Gemeinsamer Bundesausschuss

Anlage 1 zur Zusammenfassenden Dokumentation:

Organisiertes Programm zur Früherkennung von Zervixkarzinomen

Volltexte der schriftlichen Stellungnahmen 2016

Arbeitsgemeinschaft
zytologisch tätiger Ärzte in Deutschland e.V.

AZÄD

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München, 30. Mai 2016

Stellungnahme zu den Beschlußentwürfen von GKV, KBV und Patienten-vertretung zur Änderung der Krebsfrüherkennungs-Richtlinie (KFE-RL): Zervixkarzinom-Screening – Ihr Schreiben vom 3.5.2016

Sehr geehrte Damen und Herren,
sehr geehrte Frau Blümel, sehr geehrter Herr Vorsitzender,

mit Schreiben vom 3.5.2016 übersandten Sie den Beschluß des G-BA, Unterausschuß „Methodenbewertung“, vom 28.4.2016 mit dem Sie der AZÄD – Bundesverband der Zytologen – die Gelegenheit zur Stellungnahme zu den vorliegenden Beschlußentwürfen von GKV, KBV und Patientenvertretung betreffs Änderung der Krebsfrüherkennungs-Richtlinie (KFE-RL): Zervixkarzinom-Screening gegeben haben.

Für die Möglichkeit zu den verschiedenen Sachverhalten Stellung nehmen zu können, bedanke ich mich auch im Namen meines Vorstandes.

Die Stellungnahme der AZÄD enthält folgende Anlagen zu diesem Anschreiben:

1. Stellungnahme zum Gesamtkontext
2. Stellungnahme in tabellarischer Form zum Beschlußentwurf der GKV
3. Stellungnahme in tabellarischer Form zum Beschlußentwurf der KBV
4. Stellungnahme in tabellarischer Form zum Beschlußentwurf der Pat.Vertr
5. Vortragsfolien in PowerPoint-Darstellung: Vortrag Jesper Bonde
6. Vortragsfolien in PowerPoint-Darstellung: Vortrag John Smith

Mit freundlichen Grüßen

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Stellungnahme der AZÄD zu den Beschlussentwürfen von KBV, GKV und Patientenvertretung zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

Der Gemeinsame Bundesausschuss beabsichtigt, die Richtlinien für die Früherkennung von Krebserkrankungen in der Fassung vom 18. Juni 2009 zu ändern.

Hierfür liegen drei Beschlussentwürfe vor von:
1. GKV-SV, 2. KBV und 3. Patientenvertretung.

Zu den Beschlussentwürfen nimmt die AZÄD in Ergänzung zu den im E-Mail-Anhang zum Anschreiben an den G-BA tabellarisch gelisteten Punkten wie folgt Stellung:

Die Nutzenbewertung des IQWIG

Die drei Entwürfe von GKV, KBV und Patientenvertretung nehmen bei den tragenden Gründen für eine Änderung des Zervixkarzinom-Screenings Bezug auf die Nutzenbewertung des HPV Tests im Primär-Screening im Abschlußbericht S10-01 des IQWiG vom 28.11.2011 und den Rapid Report S13-03 vom 14.5.2014. In den dort zitierten fünf untersuchten Studien wurden unterschiedliche Screening-Strategien eingesetzt. Das IQWiG konnte keine Empfehlung für eine bestimmte Strategie zum Einsatz der HPV-Diagnostik aussprechen.
Zu den wenigen Gemeinsamkeiten der Studien gehörte, dass das Screening-Intervall mindestens 3 Jahre für die Zytologie betrug und das Screening in einem populationsweit organisierten und qualitätsgesicherten Kontext stattfand. Aus der Nutzenbewertung ergab sich für eine HPV-Diagnostik allein oder in Kombination mit einem Zytologie basierten Verfahren gegenüber einer ausschließlich Zytologie-basierten Strategie im Rahmen der Früherkennung des Zervixkarzinoms im Primärscreening ein Hinweis auf einen Nutzen hinsichtlich einer Reduktion des kombinierten Endpunktes CIN3+. Auch bei der Inzidenz des invasiven Zervixkarzinoms, einer Komponente des kombinierten Endpunktes, zeigten sich Hinweise darauf, dass eine HPV-Diagnostik allein oder in Kombination mit einem Zytologie basierten Verfahren zu einer niedrigeren Zervixkarzinom-Inzidenz führte als die Anwendung eines Zytologie-basierten Verfahrens allein. Eine Empfehlung für eine bestimmte Strategie zum Einsatz der HPV-Diagnostik konnte nicht ausgesprochen werden.

Inwieweit die Erkenntnisse des IQWiG, die auf einem 3-Jahres Screening-Intervall oder länger für die Zytologie beruhen, auf ein 1-Jahres-Intervall übertragen werden können, wurde nicht evaluiert. Es ist bekannt, dass längere Screening-Intervalle einen negativen Einfluss auf die Reduktion der Zervixkarzinom-Inzidenz haben (1). England verzeichnet einen Inzidenzrückgang von 44% bei einem Screening-Intervall von 3 bzw. 5 Jahren (2), Finnland 66% bei einem 5-Jahresintervall (3, 7), während Deutschland einen Inzidenzrückgang von 74% bei einem 1-Jahresintervall verzeichnet (3, 4). In Deutschland treten die meisten Zervixkarzinome bei Nicht-Teilnehmerinnen des Screening-Programmes auf (5).

Der Inzidenzrückgang invasiver Zervixkarzinome liegt bei einem 1-Jahres Screening-Intervall wie in Deutschland höher als bei einem 3-Jahresintervall oder länger wie in Finnland oder anderen europäischen Ländern, z.B. England.

Anders als in Deutschland hat sich in einigen anderen europäischen Ländern mit längeren Screeningintervallen ein "graues Screening" etabliert, bei dem Patientinnen zytologische Abstrichuntersuchungen als Krebsvorsorge außerhalb des organisierten Programms privat in Anspruch nehmen. Das graue Screening mit verkürzten Abstrichintervallen führt somit zur Detektion von Läsionen außerhalb des offiziellen Screening-Programms. In Finnland finden 55% der Abstrichuntersuchungen opportunistisch im grauen Screening statt (6).

Der Hinweis auf die Überlegenheit eines HPV-Primärscreenings im Vergleich zum Zytologie-basierten Verfahren im 3-Jahres-Rhythmus oder länger und die daraus abgeleiteten Folgerungen können nicht auf ein 1-Jahres-Screening-Intervall übertragen werden.
Da keine repräsentative Studie zum Vergleich eines 1-jährlichen Zytologie-Screenings mit einem HPV-Primärscreening vorliegt, ist unklar, welche Strategie die überlegene ist.

Daten aus den USA lassen die Sicherheit des HPV Test bezweifeln:

Studien zeigen, dass 19% der invasiven Zervixkarzinome ein negatives HPV-Testergebnis haben (8). Auch Daten zweier großer zytologischer Laboratorien aus Deutschland zeigen ähnlich hohe falsch-negativ Raten bei invasiven Zervixkarzinomen, insbesondere bei Adenokarzinomen der Cervix uteri. Eine postulierte Sensitivitätsrate von über 98 % lässt sich in der Routinediagnostik der Praxis nicht darstellen (9).

In der Athena Studie lag die Detektionsrate von CIN3+ Läsionen beim HPV-Primärscreening bei nur 58%. Das HPV-Primärscreening schnitt in der Athena Studie besser ab als die Zytologie, weil der Vergleich mit qualitativ weit unterdurchschnittlichen Zytologie-Laboratorien gezogen wurde (10).
Das Screeningintervall betrug in der Athena-Studie 3 Jahre.

Die Qualitätssicherungsvereinbarung QSV 135,2 SGB V

Die Qualitätssicherungsvereinbarung Zervix-Zytologie regelt die Modalitäten präventiver, kurativer und im Rahmen der Empfängnisregelung stattfindender zytologischer Untersuchungen in der vertragsärztlichen Versorgung. Seit 2014 sind die Jahresstatistiken zytologischer Untersuchungen von den Kassenärztlichen Vereinigungen an die KBV zu übermitteln, um den Partnern des Bundesmantelvertrages (GKV und KBV) Auswertungen zum Zweck der Evaluation und ggf. Weiterentwicklung der Qualitätssicherung zur Verfügung zu stellen.

Die vorliegenden statistischen Zahlen verweisen auf die hohe Treffsicherheit der Zytologie. Der hohe Vorhersagewert für positive zytologische Befunde bei Läsionen begründet die besondere Eignung der Zytologie im Screening. Nach einer Gruppe IV findet sich in durchschnittlich 82% der abgeklärten Fälle eine schwere Epitheldysplasie oder ein Carcinoma in situ (zusammengefasst CIN 3), in durchschnittlich 94% eine mindestens mäßiggradige Dysplasie (CIN2+ und höher).

Auch die neuesten vorliegenden Daten aus der KV-Jahresstatistik zeigen, dass neben Läsionen der Cervix uteri durch die zytologische Untersuchung weitere Malignome extrazervikaler Lokalisation gefunden werden: pro Jahr etwa 2.000 Fälle, vorwiegend Endometriumkarzinome.

Eine wichtige Erkenntnis aus der erstmals seit 2013 verwertbaren Jahresstatistik zur Zervixkarzinom-Früherkennung in Deutschland ist die über Jahre annähernd konstante Häufigkeit auffälliger zytologischer Befunde ab Gruppe III (etwa 1,6%).

Diese geringe Positivrate bestätigt die Eignung der zytologischen Untersuchung als Suchtest, da sich die Anzahl nachfolgender Kontrollen und Abklärungsuntersuchungen und damit der Anteil beunruhigter Früherkennungsteilnehmerinnen sowie die Kosten auf niedrigem Niveau bewegen.

Für das Jahr 2012 liegen für 48.904 Patientinnen histologische Befunde im Rahmen von Abklärungsuntersuchungen nach pathologischen zytologischen Diagnosen vor. **Das entspricht einer Abklärungsrate von 0,3% bezogen auf 16,2 Millionen untersuchter Frauen, eine in Bezug auf Studien zur HPV-Prävalenz (s. weiter unten) unvergleichbar niedrige Zahl abklärungsbedürftiger Befunde bei nachgewiesen hoher Treffsicherheit der Methode** (11).

Für 2016 vom RKI für die Inzidenz des Zervixkarzinoms prognostizierte Zahlen weisen einen weiteren Rückgang der Gebärmutterhalskrebserkrankungen in Deutschland aus.

Optionsmodell HPV versus Zytologie

Die AZÄD sieht mit Sorge, dass der Studienarm des HPV-Primärscreenings im geplanten Optionsmodell im Vergleich zu dem in Deutschland etablierten 1-jährlichen Intervall mit Zytologie-Screening bisher nicht an einer breiten Bevölkerungszahl untersucht wurde. Die bekannt hohen Raten HPV-Test negativer Karzinome lassen eine Zunahme der Zervixkarzinom-Inzidenz befürchten. Auch ethische Gründe verbieten deshalb eine Umstellung der Screening-Strategie auf ein neues in Feldversuchen nicht getestetes Verfahren, welches zum Nachteil der Gesundheit von Frauen in Deutschland führt.

HPV-Prävalenzen

Ein routinemäßiges HPV-Primärscreening findet bisher in keinem europäischen Land statt. Pilotstudien in England und Dänemark zeigen eine wesentlich höhere Prävalenz an HPV-positiven Patientinnen als zunächst angenommen. Die Prävalenzen betragen in Abhängigkeit vom verwendeten HPV-Testverfahren zwischen 9% (Aptima-Test) und 16% (Cobas-Test) bei Patientinnen, die älter als 30 Jahre sind (12). In England wurde sogar der Cut Off Level des Hybrid Capture HPV-Tests von 1 auf 2 (RLU>2) erhöht, um weniger HPV-positive Patientinnen zu generieren (13).
Angesichts der hohen HPV-Prävalenzraten muss bezweifelt werden, dass eine ausreichende Kapazität von Kolposkopie- bzw. Abklärungs-Sprechstunden in Deutschland für das daraus resultierende Abklärungsprozedere zur Verfügung steht. Nach den WHO Screening-Kriterien von Wilson und Jungner (14, 15) müssen aber Einrichtungen (Ressourcen) a priori verfügbar sein, die den erhöhten Versorgungsbedarf, der durch bevölkerungsbasierte Screening-Programme anfällt, abdecken.
Sollte das Optionsmodell wie geplant umgesetzt werden, müssen alle derzeitigen Leistungserbringer bei der Zervixkarzinomprävention (Gynäkologen und Pathologen), welche die entsprechenden Voraussetzungen erfüllen, HPV-Untersuchungen durchführen können.

Schaden und Akzeptanz

Die WHO Kriterien von Wilson und Jungner postulieren, dass das Risiko eines mit den Screening-Maßnahmen assoziierten physischen und psychischen Schadens nachweisbar geringer sein muss als der Nutzen (substantieller/moderater Nettonutzen). Der Beweis liegt nicht vor. Der Bericht des IQWIG konnte den Schaden bei der Nutzenbewertung des HPV-Tests im Primärscreening nicht bewerten. Positive HPV-Testergebnisse werden einen negativen Einfluss auf psychosoziale Aspekte bei den betroffenen Frauen haben. Übertherapien werden die Folge sein. Inwieweit in Kenntnis darüber die Akzeptanz und Compliance der Patientinnen gegeben sein wird, muss bezweifelt werden (16).

Datensicherheit

Die AZÄD sieht eine Gefährdung der Datensicherheit durch die geplante personen-gebundene Speicherung von Diagnosedaten. Die zunehmende Bürokratisierung und Erfassung von sensiblen Patienten-Daten verursacht dazu enorme Kosten.
Diese finanziellen Mittel werden aber in der primären Patientenversorgung benötigt.
In wieweit die zu erhebenden Daten vollständig oder überhaupt zu erfassen sind ist fraglich.
Ebenso ist zu bezweifeln, ob die Festlegung der Patientinnen auf einen Studienarm, ohne das einmal gewählte Screening wechseln zu können, realisierbar ist. Es wird nicht möglich sein, Patientinnen, die sich für eine der angebotenen Optionen entschieden haben, daran zu hindern, die Alternativmethode in Form von IGE-Leistungen oder zytologische Untersuchungen im Rahmen der Empfängnisregelung oder kurativen Leistungen zu nutzen.

Auch wird eine Optionsfestlegung durch Arztwechsel der Patientinnen unterlaufen.

2015 wurde auf dem Deutschen Ärztetag die Gefährdung der Datensicherheit im Rahmen des Optionsmodells erörtert. Der Ärztetag hat daraufhin folgenden Beschluss gefasst:

„Der Deutsche Ärztetage fordert die Bundesregierung auf, die zunehmende und kostenintensive Bürokratisierung im Gesundheitswesen zu stoppen und den Datenschutz unserer Patientinnen zu wahren." (Beschluss VI-59, 2015) (17).

Die zahlreichen Diskussionen über die Datensicherheit im Zusammenhang mit dem Optionsmodell zeigen, daß ein weiterreichendes, dazu kostenintensives personenbezogenes Überwachungssystem überflüssig ist, da die vorhandenen Strukturen von GKV und KBV gemäß SGB V zum Zweck der Evaluation und ggf. Weiterentwicklung der Qualitätssicherung ausreichen.

Fazit

Bis heute gibt es in Europa kein Land mit einem HPV-Primärscreening.
Europäische Pilotstudien sind nicht ausreichend evaluiert und noch nicht abgeschlossen. Beweise, Hinweise oder Anhaltspunkte, welche die Überlegenheit eines HPV-Primärscreenings mit einem 5-Jahresintervall gegenüber einem 1-jährlichen Zytologie-Screening belegen, liegen nicht vor.

Die vorliegenden statistischen Zahlen für die bestehende Zytologie-basierte Prävention des Zervixkarzinoms verweisen auf die hohe Treffsicherheit der Zytologie. Der hohe Vorhersagewert für positive zytologische Befunde bei Läsionen begründet die besondere Eignung der Zytologie im Screening. Neben Läsionen der Cervix uteri werden durch die zytologische Untersuchung pro Jahr ca. 2.000 extrazervikale Malignome gefunden.

Die Zahlen über HPV-negativ getestete invasive Zervixkarzinome und die in Erwägung gezogene Änderung des bestehenden Krebsfrüherkennungsprogrammes lassen eine Gefährdung der Patientinnen bei einem HPV-Primärscreening befürchten. Europäische Pilotstudien zeigen, dass die HPV-Prävalenzdaten höher liegen als erwartet.
90% der Patientinnen werden hinsichtlich der Zielläsion falsch positiv getestet. Der Schaden ist nicht kalkulierbar. Die Akzeptanz der Patientinnen für diese Methode wird durch die hohe Zahl von unnötigen Abklärungsuntersuchungen nicht gegeben sein.

Die AZÄD lehnt die Beschlussentwürfe in wesentlichen Punkten ab. Detailliert begründete Anmerkungen zu den Entwurfstexten von GKV, KBV und Patientenvertretung sind weiter unten aufgeführt. Die dortigen Begründungstexte entsprechen den Ausführungen der Deutschen Gesellschaft für Zytologie (DGZ), die von der AZÄD vollinhaltlich mitgetragen werden.

Da Daten zu Effektivität und Qualität des HPV-Primärscreenings nicht vorliegen und WHO-Kriterien für einen Screening-Test nicht erfüllt werden, fordert der Bundesverband der Zytologen (AZÄD) den G-BA auf, eine Änderung der Richtlinie über die Früherkennung von Krebserkrankungen, hier zum Zervixkarzinom-Screening, nur aufgrund evidenzbasierter Nachweise herbeizuführen.

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AZÄD S. Dominik, B. Jordan – München, den 30. Mai 2016

Gemeinsamer Bundesausschuss

Stellungnahme zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

Beschlussentwurf GKV

Deutsche Gesellschaft für Zytologie – AZÄD - Bundesverband der Zytologen	
23. Mai 2016 – 30. Mai 2016	
Stellungnahme / Änderungsvorschlag	**Begründung**
Beschlussentwurf ***§ 28 (2) e*** ***statt***: *Die Zytologiebefunde Pap I und Pap IIa sind unauffällige Befunde und werden nur bei klinischen Auffälligkeiten oder ausdrücklichen Wunsch der Versicherten mitgeteilt.* ***richtig***: *Der zytologische Befund einer Gruppe I ist ein unauffälliger Befund und erübrigt eine Befundmitteilung.*	Die Bezeichnung der zytologischen Befunde als „PAP“ entstammt der Nomenklatur von George Papanicolaou und ist in Deutschland seit den 1970er Jahren obsolet. Wie schon in der Vorgängerversion von 1990 werden die zytologischen Befunde nach der Münchner Nomenklatur III als Befundgruppen („**Gruppe** I-V“) klassifiziert [1]. Ein Befund der Gruppe II-a ist morphologisch tatsächlich unauffällig, wird jedoch vom Zytologen vergeben, weil die untersuchte Frau aufgrund pathologischer Vorbefunde einem erhöhten Risiko unterliegt. Deshalb sind mit diesem Befund je nach Vorbefund Empfehlungen für weitere Maßnahmen verknüpft. In diesem Sinne ist die Gruppe II-a im Rahmen des Abklärungsprozedere (nach auffälliger Zytologie, Histologie oder Kolposkopie) einzuordnen und nicht als „unauffällig“.
Beschlussentwurf ***§ 28 (3) d und § 29 (2) a*** *Die Zytologie-Triage ist nicht erforderlich, wenn ein HPV-Test verwendet wird, der Informationen zu den Genotypen HPV 16 und HPV 18 liefert und mindestens einer dieser Genotypen positiv ist.* ***ersatzlos streichen***	Diese Vorgabe entstammt wie andere Abklärungsstrategien der von uns abgelehnten Konsultationsfassung der S3-Leitlinie und war dort sogar nur als „Empfehlung“ (nicht als „starke Empfehlung“) mit einem sehr niedrigen Evidenzgrad (Grade +) ausgewiesen. In den europäischen Leitlinien findet sich dazu keine Aussage. HPV 16 gehört zu den häufigsten Genotypen, die bei einem HPV-Test nachgewiesen werden und sind bei erstmaligem Nachweis überwiegend Ausdruck einer passageren Infektion. Daher sollte wie beim Nachweis anderer HPV Genotypen mit kanzerogenem Potential eine zytologische Untersuchung erfolgen. Auch bei einer HPV-Infektion mit den Genotypen 16 und 18 können sowohl kolposkopische Normalbefunde vorliegen (z.B. im Falle einer Virusinfektion ohne Läsion) als auch kolposkopische minor changes (Metaplasie oder CIN1) oder major changes (CIN2 oder CIN3), des Weiteren verhindern bestimmte klinische Konstellationen einen aussagekräftigen kolposkopischen Befund. Da die Kolposkopie z. B. den risikolosen Befund einer Metaplasie nicht von dem einer CIN 1 zu unterscheiden vermag und bei diesen minor changes auch Biopsien eine erhebliche Unsicherheit aufweisen [2], sollte bei einer kolposkopischen Untersuchung ein zytologischer Befund vorliegen.
Beschlussentwurf	Diese für den Gesetzestext vorgesehenen Vorgaben für die

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§ 29 *1. Abklärungsalgorithmus …* *a. Bei den Primärscreeningbefunden Pap III-p, III-x, III-e, III-g soll bereits innerhalb von 3 Monaten ein HPV-Test durchgeführt werden, bei II-p, II-g, II-e, IIID1 erst in 6 Monaten. Bei einem positiven HPVTest soll innerhalb von 3 Monaten eine Abklärungskolposkopie erfolgen. Bei einem negativen HPV-Test soll nach 12 Monaten eine klinische Untersuchung und Ko-Testung (Zytologie und HPV-Test) erfolgen. Ist mindestens einer dieser Tests positiv, soll innerhalb 3 Monaten eine Abklärungskolposkopie erfolgen. Bei Frauen unter 25 Jahren soll nur in begründeten Ausnahmefällen eine Abklärungskolposkopie durchgeführt werden. Stattdessen soll die klinische Untersuchung und Ko-Testung (Zytologie und HPV-Test) im Abstand von mindestens 12 Monaten wiederholt werden.* *b. Bei den Primärscreeningbefunden Pap III-D2 soll innerhalb eines Monats eine Abklärungskolposkopie erfolgen.*	Abklärung auffälliger zytologischer Befunde sind offenbar ohne Sachkenntnis erstellt, fachlich unhaltbar und gefährden deshalb die Patientinnen, wie die folgenden Beispiele zeigen. - Hinter den Gruppen III-p und III-g kann sich sowohl eine CIN2/3 bzw. ein AIS verbergen als auch ein invasives Plattenepithel- oder Adenokarzinom: Dies ist Inhalt des Wortgutachtens, das der Zytologe der Befundgruppe beifügt und wovon sinnvollerweise das weitere Prozedere abhängt [3]. Es wäre für die Patientin fatal und für den Frauenarzt justiziabel, z.B. bei Gruppe III-p mit Karzinomverdacht womöglich erst in 3 Monaten einen HPV-Test durchzuführen anstatt einer sofortigen Kolposkopie. Bei Gruppe III-e ist es notwendig, ein Endometriumkarzinom auszuschließen bzw. zu diagnostizieren, bei Gruppe III-x ein Malignom des Uterus oder anderen Ursprungs – hier handelt es sich prinzipiell um nicht HPV-assoziierte Erkrankungen, sodass der HPV-Test keinen sinnvollen Beitrag für die Abklärung liefert und gegebenenfalls sogar zu einer Diagnoseverschleppung führen kann. Nach den 2015 publizierten Empfehlungen der Arbeitsgemeinschaft Zervixpathologie und Kolposkopie [2] ist eine Kolposkopie nach einer erstmalig vergebenen Gruppe III nur verzichtbar, wenn nach dem Wortgutachten des Zytologen kein Karzinomverdacht besteht. - Ein HPV-Test bei einer Gruppe IIID1 ist wenig effektiv, da er in mehr als 80% positiv ist [4]. Die adäquate Abklärung einer Gruppe IIID1 ist eine zytologische Untersuchung in 6 Monaten und bei Persistenz dieses Befundes über mehr als 12 Monate eine Kolposkopie. Die Kolposkopie dient hier nicht der Bestätigung der Diagnose einer CIN1, sondern dem Ausschluss einer höhergradigen CIN bzw. eines Karzinoms. - Eine Kolposkopie sollte auch bei Frauen unter 25 Jahren z.B. bei mehr als 12 Monate persistierender Gruppe IIID1, mehr als 6 Monate persistierender Gruppe IIID2 oder bei Gruppe III-p oder III-g erfolgen, da sich in diesen Fällen nicht selten eine CIN3 findet. - Eine unmittelbare Kolposkopie bei einer erstmalig aufgetretenen Gruppe IIID2 entspricht einer Überdiagnostik. Nach den Empfehlungen der Arbeitsgemeinschaft Zervixpathologie und Kolposkopie [2] wird bei erstmaliger Gruppe IIID2 ohne zusätzliche Risiken eine Kolposkopie innerhalb von 3-6 Monaten

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	favorisiert. Zusammenfassend sind – unabhängig von den im Beschlussentwurf zum Abklärungsprozedere gemachten wissenschaftlich unhaltbaren und laienhaften Vorgaben - detaillierte Vorschriften in einem Gesetzestext grundsätzlich abzulehnen. Komplexe medizinische Sachverhalte mit sich verändernden diagnostischen und therapeutischen Optionen müssen außerdem der individuellen Situation der Patientin angepasst werden, um Schaden von ihr abzuwenden.
§ 29 2. c. *„PAP IIIc“?*	Diese Gruppe ist nicht Bestandteil der Münchner Nomenklatur III.
Tragende Gründe ***2.2. Nutzenbewertung des HPV-Tests im Primärscreening*** *…, so dass inzwischen neben dem Pap-Test auch ein HPV-Tests zur Früherkennung des Zervixkarzinoms verwendet werden kann.*	Die Aussage, dass „auch ein HPV-Test zur Früherkennung des Zervixkarzinoms verwendet werden kann“, ist falsch: mit einem positiven HPV-Test weist man nur eine HPV-Infektion im Range eines Risikofaktors nach, nicht aber ein Zervixkarzinom oder seine Vorstufen. Bei einem positiven HPV-Test liegt nur zu 3-4% eine therapiepflichtige Krebsvorstufe und extrem selten ein Zervixkarzinom vor. Im Gegensatz zu diesem extrem schlechten positiven Prädiktionswert wird der vergleichsweise hohe negative prädiktive Wert gern hervorgehoben, der aber mit ca. 90% für einen Screening-Test mit 5jährigem Intervall ebenfalls inakzeptabel ist (s.u.).
Tragende Gründe ***2.3.3. Screeningstrategien S. 5/6*** *…Es wird ein HPV-basiertes Primärscreening mit mindestens 5 Jahresintervall und unmittelbarer Zytologie-Triage ab einem Alter von 35 Jahren in einem organisierten Programm empfohlen. Das HPV-basierte Screening sollte nicht vor dem Alter von 30 Jahren begonnen werden. Für das Alter 30 – 34 Jahre gibt es keine eindeutige Evidenz für oder gegen ein HPV-basierte Screening.* *…Das HPV-basierte Screening wird Frauen bereits ab dem Alter von 30*	Ein HPV-Test in fünfjährigem Intervall ist als Maßnahme zur Vorsorge nicht geeignet. Der alleinige HPV-Test ist von einer beachtlichen Falsch-Negativ Rate in der Detektion hochgradiger Läsionen und invasiver Karzinome behaftet [5-11]. Insbesondere auch frühinvasive Karzinome weisen eine stark reduzierte Viruslast in der Läsion auf und entgehen damit den HPV-Screening-Verfahren [12]. Folglich ist bei dem vorgeschlagenen 5-Jahres-Modell mit einer Häufung von Intervallkarzinomen zu rechnen [13]. HPV-unabhängige Malignome, die im zytologischen Screening gefunden werden können, werden im primären HPV-Screening als Screeningversager in Kauf genommen. Dies steht ethisch im Widerspruch zum etablierten Vorsorgesystem, in dem keine Patientengruppe definiert ist, die von vornherein von einem Screeningerfolg ausgeschlossen wird. Die Akzeptanz in der weiblichen Bevölkerung ist voraussichtlich auch in Deutschland gering mit folglich starker Zunahme eines sogenannten grauen Screenings [14]. In Finnland, das das angesprochene 5-Jahres-Modell mit Register und Einladung der Screening-Teilnehmerinnen seit Jahren praktiziert, wurden 2000-2008 lediglich etwa 11% der invasiven Zervixkarzinome innerhalb des organisierten Screenings entdeckt [15-17]. Ein

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Jahren angeboten, da die Inzidenz des invasiven Karzinoms bereits in diesem Alter einen deutlichen Anstieg zeigt und am in situ Karzinom erkranken Frauen im Mittel bereits mit 34 Jahren (RKI: Krebs in Deutschland 2015).	„graues“ Screening in Deutschland im Rahmen der Individuellen Gesundheitsleistungen („IGeL“) ginge zu Lasten der nicht teilnehmenden und häufig sozial unterprivilegierten Frauen mit der höchsten Inzidenz an Zervixkarzinomen. Ein primäres HPV-Screening führt zu einer unverhältnismäßig hohen Zahl von Frauen mit einem positiven Testergebnis ohne entsprechende Erkrankung, da die nachgewiesene Virus-DNA nur die Infektion, nicht aber eine Läsion dokumentiert. Die Screening-Teilnehmerinnen würden somit der Gefahr einer Überdiagnostik und Übertherapie ausgesetzt, unnötige Ängste der positiv getesteten Frauen bedeuten eine Reduktion ihrer Lebensqualität [18-20]. Die Empfehlung aus den 2015 von der Europäischen Kommission veröffentlichten Supplements zu den Europäischen Leitlinien, das primäre HPV-Screening mit 35 Jahren zu beginnen [21], wird mit der Begründung ignoriert, dass die Inzidenz des invasiven Karzinoms über 30 bereits deutlich ansteigt und an einer Präkanzerose im Range eines Carcinoma in situ (CIN3) Frauen im Mittel bereits mit 34 Jahren erkranken. Aus den zugänglichen Daten des Robert-Koch-Instituts geht allerdings nicht hervor, ob nicht die Zunahme der Karzinome ab 30 vor allem durch eine Zunahme frühinvasiver Karzinome bedingt ist, wie das in Mecklenburg-Vorpommern der Fall ist [22]. Unabhängig davon, dass das primäre HPV-Screening aus den oben angeführten Gründen ohnehin abzulehnen ist, bedeutet ein Beginn mit bereits 30 Jahren eine Gefährdung der Teilnehmerinnen vor allem wegen der extrem hohen Anzahl falsch positiver Befunde und damit verbundener Überdiagnostik und Übertherapie gerade dieser Frauen im bevorzugten Gebäralter. Es ist unverständlich, warum das 30. Lebensjahr bei der vorliegenden Datenlage und sogar in Widerspruch zu den ansonsten stets herangezogenen Europäischen Leitlinien als Eintrittsalter für das primäre HPV-Screening empfohlen wird. Aus der Erkenntnis, dass Frauen < 30 Jahren häufiger HPV-positiv sind als Frauen > 30 Jahren, wird die Festlegung für ein zytologisches Screening für Frauen < 30 Jahren und ein HPV-Screening > 30 Jahren getroffen. Der Abfall der HPV-Prävalenz erfolgt in Abhängigkeit vom Lebensalter in kleinen Schritten [23, 24]. Die HPV-Prävalenz von 31-jährigen Frauen unterscheidet sich nur marginal von denen 29-jähriger. Bei 35-jährigen Frauen liegt sie lediglich wenige Prozentpunkte unter der von 30-jährigen. Erst nach dem 40. Lebensjahr kommt es zu einem deutlicheren Abfall der HPV-Prävalenz. Die Grenzwertfestlegung bei 30 Jahren für Screeningverfahren und -intervall erfolgt somit willkürlich. Eine sinnvolle Alternative zum jährlichen zytologischen Screening auch nach dem 30. Lebensjahr wäre hingegen das

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	sogenannte Co-Testing ab dem 35. Lebensjahr (zytologische Untersuchung in Kombination mit einem adäquaten HPV-Test) in einem dreijährigen Intervall: die Kompensation der Schwäche der einen Methode durch die Stärke des anderen Verfahrens gewährleistet die Sicherheit für die teilnehmenden Frauen (die geringere Sensitivität der Zytologie und ihre hohe positive Prädiktion im Zusammenspiel mit der hohen negativen Prädiktion und schlechten Spezifität des HPV-Testes). Der Erfolg dieser Vorgehensweise ist in der aktuellen Literatur belegt [8-10, 20, 25, 26]. Insbesondere bei einer Intervallverlängerung von mehr als drei Jahren besteht die Gefahr einer Reduktion der Teilnahmerate am organisierten Screening [27]. Dies muss unbedingt vermieden werden, da unter den Zervixkarzinom-Patientinnen die Nicht-Teilnehmerinnen die meisten und die fortgeschrittenen Karzinome aufweisen [22].
2.3.3. Screeningstrategien S. 6 *Wenn für das TriageVerfahren die konventionelle Zytologie verwendet wird, gibt es zwei Möglichkeiten für die Organisation des Triage-Verfahrens:* *a) Es wird bei allen Frauen, die das HPV-basierte Screening wählen, mit dem Abstrich für den HPV-Test noch ein zusätzlicher Abstrich für die Zytologie abgenommen. Der Abstrich für die konventionelle Zytologie muss auf einem Objektträger fixiert und beim Gynäkologen oder im Labor aufbewahrt werden, bis das Ergebnis des HPV-Tests vorliegt. Ca. 10% der HPV-Tests sind positiv. Das bedeutet, dass ca. 90% der angefertigten Objektträger verworfen werden.* *b) Es wird bei allen Frauen, die das HPV-basierte Screening wählen, nur ein Abstrich für den HPV-Test abgenommen. Wenn der HPV-Test positiv ist, muss die Frau erneut einbestellt*	a) Diese Vorgehensweise ist als indiskutabel abzulehnen. Sie würde bedeuten, dass Untersuchungsmaterial vorliegt, aber keine Untersuchung vorgenommen wird – rechtlich ist dies wahrscheinlich nicht zulässig, insbesondere wenn bei Auftreten von Intervallkarzinomen nachträglich festgestellt wird, dass zum Zeitpunkt der Abnahme für den HPV-Test bereits zytologisch ein Hochrisikobefund hätte nachgewiesen werden können. In der gynäkologischen Praxis könnten diese Objektträger nicht aufbewahrt werden, weil ohne Eindeckung die Gefahr des Materialverlustes besteht. Ein Eindecken des Objektträgers setzt aber die Färbung voraus, sodass die Archivierung nur im zytologischen Labor nach Färbung und Eindeckung erfolgen könnte. Natürlich muss dann auch eine ordnungsgemäße Registrierung incl. Erfassung der Patientendaten vorgenommen werden. Dies müsste in der Gebührenordnung entsprechend als Leistung aufgeführt und bezahlt werden, b) Als einziges Gegenargument gegen eine Einbestellung der Frauen wird genannt: „*Bei diesem Vorgehen besteht das Risiko, dass ein positiver HPV-Test nicht oder verzögert abgeklärt wird.*“ Dieses „Risiko“ besteht bei jedem auffälligen Screening-Befund und ist somit irrelevant.

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und ein Abstrich für die konventionelle Zytologie abgenommen werden. Bei diesem Vorgehen besteht das Risiko, dass ein positiver HPV-Test nicht oder verzögert abgeklärt wird.	
2.3.4. Abklärungsdiagnostik S. 7 *Das zytologiebasierte Screening ist unauffällig bei Pap I und Pap IIa gemäß der Münchner Nomenklatur III. … In diesen Fällen wird das Primärscreening in den vorgegeben Zeitabständen durchgeführt.*	***Begründung s.o. Beschlussentwurf § 28 (2) e*** einfach nur „II-a“ streichen
2.3.4. Abklärungsdiagnostik S. 7/8 *Für das Management auffälliger Screeningbefunde werden für die verschiedenen Screeningstrategien Algorithmen für die Abklärungsdiagnostik vorgegeben. Die Abklärungsdiagnostik orientiert sich an den Empfehlungen der aktuellen deutschen S3 Leitlinien zur Prävention des Zervixkarzinoms (Konsultationsfassung vom 01.03.2016).* ***S.7 und 8*** *(Schema)* ***S. 8*** *Bereits bei Minor Changes ist eine Abklärung durch eine Biopsie erforderlich.*	Gemeinsam mit den anderen an der Versorgung der Frauen im Rahmen des Zervixkarzinom-Früherkennungsprogramms beteiligten Ärzte (Berufsverband der Frauenärzte, Arbeitsgemeinschaft Zervixpathologie und Kolposkopie der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe, Arbeitsgemeinschaft Zytologisch Tätiger Ärzte in Deutschland, Bundesverband deutscher Pathologen und Berufsverband zytologisch tätiger Akademiker in Deutschland) hat die Deutsche Gesellschaft für Zytologie die o.g. Konsultationsfassung der S3-Leitlinie am 10.04.2016 abgelehnt. Dafür waren vor allem fachliche Defizite des Leitlinien-Entwurfs maßgeblich, die sich auch in den vorgeschlagenen Abklärungsalgorithmen niederschlagen. Die Begründung dafür ist in unserem Ablehnungsschreiben enthalten (das der G-BA am 10.04. 2016 erhalten hat) und soll hier nicht im Einzelnen wiedergegeben werden. Bereits weiter oben haben wir aufgeführt, aus welchen Gründen die für den Richtlinientext vorgesehenen Vorgaben für die Abklärung strikt abzulehnen sind. Als weiteres Beispiel für inakzeptable pauschale Vorgaben widerspricht diese Forderung den gültigen Empfehlungen zur Kolposkopie. Es gibt keine Indikation für eine Biopsie bei „minor changes“, da derartige Befunde in der Regel physiologische Veränderungen sind oder maximal einer CIN1 entsprechen. Ausnahmen sind diskrepante Befunde (z.B. zytologisch Gruppe IV, V, Gruppe III mit Wortgutachten „Karzinom denkbar“ in Kombination mit kolposkopischen „minor changes“). Hier sind Target-Biopsien, ggf. Random-Biopsien, ggf. eine Zervix-Kürettage indiziert [2]**.**

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	Grundsätzlich bei „minor changes“ durchgeführte Biopsien bedeuten Überdiagnostik: nicht indizierte invasive Eingriffe, die die Integrität eines Organs verletzen. Sie würden außerdem zu einer nicht vertretbaren Zahl histologischer Abklärungen führen.
2.4. Fazit *… Durch die Anwendung des HPV-Tests im Primärscreening kann die Inzidenz von invasiven Zervixkarzinomen weiter gesenkt werden.*	Diese Behauptung ist nicht belegt. Sie entstammt nicht dem IQWiG-Bericht. Weder in den dabei ausgewerteten Studien noch in irgendeiner anderen Publikation findet sich dafür Evidenz, insbesondere nicht für industrialisierte Länder.

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Gemeinsamer Bundesausschuss

Stellungnahme zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

Beschlussentwurf KBV

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Stellungnahme / Änderungsvorschlag	**Begründung**
Beschlussentwurf ***§ 24***	Im Vergleich zu den entsprechenden Passagen in den Entwürfen von GKV und Patientenvertretung ist zu unterstützen, dass im KBV-Entwurf die frühinvasiven Zervixkarzinome (ca. 25% aller Karzinome) ihrer exzellenten Prognose wegen wie die Krebsvorstufen als Zielläsion der Früherkennung benannt werden.
Tragende Gründe ***2.3.3 Screeningstrategien*** *Es wird ein HPV-basiertes Primärscreening mit mindestens 5 Jahresintervall und unmittelbarer Zytologie-Triage ab einem Alter von 35 Jahren in einem organisierten Programm empfohlen. Das HPV-basierte Screening sollte nicht vor dem Alter von 30 Jahren begonnen werden. Für das Alter 30 – 34 Jahre gibt es keine eindeutige Evidenz für oder gegen ein HPV-basierte Screening.* *…Das HPV-basierte Screening wird Frauen bereits ab dem Alter von 30 Jahren angeboten, da die Inzidenz des invasiven Karzinoms bereits in diesem Alter einen deutlichen Anstieg zeigt und am in situ Karzinom Frauen im Mittel bereits mit 34 Jahren erkranken …*	Ein HPV-Test in fünfjährigem Intervall erscheint als Maßnahme zur Vorsorge nicht geeignet. Der alleinige HPV-Test ist von einer beachtlichen Falsch-Negativ-Rate in der Detektion hochgradiger Läsionen und invasiver Karzinome behaftet [1-7]. Insbesondere auch frühinvasive Karzinome weisen eine stark reduzierte Viruslast in der Läsion auf und entgehen damit den HPV-Screening-Verfahren [8]. Folglich ist bei dem vorgeschlagenen 5-Jahres-Modell mit einer Häufung von Intervallkarzinomen zu rechnen [9]. HPV-unabhängige Malignome, die im zytologischen Screening gefunden werden können, werden im primären HPV-Screening als Screeningversager in Kauf genommen. Dies steht ethisch im Widerspruch zum etablierten Vorsorgesystem, in dem keine Patientengruppe definiert ist, die von vornherein von einem Screeningerfolg ausgeschlossen wird. Die Akzeptanz in der weiblichen Bevölkerung ist voraussichtlich auch in Deutschland gering mit folglich starker Zunahme eines sogenannten grauen Screenings [10]. In Finnland, das das angesprochene 5-Jahres-Modell mit Register und Einladung der Screening-Teilnehmerinnen seit Jahren praktiziert, wurden 2000-2008 lediglich etwa 11% der invasiven Zervixkarzinome innerhalb des organisierten Screenings entdeckt [11-13]. Ein „graues“ Screening in Deutschland im Rahmen der Individuellen Gesundheitsleistungen („IGeL“) ginge zu Lasten der nicht teilnehmenden und häufig sozial unterprivilegierten Frauen mit der höchsten Inzidenz an Zervixkarzinomen. Ein primäres HPV-Screening führt zu einer unverhältnismäßig hohen Zahl von Frauen mit einem positiven Testergebnis ohne entsprechende Erkrankung, da die nachgewiesene Virus-DNA nur die Infektion, nicht aber eine Läsion dokumentiert. Die Screening-Teilnehmerinnen würden somit der Gefahr einer Überdiagnostik und Übertherapie ausgesetzt, unnötige Ängste der positiv getesteten Frauen bedeuten eine Reduktion ihrer Lebensqualität [14-16].

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	Die Empfehlung aus den 2015 von der Europäischen Kommission veröffentlichten Supplements zu den Europäischen Leitlinien, das primäre HPV-Screening mit 35 Jahren zu beginnen [17], wird mit der Begründung ignoriert, dass die Inzidenz des invasiven Karzinoms über 30 bereits deutlich ansteigt und an einer Präkanzerose im Range eines Carcinoma in situ (CIN3) Frauen im Mittel bereits mit 34 Jahren erkranken. Aus den zugänglichen Daten des Robert-Koch-Instituts geht allerdings nicht hervor, ob nicht die Zunahme der Karzinome ab 30 vor allem durch eine Zunahme frühinvasiver Karzinome bedingt ist, wie das in Mecklenburg-Vorpommern der Fall ist [18]. Unabhängig davon, dass das primäre HPV-Screening aus den oben angeführten Gründen ohnehin abzulehnen ist, bedeutet ein Beginn mit bereits 30 Jahren eine Gefährdung der Teilnehmerinnen vor allem wegen der extrem hohen Anzahl falsch positiver Befunde und damit verbundener Überdiagnostik und Übertherapie gerade dieser Frauen im bevorzugten Gebäralter. Es ist unverständlich, warum das 30. Lebensjahr bei der vorliegenden Datenlage und sogar in Widerspruch zu den ansonsten stets herangezogenen Europäischen Leitlinien als Eintrittsalter für das primäre HPV-Screening empfohlen wird. Aus der Erkenntnis, dass Frauen < 30 Jahren häufiger HPV-positiv sind als Frauen > 30 Jahren, wird die Festlegung für ein zytologisches Screening für Frauen < 30 Jahren und ein HPV-Screening > 30 Jahren getroffen. Der Abfall der HPV-Prävalenz erfolgt in Abhängigkeit vom Lebensalter in kleinen Schritten [19, 20]. Die HPV-Prävalenz von 31-jährigen Frauen unterscheidet sich nur marginal von denen 29-jähriger. Bei 35-jährigen Frauen liegt sie lediglich wenige Prozentpunkte unter der von 30-jährigen. Erst nach dem 40. Lebensjahr kommt es zu einem deutlicheren Abfall der HPV-Prävalenz. Die Grenzwertfestlegung bei 30 Jahren für Screeningverfahren und -intervall erfolgt somit willkürlich. Eine sinnvolle Alternative zum jährlichen zytologischen Screening auch nach dem 30. Lebensjahr wäre hingegen das sogenannte Co-Testing ab dem 35. Lebensjahr (zytologische Untersuchung in Kombination mit einem adäquaten HPV-Test) in einem dreijährigen Intervall: die Kompensation der Schwäche der einen Methode durch die Stärke des anderen Verfahrens gewährleistet die Sicherheit für die teilnehmenden Frauen (die geringere Sensitivität der Zytologie und ihre hohe positive Prädiktion im Zusammenspiel mit der hohen negativen Prädiktion und schlechten Spezifität des HPV-Testes). Der Erfolg dieser Vorgehensweise ist in der aktuellen Literatur belegt [4-6, 16, 21, 22]. Insbesondere bei einer Intervallverlängerung von mehr als drei Jahren besteht die Gefahr einer Reduktion der Teilnahmerate am organisierten Screening [23]. Dies muss

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	unbedingt vermieden werden, da unter den Zervixkarzinom-Patientinnen die Nicht-Teilnehmerinnen die meisten und die fortgeschrittenen Karzinome aufweisen [18].
2.3.4 Abklärungsdiagnostik	Wir begrüßen ausdrücklich, dass in diesem Entwurf für das Management auffälliger Screening-Befunde keine detaillierten Algorithmen vorgegeben werden. Bei der Vielfalt von Befundkonstellationen und unterschiedlichsten Gegebenheiten für die einzelne Screening-Teilnehmerin ist ein allgemeingültiger Algorithmus nicht festzuschreiben, im Übrigen fehlt dafür die Evidenz. Bei Vorliegen einer akzeptierten S3-Leitlinie zur Prävention des Zervixkarzinoms könnten deren Empfehlungen angewendet werden. Dies ist in absehbarer Zeit leider nicht der Fall, da die Konsultationsfassung vom 29.03.2016 von sämtlichen potentiellen Anwendern als fehlerbehaftet und nicht umsetzbar eingestuft wurde. Deshalb ist nach wie vor eine Abklärung entsprechend der Empfehlungen der Münchner Nomenklatur III (Addendum, publiziert im Januar 2015 in „Frauenarzt“ [24]) und der Empfehlungen der Arbeitsgemeinschaft Zervixpathologie und Kolposkopie (publiziert im September 2015 in gyn [25]) vorzunehmen. Die notwendigen Maßnahmen werden im Konsens mit der Patientin an ihre individuelle Situation angepasst.
Anlage I ***HPV-Impfstatus*** ***Zytologische Untersuchung*** *1. Abstrich-Qualität* *Material nicht verwertbar* *Endozervikale Zellen vorhanden / nicht vorhanden* *2. Proliferationsgrad* *3. Flora* *4. Befundgruppe* *5. Bemerkung ggf. Freitext* *6. Empfohlene Maßnahme* *Zytologische Kontroll-Untersuchung (ggf. nach Entzündungsbehand-lung/Östrogenbehandlung bzw. nach Intervall) HPV-Test* *Kolposkopie ggf. inkl. Histologie* *Sonstiges*	Hier sollte der Impfstoff erfasst werden (bisher kamen 2fach- und 4fach-Impfstoffe zum Einsatz, jetzt auch ein nonavalenter Impfstoff). 2. und 3. müssen zwar vom Zytologen im Befund dokumentiert werden, sind jedoch im Rahmen der elektronischen Dokumentation zur Datenerfassung entbehrlich. 5. und 6. sollte unbedingt nur als Freitext erfasst werden

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Gemeinsamer Bundesausschuss

Stellungnahme zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

Beschlussentwurf Patientenvertretung

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Stellungnahme / Änderungsvorschlag	**Begründung**
Beschlussentwurf ***§ 28 (2) e*** ***statt***: *Die Zytologiebefunde Pap I und Pap IIa sind unauffällige Befunde und werden nur bei klinischen Auffälligkeiten oder ausdrücklichen Wunsch der Versicherten mitgeteilt.* ***richtig***: *Der zytologische Befund einer Gruppe I ist ein unauffälliger Befund und erübrigt eine Befundmitteilung.*	Die Bezeichnung der zytologischen Befunde als „PAP“ entstammt der Nomenklatur von George Papanicolaou und ist in Deutschland seit den 1970er Jahren obsolet. Wie schon in der Vorgängerversion von 1990 werden die zytologischen Befunde nach der Münchner Nomenklatur III als Befundgruppen („**Gruppe** I-V“) klassifiziert [1]. Ein Befund der Gruppe II-a ist morphologisch tatsächlich unauffällig, wird jedoch vom Zytologen vergeben, weil die untersuchte Frau aufgrund pathologischer Vorbefunde einem erhöhten Risiko unterliegt. Deshalb sind mit diesem Befund je nach Vorbefund Empfehlungen für weitere Maßnahmen verknüpft. In diesem Sinne ist die Gruppe II-a im Rahmen des Abklärungsprozedere (nach auffälliger Zytologie, Histologie oder Kolposkopie) einzuordnen und nicht als „unauffällig“.
Beschlussentwurf ***§ 28 (3) d und § 29 (2) a*** *Die Zytologie-Triage ist nicht erforderlich, wenn ein HPV-Test verwendet wird, der Informationen zu den Genotypen HPV 16 und HPV 18 liefert und mindestens einer dieser Genotypen positiv ist.* ***ersatzlos streichen***	Diese Vorgabe entstammt wie andere Abklärungsstrategien der von uns abgelehnten Konsultationsfassung der S3-Leitlinie und war dort sogar nur als „Empfehlung“ (nicht als „starke Empfehlung“) mit einem sehr niedrigen Evidenzgrad (Grade +) ausgewiesen. In den europäischen Leitlinien findet sich dazu keine Aussage. HPV 16 gehört zu den häufigsten Genotypen, die bei einem HPV-Test nachgewiesen werden und sind bei erstmaligem Nachweis überwiegend Ausdruck einer passageren Infektion. Daher sollte wie beim Nachweis anderer HPV Genotypen mit kanzerogenem Potential eine zytologische Untersuchung erfolgen. Auch bei einer HPV-Infektion mit den Genotypen 16 und 18 können sowohl kolposkopische Normalbefunde vorliegen (z.B. im Falle einer Virusinfektion ohne Läsion) als auch kolposkopische minor changes (Metaplasie oder CIN1) oder major changes (CIN2 oder CIN3), des Weiteren verhindern bestimmte klinische Konstellationen einen aussagekräftigen kolposkopischen Befund. Da die Kolposkopie z. B. den risikolosen Befund einer Metaplasie nicht von dem einer CIN 1 zu unterscheiden vermag und bei diesen minor changes auch Biopsien eine erhebliche Unsicherheit aufweisen [2], sollte bei einer kolposkopischen Untersuchung ein zytologischer Befund vorliegen.

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Beschlussentwurf ***§ 29*** *1. Abklärungsalgorithmus …* *a. Bei den Primärscreeningbefunden Pap III-p, III-x, III-e, III-g soll bereits innerhalb von 3 Monaten ein HPV-Test durchgeführt werden, bei II-p, II-g, II-e, IIID1 erst in 6 Monaten. Bei einem positiven HPVTest soll innerhalb von 3 Monaten eine Abklärungskolposkopie erfolgen. Bei einem negativen HPV-Test soll nach 12 Monaten eine klinische Untersuchung und Ko-Testung (Zytologie und HPV-Test) erfolgen. Ist mindestens einer dieser Tests positiv, soll innerhalb 3 Monaten eine Abklärungskolposkopie erfolgen. Bei Frauen unter 25 Jahren soll nur in begründeten Ausnahmefällen eine Abklärungskolposkopie durchgeführt werden. Stattdessen soll die klinische Untersuchung und Ko-Testung (Zytologie und HPV-Test) im Abstand von mindestens 12 Monaten wiederholt werden.* *b. Bei den Primärscreeningbefunden Pap III-D2 soll innerhalb eines Monats eine Abklärungskolposkopie erfolgen.*	Diese für den Gesetzestext vorgesehenen Vorgaben für die Abklärung auffälliger zytologischer Befunde sind offenbar ohne Sachkenntnis erstellt, fachlich unhaltbar und gefährden deshalb die Patientinnen, wie die folgenden Beispiele zeigen. - Hinter den Gruppen III-p und III-g kann sich sowohl eine CIN2/3 bzw. ein AIS verbergen als auch ein invasives Plattenepithel- oder Adenokarzinom: Dies ist Inhalt des Wortgutachtens, das der Zytologe der Befundgruppe beifügt und wovon sinnvollerweise das weitere Prozedere abhängt [3]. Es wäre für die Patientin fatal und für den Frauenarzt justiziabel, z.B. bei Gruppe III-p mit Karzinomverdacht womöglich erst in 3 Monaten einen HPV-Test durchzuführen anstatt einer sofortigen Kolposkopie. Bei Gruppe III-e ist es notwendig, ein Endometriumkarzinom auszuschließen bzw. zu diagnostizieren, bei Gruppe III-x ein Malignom des Uterus oder anderen Ursprungs – hier handelt es sich prinzipiell um nicht HPV-assoziierte Erkrankungen, sodass der HPV-Test keinen sinnvollen Beitrag für die Abklärung liefert und gegebenfalls sogar zu einer Diagnoseverschleppung führen kann. Nach den 2015 publizierten Empfehlungen der Arbeitsgemeinschaft Zervixpathologie und Kolposkopie [2] ist eine Kolposkopie nach einer erstmalig vergebenen Gruppe III nur verzichtbar, wenn nach dem Wortgutachten des Zytologen kein Karzinomverdacht besteht. - Ein HPV-Test bei einer Gruppe IIID1 ist wenig effektiv, da er in mehr als 80% positiv ist [4]. Die adäquate Abklärung einer Gruppe IIID1 ist eine zytologische Untersuchung in 6 Monaten und bei Persistenz dieses Befundes über mehr als 12 Monate eine Kolposkopie. Die Kolposkopie dient hier nicht der Bestätigung der Diagnose einer CIN1, sondern dem Ausschluss einer höhergradigen CIN bzw. eines Karzinoms. - Eine Kolposkopie sollte auch bei Frauen unter 25 Jahren z.B. bei mehr als 12 Monate persistierender Gruppe IIID1, mehr als 6 Monate persistierender Gruppe IIID2 oder bei Gruppe III-p oder III-g erfolgen, da sich in diesen Fällen nicht selten eine CIN3 findet. - Eine unmittelbare Kolposkopie bei einer erstmalig aufgetretenen Gruppe IIID2 entspricht einer Überdiagnostik. Nach den 2015 publizierten Empfehlungen der Arbeitsgemeinschaft Zervixpathologie und Kolposkopie [2] wird bei erstmaliger Gruppe IIID2

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	ohne zusätzliche Risiken eine Kolposkopie innerhalb von 3-6 Monaten favorisiert. Zusammenfassend sind – unabhängig von den im Beschlussentwurf zum Abklärungsprozedere gemachten wissenschaftlich unhaltbaren und laienhaften Vorgaben - detaillierte Vorschriften in einem Gesetzestext grundsätzlich abzulehnen. Komplexe medizinische Sachverhalte mit sich verändernden diagnostischen und therapeutischen Optionen müssen außerdem der individuellen Situation der Patientin angepasst werden, um Schaden von ihr abzuwenden.
§ 29 2. c. *„PAP IIIc“?*	Diese Gruppe ist nicht Bestandteil der Münchner Nomenklatur III.
Tragende Gründe ***2.2. Nutzenbewertung des HPV-Tests im Primärscreening*** *…, so dass inzwischen neben dem Pap-Test auch ein HPV-Tests zur Früherkennung des Zervixkarzinoms verwendet werden kann.*	Die Aussage, dass „auch ein HPV-Test zur Früherkennung des Zervixkarzinoms verwendet werden kann“, ist falsch: mit einem positiven HPV-Test weist man nur eine HPV-Infektion im Range eines Risikofaktors nach, nicht aber ein Zervixkarzinom oder seine Vorstufen. Bei einem positiven HPV-Test liegt nur zu 3-4% eine therapiepflichtige Krebsvorstufe und extrem selten ein Zervixkarzinom vor. Im Gegensatz zu diesem extrem schlechten positiven Prädiktionswert wird der vergleichsweise hohe negative prädiktive Wert gern hervorgehoben, der aber mit ca. 90% für einen Screening-Test mit 5jährigem Intervall ebenfalls inakzeptabel ist (s.u.).
Tragende Gründe ***2.3.1. Ziele und Grundlagen des Zervixkarzinom-Screenings*** *… Gleichzeitig ist eine Minimierung der Belastungen, die mit einem Früherkennungsprogramm verbunden sein können, zu gewährleisten (z.B. unnötige Sorge durch falsch-positive Befunde, Gefahr der Überdiagnose und Übertherapie, Gefahr der Scheinsicherheit bzw. Gefährdung durch falsch-negative Befunde…)*	Als ein Ziel des Zervixkarzinom-Screenings wird hier die Minimierung falsch positiver Screening-Ergebnisse angestrebt. In Widerspruch dazu steht die Befürwortung eines primären HPV-Screening, das mit einer ca. 95%igen Falsch-positiv-Rate vergesellschaftet ist. Als weiteres Ziel wird die Minimierung falsch negativer Screening-Befunde genannt. Auch diese Zielstellung wird durch die Propagierung eines primären alleinigen HPV-Screening mit fünfjährigen Intervallen konterkariert, weil falsch negative HPV-Tests kombiniert mit großem Intervall die Screening-Teilnehmerinnen gefährden (s.u.).
Tragende Gründe ***2.3.3. Screeningstrategien S. 8***	Ein HPV-Test in fünfjährigem Intervall erscheint als Maßnahme zur Vorsorge nicht geeignet. Der alleinige HPV-Test ist von einer beachtlichen Falsch-

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…Es wird ein HPV-basiertes Primärscreening mit mindestens 5 Jahresintervall und unmittelbarer Zytologie-Triage ab einem Alter von 35 Jahren in einem organisierten Programm empfohlen. Das HPV-basierte Screening sollte nicht vor dem Alter von 30 Jahren begonnen werden. Für das Alter 30 – 34 Jahre gibt es keine eindeutige Evidenz für oder gegen ein HPV-basierte Screening. *…Das HPV-basierte Screening wird Frauen bereits ab dem Alter von 30 Jahren angeboten, da die Inzidenz des invasiven Karzinoms bereits in diesem Alter einen deutlichen Anstieg zeigt und am in situ Karzinom erkranken Frauen im Mittel bereits mit 34 Jahren (RKI: Krebs in Deutschland 2015).*	Negativ Rate in der Detektion hochgradiger Läsionen und invasiver Karzinome behaftet [5-11]. Insbesondere auch frühinvasive Karzinome weisen eine stark reduzierte Viruslast in der Läsion auf und entgehen damit den HPV-Screening-Verfahren [12]. Folglich ist bei dem vorgeschlagenen 5-Jahres-Modell mit einer Häufung von Intervallkarzinomen zu rechnen [13]. HPV-unabhängige Malignome, die im zytologischen Screening gefunden werden können, werden im primären HPV-Screening als Screeningversager in Kauf genommen. Dies steht ethisch im Widerspruch zum etablierten Vorsorgesystem, in dem keine Patientengruppe definiert ist, die von vornherein von einem Screeningerfolg ausgeschlossen wird. Die Akzeptanz in der weiblichen Bevölkerung ist voraussichtlich auch in Deutschland gering mit folglich starker Zunahme eines sogenannten grauen Screenings [14]. In Finnland, das das angesprochene 5-Jahres-Modell mit Register und Einladung der Screening-Teilnehmerinnen seit Jahren praktiziert, wurden 2000-2008 lediglich etwa 11% der invasiven Zervixkarzinome innerhalb des organisierten Screenings entdeckt [15-27]. Ein „graues“ Screening in Deutschland im Rahmen der Individuellen Gesundheitsleistungen („IGeL“) ginge zu Lasten der nicht teilnehmenden und häufig sozial unterprivilegierten Frauen mit der höchsten Inzidenz an Zervixkarzinomen. Ein primäres HPV-Screening führt zu einer unverhältnismäßig hohen Zahl von Frauen mit einem positiven Testergebnis ohne entsprechende Erkrankung, da die nachgewiesene Virus-DNA nur die Infektion, nicht aber eine Läsion dokumentiert. Die Screening-Teilnehmerinnen würden somit der Gefahr einer Überdiagnostik und Übertherapie ausgesetzt, unnötige Ängste der positiv getesteten Frauen bedeuten eine Reduktion ihrer Lebensqualität [18-20]. Die Empfehlung aus den 2015 von der Europäischen Kommission veröffentlichten Supplements zu den Europäischen Leitlinien, das primäre HPV-Screening mit 35 Jahren zu beginnen [21], wird mit der Begründung ignoriert, dass die Inzidenz des invasiven Karzinoms über 30 bereits deutlich ansteigt und an einer Präkanzerose im Range eines Carcinoma in situ (CIN3) Frauen im Mittel bereits mit 34 Jahren erkranken. Aus den zugänglichen Daten des Robert-Koch-Instituts geht allerdings nicht hervor, ob nicht die Zunahme der Karzinome ab 30 vor allem durch eine Zunahme frühinvasiver Karzinome bedingt ist, wie das in Mecklenburg-Vorpommern der Fall ist [22]. Unabhängig davon, dass das primäre HPV-Screening aus den oben angeführten Gründen ohnehin abzulehnen ist, bedeutet ein Beginn mit bereits 30 Jahren eine Gefährdung der Teilnehmerinnen vor allem wegen der extrem hohen Anzahl falsch positiver Befunde und damit verbundener Überdiagnostik

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	und Übertherapie gerade dieser Frauen im bevorzugten Gebäralter. Es ist unverständlich, warum das 30. Lebensjahr bei der vorliegenden Datenlage und sogar in Widerspruch zu den ansonsten stets herangezogenen Europäischen Leitlinien als Eintrittsalter für das primäre HPV-Screening empfohlen wird. Aus der Erkenntnis, dass Frauen < 30 Jahren häufiger HPV-positiv sind als Frauen > 30 Jahren, wird die Festlegung für ein zytologisches Screening für Frauen < 30 Jahren und ein HPV-Screening > 30 Jahren getroffen. Der Abfall der HPV-Prävalenz erfolgt in Abhängigkeit vom Lebensalter in kleinen Schritten [23, 24]. Die HPV-Prävalenz von 31-jährigen Frauen unterscheidet sich nur marginal von denen 29-jähriger. Bei 35-jährigen Frauen liegt sie lediglich wenige Prozentpunkte unter der von 30-jährigen. Erst nach dem 40. Lebensjahr kommt es zu einem deutlicheren Abfall der HPV-Prävalenz. Die Grenzwertfestlegung bei 30 Jahren für Screeningverfahren und -intervall erfolgt somit willkürlich. Eine sinnvolle Alternative zum jährlichen zytologischen Screening auch nach dem 30. Lebensjahr wäre hingegen das sogenannte Co-Testing ab dem 35. Lebensjahr (zytologische Untersuchung in Kombination mit einem adäquaten HPV-Test) in einem dreijährigen Intervall: die Kompensation der Schwäche der einen Methode durch die Stärke des anderen Verfahrens gewährleistet die Sicherheit für die teilnehmenden Frauen (die geringere Sensitivität der Zytologie und ihre hohe positive Prädiktion im Zusammenspiel mit der hohen negativen Prädiktion und schlechten Spezifität des HPV-Testes). Der Erfolg dieser Vorgehensweise ist in der aktuellen Literatur belegt [8-10, 20, 25, 26]. Insbesondere bei einer Intervallverlängerung von mehr als drei Jahren besteht die Gefahr einer Reduktion der Teilnahmerate am organisierten Screening [27]. Dies muss unbedingt vermieden werden, da unter den Zervixkarzinom-Patientinnen die Nicht-Teilnehmerinnen die meisten und die fortgeschrittenen Karzinome aufweisen [22].
2.3.4. Abklärungsdiagnostik S. 10 *Das zytologiebasierte Screening ist unauffällig bei Pap I und Pap IIa gemäß der Münchner Nomenklatur III. … In diesen Fällen wird das Primärscreening in den vorgegeben Zeitabständen durchgeführt.*	***Begründung s.o. Beschlussentwurf § 28 (2) e*** einfach nur „II-a“ streichen
2.3.4. Abklärungsdiagnostik	Gemeinsam mit den anderen an der Versorgung der Frauen im Rahmen des Zervixkarzinom-Früherkennungsprogramms

Deutsche Gesellschaft für Zytologie – AZÄD - Bundesverband der Zytologen	
23. Mai 2016 – 30.Mai. 2016	
Für das Management auffälliger Screeningbefunde werden für die verschiedenen Screeningstrategien Algorithmen für die Abklärungsdiagnostik vorgegeben. Die Abklärungsdiagnostik orientiert sich an den Empfehlungen der aktuellen deutschen S3 Leitlinien zur Prävention des Zervixkarzinoms (Konsultationsfassung vom 01.03.2016). ***S.10/11*** *(Schema)* ***S. 11*** *Bereits bei Minor Changes ist eine Abklärung durch eine Biopsie erforderlich.*	beteiligten Ärzte (Berufsverband der Frauenärzte, Arbeitsgemeinschaft Zervixpathologie und Kolposkopie der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe, Arbeitsgemeinschaft Zytologisch Tätiger Ärzte in Deutschland, Bundesverband deutscher Pathologen und Berufsverband zytologisch tätiger Akademiker in Deutschland) hat die Deutsche Gesellschaft für Zytologie die o.g. Konsultationsfassung der S3-Leitlinie am 10.04.2016 abgelehnt. Dafür waren vor allem fachliche Defizite des Leitlinien-Entwurfs maßgeblich, die sich auch in den vorgeschlagenen Abklärungsalgorithmen niederschlagen. Die Begründung dafür ist in unserem Ablehnungsschreiben enthalten (das der G-BA am 10.04.2016 erhalten hat) und soll hier nicht im Einzelnen wiedergegeben werden. Bereits weiter oben haben wir aufgeführt, aus welchen Gründen die für den Richtlinientext vorgesehenen Vorgaben für die Abklärung strikt abzulehnen sind. Als weiteres Beispiel für inakzeptable pauschale Vorgaben widerspricht diese Forderung den gültigen Empfehlungen zur Kolposkopie. Es gibt keine Indikation für eine Biopsie bei „minor changes“, da derartige Befunde in der Regel physiologische Veränderungen sind oder maximal einer CIN1 entsprechen. Ausnahmen sind diskrepante Befunde (z.B. zytologisch Gruppe IV, V, Gruppe III mit Wortgutachten „Karzinom denkbar“ in Kombination mit kolposkopischen „minor changes“). Hier sind Target-Biopsien, ggf. Random-Biopsien, ggf. eine Zervix-Kürettage indiziert [2]**.** Grundsätzlich bei „minor changes“ durchgeführte Biopsien bedeuten Überdiagnostik: nicht indizierte invasive Eingriffe, die die Integrität eines Organs verletzen. Sie würden außerdem zu einer nicht vertretbaren Zahl histologischer Abklärungen führen.
6. Fazit und Ausblick *… Durch die Anwendung des HPV-Tests im Primärscreening kann die Inzidenz von invasiven Zervixkarzinomen weiter gesenkt werden.*	Diese Behauptung ist nicht belegt. Sie entstammt nicht dem IQWiG-Bericht. Weder in den dabei ausgewerteten Studien noch in irgendeiner anderen Publikation findet sich dafür Evidenz, insbesondere nicht für industrialisierte Länder.

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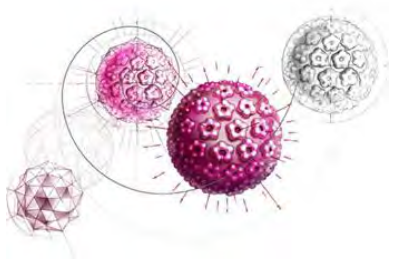
The Danish Cervical Cancer Screening Experience: Importance of HPV assay choice, and a full cervical cancer solution to accommodate changes over time.”

Jesper Bonde
Copenhagen University Hospital, Hvidovre



DISCLOSURE STATEMENT

Jesper Bonde,
PhD, Dipl.Med.Sci
Senior Researcher

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Molecular Pathology
Dept. Pathology & Clinical Research Centre
Copenhagen University Hospital,
Hvidovre, Denmark

AxLab
BD Diagnostics
Genomica
Hologic/Gen-Probe
Qiagen
Roche Diagnostics
Roche Pharma

The HORIZON study is a independent investigator driven study

The CSi study is an independent investigator driven study

The company partners accepted and acknowledged the protocol prior to the study

All instrumentation and software were manufacturer issued, and maintained for the duration of the study in both studies

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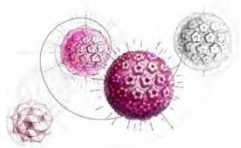
The European BD Onclarity CE-IVD trial is sponsored by BD Diagnostics



Todays Presentation

Introduction:
The rationale of Primary HPV screening
The Danish Screening Program

Experiences from two Danish HPV screening trials:
The HORIZON Study
The BD Onclarity CE-IVD trial

Perspective:
The immediate future design for molecular HPV screening

The Outsider:
Self taken samples & HPV tests

Conclusion

The vision & challenges of primary HPV screening

Cervical cancer
is the *only* fully preventable cancer

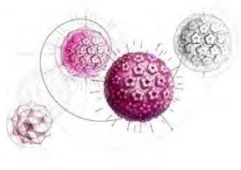
But vaccine alone will not be enough….

11 High Risk Genotypes causing cancer is not included in the vaccine

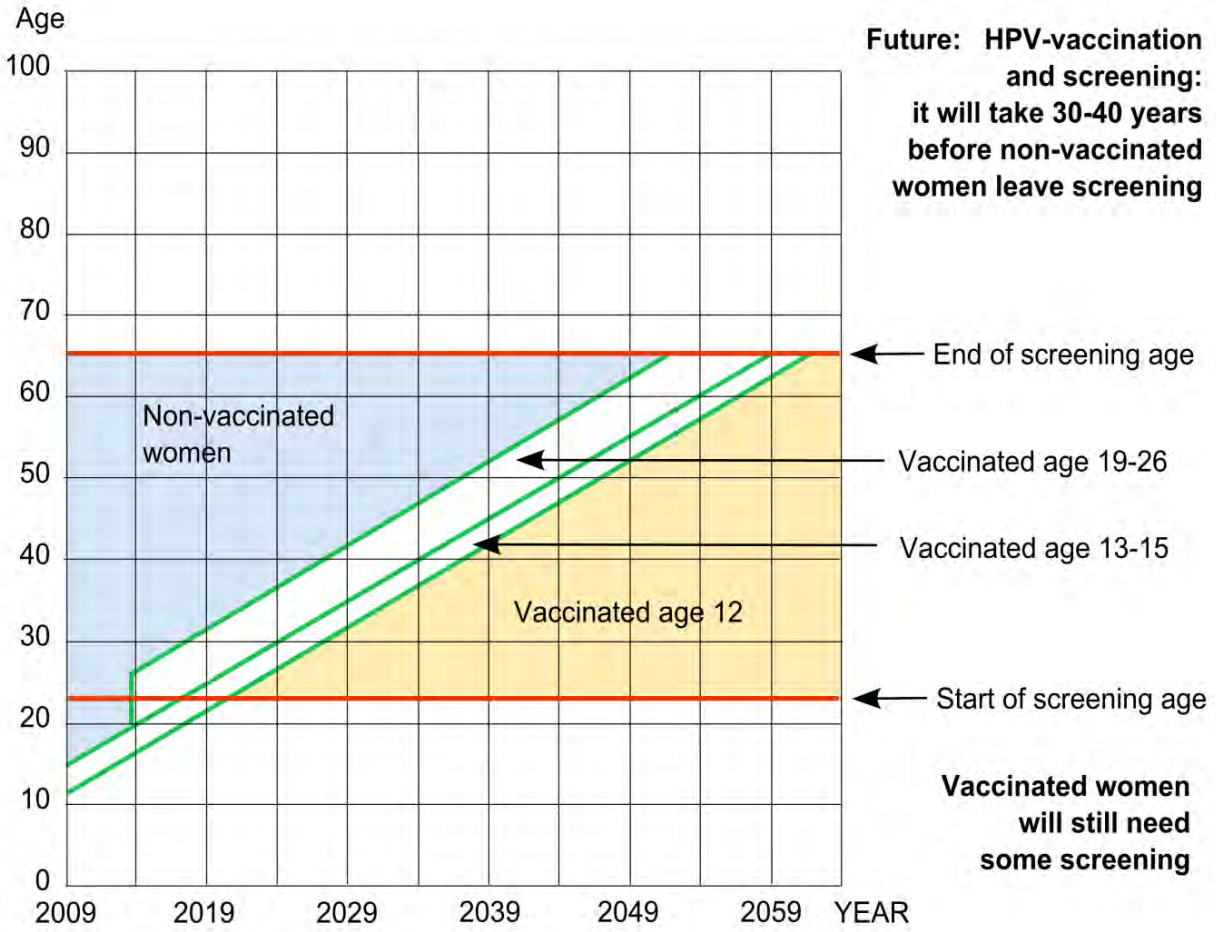
In women ≥35 years genotypes HPV31, 33, 51, 52 and 58 plays a larger role in disease than HPV16 and HPV18

(Sideri et al, 2012, EIO report)

Vaccine & screening must walk hand-in-hand



A double challenge – a window of opportunity



[Lynge et al., forthcoming]

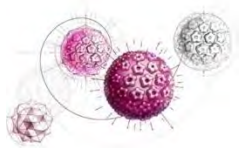
The Vision

Today

Molecular HPV testing allows for improvements in cervical cancer prevention and screening, either as triage modality or as stand alone screening test

Tomorrow

The introduction of DNA and RNA based methods opens up a wide new horizon of methodologies to make the screening individualized and highly specific for disease detection



Molecular HPV technology offers a new approach
The Premise – clinical perspective

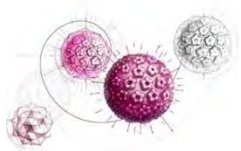
All cervical cancers caused by HR-HPV infection, active or latent over a period of years

High sensitivity CIN2+ in the range of >90% favours HPV assays over cytology (Very variable - from 55%-80%)

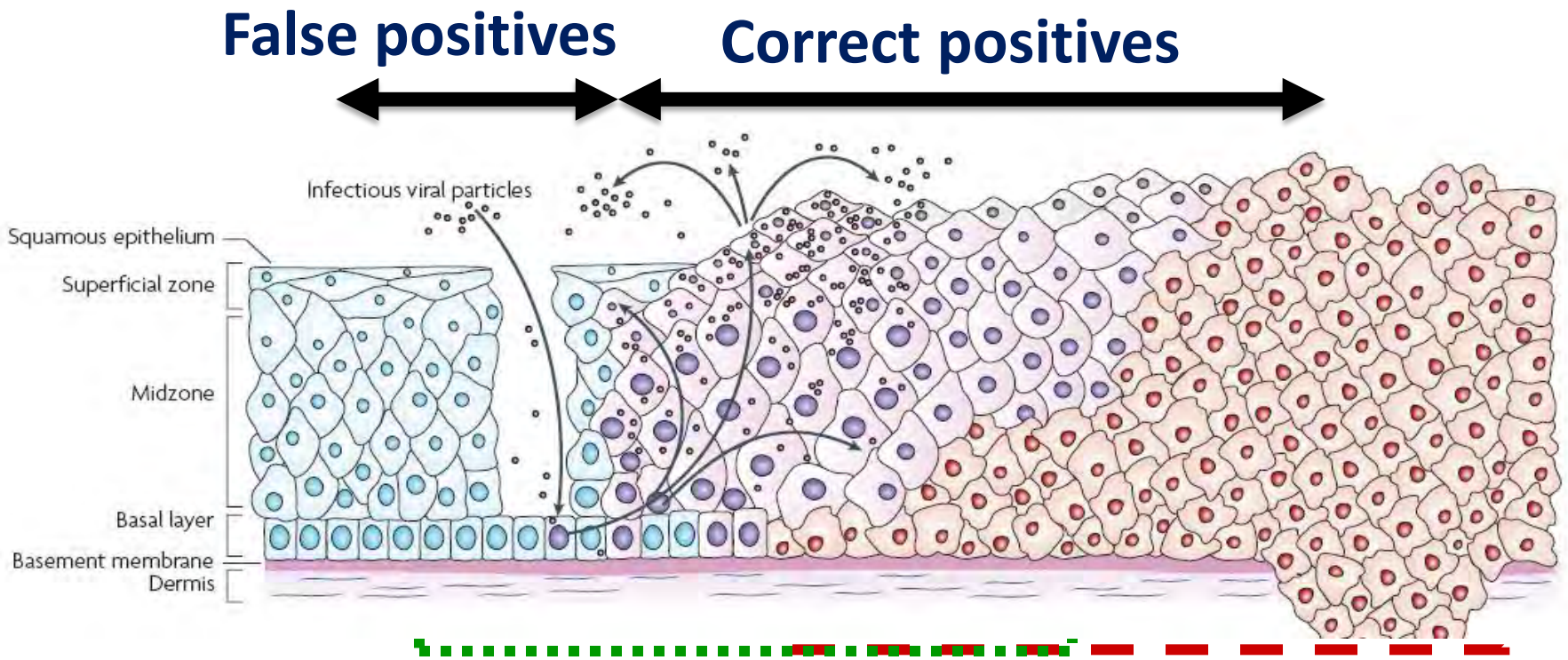
Of current cervical screening technologies, molecular HPV testing offers by far best negative predictive value for detection of high grade CIN

(Dillner et al. BMJ, 2008, Ronco et al. 2014)

A negative test result provides long term confidence that disease is not imminent



The Challenge of primary HPV screening



HPV-DNA test
Sensitivity ≥ 95-97%

Pap-Smear
Sensitivity ≥60%

Figure from Nature Biotechnology

Molecular HPV technology offers a new approach

The Premise – Laboratory perspective

Molecular HPV testing is more reproducible than cytology

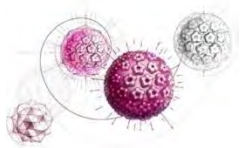
Molecular HPV testing can be automated and QA/QC controlled

Not prone to intra-observer variability as cytology

National and international QA/QC programs will eventually allow for performance evaluation in order to secure uniform services

Negative predictive value of HPV tests means longer, safe intervals reducing the cost of screening allowing a re-focusing on those women who really need follow up and/or treatment

Our staff runs both cytology and molecular testing in a integrated, rotational routine; integration leads to superior service.



The Danish Screening Program;

HPV testing in triage and primary screening…

The national Danish cervical screening program

Cervical cancer screening programs started in Denmark in late 1960´s

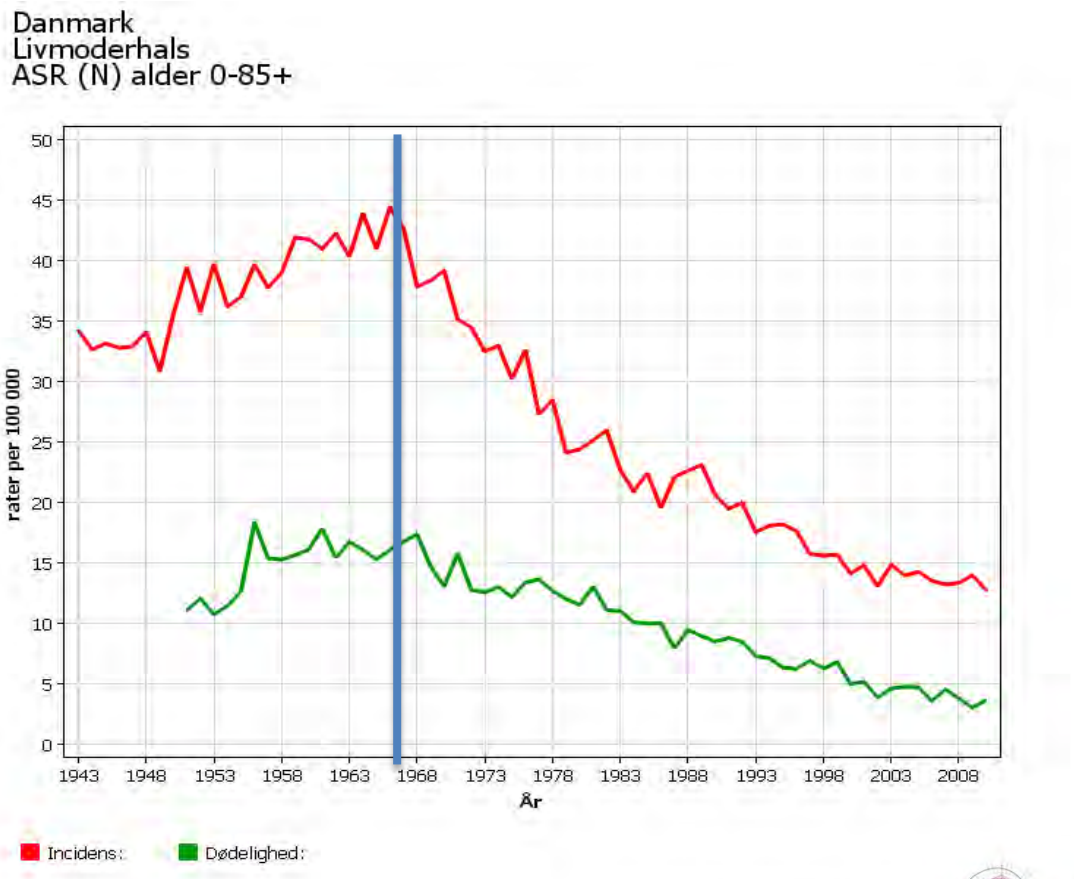
Current coverage is 76%

By screening early stages can be diagnosed

When early stages are treated, invasive disease can be avoided

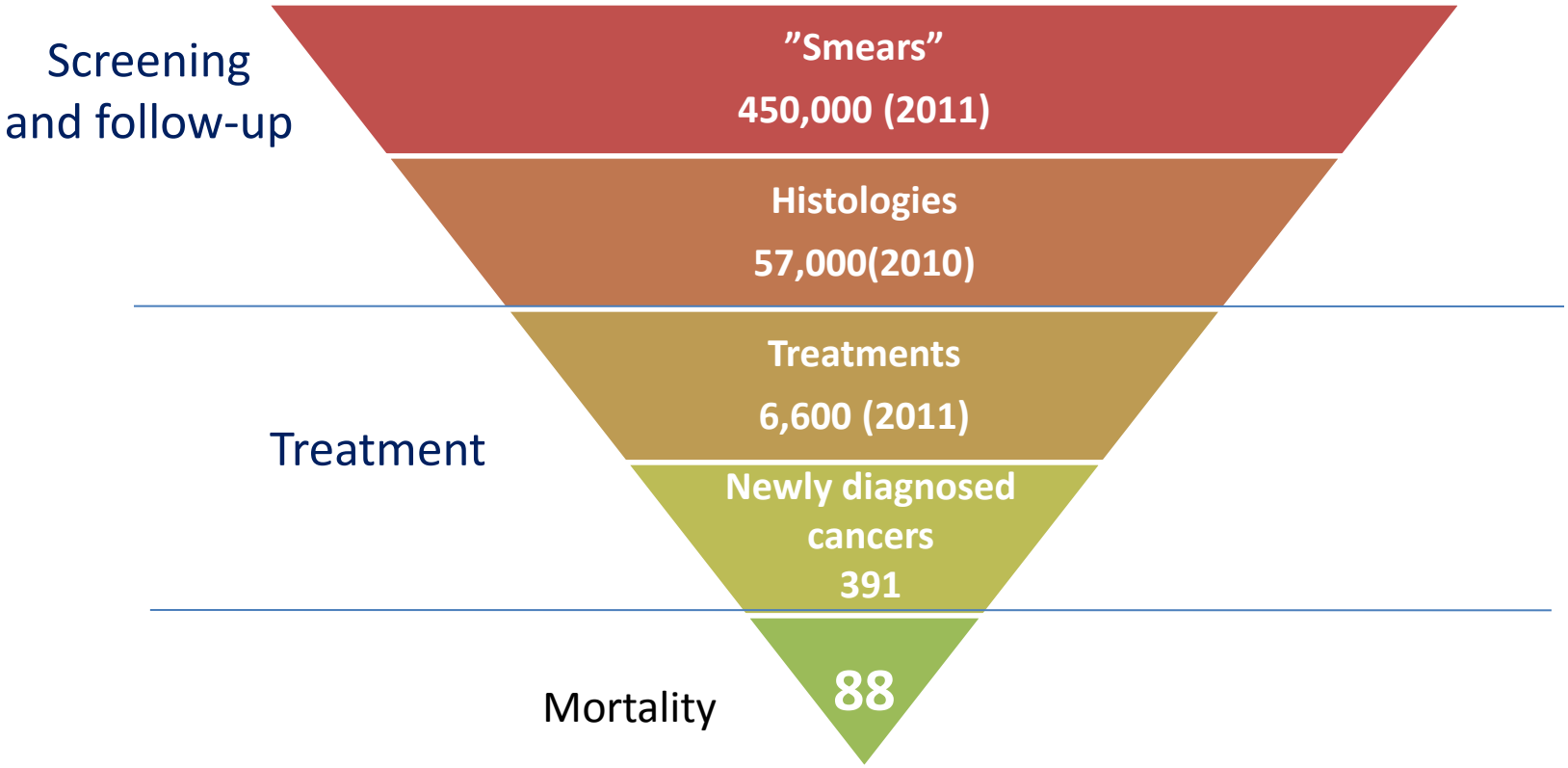
It worked

However, 20% of all women with cervical cancer had a recent normal cytology (*Ingemann-Hansen et al, BJC, 2008*)

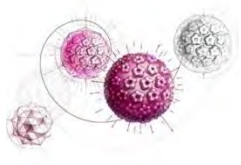


The national Danish cervical screening program

Population :1,560,000 women nationwide (23-65 years)



”For every saved cancer, 6-8 women are treated for cell abnormalities.”
Barken et al, Int. J. Cancer 2011



The current screening in Denmark

Screening population :1,560,000 women nationwide (23-65 years)

Who is offered screening?

All women 23-49 years: Every 3rd year
All women ≥50-65: Every 5th year

”Smears”

Denmark: Approx. 450,000/ annually
Hvidovre Hospital: Approx. 160,000 / annually

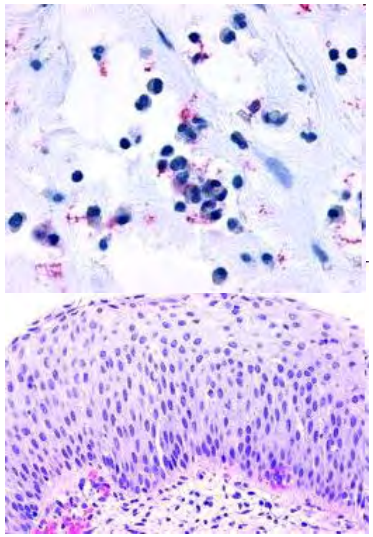
Type of collection media

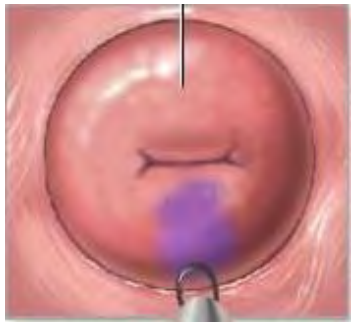
All “smears” are LBC, less than 5% pap´s.
LBC is 80% SurePath, 20% Thinprep

Automated reading

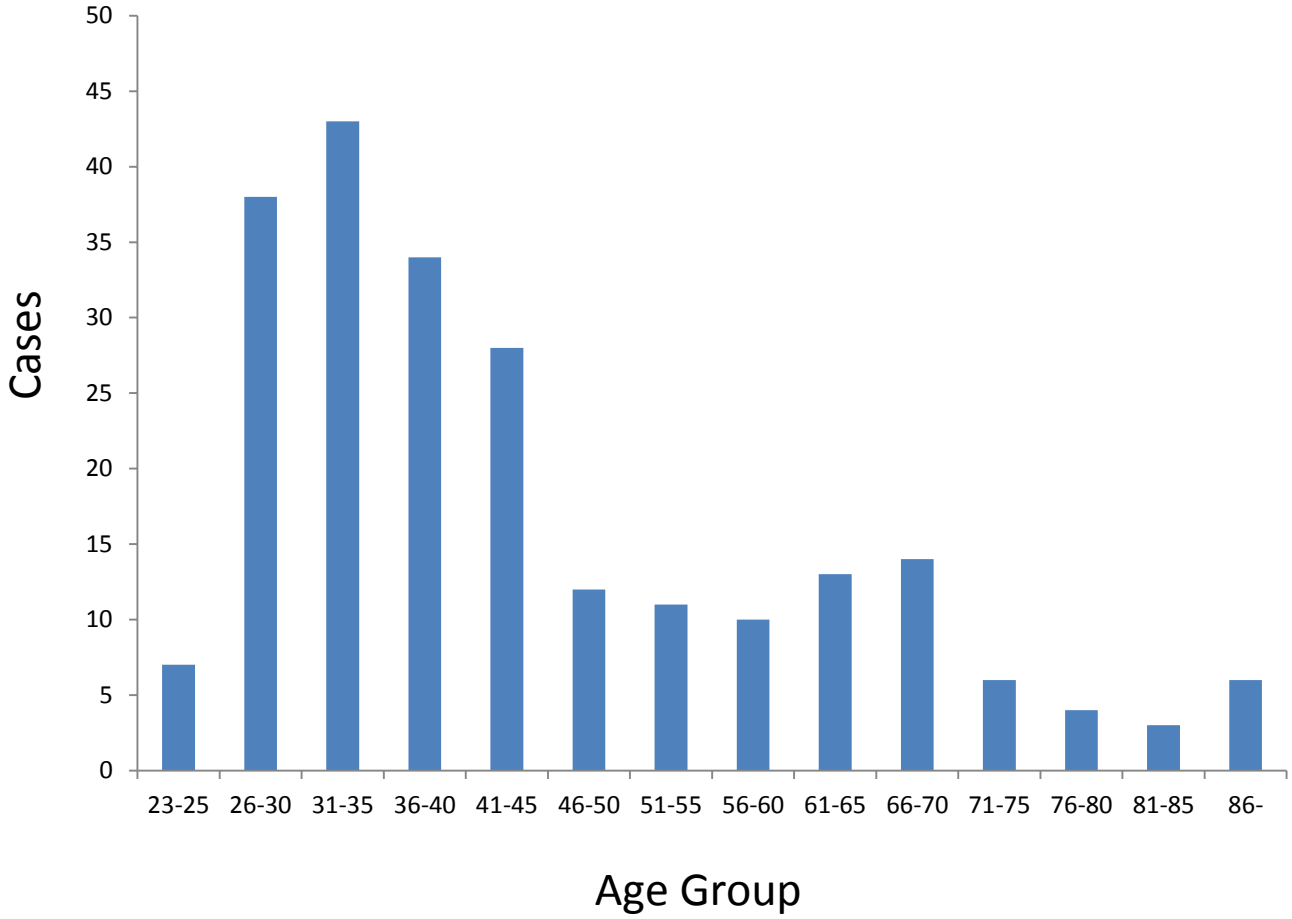
Focal point computer assisted screening is widely used; increases speed of production, 40% of lowest fractiles answered directly from the system to the national Patobank

Consolidation of screening units into large units improves consistency and service





Cervical Cancers; Capital Region 2008-2013 By age



Current indications for HPV tests by the Danish Health and Medicines Authority, 2012

Triage (ASCUS ≥30 years)

1st control after conisation (LEEP)

Primary screening ≥60 years
(Check out test, DNA only, from 2013)

Annual turnover of HPV tests:

75,000 National/25,000 at Hvidovre Hospital from 2013

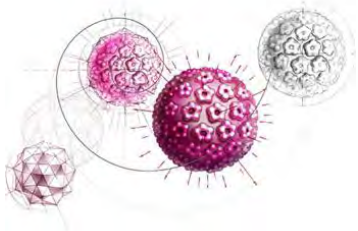
Equals:
1 of 6 LBC samples in our lab will have an HPV test by full implementation of these indications

First country to indicate primary HPV screening

Small Country

Small Numbers

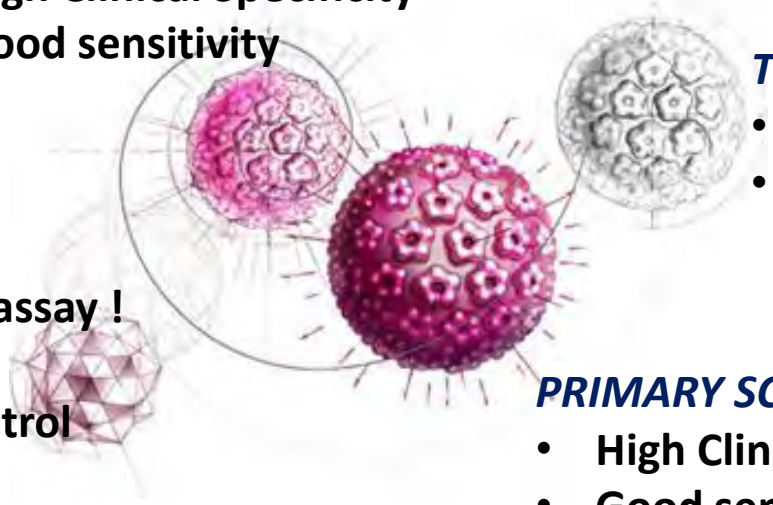
What do we need from a molecular HPV screening test ?



Embedded vaccine monitoring in organised screening requires extended genotyping

TRIAGE
- **High Clinical Specificity**
- **Good sensitivity**

SELF SAMPLING
- **High sensitivity**
- **Clinical specificity?**
- **Robustness of chosen assay !**
- **Reproducibility!**
- **Sample sufficiency control**



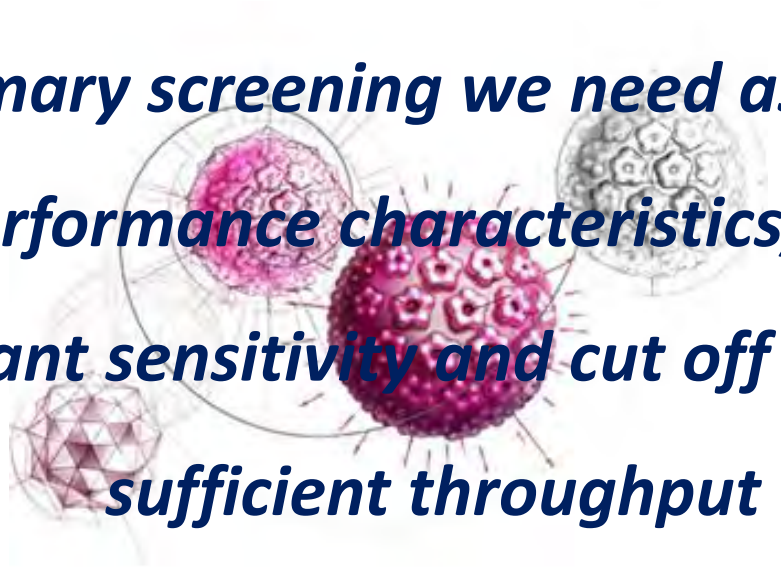
TEST of CURE
- **High sensitivity**
- **Genotyping*?***

PRIMARY SCREENING
- **High Clinical Specificity**
- **Good sensitivity**
- **Reproducibility**
- **(Sample sufficiency control?)**

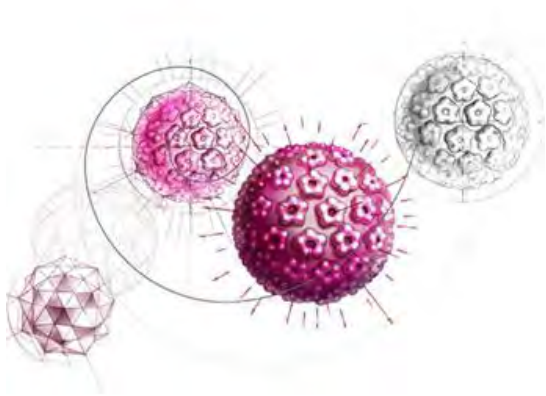
EXIT TEST
- **High sensitivity**
- **Sample sufficiency control**

Can we get all that in one assay?

For primary screening we need assays with good performance characteristics, screening relevant sensitivity and cut off´s, and a sufficient throughput



Finding a cervical screening solution to accommodate changes over time…

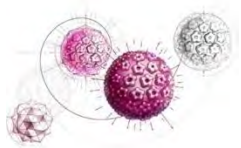


Why the HORIZON Study ?

We wanted to test the four candidate assays already running as triage assays in Denmark for proficiency in primary HPV screening

We wanted to generate SurePath based experiences in primary HPV screening

We wanted to test lab-performance our self



The Assays on the HORIZON

The HORIZON Study

Four HPV assays – four different technologies

- ***HC2®*** *Hybridization assay with HR HPV detection*
- ***Cobas®HPV test*** *Real-time PCR assay, with co-detection of HPV HR and 16 and 18*
- ***APTIMA®*** *RNA assay with HR HPV detection*
- ***CLART®*** *PCR-Microarray assay with simultaneous detection of 35 genotypes*

QiaSymphony RCS HC2® work flow

Roche cobas®4800 workflow

Gen-Probe PANTHER® APTIMA workflow

Genomica CLART®HPV2

The HORIZON Study Set-up

*Comparing **APTIMA, CLART, cobas & HC2 HPV assays***
in PRIMARY cervical cancer screening

Clinical and analytical assay performance in a true screening study sample

---

5064 unselected samples taken straight from our routine

Tested on cytology plus the four HPV tests in a split sample fashion

All cytology positive followed up according to national guidelines

All HPV+ (on any test) cytology normal invited for an additional screening round at 18 months after baseline

= The Horizon Study

The HORIZON Study Aims

*Comparing **APTIMA, CLART, cobas & HC2 HPV assays***
in PRIMARY cervical cancer screening

Clinical and analytical assay performance in a ***true*** screening study sample

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Evaluation parameters

Intra-laboratory assay reproducibility on screening samples

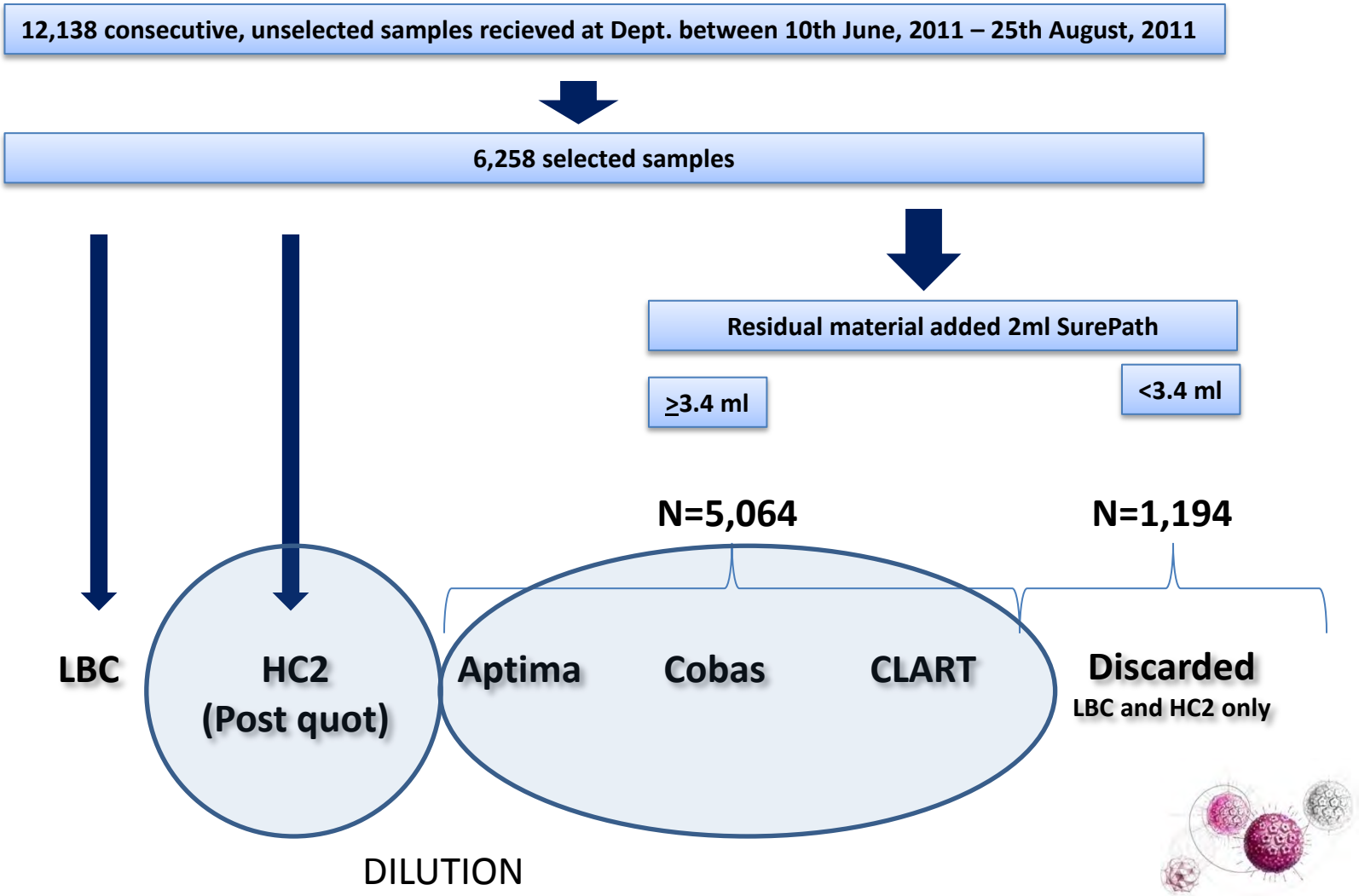
Evaluation of assay specific cross reactivity profiles to LR HPV genotypes

SurePath and HPV assays

Cross comparison of assays in primary screening of women ≥30 years

The HORIZON Study

Design & Inclusion



Assay Performance Indicators

Intra-laboratory assay

Reproducibility

Implications for primary screening

Importance of intra-laboratory reproducibility

Need to trust your system
In primary screening each sample will run only once
Need to know the limitations of the systems to design National QA &QC procedures & guidelines

Negative reproducibility:

Important for the safety of extended screening intervals for HPV negative

Positive reproducibility:

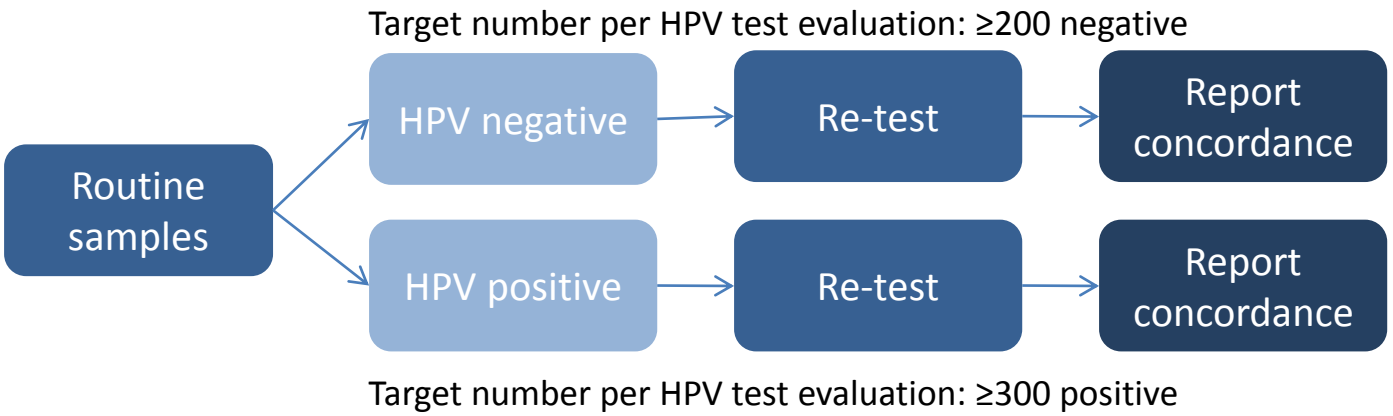
Important for frequency of false positive tests

Overall reproducibility:

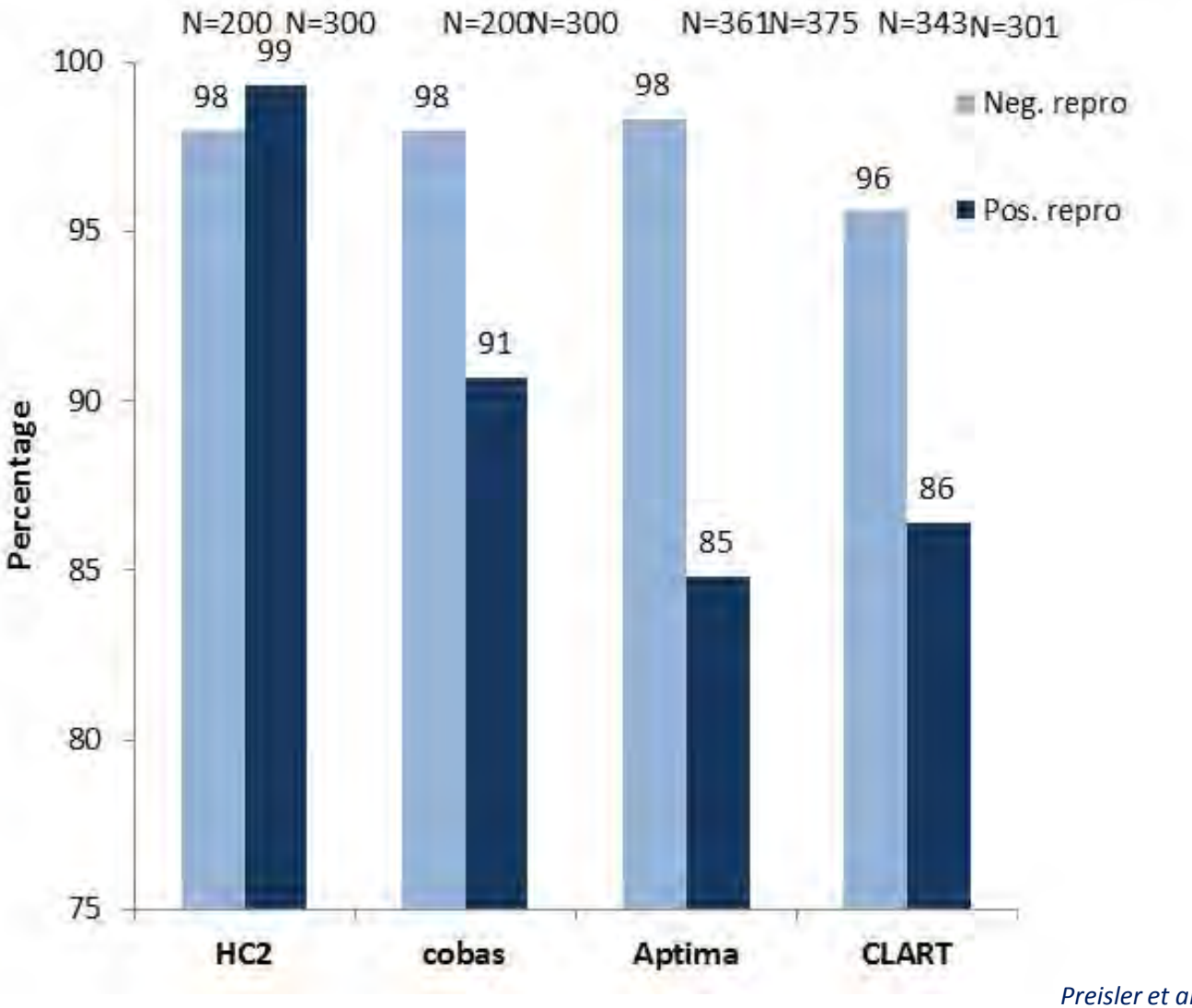
Important for lab performance

Intra-laboratory reproducibility

LBC routine SurePath samples was selected for this study
Batches were not overlapping



Negative, positive and overall assay reproducibility with respect to prevalence findings



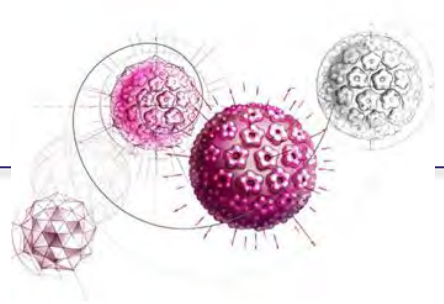
Preisler et al., PLOS One, 2013

Bonde et al., forthcoming

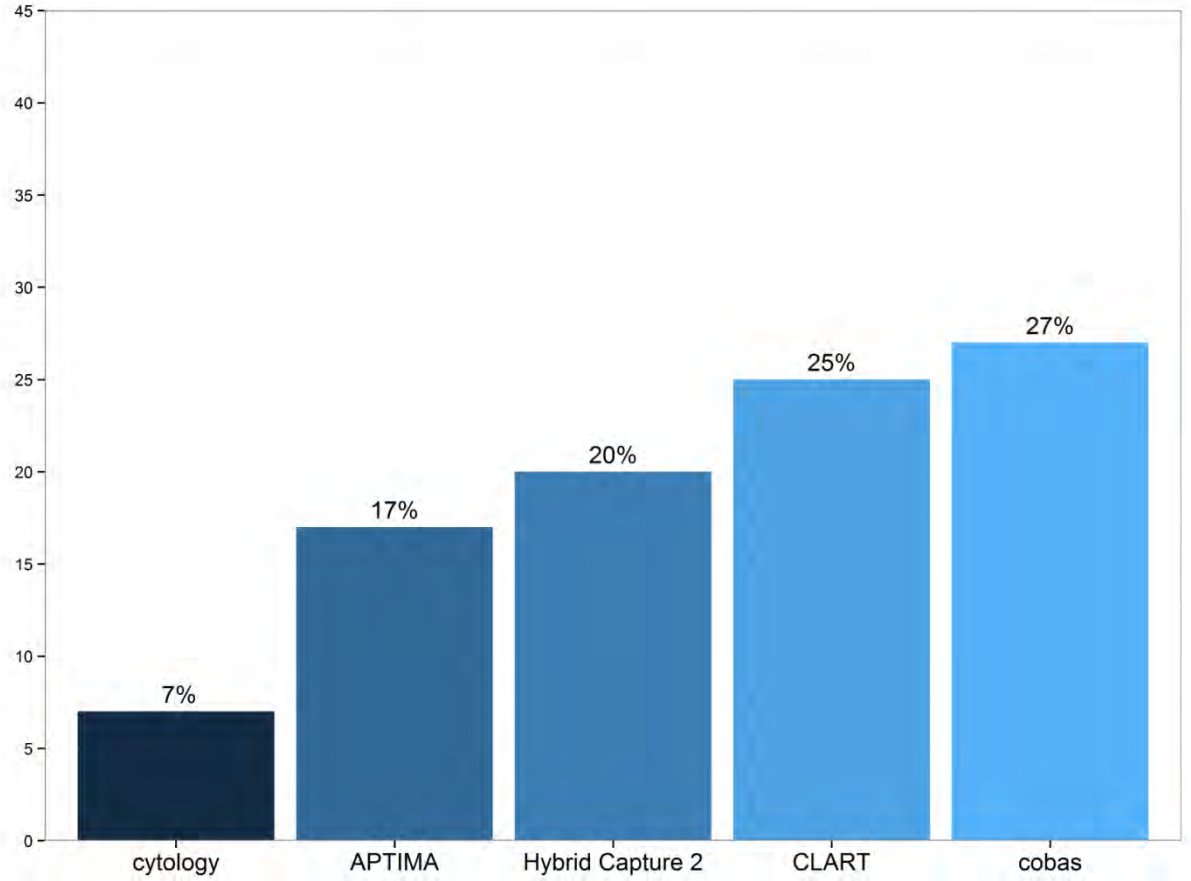
Rebolj et al., J Mol. Diag, 2013

The HORIZON Study

Main results from baseline and the 18 month follow up invitation

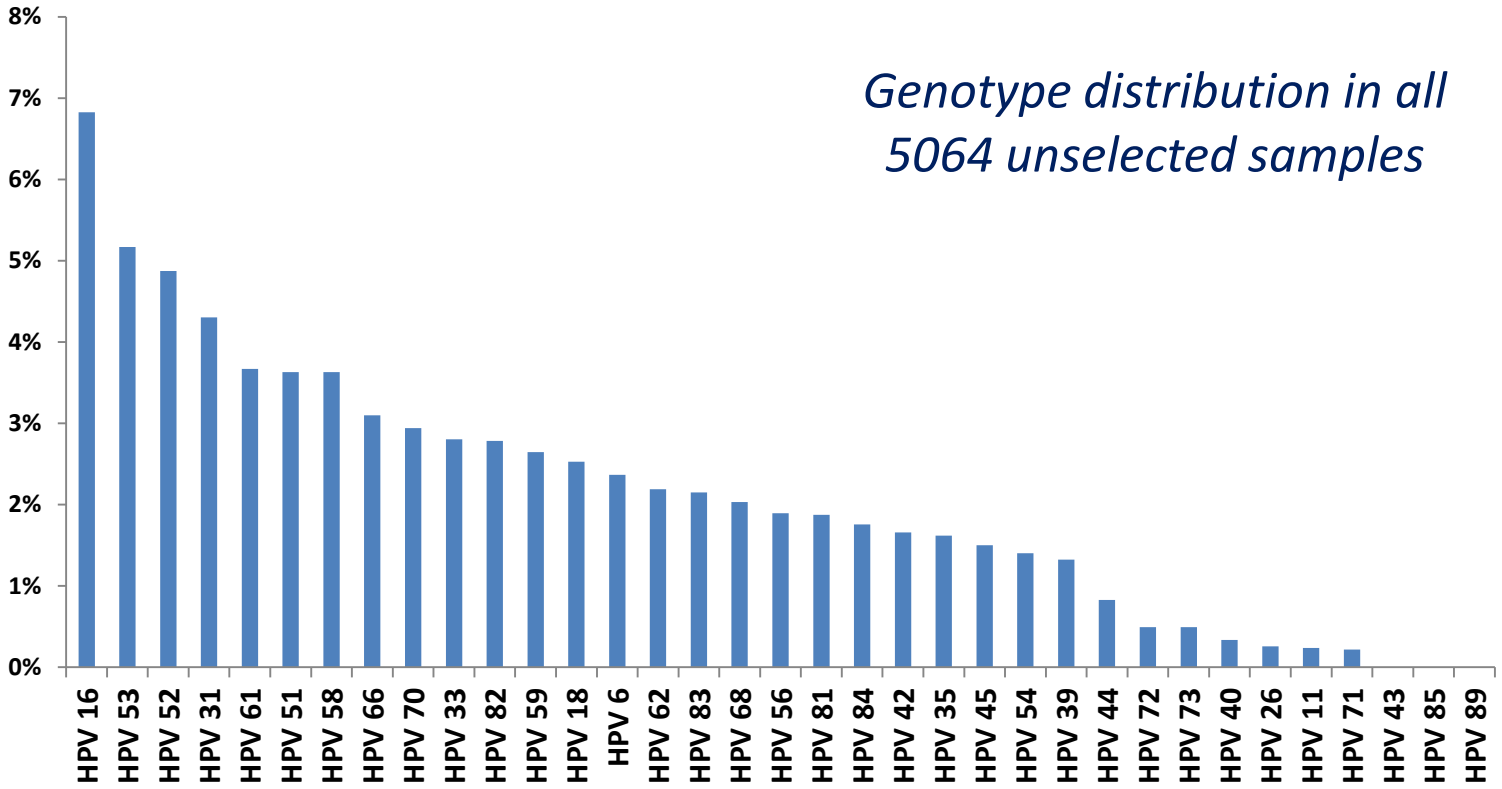


Baseline data from the HORIZON study



Preisler et al., PLOS ONE, 2013
Rebolj et al., J.Mol.Med 2013
Goldman et al., Vaccine 2013
Rebolj et al, Plos One 2014
Bonde et al., forthcoming

Baseline data from the HORIZON study

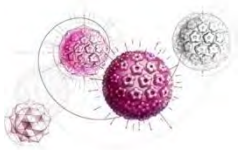


Genotype distribution in all 5064 unselected samples

Goldman et al., Vaccine 2013
Bonde et al., forthcomming

Agreement of the four HPV assays

	All 5,064 samples	23-29 years	30-65 years	30-65 years		*30-65 years, primary screening samples*	
				Screening samples	*Follow-up samples*	*Normal cytology*	*Abnormal cytology*
N	5,064	1,534	3,256	2,881	375	**2,741**	**127**
N (%) ≥1 test pos	1,636 (100%)	731 (100%)	771 (100%)	630 (100%)	141 (100%)	**537 (100%)**	**93 (100%)**
1 test pos	28%	18%	38%	40%	30%	**45%**	**14%**
2 test pos	20%	21%	20%	21%	19%	**22%**	**13%**
3 test pos	52%	61%	41%	39%	50%	**34%**	**73%**



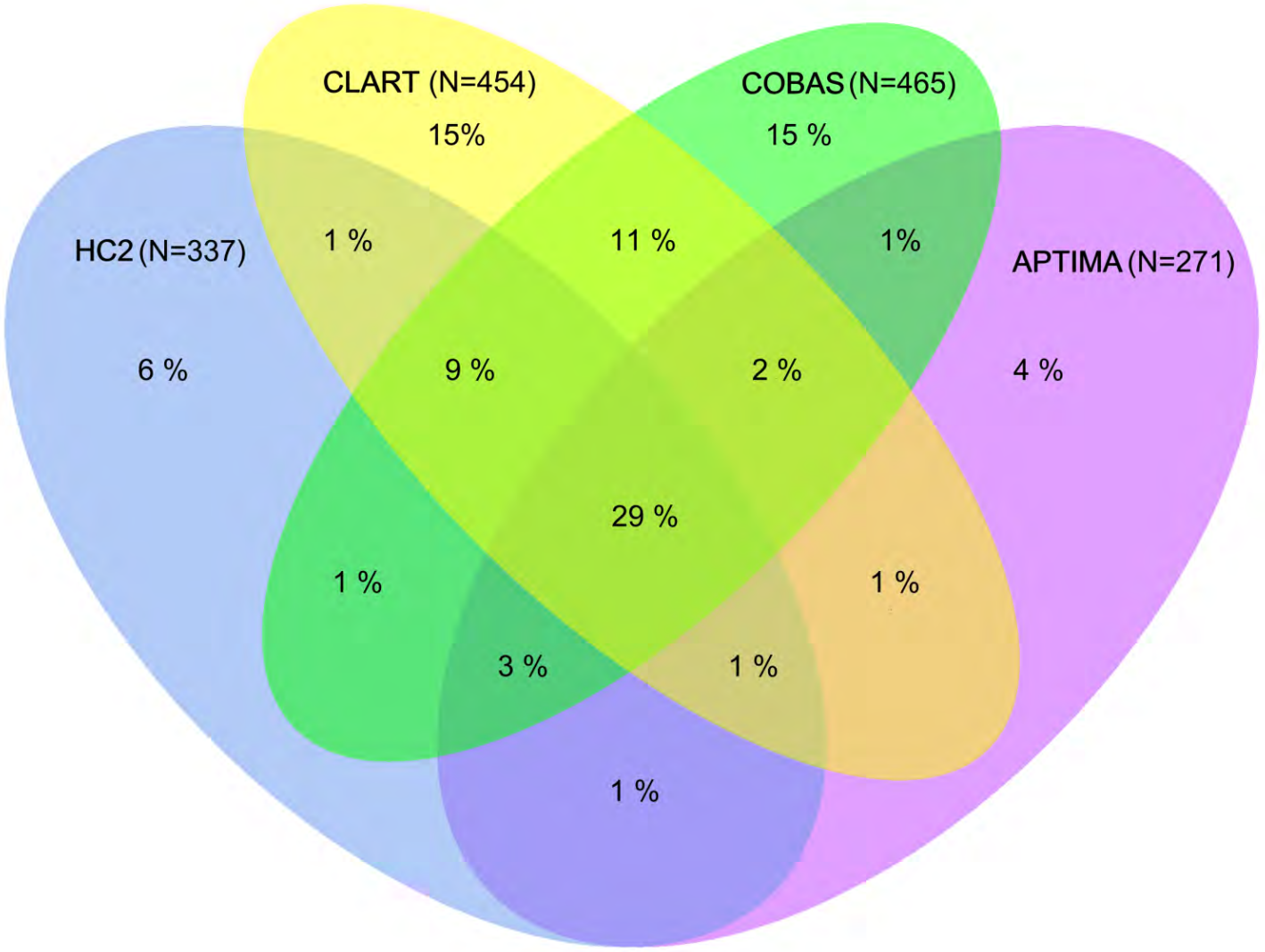
[Rebolj et al., Plos One 2014]

Agreement of the four HPV assays: Primary screening, 30-65 years

Sum of all proportions: 100% (all women testing positive on at least one HPV assay)

Only 29% of all HPV+ samples tested positive on all 4 assays

All combinations of positive tests for the four assays were observed in the data



[Rebolj et al., Plos One 2014]

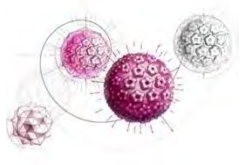
And this means:

Concordance in HPV assay positivity is
Age, sceening history, cytology dependent

Poorer in women ≥30 years
Poorer in screening samples
Poorer in women with normal cytology

And this means:

That assay choice should be based upon evidence of performance from many studies, not only a few



The HORIZON Study

Different HPV tests, Different Horizons

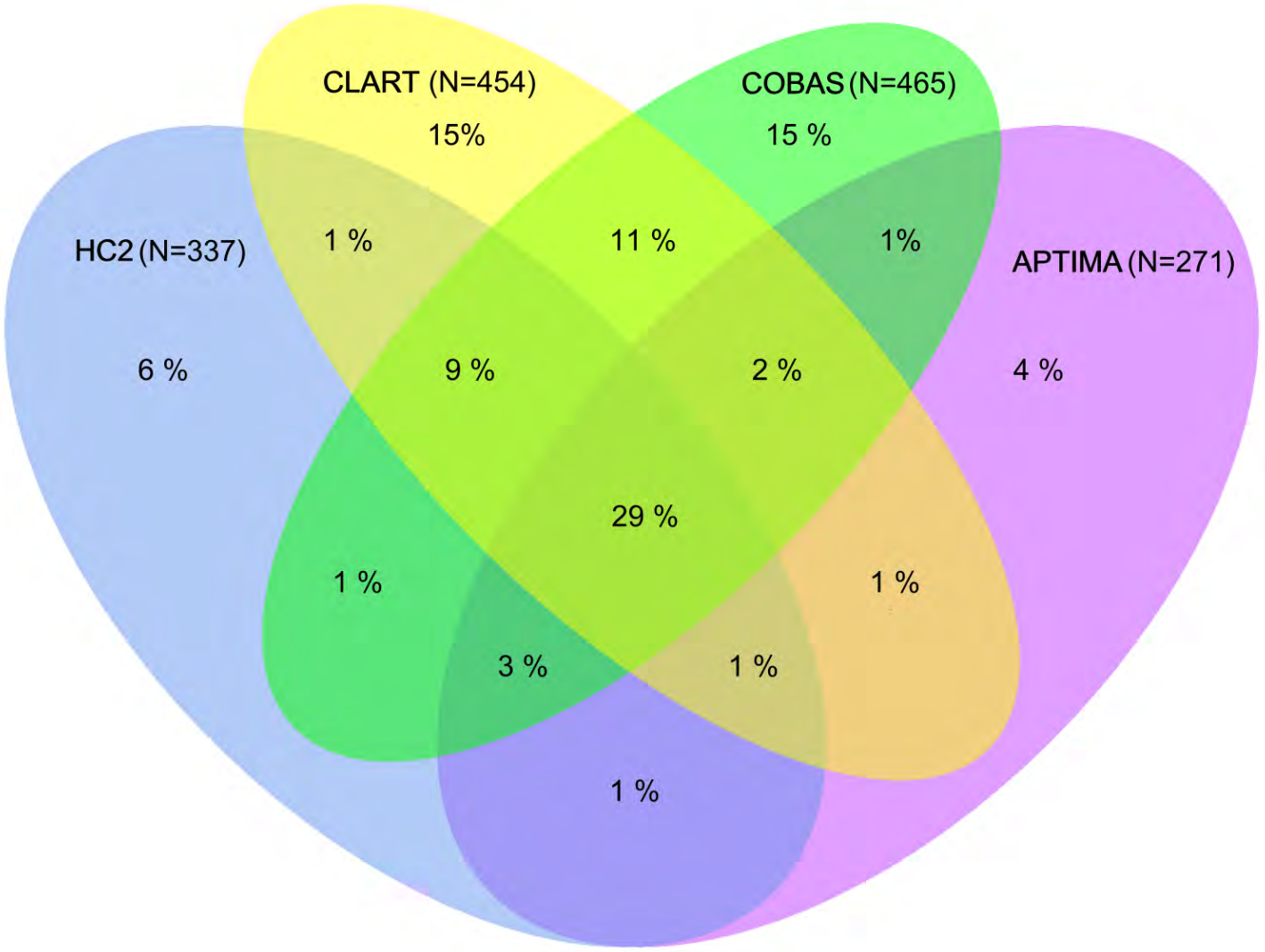
What are the clinical consequences of these findings?

Agreement of the four HPV assays: Primary screening, 30-65 years

Sum of all proportions: 100% (all women testing positive on at least one HPV assay)

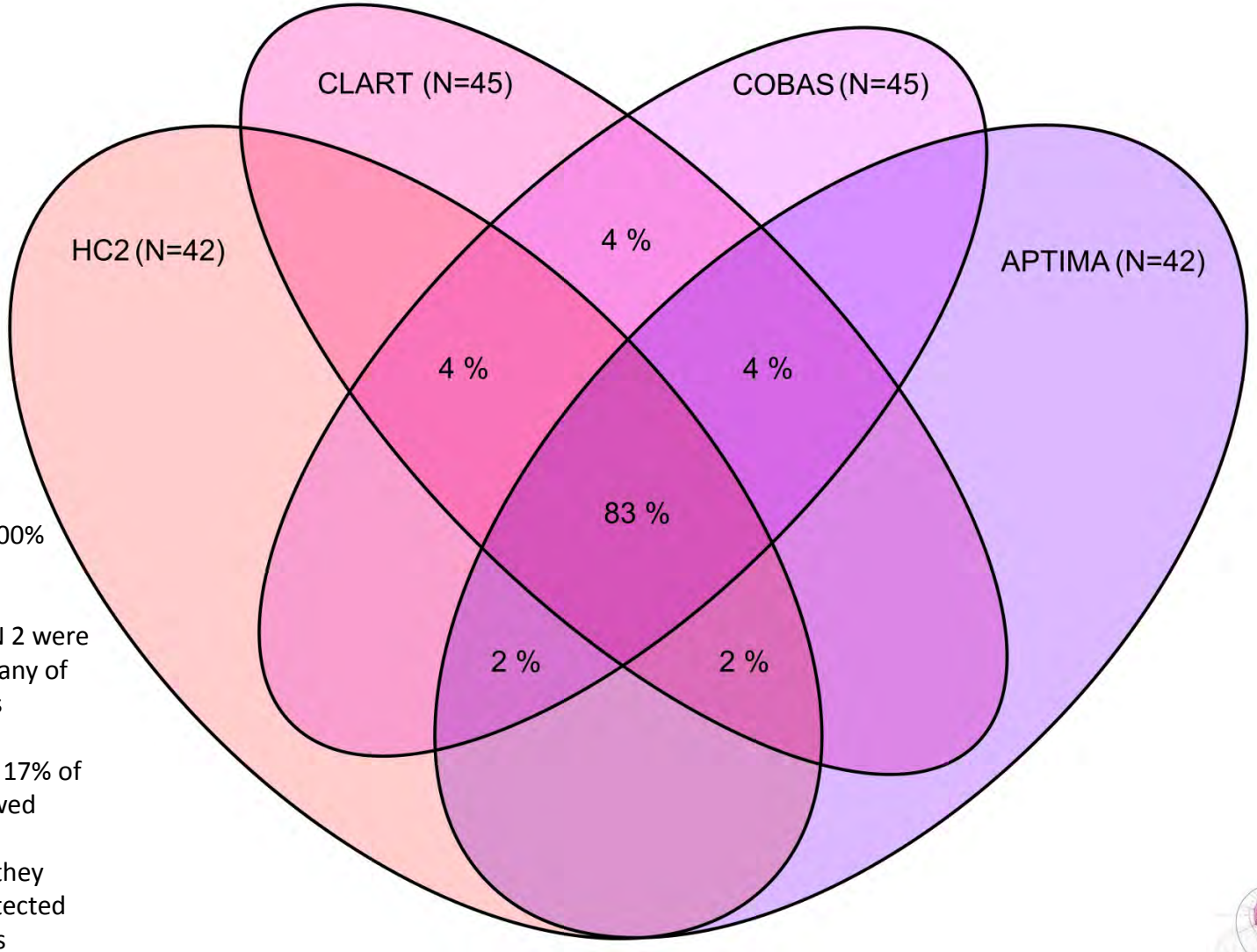
Only 29% of all HPV+ samples tested positive on all 4 assays

All combinations of positive tests for the four assays were observed in the data



[Rebolj et al., Plos One 2014]

Detection of ≥CIN 2 (preliminary)

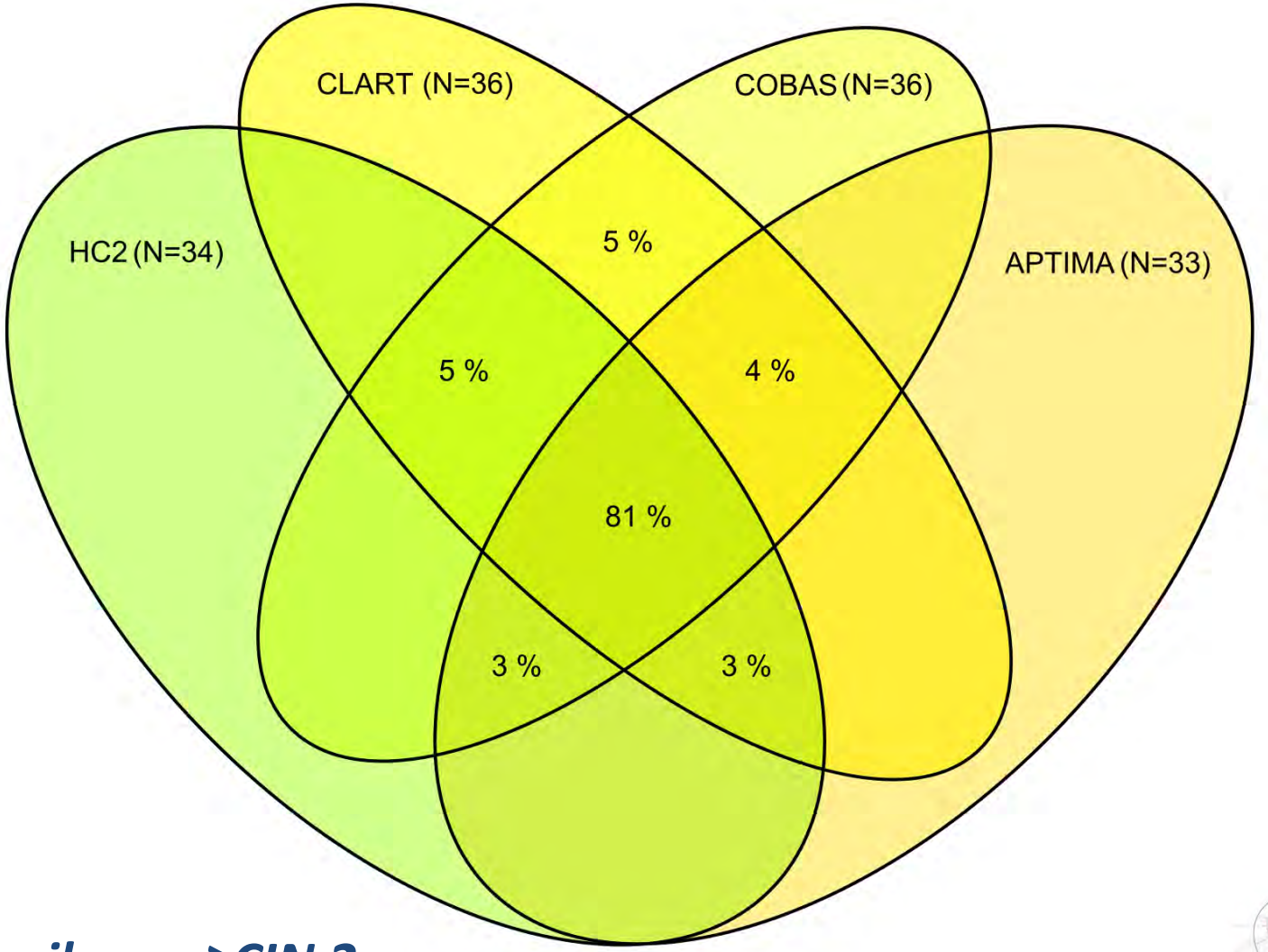


Sum of all proportions: 100% (all ≥CIN 2)

83% of all ≥CIN 2 were detected with any of the four assays

The remaining 17% of all ≥CIN 2 showed relatively good concordance: they were often detected by three assays

Detection of ≥CIN 3 (preliminary)



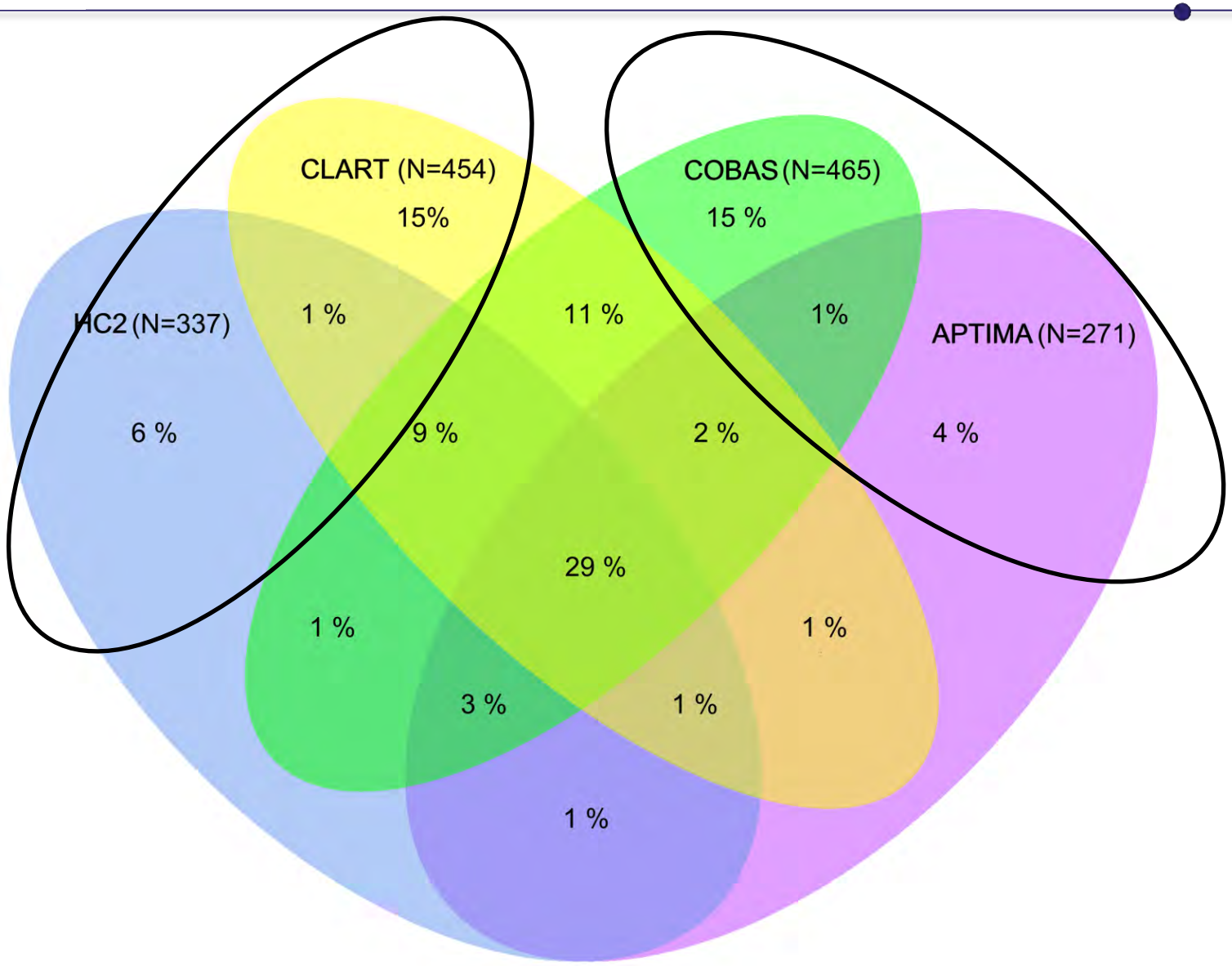
Very similar as ≥CIN 2

Agreement of the four HPV assays: Primary screening, 30-65 years

Sum of all proportions: 100% (all women testing positive on at least one HPV assay)

Only 29% of all HPV+ samples tested positive on all 4 assays

All combinations of positive tests for the four assays were observed in the data



[Rebolj et al., Plos One 2014]

False-positive tests

2,869 women aged 30-65 years with screening samples

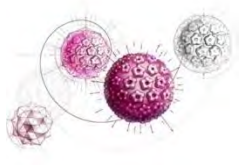
Screening test	% testing positive	% with CIN 3+	% with a false-positive test
Hybrid Capture 2	12%	1.2%	11%
cobas	16%	1.3%	15%
CLART	16%	1.3%	15%
APTIMA	9%	1.2%	8%

[Rebolj et al., in preparation]

The HORIZON Study

Different HPV tests, Different Horizons

Detection of cancers



3 women had cervical cancer

Cytology	HC2 result (rlu/co)	Cobas result (CT)	CLART result (genotypes)	APTIMA (s/co)
HSIL	Positive (11.8)	Positive, HPV 16 (28.6)	Positive (HPV 16)	Positive (13.90)
HSIL	Positive (21.43)	Positive, HPV 18 (39.5)	Negative	Positive (0.84)
HSIL	Positive (92.02)	Negative*	Positive (HPV 16)	Positive (11.10)

* CT-β: 28.9

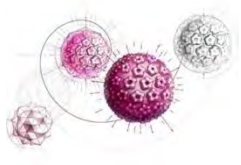
Summary

Assays find more or less the same CIN lesions…
(= a prerequisite for high sensitivity)

…but whether or not a given woman will be referred to follow-up:

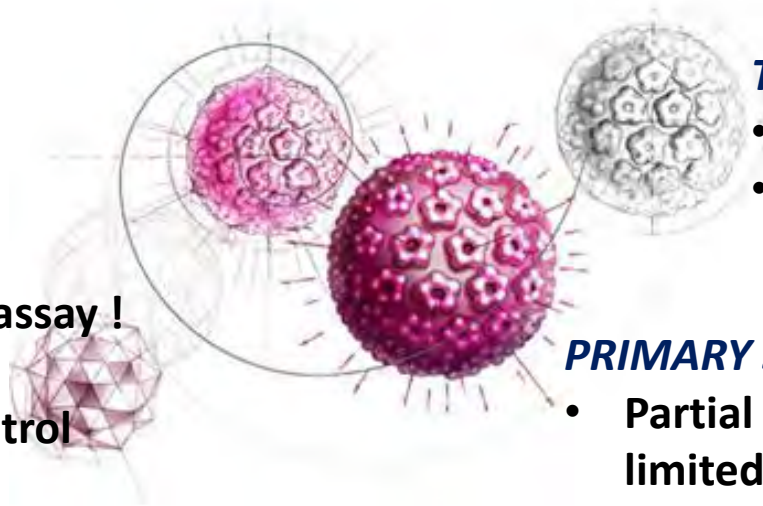
Repeat testing
Colposcopy, biopsies
Treatment

depends on the HPV assay used for testing



So where does this leave us…..?

TRIAGE of HPV positives



SELF SAMPLING
- **High sensitivity**
- **Clinical specificity?**
- **Robustness of chosen assay !**
- **Reproducibility!**
- **Sample sufficiency control**

TEST of CURE
- **High Sensitivity**
- **Genotyping**

PRIMARY SCREENING
- **Partial genotyping is a time limited ”pleasure”**
- **Clinical Specificity**
- **Sufficiency controls**

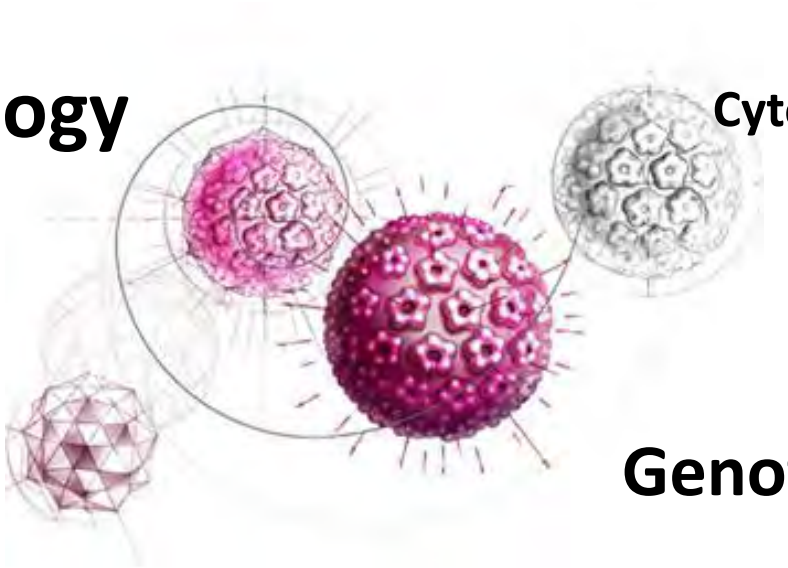
EXIT TEST
- **High sensitivity**
- **Genotyping**
- **Sample sufficiency control**
- **No need for triage, straight to colpo?**

The New Role of Cytology

Possible HPV screening Triage modalities

Cytology

Cytology p16/Ki67
MCM



Genotyping

Biomarkers…

Methylation markers

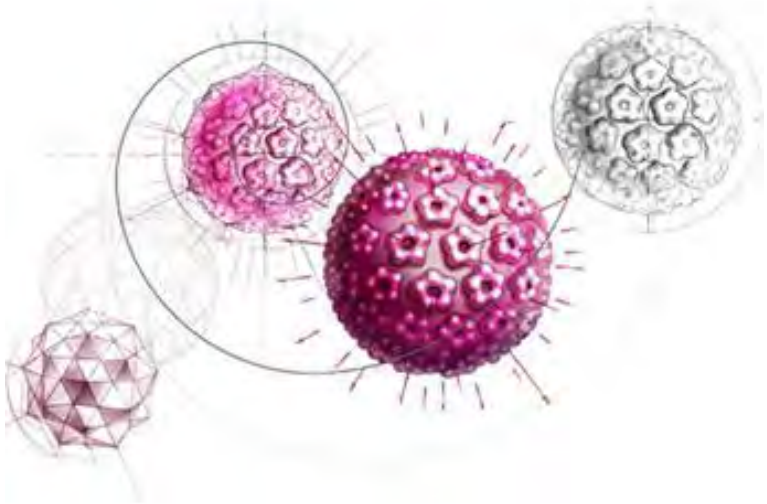
What do we need from Molecular HPV screening tests?

Can we get everything in one assay?

Common denominators:

No but we keep looking..

The added value of genotyping information



Molecular Pathology
Department of Pathology
Hvidovre Hospital

The BD Onclarity™ HPV Assay
Results from the multi-center European CE-IVD trial

European Institute of Oncology
Gynecology Division
Milano

BD Onclarity-ThinPrep evaluation

Copenhagen University Hospital, Hvidovre
Department of Pathology
Copenhagen

BD Onclarity-SurePath evaluation

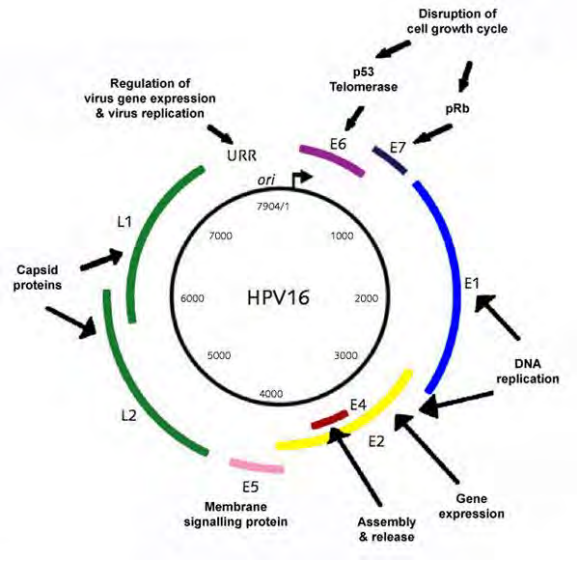
What is the BD Onclarity™ HPV Test…

Molecular Pathology
Department of Pathology
Hvidovre Hospital

The BD Onclarity HPV assay design
and study reference tests

HPV assay	Targeted HPV genotypes	Detection technology	DNA/RNA, and targeted HPV gene	Controls
BD Onclarity™ HPV Assay	**14 HR** 16, 18, 31, 45, 51, 52 33/58, 56/59/66, 35/39/68	Real-time PCR	DNA, E6-E7	Sample by sample Beta globin for sample sufficiency and assay performance

- The first clinical HPV test targeted at E6/E7 ***DNA*** with extended genotyping.
- 3-well assay with 9 separate HPV genotype readouts
- Multiple readouts
- Human β-globin control (IC) in each well



The Viper LT™ design
–from the Lab perspective

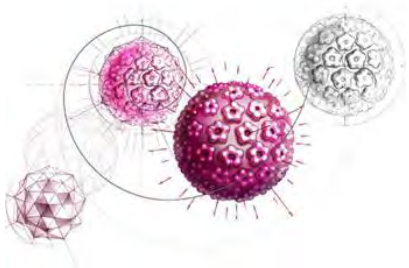
Lab Performance

- Fully automated specimen processing and molecular testing
  - Walk-away convenience with load and go
  - Automatic system checks prior to and during each run
- Delivers up to 90+ to 120 results per working day
  - Equals around 25.000 test per instrument per working year (260 working days)
- 20 minutes or so of total hands-on, active time per run
- On-board sample DNA extraction reduces manual processing steps, and reduces need for auxiliary equipment
- Automated sample processing, ready-to-use reagents
- Works on SurePath™ *and* ThinPrep™

Assay Performance Indicators

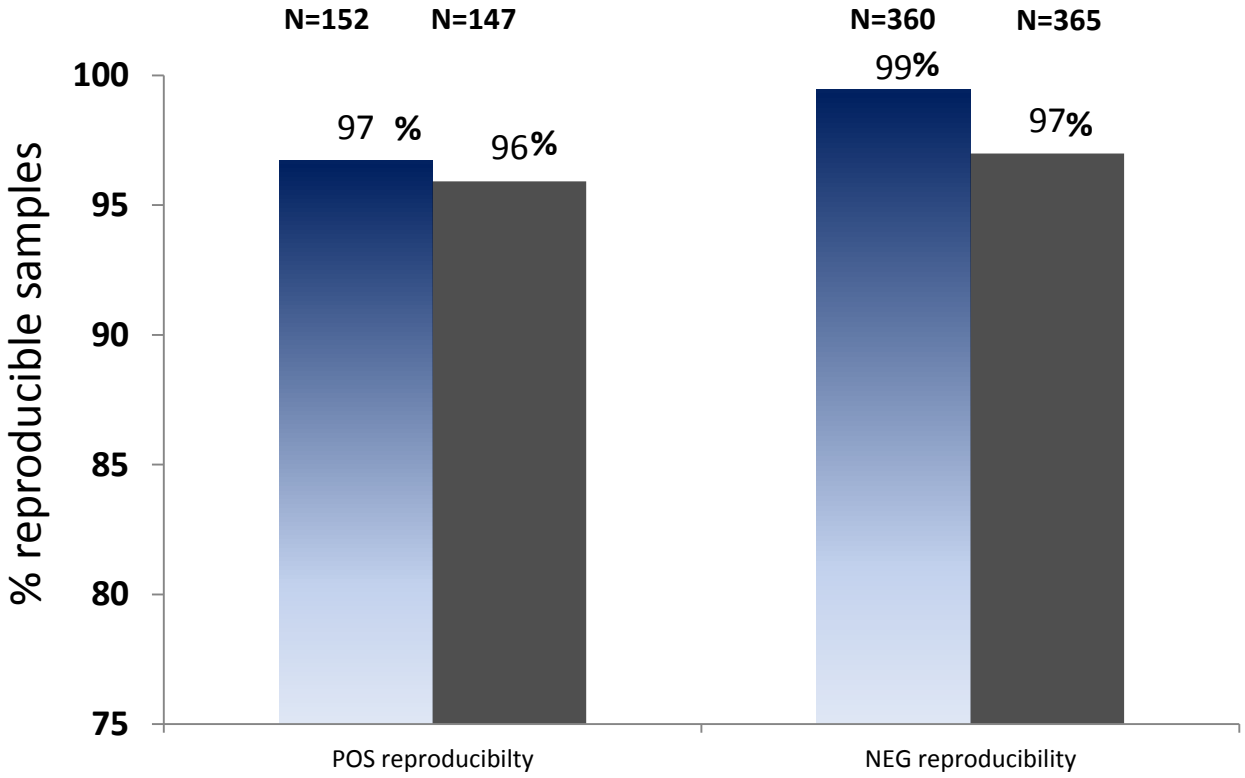
Inter and Intra laboratory assay

Reproducibility



Intra-Lab Reproducibility of BD Onclarity

Same samples tested twice in Copenhagen



Material: 512 routine ThinPrep screening samples

HPV prevalence in unselected samples: 15.5 %

Average test time difference between the two tests: 5 days

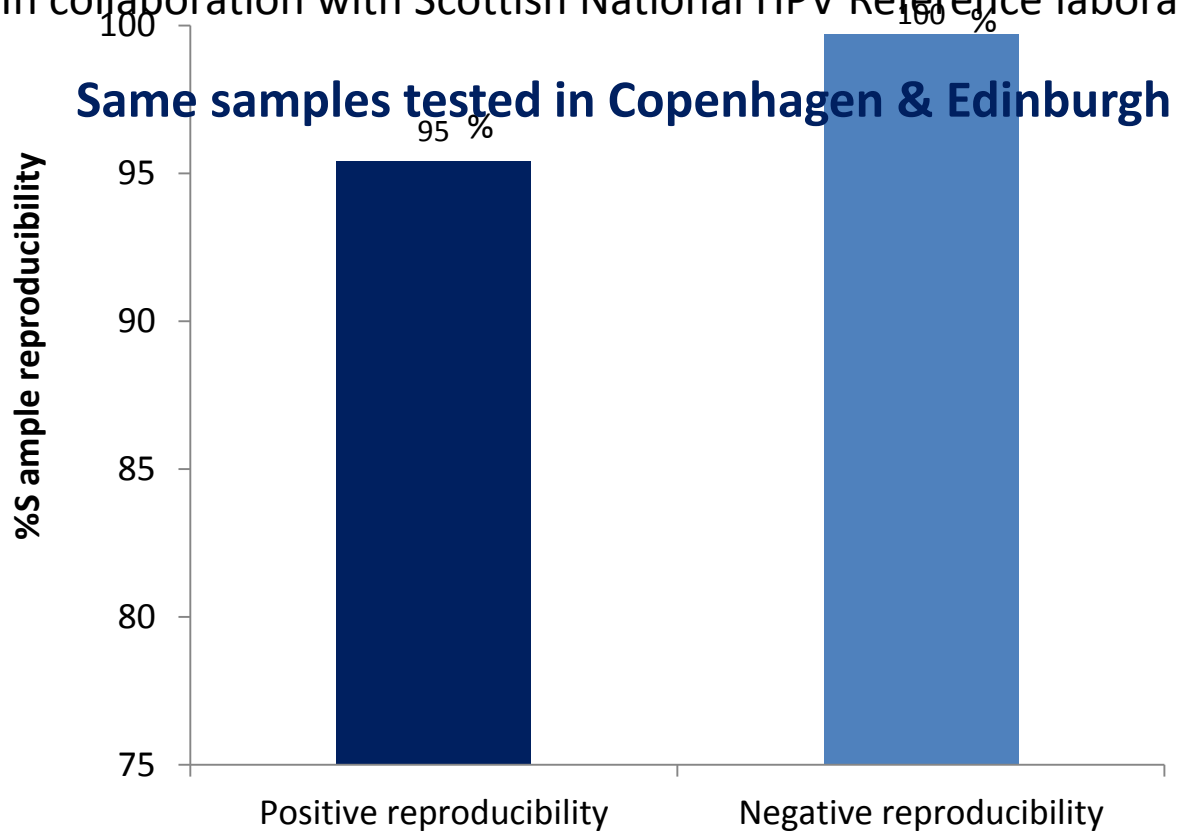
Overall intra-lab repro: 98.6% (kappa=0.967)

[Ejegod et al., J. Med. Micro.Diag, Dec, 2013]

Inter-Lab Reproducibility of BD Onclarity

In collaboration with Scottish National HPV Reference laboratory

Same samples tested in Copenhagen & Edinburgh



Material: 512 routine ThinPrep screening samples

Average test time span between Copenhagen and Edinburgh: 9 days

Overall Inter-Lab repro: 98.4% (kappa=0.962)

[Ejegod et al., J. Med. Micro.Diag, Dec, 2013]

Summary of clinical study data,

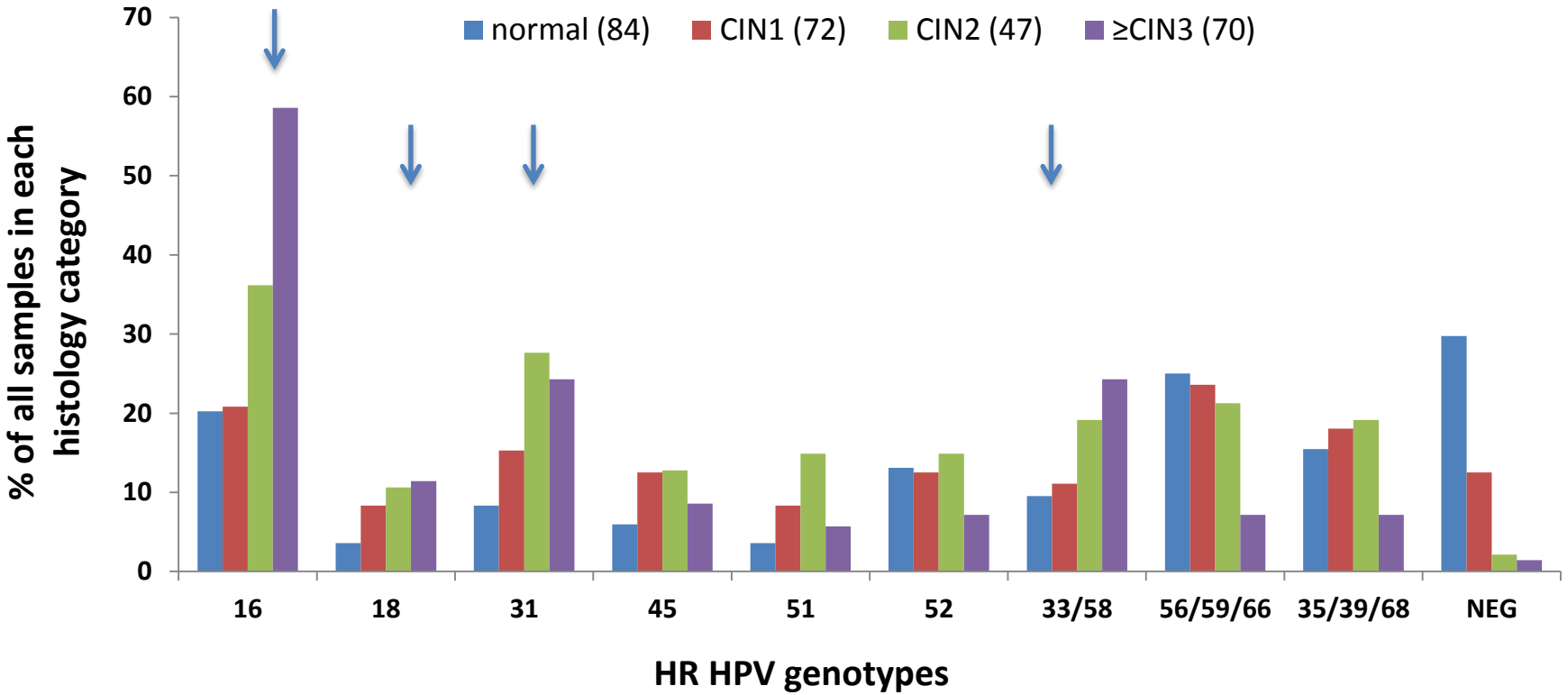
SurePath taken samples, referral population

≥CIN2 and ≥CIN3 based on histology result for prospective specimens, adjudicated.

Diagnostics index	Histology category	# Total	*Digene* HC2	BD Onclarity
Sensitivity	≥CIN2	115	**113/115 (98,3%)** 95% CI: 0,939-0,998	**113/115 (98,3%)** 95% CI: 0,939-0,998
	≥CIN3	68	68/68 (100%) 95% CI: 0,947-1,000	67/68 (98,5%) 95% CI: 0,921-0,1,000
Relative sensitivity	<CIN2	115	1,0	1,0 (0,97-1,03)
	<CIN3	68	1,0	0,99 (0,96-1,01)
Specificity	<CIN2	154	**33/154 (21,4%)** 95% CI: 0,152-0,288	**33/154 (21,4%)** 95% CI: 0,152-0,288
	<CIN3	201	35/201 (17,4%) 95% CI: 0,124-0,234	34/201 (16,9%) 95% CI: 0,1
Relative specificity	<CIN2	154	1,0	1,0 (0,65-1,53)
	<CIN3	201	1,0	0,97 (0,63-1,49)

The value of genotype information

Genotype distribution vs. Histology



Not surprisingly, HPV16 and 18 findings increase with increasing CIN grade

However, as the data indicates genotypes HPV31 and 33/58 are of equal importance if genotyping is to be used for HPV testing, i.e. in differential screening follow up modalities

Conclusions

BD Onclarity HPV test

- Focus on good lab performance characteristics
  - *Excellent inter and intra lab repro in ThinPrep*
  - *SurePath inter and Intra lab repro study underway*
- Clinical sensitivity and specificity for CIN2+ non-inferior to HC2 (Meijer criterion)
  - *Proven for referral population*
  - *NILM study in SurePath underway*
- Automated integration Totalys-VIPER is a full molecular-cytology workflow

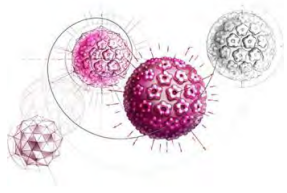
Perspectives
HORIZON & VIPER TRIALS

- For high prevalence populations, false positives will pose a challenge
  - Cytology as triage is currently the best option to reduce the number of immediate referrals without giving away the benefits of primary HPV screening (Meijer et al).

- HPV16/18 triage leads to overtreatment if used for direct referral in high prevalence populations (HORIZON)

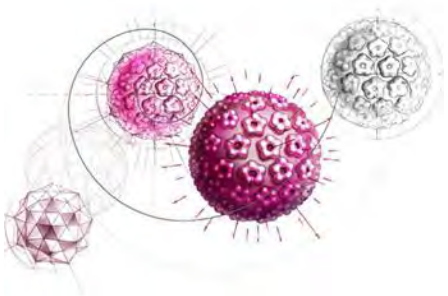
- Extended genotyping allows for a more individual focus and allows for assessment of clearance versus persistence. (HORIZON & Onclarity)

- **Integration between molecular HPV testing and cytology is required for the immediate future until new methods come online….**



Primary HPV Screening any day soon…?

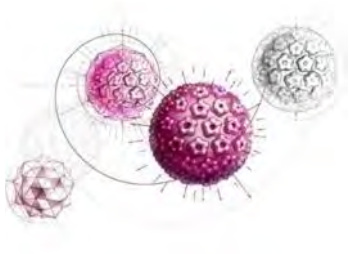
The game changer



Molecular Pathology
Department of Pathology
Hvidovre Hospital

HPV-BASED SELF-SAMPLING TO IMPROVE CERVICAL SCREENING COVERAGE

Copenhagen Self-sampling Initiative - CSi



Why self sampling

The definitively most efficient way to improve screening efficacy is to raise attendance rate

---

Self sampling offers itself to molecular HPV testing, but can not be done using cytology

---

The aim of self sampling is to get more women to go for a regular screening test

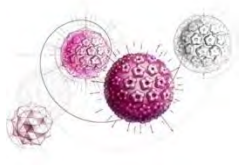
---

Copenhagen Self-sampling Initiative

By mandate of recommendation from the National Board of Health, 2012, to initiate pilot implementation of self-sampling

Funds from the Capital Region (Strategic Development Funds) to the Pathology Department, 2013

Implementation 2014



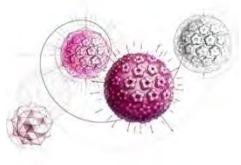
Copenhagen Self-sampling Initiative

Will approach all 20-25.000 non-responders and suggest a "home sample"

Innovative patient safety approach

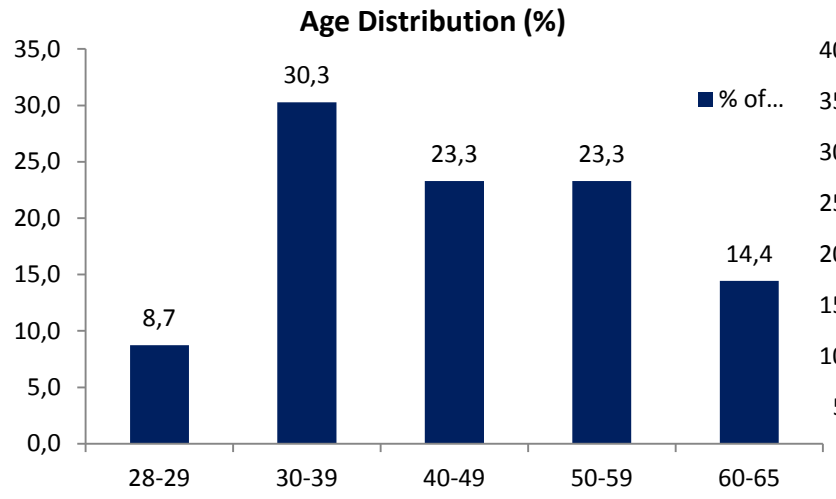
Innovative communication approach

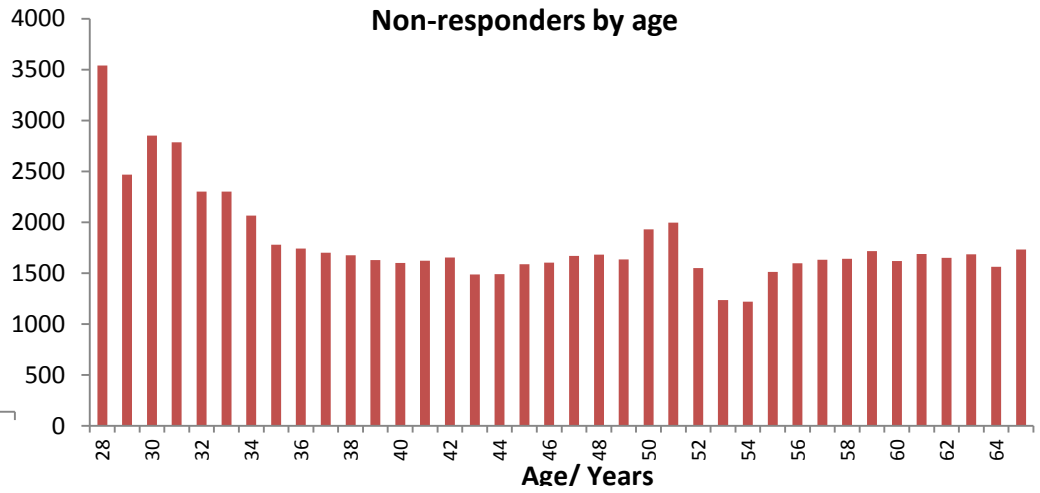
Split sample evaluation of three different HPV DNA technologies

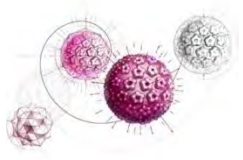


Copenhagen Self-sampling Initiative

Who are these women?



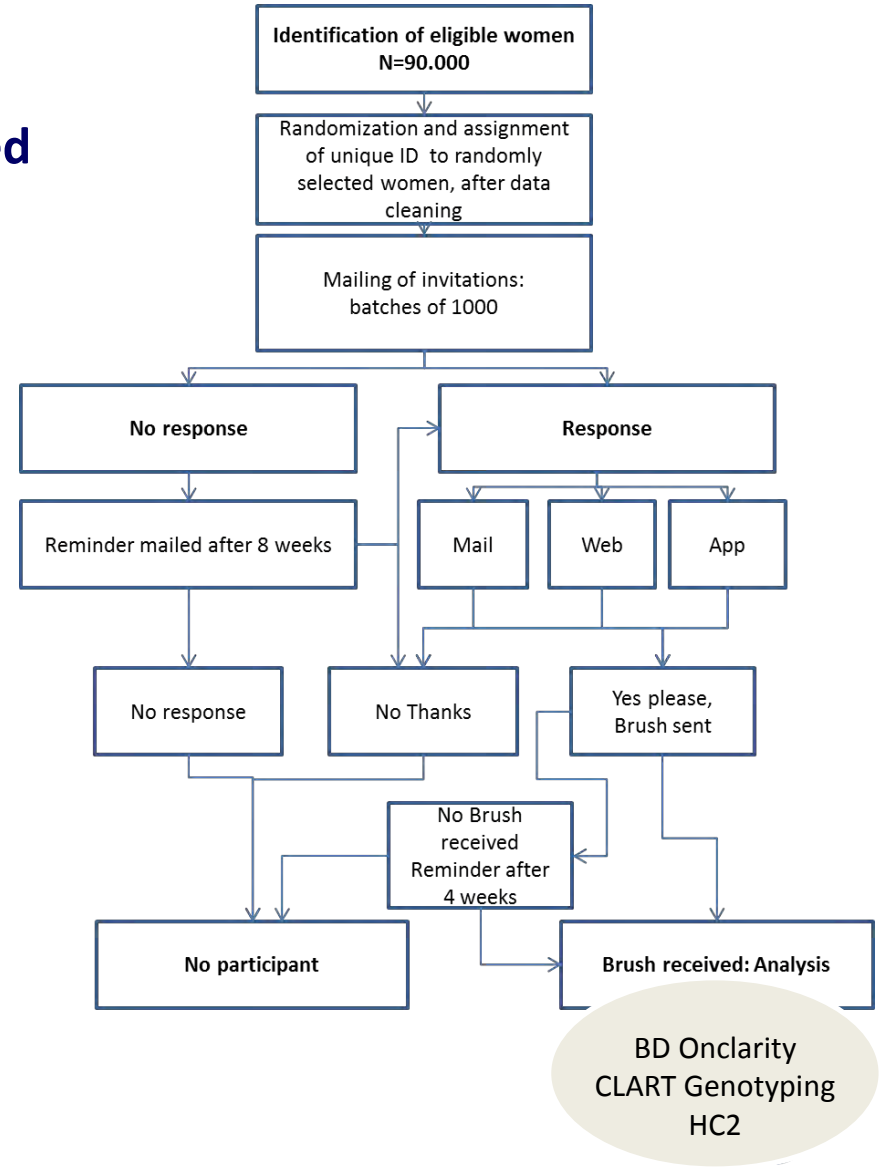




Copenhagen Self-sampling Initiative

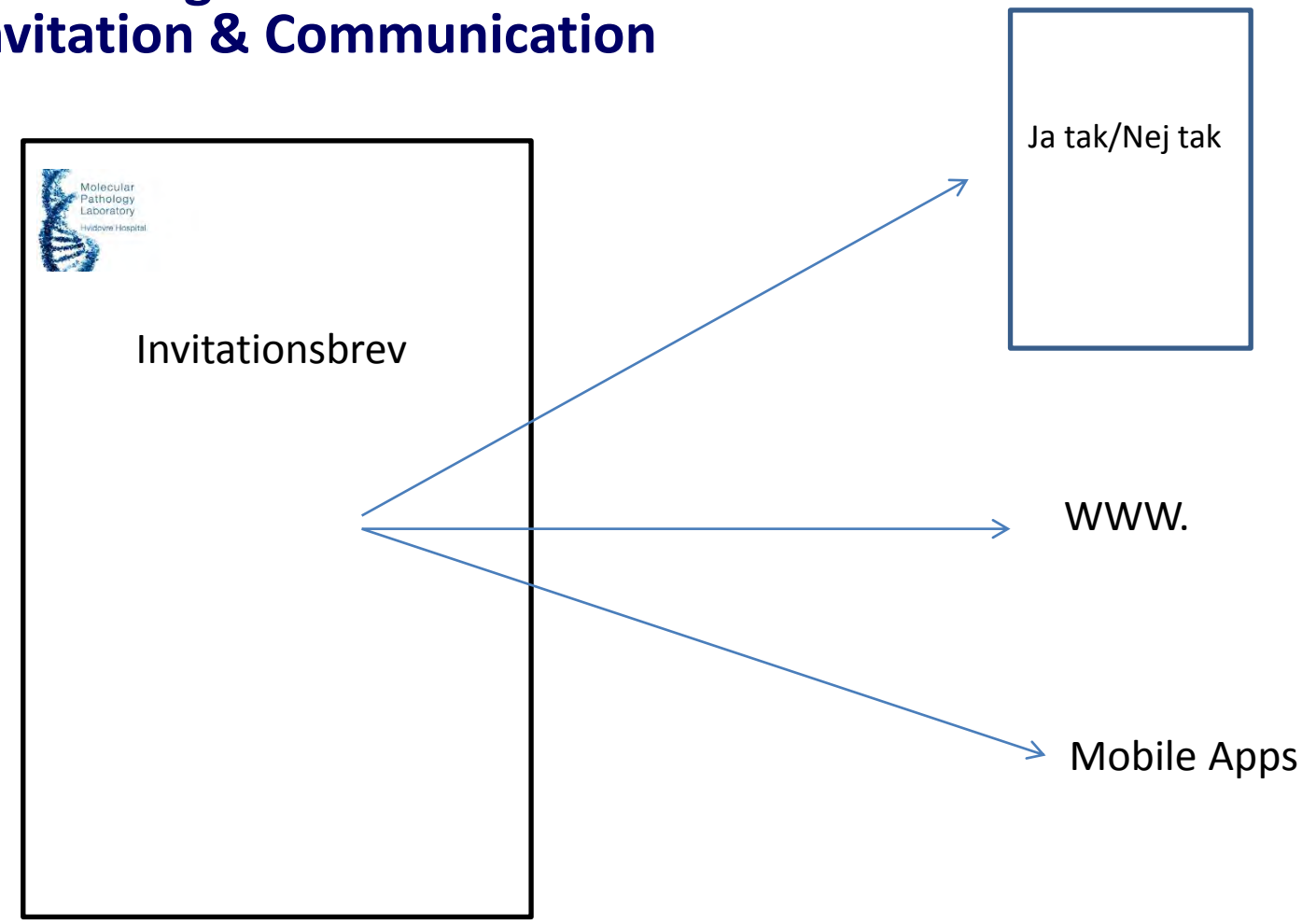
Pilot design

Target : 5000 returned brushes for analysis

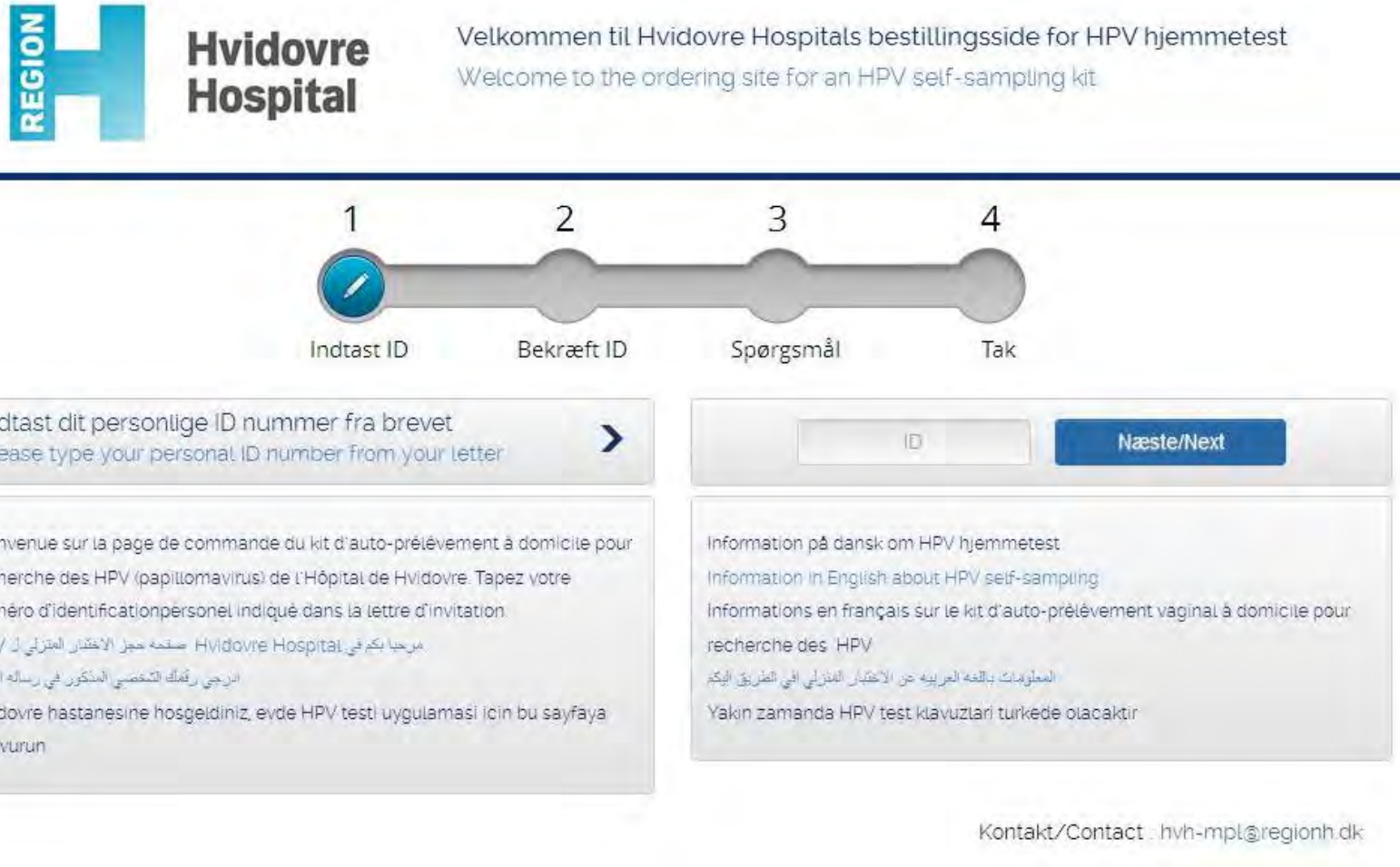


Copenhagen Self-sampling Initiative

Pilot design: 12-03-14-4444
Invitation & Communication



Innovative Communication
Opt-In www/App

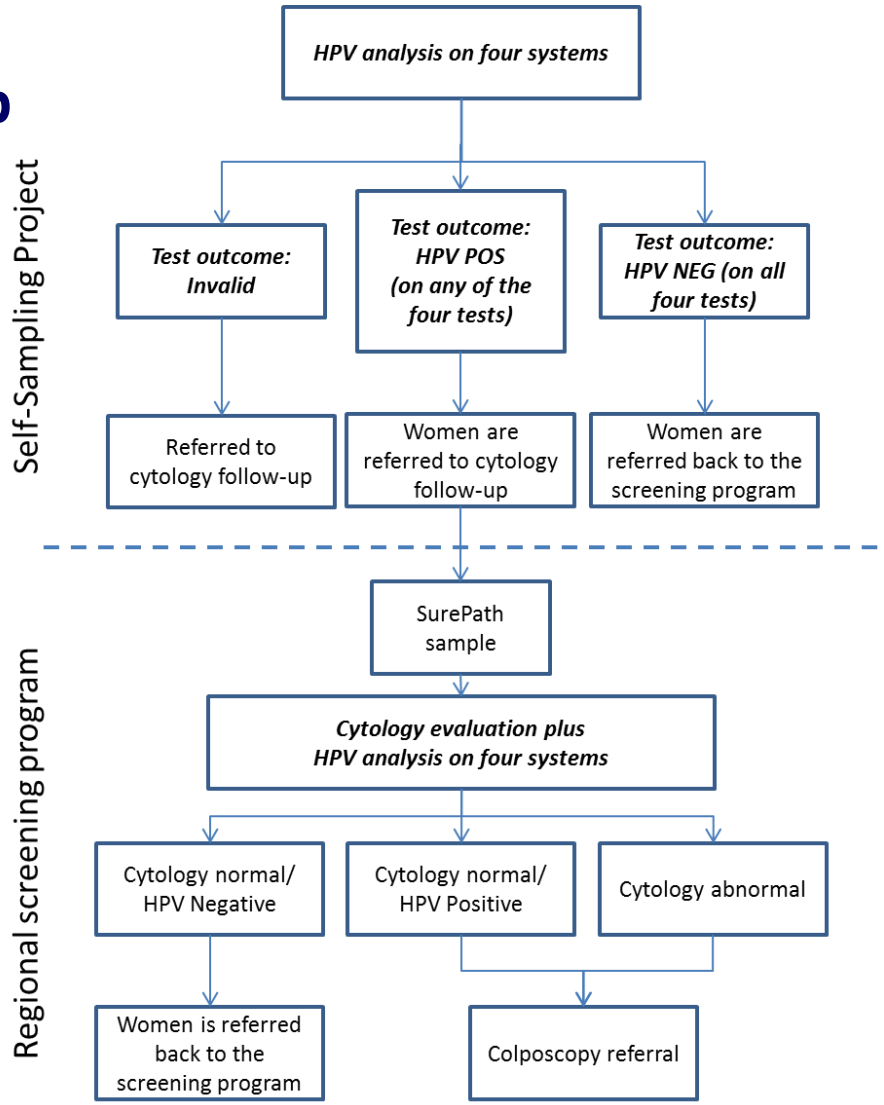


Copenhagen Self-sampling Initiative

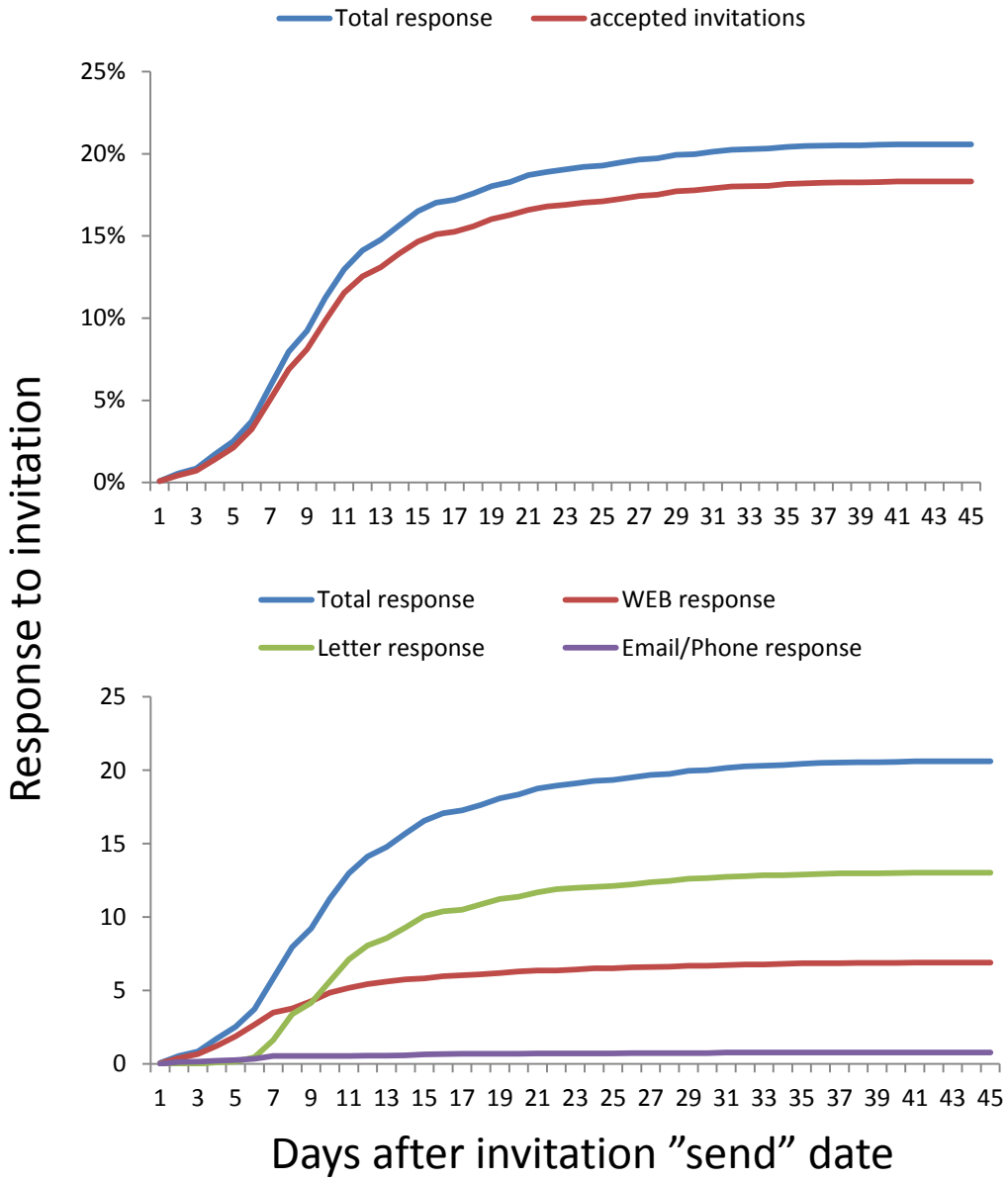
The Brush

Copenhagen Self-sampling Initiative

Pilot design: Test&Follow up

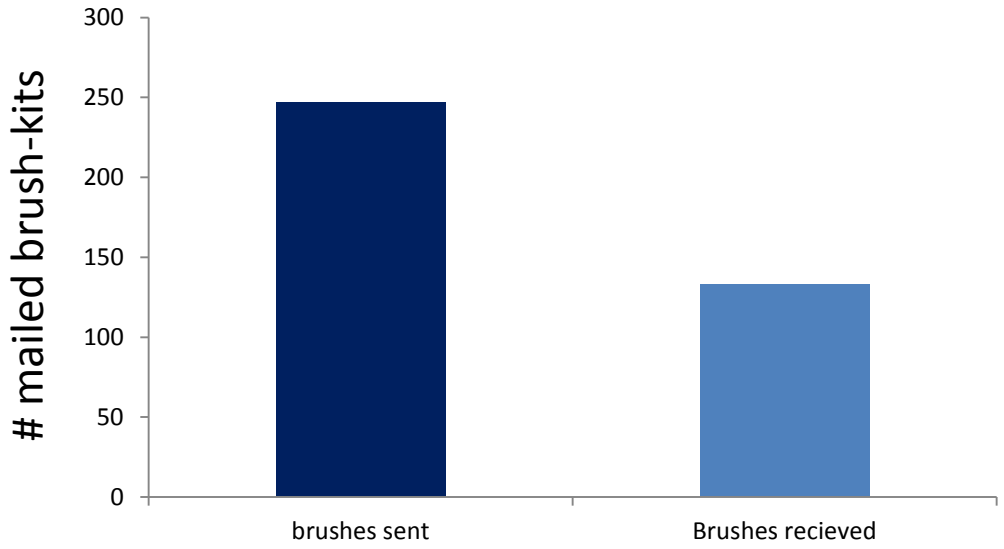


After one month, what has happened is…

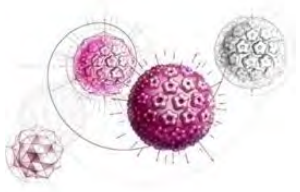


After one month, what has happened is…

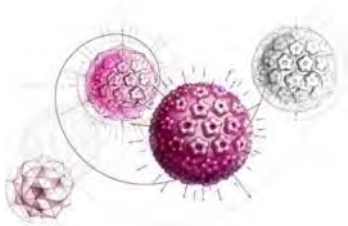
54% return rate, *prior* to reminder



14% prevalence on *any* of the three HPV tests



Acknowledgement



The Horizon study group

-a multi-disciplinary team

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Presented data reflect the work of the whole team
Opinions presented in the talk are mine, with team discussions gratefully acknowledged

The BD Onclarity EU CE-IVD Trial Group:

Acknowledgement

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Silvestro Carinelli, MD
Eugenia Tomas-Roldan, Nurse
&
Mario Sideri, MD

Corporate Sponsor
Becton Dickinson and Company (BD Diagnostics)

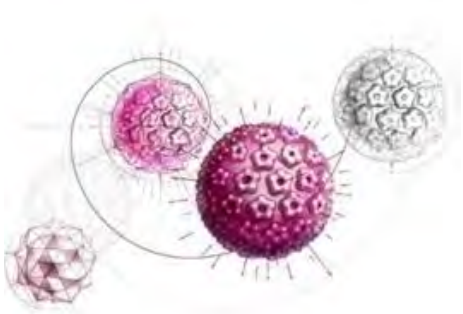
In Memory of

Mario Giovanni Sideri
1953
- 28th June 2014

Your booming voice will be missed…

Thank you for your attention

Jesper.Hansen.Bonde@regionh.dk



BD Europe Heidelberg 2014

HPV testing in the NHSCSP The story so far

Dr J H F Smith
Royal Hallamshire Hospital, Sheffield
East Pennine Cytology Training Centre

East Pennine Cytology Training Centre
TRAINING STAFF FOR A QUALITY SERVICE

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Cancer of the Cervix: Death by Incompetence

The most successful programmes:

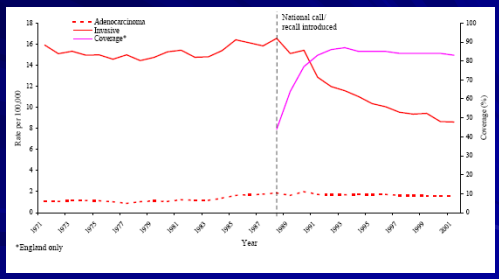
- 'are organised as public health cancer control programmes, specifically directed towards a reduction of mortality'
- 'call the age groups at greatest and most immediate risk (30+) and keep on trying. Concentrate first upon women who have never had a smear at all. They use population registers'
- 'someone is in charge…and can be held to account'

Lancet 1985; ii: 363-364

Cervical Screening in England and Wales after 1988

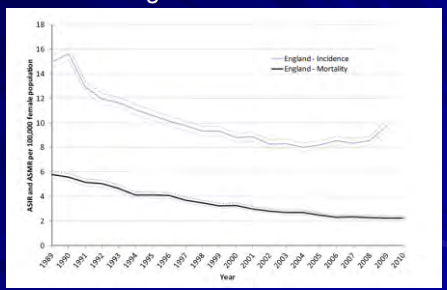
- Computerised call/recall
- Target age range 20-64 years
- Screening managers
- Family physician (GP) contract
- Quality assurance programmes
- Improved training
- Director NHSCSP

Age-standardised incidence of invasive cervical cancer (total) and adenocarcinoma of the cervix. England and Wales 1971-2001



Cancer Trends: Office for National Statistics

Cervical cancer incidence and mortality, England 1989-2010

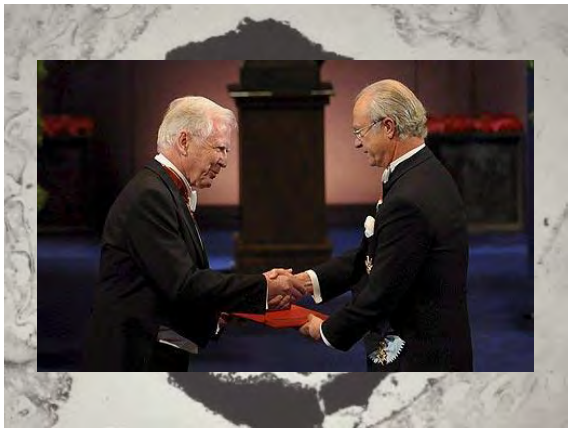


www.ncin.org.uk/view.aspx?rid=1669

Cervical Screening in England and Wales after 1988

- Screening saves at least 1100 and up to 4000 lives per annum
- Impact on both squamous cell carcinoma and adenocarcinoma
- Annual deaths below 1000 per annum
- 78.3% eligible women screened every 5 years:
  - 71.5% women aged 25-49 every 3 years
  - 77.5% women aged 50-64 every 5 years

Peto et al. Lancet 2004; 364: 249
Sasieni. Lancet 2001; 357:1490



Epidemiologic classification of HPV

High risk types: high grade CIN and cancer

16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82

Low risk types: low grade CIN and condyloma

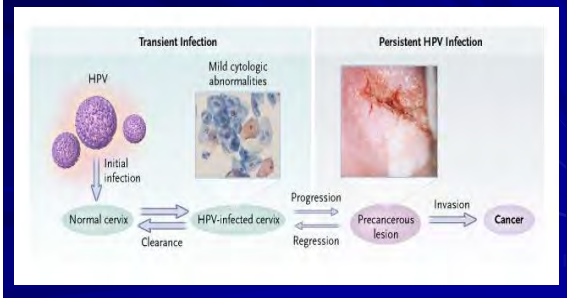
6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108

Probable high risk types

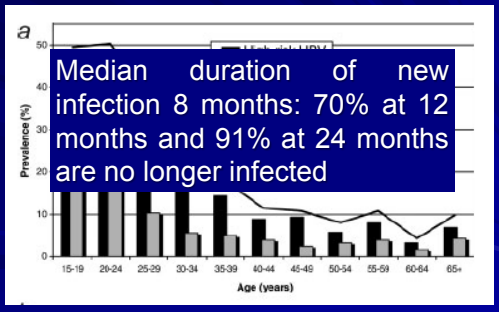
26, 53, 66

Munoz et al. NEJM 2003; 348: 518

The natural history of HPV infection and cervical cancer



Age specific prevalence HPV



Median duration of new infection 8 months: 70% at 12 months and 91% at 24 months are no longer infected

HPV Testing in Cervical Screening

- Positive predictive value high risk HPV is very low
- Negative predictive value high risk HPV is very high
- Low long term risk of CIN 3+ in HPV negative women

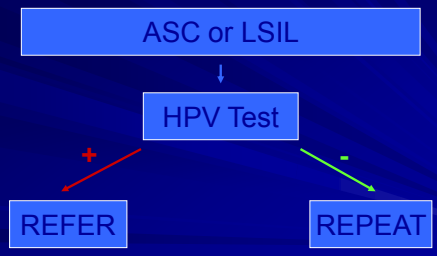
Kitchener et al. Eur J Cancer 2011; 47: 864
Elfstrom BMJ 2014; 348: g130

HPV Testing in Cervical Screening

- Triage low grade abnormality
- Follow up after treatment

- Primary screening with triage to:
  - Cytology
  - Colposcopy
  - VIA
  - VILI

Triage of low-grade smears



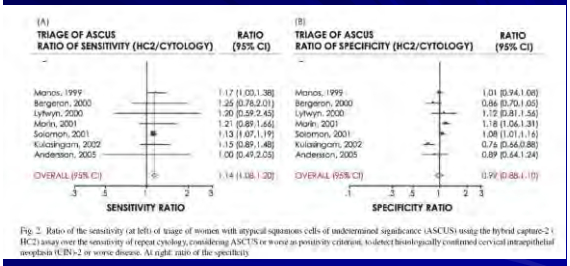


Fig. 2. Ratio of the sensitivity (at left) of triage of women with atypical squamous cells of undetermined significance (ASCUS) using the hybrid capture-2 (HC2) assay over the sensitivity of repeat cytology, considering ASCUS or worse as positivity criterion, to detect histologically confirmed cervical intraepithelial neoplasia (CIN)-2 or worse disease. At right: ratio of the specificity

Arbyn et al. Vaccine 2006; 24S3: 78

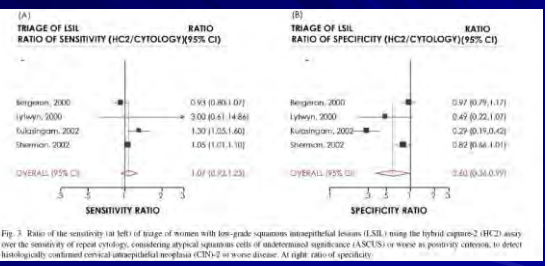


Fig. 3. Ratio of the sensitivity (at left) of triage of women with low-grade squamous intraepithelial lesions (LSIL) using the hybrid capture-2 (HC2) assay over the sensitivity of repeat cytology, considering atypical squamous cells of undetermined significance (ASCUS) or worse as positivity criterion, to detect histologically confirmed cervical intraepithelial neoplasia (CIN)-2 or worse disease. At right: ratio of specificity

Arbyn et al. Vaccine 2006; 24S3: 78

HPV* triage of low grade cytology

	Sensitivity	Specificity
Borderline/ASCUS	↑	↔
Mild dyskaryosis/LSIL	↑	↓

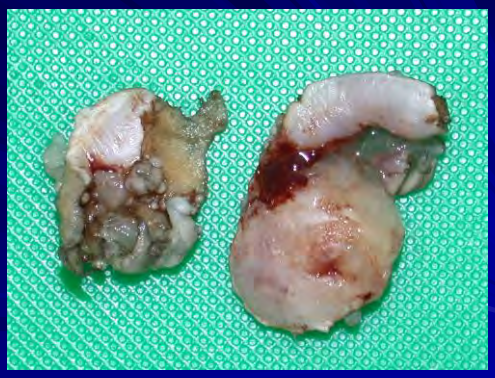
* Hybrid Capture-2 (HC2) assay

Arbyn et al. Vaccine 2006; 24S3: 78

HPV triage in NHS LBC pilot

- HPV triage is feasible
- It is acceptable to women
- May lead to increased detection of CIN2+
- It accelerates the diagnosis of high-grade CIN
- It avoids the need for repeated cytology
- It is cost effective in terms of quality and of life years saved

Legood. BMJ 2006; 332: 79-83
Moss. BMJ 2006; 332: 83-85



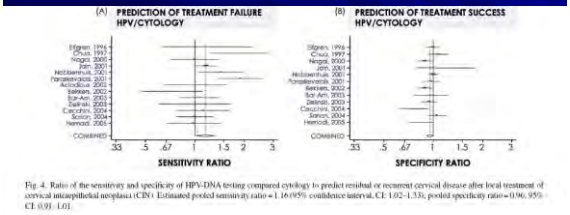


Fig. 4. Ratio of the sensitivity and specificity of HPV-DNA testing compared cytology to predict residual or recurrent cervical disease after local treatment of cervical intraepithelial neoplasia (CIN). Estimated pooled sensitivity ratio = 1.16 (95% confidence interval, CI: 1.02–1.33); pooled specificity ratio = 0.96; 95% CI: 0.91–1.01.

Arbyn et al. Vaccine 2006; 24S3: 78

Follow up after Treatment

- Currently women treated for CIN 2 or worse are followed by annual sampling for at least 10 years before returning to routine screening
- Women treated for CIN 3 should continue surveillance beyond the age limit of regular screening

NHSCSP Publication 20. 2004

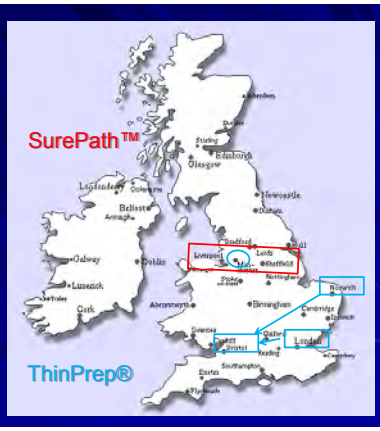
Strander et al. BMJ 2007; 370: 1764

Sentinel Site Study

A person employed to keep watch for some anticipated event

Hybrid Capture 2

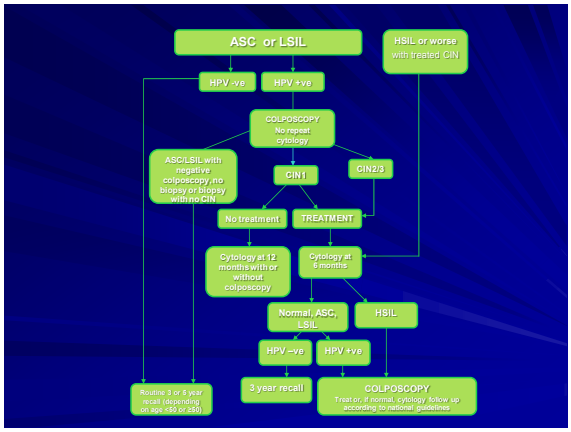
RLU>2



Sentinel sites

6 centres. Using HC II

- HPV triage
  - ASC / LSIL - HPV positive = refer
  - ASC / LSIL - HPV negative = routine recall
- Follow up after treatment – 'test of cure'
  - If cytology and HPV negative at 6 months = routine recall: 3 or 5 years depending on age



Sentinel Site Triage Results

- HPV positive rates
  - ASC 53.7% (range 34.8% - 73.3%)
  - LSIL 83.9% (range 73.4% - 91.6%)
  - Low grade overall **64.4%**
  - PPV HPV +ve for CIN 2+ 16.3% (9.3 – 21.1%)
  - PPV HPV +ve for CIN 3+ 6.1% (2.5 – 11.5%)

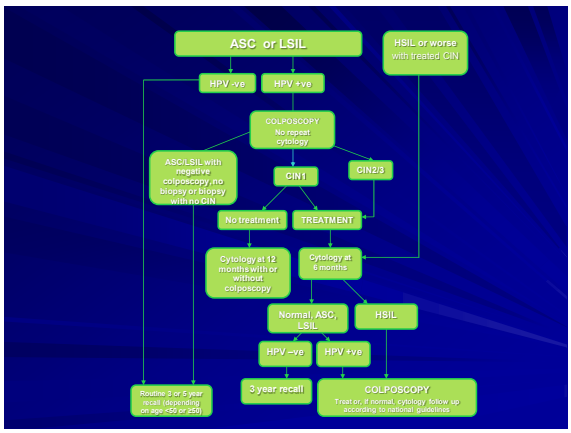
British Journal of Cancer 2011; 105: 983-988

Sentinel Site Test of Cure Results

- 78% HPV & cytology negative at 6 months and could revert to normal recall

Detection of CIN in ToC

PPV	CIN 2+	CIN 3+
HSIL	13.6%	8.5%
Normal/ASC/LSIL and HPV +ve	2.9%	0.4%



Cytology/HPV +ve and Colp -ve

- Cumulative incidence CIN 2+ after 3 years = 4.4%
  (1.2% normal screened population)
- Cumulative incidence CIN 3+ after 3 years = 2.4%
  (0.7% normal screened population)
- No cases of invasive disease

Kelly et al BJOG 2012; 119: 20

Advantages of HPV Triage and ToC

- Detection of high-grade CIN leading to earlier treatment and early discharge
- Early return of women with low-grade cytology and HR-HPV negative to routine recall
- Early return of women treated for CIN who were cytology negative and HR-HPV negative to routine recall.

Figure 1 A woman with CIN 3, (a) with and (b) without HPV triage and test of cure

(a) HPV triage and test of cure	(b) Standard treatment
• Routine screen • Borderline cytology, HPV+ • Colposcopy at 8 weeks from date of test • CIN3 detected • Treated with LLETZ • Test of cure at 6 months, negative • 3 year recall • Time for whole episode: 9 months	• Routine screen • Borderline cytology • Repeat at 6 months, borderline cytology • Repeat at 6 months, borderline cytology • Colposcopy 14 -18 months from date of initial test • CIN 3 detected • Treated with LLETZ • Annual follow up for 10 years • Time for whole episode: 12 years

HPV Triage and Test of Cure: Implementation Guidance. NHSCSP. July 2011

What will be the impact of HPV testing on cytology laboratory practice?

Impact on National Workload

Combined effect HPV triage & test of cure

HPV triage	175,000 fewer tests
Test of cure	428,000 fewer tests
Total	603,000 fewer tests

Total cost saving of €26 million/year = 13% saving

Impact on Cytology Reporting

- The potential to
  - make us lazy
  - alter our reporting parameters

Will HPV triage make screening staff lazy?

- Why worry about whether abnormality is ASC or LSIL when management will be decided by the HPV test?
- In sample with ASC/LSIL do you spend time thoroughly checking to exclude HSIL when management will be decided by the HPV test?
- Professional integrity should mean that we still try and categorise correctly

Will HPV triage make screening staff lazy?

- Pathologists must be careful NOT to over use HPV testing.
  - Remember a significant proportion of young women will test HPV positive irrespective of whether they have disease or not
  - Adds cost
  - Decreases specificity
  - Impacts on colposcopy clinic workloads
  - Creates unnecessary anxiety in women

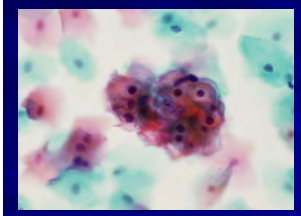
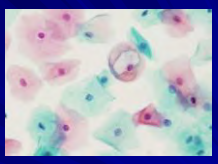
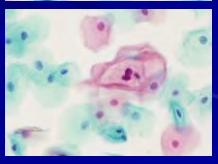
Will HPV triage alter reporting parameters?

- Increased use of ASC to improve management?
  - In past, if unsure but favouring high grade (ASC-H), guidance was to code as HSIL (moderate) and refer to colposcopy
  - With HPV testing more benefit is gained by coding as ASC and request an HPV test
  - If HPV test is negative colposcopy and anxiety are avoided, and money saved

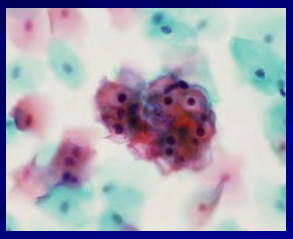
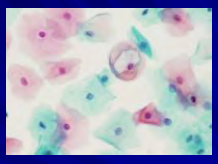
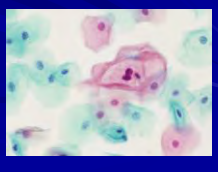
What are the main benefits of HPV triage in reporting?

- Very useful in
  - Minimal changes in poor attendees
  - Atrophic samples
  - Hyperchromatic crowded cell groups (HCCGs)

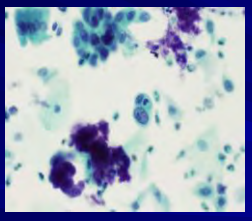
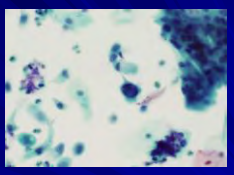
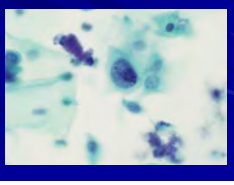
Age 29 - Minimal LSIL in poor attendee

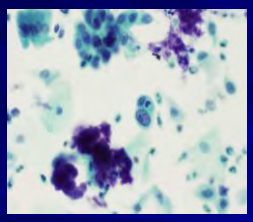
HPV negative » routine recall

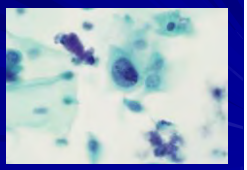
Age 51 – early atrophy/degeneration v HSIL

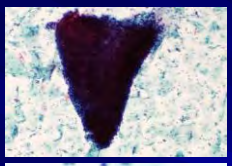
Age 51 – early atrophy / degeneration v HSIL

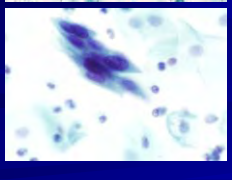
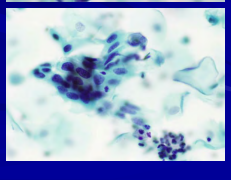


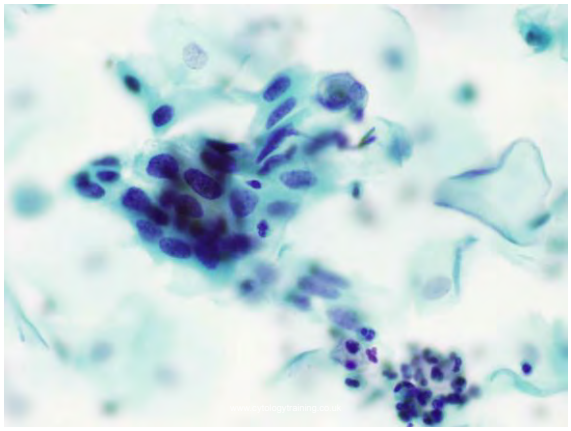
- HPV positive
- Biopsy = CIN 3



Age 50 – HCCGs - HSIL?

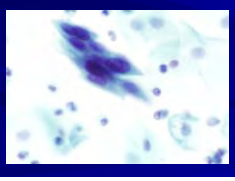
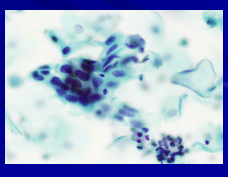


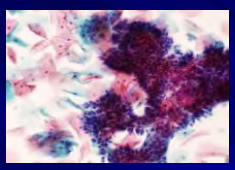
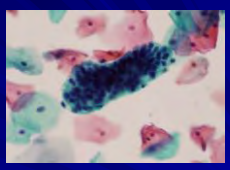


Age 50 – HCCGs - HSIL?

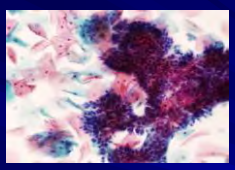
- HPV negative

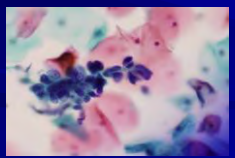
Age 44 AGC NOS

Age 44 AGC NOS



- HPV negative




Impact of HPV triage and ToC 5 years on

- Overall reduced workload – impact on screening sensitivities
- Fewer abnormal slides impacting on consultant/AP* reporting numbers
- Established protocol
  - Simplified management decisions
  - Improved laboratory workflow

*Advanced biomedical scientist practitioner

Main Challenges for Laboratories

- Impact on morale of staff
- Understanding protocols
- Access to appropriate follow up information
- Clinical liaison with gynaecologists

Impact on colposcopy

- Colposcopy DNA (no show) Rates
  - Reduced from approximately 20 to 10%
  - Repeated across the NHSCSP could avoid approximately 17,600 missed appointments

Conclusion

- HPV triage / ToC **is good for women**
  - Speeds up referral
  - Avoids referral for those that don't need it
  - Reduces number of repeat cytology tests
  - Returns women to normal recall earlier

Are all HPV testing platforms the same?

- TP/HC2 = 54%
- TP/HC2 = 56%
- TP/HC2 = 55.5%
- TP/Roche = 69.4%
- SP/Abbott = 80%
- SP/Roche = 55.7%
- SP/Roche = 72.3%

Changing platforms overall

Cytology	% Test positive HC II	% Test positive Cobas-4800
Negative	12.4	26.4
ASC/AGC	77.0	69.4
LSIL	94.2	89.6
OVERALL	**40.1**	**54.0**

Changing platforms in ToC

	HC II	Roche Cobas-4800
Median age	30 (18-66)	29 (20-68)
Negative cytology	95.1%	96.6%
Negative HR HPV +ve	13.5%	26.1%
Low grade HR HPV +ve	1.5%	3.69%
Significant disease (CIN 2+)	3.14%	2.53%

Primary HPV Screening

Sensitivity and specificity of HC2

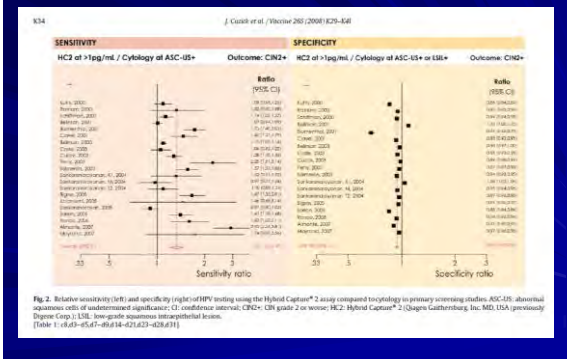
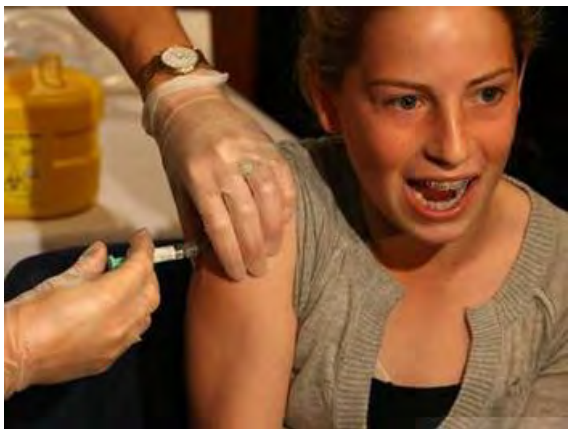


Fig. 2. Relative sensitivity (left) and specificity (right) of HPV testing using the Hybrid Capture® 2 assay compared to cytology in primary screening studies. *ASC-US*: abnormal squamous cells of undetermined significance; CI: confidence interval; CIN2+: CIN grade 2 or worse; HC2: Hybrid Capture® 2 (Qiagen Gaithersburg, Inc. MD, USA [previously Digene Corp.]); LSIL: low-grade squamous intraepithelial lesion.

Primary Screening by HPV Testing

- Sensitivity of HPV testing by HC 2 (80- 100%) is higher than conventional cytology, but specificity is lower (51-95%)
- Focus intensive screening on HPV positive women
- Direct referral for colposcopy of all women aged 30-35 who are HPV positive in one screening round would detect almost all high-grade CIN and invasive cancer (Meijer 2000)



Estimating the long-term impact of a prophylactic human papillomavirus 16/18 vaccine on the burden of cervical cancer in the UK

- 100% coverage of a 12-year old cohort of girls would lead to:
  - 75000 fewer abnormal cytology tests
  - 442000 fewer cytology tests including follow up tests

Estimates most sensitive to age of vaccination and coverage

Kohli et al. Br J Cancer 2007; 96: 143

Estimating the long-term impact of a prophylactic human papillomavirus 16/18 vaccine on the burden of cervical cancer in the UK

- 100% coverage of a 12-year old cohort of girls would lead to:
  - 66% reduction in prevalence of CIN 2/3
  - 76% reduction in cervical cancer deaths
  - 25% reduction in abnormal cytology tests
  - 33% reduction in diagnostic tests and CIN treatments

  Results sensitive to increase in vaccination age and coverage

Kohli et al. Br J Cancer 2007; 96: 143

Predicted impact of vaccination against human papillomavirus 16/18 on cancer incidence and cervical abnormalities in women aged 20-29 in England

- Assuming 80% coverage:
  - 63% reduction in invasive cancer
  - 51% reduction in CIN 3
  - 27% reduction in cytological abnormalities by age 30

Cuzick et al. Br J Cancer 2010; 102: 933

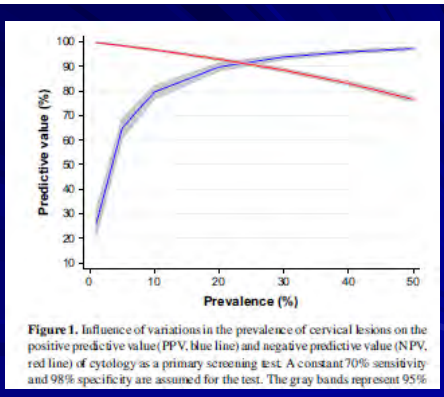


Figure 1. Influence of variations in the prevalence of cervical lesions on the positive predictive value (PPV, blue line) and negative predictive value (NPV, red line) of cytology as a primary screening test. A constant 70% sensitivity and 98% specificity are assumed for the test. The gray bands represent 95%

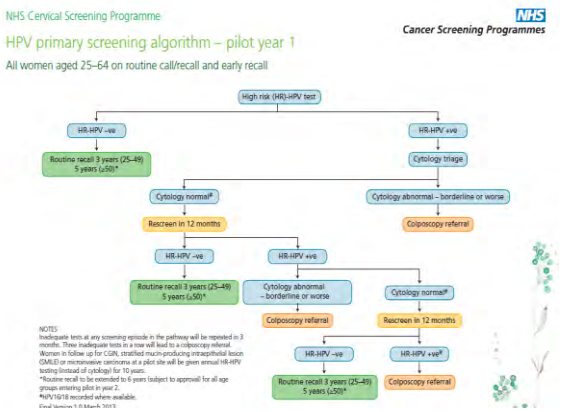
Franco et al. Arch Med Res 2009; 40: 478

Is cytology the best way to screen a vaccinated population?

- HPV testing in primary screening
  - 20-40% greater sensitivity but 5-10% lower specificity
  - Highly standardised and validated assay system – maintain performance characteristics under low prevalence conditions
  - Monitor the epidemiology of HPV infection
  - Incidence of HPV infection in vaccinated women

Sentinel Site Conversion

	Workload	Primary HPV tests
Bristol	33%	20,000
Liverpool	33%	15,000
Manchester	40%	47,000
Norwich	20%	11,500
Northwick Park	25%	20,000
Sheffield	33%	35,000



HPV Primary Screening in Family Practice

- All women invited for screening
- No change in sample taking
- No difference for women
- Emphasis on counseling women
- Awareness of limitations of HPV test
  - Will not identify non-HPV related cancers
  - Some cervical cancers HPV negative

Sheffield Story

- Sheffield PCT – approx 35,000 samples
- April 1st 2013 – women invited
- May 1st 2013 – HPV primary screening
- Dual testing - Cobas 4800 and HC2
- First to go live

Sheffield Story

- Laborious decapping/aliquotting
- Downtime of HPV platforms
- Laboratory and family practice computer systems not accepting codes
- No cytology result
- Confusion with new ABC 3 terminology
- STAFF

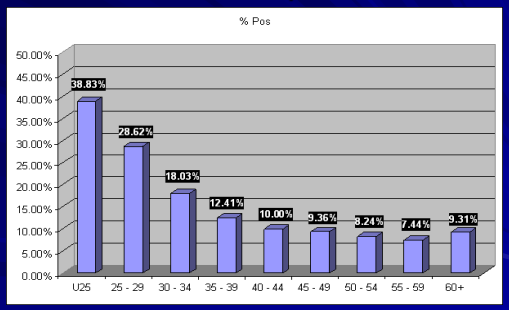
Staff

- Sudden realisation of the implications....
- HPV primary screening slides separately identified
- Screening/reporting knowing sample HPV positive
- Learning curve – which staff grades?

Sheffield Story – End April 2014

- 30,063 samples HPV tested
  - 82.78% HPV -ve
  - 16.32% HPV +ve
  - 0.9% HPV test unreliable
- 4,906 cytology slides assessed
  - Approx 70% no abnormality – repeat 12 months
  - Approx 30% abnormal cytology – refer to colp

Sheffield HPV prevalence



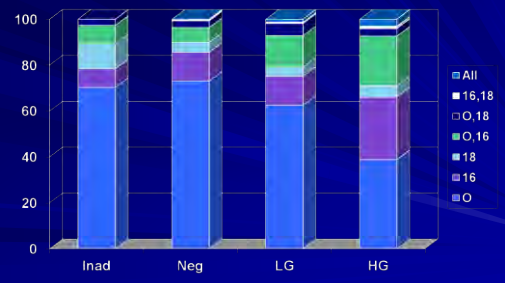
Cytology Breakdown

Cytology Grade	Number	%
Inadequate	46	0.94%
Negative	3493	71.20%
Low Grade	882	17.98%
High Grade	383	9.86%
Non-cervical cancer	1	0.02%
Total	**4906**	**100.00%**

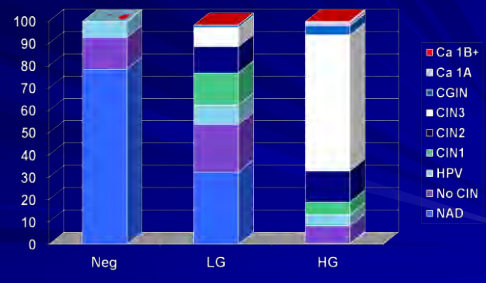
Sheffield Story

- Breakdown of HPV positive by cytology
  - 70% negative
  - 20% low grade cytology
  - 10% high grade cytology
- Predicted 16% HPV positive and 30% cytologically abnormal in 100,000 workload = 4,800 abnormal cytology specimens, comparable to conventional workload

HPV Type by Cytology (%)



Histology – HPV +ve/cytology (%)



HPV positive rates by site

Site	HPV Test	Rate (%)
Bristol (TP)	HC2/Genprobe	15
Liverpool (SP)	Genprobe	11.5
London (TP)	Abbott	12
Manchester (SP)	Abbott	12
Norwich (TP)	Roche Cobas	12
Sheffield (SP)	Roche Cobas	16

HPV primary screening pilot dual testing

- 1600 samples tested on HC2 and Cobas 4800
  - HC2 12.7% HPV +ve
  - Cobas 4800 15.7% HPV +ve

Risks of HPV Primary Screening

- Will miss some CIN and cancer
- ARTISTIC data – 10.9% CIN II and 4.3% CIN III, and 3 cancers were HPV negative
- Magee Hospital - 17% of 454 women had negative HPV test within 3 years of diagnosis of cervical cancer
- CAP Study 2012 – 25% women had negative HPV test 1 to 5 years prior to diagnosis of cervical cancer

Cuzick et al: Int J Cancer 2006;119:1095-101
Obstet Gynecol 2010; 116:76-84
J Lower Genital Tract Disease 2010; 14: 247A, 255A

However .....

- Cytology also misses cervical disease
- Of women with cervical cancer
  - 20% aged 20 - 49 had a negative test within 3.5 years of diagnosis
  - 28% aged 50 - 64 had a negative test within 5.5 years of diagnosis (NHSCSP 2012).

SUMMARY

- *HPV triage* will result in
  - An increased colposcopy and biopsy workload initially
  - A cheaper, more effective and speedier service for women with low grade abnormality
  - A sustained reduction in cytology workload

SUMMARY

- *HPV test of cure* will result in
  - A sustained reduction in cytology workload

SUMMARY

- *HPV vaccination* will progressively decrease the prevalence of HPV-related cervical disease and related cytological and histological abnormalities
- Cytology based screening will become less sensitive and specific and replaced by HPV primary screening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Bundesärztekammer
Arbeitsgemeinschaft der deutschen Ärztekammern

Berlin, 31.05.2016

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Gemeinsamer Bundesausschuss
Frau Heike Blümel
Wegelystr. 8
10623 Berlin

Stellungnahme der Bundesärztekammer gem. § 91 Abs. 5 SGB V über eine Änderung der Krebsfrüherkennungs-Richtlinie (KFE-RL): Zervixkarzinom-Screening
Ihr Schreiben vom 03.05.2016

Sehr geehrte Frau Blümel,

als Anlage senden wir Ihnen unsere Stellungnahme in o. g. Angelegenheit.
Für Ihre Hinweise auf die Gelegenheit zur zusätzlichen mündlichen Stellungnahme danken wir – wir werden hiervon in der bezeichneten Angelegenheit keinen Gebrauch machen.

Mit freundlichen Grüßen

Dr. rer. nat. Ulrich Zorn, MPH
Leiter Dezernat 3

Anlage

Stellungnahme der Bundesärztekammer

gem. § 91 Abs. 5 SGB V
über eine Änderung der Krebsfrüherkennungs-Richtlinie (KFE-RL):
Zervixkarzinom-Screening (Teilbeschluss)

Berlin, 31.05.2016

Bundesärztekammer
Herbert-Lewin-Platz 1
10623 Berlin

Hintergrund

Die Bundesärztekammer wurde mit Schreiben vom 03.05.2016 durch den Gemeinsamen Bundesausschuss (G-BA) zur Stellungnahme gemäß § 91 Abs. 5 SGB V bezüglich einer Änderung der Krebsfrüherkennungs-Richtlinie (KFE-RL) – Zervixkarzinom-Screening – aufgefordert.

Die vom G-BA gemäß § 92 Abs. 1 Satz 2 Nr. 3, Abs. 4 und § 25 Abs. 4 SGB V beschlossene Krebsfrüherkennungs-Richtlinie (KFE-RL) regelt das Nähere über die ärztlichen Maßnahmen zur Früherkennung von Krebserkrankungen nach § 25 Abs. 2 und 3 SGB V.

Mit Inkrafttreten des Krebsfrüherkennungs- und -registergesetzes (KFRG) im Jahr 2013 wurde ein rechtlicher Rahmen für die inhaltliche und organisatorische Weiterentwicklung der Krebsfrüherkennung geschaffen. Bislang opportunistische Screeningprogramme sollen in organisierte Screeningprogramme überführt werden. Durch das Gesetz sollen die Strukturen, die Reichweite, die Wirksamkeit und die Qualität der bestehenden Krebsfrüherkennungsangebote nachhaltig verbessert werden.

Der G-BA hat gemäß dieser gesetzlichen Ziele ein Konzept für ein organisiertes Zervixkarzinom-Screening-Verfahren entwickelt. Vor dem Hintergrund neuer Technologien war auch das Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) mit einer Nutzenbewertung von HPV-Tests im Primärscreening involviert. Das Hauptziel der Untersuchung des IQWiG war laut tragenden Gründen die vergleichende Nutzenbewertung der HPV-Diagnostik allein oder in Kombination mit einem zytologiebasierten Verfahren im Primärscreening gegenüber einer Strategie, die ausschließlich zytologiebasierte diagnostische Testverfahren im Primärscreening einsetzt, hinsichtlich patientenrelevanter Endpunkte. Darüber hinaus zielte die Untersuchung darauf ab, verschiedene Screeningstrategien, welche zytologische und HPV-basierte diagnostische Verfahren im Primärscreening miteinander kombinieren, hinsichtlich patientenrelevanter Endpunkte untereinander zu vergleichen.

Aus der Nutzenbewertung ergab sich für eine HPV-Diagnostik allein oder in Kombination mit einem zytologiebasierten Verfahren gegenüber einer ausschließlich zytologiebasierten Strategie im Rahmen der Früherkennung des Zervixkarzinoms im Primärscreening aus Sicht des G-BA ein Hinweis auf einen Nutzen hinsichtlich patientenrelevanter Endpunkte. Unter Verweis auf sehr unterschiedliche Screeningstrategien in den ausgewerteten Studien möchte sich der G-BA nicht auf eine bestimmte Strategie zum Einsatz der HPV-Diagnostik festlegen.

Die Früherkennung des Zervixkarzinoms soll in der Krebsfrüherkennungs-Richtlinie als organisiertes Programm separat geregelt werden und die klinische Untersuchung zur Früherkennung von Krebserkrankungen des Genitales und der Brust bei Frauen erhalten bleiben. Frauen ab dem Alter von 20 Jahren sollen diese Untersuchung weiterhin jährlich in Anspruch nehmen können, wenn in dem jeweiligen Kalenderjahr keine klinische Untersuchung im Rahmen der Früherkennung des Zervixkarzinoms durchgeführt wurde.

Der vorgesehene Beschluss zur Neuorganisation der Früherkennung des Zervixkarzinoms soll die Grundlage für weitere Beschlüsse zur Weiterentwicklung in ein organisiertes Programm sein. Weitere Beschlüsse zu einer Versicherteninformation, zum Einladungsschreiben sowie zur detaillierten Konzeption der Evaluationsfragestellungen und Regelung der Datenzusammenführung sollen folgen.

Die Bundesärztekammer nimmt zum Beschlussentwurf wie folgt Stellung:

Aus Sicht der Bundesärztekammer ist der mit dem Krebsfrüherkennungs- und -registergesetz unter anderem intendierte Ansatz, opportunistische in organisierte Screeningprogramme zu überführen, grundsätzlich begrüßenswert. Insbesondere dem Aspekt, durch die Weiterentwicklung von Krebsfrüherkennung den potentiellen Teilnehmerinnen und Teilnehmern nicht nur evidenzbasierte, qualitätsgesicherte und in die Versorgungsstrukturen systematisch integrierte Programme anzubieten, sondern auch die ausgewogen informierte Entscheidung für oder gegen die Teilnahme an einem Screening zu unterstützen, kann dadurch verstärkt Rechnung getragen werden.

Im Falle der Neukonzeption eines Zervixkarzinom-Screenings im Kontext der Richtlinienkompetenz des G-BA zur Früherkennung von Krebserkrankungen stützt sich der vorgelegte Entwurf zur Änderung der bestehenden Richtlinie maßgeblich auf eine beim IQWiG in Auftrag gegebene Nutzenbewertung von HPV-Tests im Primärscreening zur Früherkennung des Zervixkarzinoms. Danach erlaubt die verfügbare Datenlage keine Empfehlung für eine bestimmte Screeningstrategie, ergab aber aus Sicht des IQWiG einen Hinweis auf einen Nutzen einer HPV-Diagnostik allein oder in Kombination mit einem zytologiebasierten Verfahren gegenüber einer ausschließlich zytologiebasierten Strategie.

Die existierenden – und damit für den G-BA maßgeblich handlungsauslösenden – Europäischen Leitlinien für ein Zervixkarzinom-Screening beinhalten mit ihren im Jahr 2015 veröffentlichten Supplements konkrete Empfehlungen für ein HPV-basiertes Primärscreening (mindestens 5-Jahresintervall und unmittelbare Zytologie-Triage ab einem Alter von 35 Jahren in einem organisierten Programm).

Vor diesem Hintergrund erscheint die vorgelegte Konzeption zur Neuorganisation der Früherkennung des Zervixkarzinoms im Rahmen der G-BA-Richtlinie zur Krebsfrüherkennung insgesamt plausibel, wenngleich die Problematik des nicht oder nur eingeschränkten Erreichens der besonders vulnerablen Subgruppen innerhalb der Zielpopulation wahrscheinlich auch nach der Umgestaltungen des Screenings persistieren wird.

Allein die erforderliche Umsetzung der Eckpunkte für die Rahmenbedingungen für das Screening gemäß § 25a Abs. 1 Satz 2 Nrn. 1 – 4 SGB V, die in den tragenden Gründen des Beschlussentwurfs auch vollständig zitiert werden, dürfte – unabhängig von der methodisch-technischen Fragestellung zur Güte der jeweiligen Testverfahren – positive Effekte erzielen, etwa mit Blick auf die Schaffung systematischer Grundlagen für die überaus wünschenswerte und auch notwendige Evaluationen solcher Maßnahmen.

Mit Blick auf die konkret in der Richtlinie vorgesehenen Regelungen zur Durchführung der Zervixkarzinom-Früherkennung sei noch auf folgende Details hingewiesen:

In § 24 „Ziele und Grundlagen des Zervixkarzinomscreenings“ wird in den Beschlussvorschlägen teilweise explizit hervorgehoben, dass sich das erklärte Ziel der Senkung der Zervixkarzinom-Inzidenz und der Zervixkarzinom-Mortalität lediglich auf die „anspruchsberechtigte“ Bevölkerungsgruppe beziehe.

Dies ist selbstverständlich insofern korrekt, als dass sich Effekte von Leistungen nur dann zeigen können, wenn diese Leistungen auch stattfinden bzw. in Anspruch genommen werden. Es sollte jedoch bedacht werden, dass sich die Intention von Krebsfrüherkennung grundsätzlich auf die Bevölkerung insgesamt bezieht, jedenfalls unter epidemiologischen bzw. biologischen Aspekten. Der mögliche Umkehrschluss aus der genannten Formulierung in der Richtlinie könnte bedeuten, dass der G-BA das

Potential einer Senkung krankheitsbedingter Sterblichkeit für einen Teil der Bevölkerung bewusst ignoriert – in Ermangelung des Vorliegens sozialrechtlich zu begründender Ansprüche. Die Neukonzeption einer Screeningmaßnahme – wie in diesem Fall die Neukonzeption des Zervixkarzinom-Screenings – wird sich im Versorgungsalltag nicht auf GKV-versicherte Frauen beschränken, sondern mittel- bis langfristig die Versorgungsangebote unabhängig vom Versicherungsstatus beeinflussen. Vor diesem Hintergrund sollte auf die einschränkende Bemerkung bezüglich der Anspruchsberechtigung verzichtet werden

Ebenfalls in § 24 ist in den Beschlussentwürfen übereinstimmend formuliert worden, dass es auch zu den Zielen des Programms gehöre, eine „Minimierung der Belastungen, die mit einem Früherkennungsprogramm verbunden sein können, zu gewährleisten".

Auch dies erscheint zunächst unstrittig, greift aber zu kurz. Die Reduktion der möglichen Folgen einer Inanspruchnahme eines Screeningprogramms auf „Belastungen" erweckt den Eindruck, hierbei handele es sich lediglich um mögliche Nachteile im Sinne von Komforteinbußen. Wenn dem Auftrag an den G-BA, den potentiellen Teilnehmerinnen und Teilnehmern einer jeden Früherkennungsmaßnahme eine informierte Entscheidung zur Teilnahme zu ermöglichen, Rechnung getragen werden soll, sollte bereits in den Aussagen der jeweiligen Richtlinie (und nicht nur in dem flankierenden Merkblatt) auf eine entsprechende Sprachwahl geachtet werden.

Es wäre also statt von „*Belastungen*" unmissverständlich von „*Risiken*" zu sprechen, und auch der Begriff des „*Schadens*" wäre hier konsequent.

In diesem Sinne sollte es in § 24 Abs. 1 auch nicht „…verbunden *sein können*" heißen, sondern „verbunden *sind.*"

Berlin, 31.05.2016

Dr. rer. nat. Ulrich Zorn, MPH
Leiter Dezernat 3 - Qualitätsmanagement,
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30.05.2016

Stellungnahme zur Änderung der Krebsfrüherkennungs-Richtlinie (KFE-RL): Zervixkarzinom-Screening

Sehr geehrte Damen und Herren,

mit Ihrem Schreiben vom 03.05. 2016 haben Sie die Becton Dickinson GmbH als betroffenen Medizinproduktehersteller zur Abgabe einer Stellungnahme nach § 92 Absatz 7d Satz 1 Halbsatz 2 SGB V über die geplanten Änderung der Krebsfrüherkennungs-Richtlinie Zervixkarzinomscreening aufgefordert.

Anbei senden wir Ihnen unsere Stellungnahme, die sich im Wesentlichen auf die folgenden Punkte bezieht:

- Wir unterstützen die Positionen des GKV-Spitzenverbandes und der KBV im Allgemeinen sowie der Patientenvertretung im Speziellen und unterbreiten den Vorschlag, den Zielkatalog der KFE-RL um die Zieldimension „Monitoring“ zu erweitern.
- Wir begrüßen den Einsatz der Dünnschichtzytologie als Triage und weisen darauf hin, dass sich durch die Dünnschichtzytologie neben den benannten Effizienzvorteilen auch in klinischer Hinsicht Vorteile gegenüber der konventionellen Zytologie realisieren lassen. Die sind aber abhängig vom eingesetztem Instrument und dem Alter der Screeningpopulation.
- Wir begrüßen den Einsatz der Dünnschichtzytologie als Triage und weisen darauf hin, dass sich durch die Dünnschichtzytologie neben den benannten Effizienzvorteilen auch in klinischer Hinsicht Vorteile gegenüber der konventionellen Zytologie realisieren lassen. Die sind aber abhängig vom eingesetztem Instrument und dem Alter der Screeningpopulation.
- Gegeben der hohen Relevanz der hrHPV-Typen 16 und 18 bei der Entwicklung von Zervixkarzinomen unterstützen wir den Vorschlag des GKV-Spitzenverbandes und der Patientenvertretung, bei der Detektion der hrHPV-Genotypen 16/18 im Primärscreening unmittelbar eine Abklärungskolposkopie durchzuführen.
    - Vor dem Hintergrund der damit einhergehenden therapeutischen Konsequenz für die Patientinnen sollte der verbindliche Einsatz von genotypisierenden HPV-Testverfahren Mittel der Wahl im Primärscreening sein. Das gilt zuvorderst für die

Typen 16/18 für deren Detektion bereits jetzt unmittelbare klinische Konsequenzen akzeptiert sind.
    - Ferner betrifft es aber auch die Typen 31, 33 und 52 für die sich ein mit HPV18 vergleichbares Risiko zeigen lässt.
    - Aus Gründen der Patientensicherheit und aufgrund der unmittelbar folgenden klinischen Konsequenzen ist die spezifische Detektion des HPV-Typen 45 im Primärscreening dringend zu empfehlen. Über das Primärscreening hinaus ist der Einsatz der erweiterten Genotypisierung insbesondere im Rahmen der Ko-Testung von Frauen mit auffälligem Befund vor Eintritt in das organisierte Screening sowie als HPV-Triage durchzuführen.
- Ergänzend zu den in den Richtlinienentwürfen vorgesehenen Qualitätssicherungs-maßnahmen wird vorgeschlagen, durch das Vorhalten interner Kontrollen sicherzustellen, dass jede Probe menschliche DNA enthält, um auf diese Weise die Gefahr falsch-negative Ergebnisse zu minimieren.

Im weiteren Verlauf des Verfahrens möchten wir Sie bitten Korrespondenz an folgenden Ansprechpartner zu richten:

Eike Hiemesch, Public Policy Manager

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Gemeinsamer Bundesausschuss

Stellungnahme zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

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30.05.2016	
Stellungnahme / Änderungsvorschlag	**Begründung**
Ziele des organisierten Screeningprogramms Betrifft § 24 GKV-SV § 24 KBV § 24 PatV Wir unterstützen die Positionen des GKV-Spitzenverbandes und der KBV im Allgemeinen sowie der Patientenvertretung im Speziellen und unterbreiten den Vorschlag, den Zielkatalog der KFE-RL um die Zieldimension einer epidemiologischen Überwachung (Monitoring) zu erweitern.	Mit Blick auf die Ziele eines organisierten Screeningprogramms unterstützen wir die Position des GKV-Spitzenverbandes, der KBV und der Patientenvertretung, die analog zum Nationalen Krebsplan das Vorhaben eines organisierten Zervixkarzinomscreenings in der Senkung von Neuerkrankungen an invasiven Zervixkarzinomen und der Zervixkarzinomsterblichkeit sehen. Wir erachten es darüber hinaus für wichtig, dass das Screeningprogramm die Früherkennung in einem möglichst frühen Stadium zur Zielsetzung hat, um sicherzustellen, dass die gegebenenfalls erforderlichen differenzialdiagnostischen Maßnahmen bzw. die potentiell zu ergreifenden therapeutischen Konsequenzen rechtzeitig eingeleitet werden können. Aus diesem Grund begrüßen wir die dahingehende Konkretisierung der Patientenvertretung in § 24 Abs. 1. Wir möchten ergänzend darauf hinweisen, dass ein organisiertes Screeningprogramm die Chance für ein systematisches Monitoring von möglichen Veränderungen der Epidemiologie von Hochrisiko-HPV-Typen (hrHPV) bietet. Ein derartiges Monitoring erscheint insbesondere im Kontext der zunehmenden Durchimpfungsrate gegen die hrHPV-Typen 6, 11, 16 und 18 als ein sinnvolles Instrumentarium, um eine potentiell steigende Prävalenz von HPV-Typen, die nicht durch die Impfung abgedeckt sind, zu erkennen und ggfs. Anpassungen im Screeningalgorithmus vorzunehmen. Bereits heute lässt sich zeigen, dass es infolge der Einführung der HPV-Impfung in einigen Populationen zu Prävalenzverschiebungen gekommen ist, die sich durch eine immer höhere Prävalenz von HPV-Typen, die nicht durch die Impfung abgedeckt sind, manifestiert (Deleré et

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	al. *2014, Mesher D, Panwar K, Thomas SL, et al. 2016, Kavanagh K et al.2014, Joste NE 2015, Monsonego J 2015,).* So lässt sich in jungen Populationen zeigen, dass die Prävalenz der HPV-Typen 16/18 von 20 % auf 14% gesunken ist (*Delere et al 2014*). Das gilt insbesondere für Frauen, die vor ihrer ersten sexuellen Aktivität geimpft wurden. Mesher et al. (*2016*) berichten in einer Beobachtungsstudie einen Anstieg von nicht-impfbaren Hochrisikotypen nach einer Impfperiode (das gilt insbesondere für den HPV-Typen 52). Gleichzeitig werden zunehmend Informationen über das Risiko einer Progressio*n zum Zervixkarzinom bei nicht durch die Impfung* abgedeckten hrHPV-Typen generiert, welche nahelegen, dass diese im Vergleich zu HPV 18 ein erhöhtes CIN 3+-Risiko aufweisen *(Schiffman, M, et al 2015, Stoler et al.2011, Thomsen LT 2015, Schiffman M et al. 2011, Cuzick J et al 2014, Chiang Y et al. 2013, Matsumoto K 2011)*. Darüber hinaus lässt sich zeigen, dass bei invasivem Gebärmutterhalskrebs eine hohe Prävalenz von HPV 31 und 45 vorliegt *(Matsumoto K 2011, DeSanjose S 2010, Halfon et al. 2013, Meijer, C.J., P.J. Snijders 2006)*. Die vorliegenden Daten lassen den Schluss zu, dass durch die benannten möglichen Verschiebungseffekte mittel- bis langfristig Anpassungen hinsichtlich der durch die Richtlinie zum organisierten Zervixkarzinomscreening definierten Screeningalgorithmen und folglich den angezeigten therapeutischen Konsequenzen erforderlich sein könnten. Angesichts dieser sich durch die HPV-Impfung graduell verändernden Epidemiologie von hrHPV-Typen sind wir der Ansicht, dass die Einführung des primären HPV-Screenings eine besondere Chance bietet, Prävalenzverschiebungen durch ein gezieltes Monitoring zu erkennen und im Rahmen der geplanten Evaluation gezielt auszuwerten. Neben dieser populationsbezogenen Chance bietet ein solches Monitoring zusätzlich für die einzelne Frau den

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	Vorteil, Informationen zur spezifischen Persistenz einzelner Genotypen zu sammeln. Diese Informationen können dabei helfen, das individuelle Risiko für die Entwicklung einer CIN 2+ zu bestimmen; dies ist vor allem vor dem Hintergrund der hohen Korrelation von persistenten Infektionen und der Entwicklung von CIN2+ zu berücksichtigen (*Castle P. E. et al. 2009, Chen H. C. et al. 2011, Naucler et al. 2009, Schmeink et al. 2011, Kjaer SK et al. 2011)*. Auf Basis der dargelegten Erläuterung wird empfohlen, bei Einsatz eines HPV-Genotypisierungstest alle mit diesem Test erfassbaren HPV-Typen und Gruppen zu dokumentieren und in Bezug auf das Versorgungsgeschehen in die Evaluation einzubeziehen. Die Ergebnisse dieser Auswertung könnten maßgeblich für die zielgerichtete Weiterentwicklung des organisierten Screenings nach Ablauf der Pilotphase sowie darüber hinaus sein.
Dünnschicht-Zytologie als Triageverfahren Betrifft § 29 Nr. 2 GKV-SV § 29 nr. 1-3 KBV § 29 Nr. 2 PatV Wir begrüßen den Einsatz der Dünnschichtzytologie als Triage und weisen darauf hin, dass sich durch die Dünnschichtzytologie neben den benannten Effizienzvorteilen auch in klinischer Hinsicht Vorteile gegenüber der konventionellen Zytologie realisieren lassen. Die sind aber abhängig vom eingesetztem Instrument und	Der Einsatz der Dünnschichtzytologie als Triageverfahren nach auffälligem Befund ist aus unserer Sicht geeignet, das populationsbezogene Screening auf Gebärmutterhalskrebs effizienter und effektiver zu gestalten. Zu den Vorteilen der Dünnschichtzytologie zählen eine Verringerung der Raten von Proben unbefriedigender Qualität, die standardisierte und einheitliche Darstellung von Zervixzellen auf dem Objektträger, der im Vergleich zu konventionellen Abstrichverfahren bessere Nachweis abnorm veränderter Zellen sowie die Weiterverwendung von Einzelproben zur Durchführung begleitender molekularer Testverfahren (d. h., Chlamydia trachomatis) *(Hoda RS et al 2013, Fontaine D et al 20012, Cheung AN et al 2003, Fremont-Smith M et al 2004, Kituncharoen S et al 2015, Chen C et al 2004)*. Vor diesem Hintergrund sind mit der Dünnschichtzytologie mindestens äquivalente klinische Ergebnisse im Vergleich zum Pap-Test zu erwarten.

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dem Alter der Screeningpopulation.	Der Einsatz der Dünnschichtzytologie als Reflex-Test trägt des Weiteren durch die Weiterverwendung der für den HPV-Test genommenen Probe dazu bei, Kosten zu sparen. Aus diesem Grund unterstützen wir den Ansatz des GKV-Spitzenverbandes und der Patientenvertretung, die Dünnschichtzytologie als Triage-Verfahren einzusetzen. Die Tatsache, dass sich beim Vergleich von Dünnschichtzytologie und konventioneller Zytologie in der Vergangenheit kein signifikanter Unterschied ablesen lies, ist darauf zurückzuführen, dass sich diese Metaanalysen vor allem mit Studien zu einem einzigen Entnahmeinstrument befassten. Inzwischen liegen jedoch umfassende Daten auch zu anderen Entnahmeinstrumenten vor. Neben den Effizienzvorteilen der Dünnschichtzytologie lassen sich deshalb inzwischen auch klinischen Vorteile nachzuweisen. So sind gegenüber konventionellen Abstrichverfahren signifikante Verbesserungen sowohl hinsichtlich der Verringerung der Raten von Proben unbefriedigender Qualität als auch hinsichtlich des Nachweises geringfügig veränderter abnormer Zellen nachweisbar *(Kituncharoen S et al 2015, Chen C et al 2012, Longatto-Filho A et al 2015)*. In einer Veröffentlichung zum dänischen Früherkennungsprogramm wurde berichtet, dass der Nachweis abnorm veränderter Zellen mit einigen Systemen besser gelang als mit konventionellen Abstrichverfahren (*Rask J et al 2014)*. In einer niederländischen Publikation konnte gezeigt werden, dass mittels dünnschichtzytologischen Verfahren mehr bioptisch gesicherte CINII+-Befunde erhoben werden konnten als mit konventionellen Abstrichverfahren (*Rozemeijer K et al 2015)*. Ferner konnten Rebilj et al in einer Registerstudie kenntlich machen, dass das Ausmaß des klinischen Zusatznutzens der Dünnschichtzytologie vor allem vom Alter der Screeningpopulation und den gewählten Technologien abhängt (*2015)*. Allerdings wurde in diesem Zusammenhang deutlich, dass die

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	Detektionsrate von CIN III bei Frauen im Alter von 30-44 Jahren durch den Einsatz bestimmter Instrumente signifikant verbessert werden konnte. Vor diesem Hintergrund sehen wir in dem Einsatz der Dünnschichtzytologie als Triage für Frauen mit auffälligem Befund einen ausgewogenen Ansatz, um die klinischen Vorteile und ökonomischen Potentiale zu nutzen.
Screening Algorithmus Betrifft § 28 GKV-SV § 29 KBV § 28 PatV Gegeben der hohen Relevanz der hrHPV-Typen 16 und 18 bei der Entwicklung von Zervixkarzinomen unterstützen wir den Vorschlag des GKV-Spitzenverbandes und der Patientenvertretung, bei der Detektion der hrHPV-Genotypen 16/18 im Primärscreening unmittelbar eine Abklärungskolposkopie durchzuführen. Vor dem Hintergrund der damit einhergehenden therapeutischen Konsequenz für die Patientinnen sollte der verbindliche Einsatz von genotypisierenden HPV-Testverfahren Mittel der Wahl im Primärscreening sein. Das gilt für die Typen 16/18 für	**<u>Genotypisierung im Primärscreeing</u>** Analog zur Konsultationsfassung der S3-Leitlinie Prävention des Zervixkarzinoms der AWMF soll eine Indikation zur kolposkopischen Abklärung ab einer Post-Test-Wahrscheinlichkeit für ein durchschnittliches kumulatives CIN III+ Risiko von 10% gestellt werden. Auf Basis der vorliegenden Daten ist dieses Risiko für die Genotypen 18 und 16 nachweisbar. Mit Blick auf den HPV-Arm des Optionsmodells unterstützen wir deshalb den Vorschlag des GKV-Spitzenverbandes und der Patientenvertretung, Frauen nach Detektion der HPV-Genotypen 16 und 18 unmittelbar zur Kolposkopie zu entsenden. Trotz des in beiden Vorschlägen eindeutig definierten Abklärungsalgorithmus bleibt es in der derzeitigen Fassung jedoch dem Anwender überlassen, auch tatsächlich einen genotypisierenden HPV-Test einzusetzen. Sofern sich aber aus den Ergebnissen einer HPV-Genotypisierung unmittelbare therapeutische Konsequenzen für die Patientinnen ableiten lassen, ist der verpflichtende Einsatz von genotypisierenden Testverfahren aus unserer Sicht unbedingt geboten. Dementsprechend regen wir die Anpassung der Richtlinienentwürfe dahingehend an, eine prinzipielle Empfehlung für genotypisierende HPV-Testverfahren im Primärscreening auszusprechen. **<u>Relevanz der erweiterten Genotypisierung</u>** Ein Großteil der verfügbaren HPV-Tests fasst alle 14

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deren Detektion bereits jetzt unmittelbare klinische Konsequenzen akzeptiert sind. Ferner betrifft es aber auch die Typen 31, 33 und 52 für die sich ein mit HPV18 vergleichbares Risiko zeigen lässt. Aus Gründen der Patientensicherheit und aufgrund der unmittelbar folgenden klinischen Konsequenzen ist die spezifische Detektion des HPV-Typen 45 im Primärscreening dringend zu empfehlen. Über das Primärscreening hinaus ist der Einsatz der erweiterten Genotypisierung insbesondere im Rahmen der Ko-Testung von Frauen mit auffälligem Befund vor Eintritt in das organisierte Screening sowie als HPV-Triage durchzuführen.	Hochrisiko-Typen in eine oder mehrere Gruppen zusammen. Einzelne Genotypen lassen sich nur mit einigen Tests gezielt identifizieren. Wir sind davon überzeugt, dass die gezielte Genotypisierung ein wichtiges Element für das Erreichen der Ziele eines organisierten Screenings ist. Deshalb möchten wir auf die Vorteile einer erweiterten Genotypisierung im Primärscreening hinweisen. Die Risiken, die mit den Genotypen 16, 18 und 45 verbunden sind, gelten mittlerweile als gut belegt. Obwohl HPV 16 und 18 schätzungsweise 70% der Zervixkarzinome weltweit verursachen, stellen aber auch andere Hochrisiko-HPV-Typen ein ernsthaftes Risiko für die Progression von präkanzerösen Läsionen dar (*Stoler et al. 2011)*. So haben Follow-up Studien gezeigt, dass insbesondere auch die HPV-Typen 31, 33, und 52 mit einem erhöhten Risiko zur Entwicklung eines CINIII+ einhergehen, dass vergleichbar mit dem von HPV 18 ist (*Schiffman, M, et al 2015)*. Neben den epidemiologischen Vorteilen für des Programm-Monitoring und die -Evaluation sehen wir deshalb auch klinische Vorteile für den Einsatz der gezielten Genotypisierung im Primärscreening und in der Triage. Neben dem direkten Zusammenhang zwischen der Prävalenz eines der oben genannten hrHPV-Typen gilt auch die typenspezifische Persistenz als wichtiges Indiz für die Entwicklung von Gebärmutterhalskrebs. Mit Hilfe der individuellen Genotypisierung von hrHPV-Typen lassen sich Aussagen über die typenspezifische Persistenz von Infektionen treffen und damit Einschätzungen über das Risiko einer Entwicklung von CINII+ abgeben *(Chen, H. C. et al. 2011, Castle, P. E. et al. 2009, Naucler et al. 2009, Schmeink et al., Kjaer SK, et al. 2010)*. Vor diesem Hintergrund haben Neulcer et al. HPV-DNA Tests im Primärscreening mit der konventionellen Zytologie verglichen (2009). Zum Einsatz kam dabei die Zytologie-Triage und ein wiederholter HPV-DNA Test bei Frauen mit auffälligem Befund. Dies hat zu einer um 30% erhöhten Sensitivität des Verfahrens, bei gleichbleibendem positiv-prädiktiven Wert und einer

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	vergleichsweise geringen Erhöhung der insgesamt durchgeführten Tests geführt (12%). Die Feststellung der Persistenz eines spezifischen Genotyps ist aus unserer Sicht deshalb sowohl für die HPV-Triage als auch für die Ko-Testung von Frauen, bei denen in der Vergangenheit bereits ein positiver Befund vorgelegen hat (analog zum Vorschlag der PatV), in besonderer Weise geeignet, die Sensitivität des Verfahrens zu erhöhen. **<u>Besondere Relevanz des HPV-Typs 45</u>** Ferner verdient der hrHPV-Typ 45 besondere Aufmerksamkeit. Zusammen mit HPV 31 zeigt dieser eine erhöhte Prävalenz bei invasivem Gebärmutterhalskrebs (*Matsumoto K et al. 2011, DeSanjose S, et al. 2010, Halfon et al. 2013)*. Zudem lässt sich international eine steigende Inzidenz des HPV-Typs 45 (z. B. USA Anstieg um 32.2% von 1.09/100,000 (1973-1975) auf 1.44/100,000 (2006-2007)) beobachten (*Adegoke O et al 2002)*. Das erhöhte Krebsrisiko, dass mit diesem Genotyp einhergeht, ist nicht nur auf das Plattenepithelkarzinom zurückzuführen, sondern auch mit dem Auftreten von Adenokarzinomen assoziiert. So konnte der Typ 45 zusammen mit HPV 16/18 bei 95 % aller zervikalen Adenokarzinome festgestellt werden. In 8% der Fälle war das Karzinom mit dem Auftreten der des hrHPV-Typs 45 assoziiert (HPV 16 50.5 % und HPV 18 39.8 %) (*DeSanjose S et al. 2010)*. Es ist zu berücksichtigen, dass zytologische Verfahren offensichtlich nicht in der Lage sind, zervikale Adenokarzinome zuverlässig zu erkennen. So hat eine amerikanische Studie mit 330.000 Frauen in einem 5 Jahresintervall gezeigt, dass in 17 von 27 Fällen eines Adenokarzinoms ein positiver HPV-Test aber negative zytologische Befunde vorlagen *(Katki HA et al 2011)*. Diese Beobachtung bestätigt sich auch in anderen Studien (*Kinney W et al 2011)*. Eine mögliche Erklärung für die ungünstigen Ergebnisse bei der Detektion von präkanzerösen Läsionen von Adenokarzinomen ist die

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	Tatsache, dass sie regelmäßig am oberen Ende des Gebärmutterhalses lokalisiert sind und sich deshalb mit den zytologischen Entnahmeinstrumenten nur schlecht erreichen lassen. In einer europäischen Studie konnten 351 Adenokarzinome identifiziert werden, die auf einen einzelnen HPV-Typen zurückzuführen waren. Der HPV-Typ 45 lässt sich mit modernen Testverfahren getrennt von anderen HPV-Hochrisikotypen spezifisch erkennen. Über die generelle Genotypisierung von 16/18 hinaus, halten wir es deshalb für sinnvoll, auch den Typ 45 in die Genotypisierung einzubeziehen. Anhand dieses spezifischen Befunds können Frauen direkt einer Kolposkopie unterzogen werden (*Kinney W et al 2011, Holl K et al 2015)*. Ohne eine spezifische Genotypisierung der Gruppe 45 im primären HPV-Screening besteht die Gefahr, dass das Risiko eines Adenokarzinoms bei der zytologischen Abklärung auffälliger HPV-Befunde mit großer Wahrscheinlichkeit übersehen wird.
Vorgaben zur Strukturqualität Betrifft § 30 Nr. 3 GKV-SV § 31 Nr. 4 KBv § 30 Nr. 3 PatV Ergänzend zu den in den Richtlinienentwürfen vorgesehenen Qualitätssicherungs-maßnahmen wird vorgeschlagen, durch das Vorhalten interner Kontrollen sicherzustellen, dass jede Probe menschliche DNA enthält, um auf diese Weise die Gefahr falsch-negative Ergebnisse zu minimieren.	In einem bevölkerungsbezogenen Screening ist sicherzustellen, dass die eingesetzten Tests und Verfahren mit Blick auf die Patientensicherheit höchsten Standards entsprechen. Das betrifft insbesondere die Vermeidung falsch-positiver Ergebnisse. Sie führen zu einer vermeidbaren physischen und psychischen Belastung der betroffenen Frauen und zu vermeidbaren Folgekosten für das Gesundheitssystem. Wir begrüßen, dass alle Vorschläge der beteiligten Organisationen in diesem Zusammenhang die international anerkannten Kriterien nach Meijer und Stoler heranziehen, um sicherzustellen, dass hinreichend klinisch validierte HPV-Tests im Primärscreening zur Anwendung kommen. Neben der Minimierung von falsch-positiven Ergebnissen muss jedoch auch das Auftreten von falsch-negativen Ergebnissen soweit wie möglich auszuschließen sein. Wir begrüßen, dass die beteiligten Organisationen in diesem Zusammenhang die Teilnahme an Ringversuchen nach B

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	3-2 der Richtlinie zur Qualitätssicherung in der Laboratoriumsmedizin (RiLi-BÄK) vorsehen. Gemäß dem Abschnitt 2.1.2.3 der RiLi-BÄK haben alle molekularbiologischen Verfahren darüber hinaus folgende Anforderungen zu erfüllen: • Extraktionskontrolle über Nukleinsäurebestimmung • Konformitätstestung der Reagenzien • Positiv- und Negativkontrolle • Datenbank-Abgleich der bei diesen Nachweisverfahren benutzten Primer und Sondensequenzen hinsichtlich der deklarierten Speziesspezifität Wir schlagen vor, auch diese Anforderungen ausdrücklich im Beschlusstext zu benennen, um hier rechtzeitig eine Klarstellung zu bewirken. Analog zu den tragenden Gründen des Richtlinienentwurfs der PatV sehen wir in der Möglichkeit einer Scheinsicherheit bzw. der Stellung von falsch-negativen Befunden eine vermeidbare Gefährdung des Patienten. Deshalb halten wir es zur Gewährleistung der Patientensicherheit für wichtig, dass alle Verfahren neben externen Kontrollen auch über interne Kontrollen verfügen, die sicherstellen, dass in der Probe tatsächlich menschliche DNA enthalten ist. Auf diese Weise kann das Risiko minimiert werden, dass bei Patientinnen relevante Zellveränderungen aufgrund eines ungenügenden Abstrichs bzw. dem Fehlen von DNA-Material auf dem Objektträger übersehen werden und somit dem Risiko eines potentiell falsch-negativen Testergebnisses ausgesetzt sind. Ungenügendes Zellmaterial auf dem Objektträger kann in letzter Konsequenz dazu führen, dass Betroffene nicht den erforderlichen differentialdiagnostischen Verfahren unterzogen werden; durch ein internes Kontrollverfahren der angewandten Tests kann ein solches Szenario vermieden werden.

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Bitte geben Sie das vorstehende Geschäftszeichen bei allen Antwortschreiben unbedingt an.

BETREFF **Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening**
HIER Ihr Schreiben vom 03. Mai 2016

Sehr geehrte Damen und Herren,

für die Gelegenheit zur Stellungnahme nach § 91 Abs. 5a SGB V danke ich.

I. Stellungnahme zum Beschlussentwurf des GKV-SV

1) Zu § 27: Aus dem Einladungsschreiben der Krankenkassen sollte sich die Freiwilligkeit der Inanspruchnahme der Untersuchung ergeben.

2) Zu § 28: Dort wird unter Abs. 2 Buchst.d. eine Regelung zur Weiterleitung des Abstrichs „zur zytologischen Untersuchung an eine Ärztin oder einen Arzt mit der genannten Genehmigung“ getroffen. Aus der Regelung geht nicht hervor, dass die Patientin über die Weitergabe des Abstrichs informiert ist. Für eine Weitergabe des Abstrichs sowie einen Austausch von Gesundheitsdaten zwischen der Ärztin/dem Arzt, welche(r) den Abstrich genommen hat und der Ärztin/dem Arzt welche(r) die zytologische Untersuchung durchführt, ist eine Entbindung von der Schweigepflicht zwingend erforderlich. Ein entsprechender Passus ist daher in die Regelung aufzunehmen.

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3) Zu §§ 28, 30: Der gleiche Maßstab ist hinsichtlich der Untersuchungen nach § 28 Abs. 3 sowie bei der Anwendung des Verfahrens nach § 30 Nr. 3b anzulegen. Grundsätzlich ist die Patientin über eine Weitergabe von entnommenem Material und den Austausch medizinischer Daten zum Zwecke der Untersuchung/Abklärung zu informieren.

II. Stellungnahme zum Beschlussentwurf der Patientenvertretung

Insoweit nehme ich bezüglich der Regelungen in § 27 (Einladung) und § 28 (Untersuchungen im Primärscreening) auf die Ausführungen zu den entsprechenden Paragraphen im Beschlussentwurf des GKV-SV vollumfänglich Bezug.

III. Stellungnahme zum Beschlussentwurf der KBV

1) Bezüglich der in den §§ 27 (Einladung), 28 (Zytologischen Untersuchung) und 29 (HPV-Test) getroffenen Regelungen verweise ich ebenfalls auf die zum Beschlussentwurf des GKV-SV gemachten Ausführungen.

2) Zu § 32: Ich rege an, im § 32 Abs. 1 nach dem Wort „dokumentieren“ einen Punkt einzufügen und die Wörter „und vom dokumentierenden Arzt an die jeweils zuständige KV zu übermitteln“ zu streichen.

3) Für die Regelung im Entwurf der KBV zu § 32 Abs. 2, dass der zuständige Unterausschuss des Gemeinsamen Bundesauschusses berechtigt ist „ Änderungen an den Anlagen vorzunehmen, deren Notwendigkeit sich aus der praktischen Anwendung ergibt, soweit ihr wesentlicher Inhalt nicht verändert wird“, wird rein vorsorglich davon ausgegangen, dass darunter keine Änderungen fallen, die eine datenschutzrechtliche Bedeutung haben. Insoweit wäre eine Delegation von Kompetenzen vom Plenum auf Unterausschüsse aufgrund Fehlens einer gesetzlichen Grundlage nicht hinnehmbar.

4) Zu § 33: Grundsätzlich erkenne ich die Erforderlichkeit von Qualitätssicherung, Programm-Monitoring und Evaluation an. Allerdings lässt die vorgeschlagene Regelung nicht erkennen welche Aufgaben die datenzusammenführende Stelle und die die Vertrauensstelle haben sollen. Ich rege daher dringend an, eine vom GBA zu erarbeitende Regelung mit der BfDI abzustimmen.

Mit freundlichen Grüßen
Im Auftrag

Gies

Dieses Dokument wurde elektronisch versandt und ist nur im Entwurf gezeichnet.

Gemeinsamer Bundesausschuss

Stellungnahme zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

Cepheid GmbH, Unterlindau 29, 60323 Frankfurt am Main (www.cepheidinternational.com)	
31.05.2016	
Stellungnahme / Änderungsvorschlag	**Begründung**
Zu § 25 Anspruchsvoraussetzungen **Änderungsvorschlag: Direkter Einstig in ein HPV Screening für Frauen ab 30 Jahre mit einem Screening Intervall von 3 – 5 Jahren**	Aus den Formulierungen in allen Teilbeschlüssen ist nicht ersichtlich, ob das in § 25 vorgeschlagene Optionsmodell auf die in dem Eckpunktepapier vom 19.03.2015 beschriebene sechs-jährige Übergangsfrist beschränkt sein soll oder dauerhaft Eingang in die ärztliche Versorgung findet. Die Firma Cpeheid GmbH plädiert dafür, das Optionsmodell, für die Altersklasse ab 30 Jahren, fallen zu lassen. Die Überlegenheit des HPV Screenings ist mit Studien ausreichend nachgewiesen worden. Die in der Konsultationsfassung vorliegende S3 Leitlinie Prävention des Zervixkarzinoms hat die Überlegenheit eines organisierten Screeningprogrammes, das auf HPV Testung bejaht und sogar einen Zeitraum von 3 oder 5 Jahren befürwortet (Konsultationsfassung S3 Leitlinie Prävention des Zervixkarzinoms, Seite 69). Auch haben sich alle stimmberechtigten Bänke des G-BA und die Patientenvertretung in der öffentlichen Sitzung am 20.03.2016 dahingehend einstimmig geäußert, dass man ein alleiniges HPV Screening anstrebe. Aufgrund des Nachweises der Überlegenheit des HPV Screenings (s.o.) sollte auf das Optionsmodell verzichtet werden und der direkte Einstieg in ein reines HPV Programm erfolgen.
Wegfall, bzw. Vermeidung von Ko-Testung bei unbekanntem/unklarem Befund	Vermeidung von Ko-Testung gemäß der europäischen Richtlinie 2. Ausgabe „**European guidelines for quality assurance in cervical cancer screening“** **Second edition - Supplements** Es sollte nur ein Primärtest verwendet werden, entweder Zytologie oder HPV Test. Eine Ko-Testung führt zu höheren Kosten, höhere Raten an Kolposkopien, die vermieden werden könnten und einem niedrigeren Positiven Vorhersagewert für CIN2+. **Siehe hierzu Zusammenfassung von Karsa 2015 oder European Guidelinse Seite 46 Kapitel 1.9. zweiter Absatz oder (Rec. 1.3 - 1.7) (II-A).**Rec 1.2

Cepheid GmbH, Unterlindau 29, 60323 Frankfurt am Main (www.cepheidinternational.com)	
31.05.2016	
Zu § 30 und § 31 (KBV) Vorgaben zur Strukturqualität **Verzicht auf Nennung einzelner Tests eines Herstellers, auch nicht als Referenztest**	*Zum Entwurf des § 31 Abs. 4 der KBV*: Die Nennung eines bestimmten Tests als Referenz in einer Richtlinie wird abgelehnt, da sie nicht praktikabel ist und den aktuellen medizinischen Stand der Technik nicht ausreichend abbilden kann.
Verzicht auf zusätzliche Validierungsstudien	Angesichts der dezidierten Vorgaben zur Testgüte, sind zusätzliche Vorgaben im Sinne von zusätzlichen Validierungsstudien nicht nachvollziehbar. Daher ist auf diese zu verzichten.
Generelle Anmerkung	Eine deutsche Richtlinie sollte sich an die europäischen Richtlinie anlehnen. • Die "**European guidelines for quality assurance in cervical cancer screening" Second edition – Supplements** ist unserer Stellungnahme beigefügt • Ebenfalls beigefügt ist die Zusammenfassung von Karsa aus dem Jahr 2015 Die angehängte europäische Richtlinie basiert auf dem aktuellen Kenntnisstand und der aktuellen Studienlage.

Frankfurt, 31.05.2016

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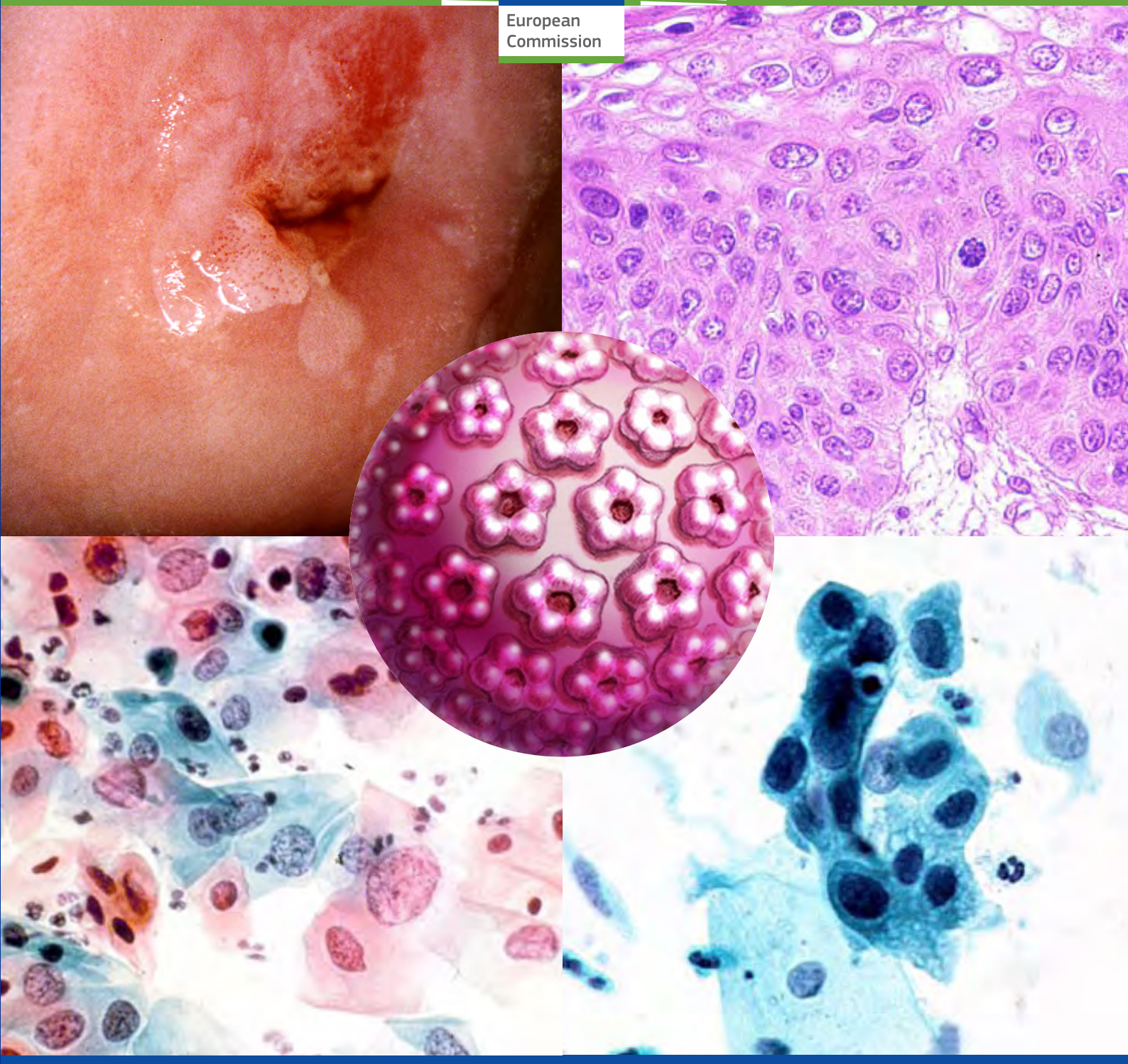

European guidelines for quality assurance in cervical cancer screening

Second edition - Supplements

Health

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Minor pertinent interests are not listed and include stock valued at no more than US$ 10 000 overall, grants that provide no more than 5% of the research budget of the expert's organization and that do not support the expert's research or position, and consulting or speaking on matters not before a court or government agency that does not exceed 2% of total professional time or compensation. All grants that support the expert's research or position and all consulting or speaking on behalf of an interested party on matters before a court or government agency are listed as significant pertinent interests.

[3] J. Cuzick has received equipment and support for studies evaluating HPV testing from Qiagen, Abbott, Hologic, Genera, Trovagene and OncoHealth. The total value does not exceed US$ 30,000. He has also received travel grants, and payment for lectures from Merck, Abbott, AstraZeneca, Nanostring and Myriad; the total amount received in the past 4 years does not exceed US$ 12,000.

[4] J. Dillner has received research grants to his university with significant funding from Merck/SPMSD, a manufacturer of HPV vaccines, for monitoring studies on HPV vaccines. He declares no personal remuneration.

[5] See footnote no. 4 indicating interest of spouse (J. Dillner).

[6] P. Giorgi Rossi is Principal Investigator of a project sponsored by the Italian Ministry of Health (data owner) for which he is in contact with Roche Diagnostics, Hologic Gen-Probe, Abbott, and Qiagen to obtain reagents and diagnostics free or at a reduced price. The total amount of discount requested does not exceed 300,000 euros.

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[11] See footnote no. 2 on page IV; the same information applies to the members of the Literature Group.

Preface

2015 marks the 30th anniversary of EU action on cancer - a long-standing priority issue for EU public health policy. The 2003 Council Recommendation on Cancer Screening is an important milestone in the activities at EU level in the field of cancer. This Recommendation sets out principles of best practice in the early detection of cancer and invites all Member States to take common action to implement national population-based screening programmes for breast, cervical and colorectal cancer, with appropriate quality assurance at all levels.

To assist the Member States with cancer screening, the Commission has published European guidelines for quality assurance in cervical cancer, breast cancer and colorectal cancer screening.

There have been considerable achievements in cancer screening as a result of coordinated work at EU level to support Member States in the implementation of national cancer screening programmes and, therefore, the completion of the Supplements to the 2nd Edition of the European Guidelines for quality assurance in cervical screening is a further milestone towards high quality cancer screening and diagnosis. Taking into account the recent developments in the field of cervical cancer, this publication illustrates the role the EU can play to reduce inequalities and to improve the health of its citizens.

I would like to thank the International Agency for Research on Cancer as well as all contributors involved in this project for their valuable contribution to this publication.

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Foreword

The current supplements to the second edition of the *European guidelines for quality assurance in cervical cancer screening* have been developed in a time of transition when primary testing for oncogenic human papilloma virus (HPV) types and vaccination against infection with the HPV types that cause most cases of cervical cancer have become complementary approaches to cervical cancer prevention in Europe. By focusing on the core topics of quality assurance in primary HPV testing, organisation of HPV-based and cytology-based screening programmes, and implementation of HPV vaccination programmes, the supplements lay the foundation for further development of the comprehensive European Guidelines in the coming years.

The original volume of the second edition was published in 2008. Many of the contributors have collaborated in the preparation of the current supplements. In presenting these we wish to thank and pay tribute to the dedication of all current and previous contributors to the European guidelines.

Brussels, Helsinki, London, Lyon, Stockholm and Turin in March 2015

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Declarations of interest
Interests of J. and L. Dillner are reported on page IV, and an interest of G. Ronco is reported on page V.

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Executive Summary

In the current twenty-eight Member States of the European Union (EU), approximately 34,000 new cases of cervical cancer and 13,000 deaths due to the disease occur annually (Ferlay et al 2013). Despite significant progress in Europe in recent decades in reducing the burden of cervical cancer, rates of death attributed to the disease are still high in many of the 'new' Member States that joined the EU after 2003: estimates of the annual age-standardized rates per 100,000 women in Hungary (6.9), the Slovak Republic (6.9), Poland (7.4), Latvia (8.2), Bulgaria (8.8) and Lithuania (9.8) are five to seven times higher, and in Romania (14.2) ten times higher than in Finland (1.4) and Malta (1.2), the EU Member States with the lowest rates in 2012. The age-standardized incidence rates of cervical cancer reveal a similar picture. The current 10-fold gradient in the mortality rates of cervical cancer among the EU Member States largely reflects the persistent absence, or inadequate implementation of cervical cancer screening programmes more than ten years after organized, population-based screening programmes following European quality assurance guidelines were unanimously recommended by the Health Ministers of the EU (Council of the European Union 2003).

Quality assurance aims to ensure that an endeavour leads to the outcome for which it is intended; this is particularly important for complex systems, such as screening programmes designed to lower the burden of cancer in the population (von Karsa et al. 2013b). The second edition of the European guidelines for quality assurance in cervical cancer screening (Arbyn et al. 2008, see also Arbyn et al. 2010) was published seven years ago. The continuing clear need to improve implementation of cervical cancer screening in the EU underlines the importance of re-emphasizing the European Guidelines through the publication of the present supplements to the second edition. The supplements have been developed in a time of transition. Vaccination of girls and possibly also of boys in the future against the human papilloma virus (HPV) types that cause approximately seventy percent of cervical cancer has become an additional, complementary option of cervical cancer prevention, the main impact of which will emerge in a few decades when currently vaccinated girls are in their thirties and forties. In addition, cytology[12] is no longer the only test suitable for use in cervical cancer screening in the EU. The evidence presented in the first of the present supplements shows that primary testing for oncogenic HPV[13] fulfils the requirements for evidence-based screening tests laid down in the Council Recommendation, provided that cervical cancer screening programmes follow the recommendations for quality assurance published in the second edition of the European Guidelines, and the present supplements.

[12] Conventional cervical cytology with Papanicolaou staining (Pap smear) and validated liquid-based cervical cytology (LBC) are evidence-based screening tests that fulfil the requirements of the Council Recommendation on Cancer Screening of 2 December 2003 if performed in accordance with the European guidelines for quality assurance in cervical cancer screening. The applicable items in the Council Recommendation of 2 December 2003 are 1(a) for conventional cervical cytology with Papanicolaou staining (Pap smear) and 1(a) in combination with 6(e) for validated liquid-based cervical cytology (LBC) (see Annex 2).

Primary testing for oncogenic HPV with validated assays also fulfils the requirements of the Council Recommendation of 2 December 2003 for evidence-based screening tests, provided the recommendations in Supplements 1 and 2 to the second edition of the European guidelines for quality assurance in cervical cancer screening are followed. The applicable items in the Council Recommendation are 6(c) and 6(e) (see Annex 2).

[13] Oncogenic *HPV* refers to the 13 high-risk HPV types (*hrHPV*): 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. These include the 12 HPV types currently classified as *carcinogenic to humans* and one type (68) classified as *probably carcinogenic to humans* in the IARC Monograph Series (Bouvard et al. 2009; IARC 2012). Unless otherwise indicated, the terms *HPV primary testing* and *HPV primary screening* used in this supplement refer to HPV testing conducted with systems based on validated hrHPV DNA assays. Oncogenic HPV also induces other cancers than those of the cervix uteri, such as vulvar, vaginal, anal and oropharyngeal cancers.

Of particular importance is the recent evidence from the second round of European randomized controlled trials showing a more pronounced effect of cervical screening using HPV primary testing compared to cytology-based screening (Ronco et al. 2014, Arbyn et al. 2012). Given the evidence for improved efficacy of HPV primary screening that is explained in the first supplement, decision-makers, advocates, professionals, and women in the EU are increasingly confronted with the question of whether or not, and if so, how these new developments should be integrated into more successful approaches to control of cervical cancer in Europe, both for the individual women affected and for the population as a whole. By focusing on the core topics of primary HPV testing in the first supplement (Ronco et al. 2015), organisation of HPV-based and cytology-based screening programmes in the second supplement (Anttila et al. 2015a), and implementation of HPV vaccination programmes in the third supplement (De Vuyst et al. 2015), the joint publication of these supplements aims to provide appropriate answers to these important questions and to lay the foundation for further development of the comprehensive European guidelines in the coming years.

Publication format

The supplements are presented in a joint volume including 62 main recommendations and conclusions, for which the strength of the evidence and the respective recommendations is graded according to a defined format. The respective recommendations are presented at the beginning of each supplement and their annotation indicates the places in the subsequent text where the evidence and the rationale pertaining to each recommendation is explained, including cross-references to other supplements and recommendations. This enables the reader to rapidly review the key content of the supplements and to identify places in the volume likely to be of interest for further reading. In addition, some statements of advisory character considered to be good practice but not sufficiently important to warrant formal grading are provided in each supplement.

Methodology

To develop the evidence-based recommendations, the approach used for the European guidelines for quality assurance in colorectal cancer screening and diagnosis (Minozzi et al. 2012) was adopted and modified slightly to take into account the different subject matter and time period of the present project. A multidisciplinary group of authors and editors experienced in quality assurance in cervical cancer screening, programme implementation and guideline development collaborated with a 'literature group' consisting of epidemiologists with special expertise in the field of cervical cancer screening and in systematic literature review. Experts in HPV vaccination were also recruited to participate in the project together with the other editors, authors and reviewers. The literature group systematically retrieved, evaluated and synthesized relevant publications dealing with cervical cancer screening and vaccination using clinical questions defined by the authors and editors. The clinical questions were elaborated according to the Patient-Intervention-Comparison-Outcome-Study (PICOS) method (Richardson et al. 1995, Greenhalgh 1997, O'Connor, Green and Higgins 2008) that was modified slightly to take into account the aim of screening to lower the burden of the disease in the population.

Bibliographic searches for most clinical questions were limited to the time period January 2000 to March 2012 and were performed on Medline, and in many cases also on Embase and the Cochrane Library. Priority was given to recent comprehensive reviews. Additional searches were conducted without date restrictions or starting before 2000 if the authors or editors who were experts in the field knew that there were relevant articles published before 2000. Where no observational data were available, outcomes simulated by mathematical models and expert opinion were accepted as the lowest level of evidence. Articles of adequate quality recommended by authors because of their clinical relevance were also included, especially in the time period after March 2012 and up to December 2014 prior to completion of final editing of the draft manuscripts that began in July 2014. Preliminary versions of the draft supplements were repeatedly reviewed and revised through multidisciplinary meetings and discussions in which authors, editors and members of the literature group participated. Prior to finalization and review by the complete group of editors, the draft manuscripts were intensively reviewed by selected editors and/or external experts.

The editorial board was responsible for the final formulation of the supplements and the grading of the evidence and strength of the recommendations. The level of evidence and the strength of each of the graded recommendations are indicated using the slightly modified scales adopted for the European guidelines for quality assurance in colorectal cancer screening (Segnan, Patnick & von Karsa 2010; Minozzi, Armaroli & Segnan 2012); see below:

Grading of recommendations and supporting evidence

For the level of evidence:

- I consistent multiple randomised controlled trials (RCTs) of adequate sample size, or systematic reviews (SRs) of RCTs, taking into account heterogeneity
- II one RCT of adequate sample size, or one or more RCTs with small sample size
- III prospective cohort studies or SRs of cohort studies; for diagnostic accuracy questions, cross-sectional studies with verification by a reference standard
- IV retrospective case-control studies or SRs of case-control studies, trend analyses
- V case series; before/after studies without control group, cross-sectional surveys
- VI expert opinion

For the strength of the respective recommendation:

- A intervention strongly recommended for all patients or targeted individuals
- B intervention recommended
- C intervention to be considered but with uncertainty about its impact
- D intervention not recommended
- E intervention strongly not recommended

Screening for cervical cancer with primary testing for human papillomavirus

The first of the present supplements (Ronco et al. 2015) aims to inform European policymakers and public health specialists, and any other interested parties about the critical issues that should be considered in weighing the potential benefit and harm of cervical screening programmes based on HPV primary testing. It includes 36 main recommendations and conclusions dealing with the suitability of HPV primary testing for use in cervical cancer screening. Key messages and topics covered in the supplement include the lack of appropriate benefit from co-testing, and the appropriate target age group and interval for HPV primary testing. Management protocols for women with positive or technically inadequate HPV primary tests, the clinical accuracy of HPV testing using self-collected samples, and the selection of tests suitable for primary screening are also covered; and other policies and professional and scientific standards, such as consideration of health economic issues, are indicated that should be adhered to in the design and implementation of quality-assured cervical cancer screening programmes based on HPV primary testing. It is not the intention of the authors and editors to promote recent research findings before they have been demonstrated to be of proven benefit in clinical practice. The supplement therefore focuses on the use of primary testing for HPV DNA in cervical cancer screening with cytology triage in the EU. As far as possible the authors and editors have attempted to achieve an equitable balance that is applicable across a wide spectrum of cultural and economic healthcare settings in the EU. As with any standards and recommendations, these should be continuously reviewed in the light of future experience.

The scientific justification for the recommendations in the first supplement is provided by over 110 publications cited in the text, including published cross-sectional and longitudinal data from eight randomized clinical trials conducted in Canada, Finland, India, Italy, Sweden, The Netherlands and the United Kingdom (Bulkmans et al. 2004, Kotaniemi-Talonen et al. 2005, Sankaranarayanan et al. 2005, Kitchener et al. 2006, Ronco et al. 2006a, Ronco et al. 2006b, Mayrand et al. 2007, Naucler et al. 2007, Ronco & Segnan 2007, Leinonen et al. 2009, Naucler et al. 2009, Sankaranarayanan et al.

2009, Anttila et al. 2010, Ronco et al. 2010, Kitchener et al. 2011, Leinonen et al. 2012, Rijkaart et al. 2012, Dijkstra et al. 2014, Ronco G et al. 2014). It should be noted that the efficacy of HPV primary testing in cervical cancer screening has been demonstrated in studies using clinician-based samples. The authors and editors emphasize that currently the clinical accuracy of HPV primary testing on self-collected samples is sufficient to conduct organized, population-based pilot programmes for women who have not attended screening despite a personal invitation and a personal reminder (see Suppl. 1, Rec. 1.32). Policy makers and professionals must be aware, however, that HPV testing on self-taken samples is less accurate than on clinician-taken samples. For this reason, self-sampling is not recommended for all women invited to screening (see Sect. 1.7 and Suppl. 2, Sect. 2.4.4 and Rec. 2.8 - 2.13).

The authors and editors also emphasize that despite the convincing evidence for more efficacious screening using HPV primary testing, appropriate screening policy and programme organization are essential to achieving an acceptable balance between benefit and harm of any screening programme. These principles are particularly important in HPV primary screening, in order to avoid substantial increase in the number of women with positive test results and additional colposcopies and treatment of no additional benefit to participating women. Following the recommendations in the present supplement will enable programmes to achieve the potential benefit of HPV primary testing in cervical cancer screening while minimizing the risks (Rec. 1.1).

While most of the recommendations in the first supplement focus on the opportunities and the challenges of HPV primary screening that set it apart from cytology-based screening; decision-makers, programme managers and professionals should also be aware of the guidance in the second Guidelines edition (Arbyn et al. 2008; Arbyn et al. 2010) that is relevant to any cervical screening programme irrespective of the method of primary testing used (see Rec. 1.34). Of prime importance in this regard are also the recommendations on programme organization, planning, monitoring and evaluation in the second supplement. The authors and editors also emphasize the importance of using reliable, validated HPV tests (see Rec. 1.33) in qualified laboratories, accredited by authorized accreditation bodies and in compliance with international standards (see Rec. 1.35) In addition, any decision to implement HPV primary testing in cervical cancer screening should take into account health economic factors, and whether correct use of the test as specified in the instructions of the manufacturer and in accordance with the recommendations in the supplement can be organized (see Rec. 1.36). The authors and editors also point out that sustainability is crucial to the success of any cervical screening programme, and in the first supplement they underline the importance of the respective recommendations in Supplement 2 and Annex 1.

Organization of cytology-based or HPV-based cervical cancer screening

The second supplement (Anttila et al. 2015a) addresses the persisting gap in the EU between knowledge of the potential of population-based cervical screening to reduce the burden of the disease in the population, on the one hand, and the extent to which this knowledge has been translated into effective national programmes to control cervical cancer, on the other hand. As pointed out in the Council Recommendation on cancer screening (Annex 2), the most effective and appropriate way for screening to reduce cervical cancer incidence and mortality is through implementation of population-based programmes following the European quality assurance guidelines. Despite this knowledge, many old and new Member States of the European Union do not have population-based screening programmes in place or have programmes that are underperforming. The supplement provides seventeen recommendations on the policy and organizational issues that are inherent to the use of cytology and HPV testing in screening programmes. First and foremost is recognition of the need to implement HPV primary screening only in organized, population-based programmes (see Rec. 2.1 in Suppl. 2). This is an important prerequisite for effective quality assurance of any cancer screening programme (see Annex 1 and 2) and one that applies particularly to HPV primary screening.

The scientific justification for the recommendations in the second supplement is provided by over 90 publications cited in the text. In light of the evidence that HPV primary screening of appropriate qual-

ity can yield better results than cytology-based screening, policy-makers in EU countries or regions with cytology-based population programmes are advised to review current policies and consider whether transition to HPV primary screening would improve the balance between harm and benefit in their programmes. Policy makers in EU countries or regions lacking any population-based cervical screening programme are advised to review current policies and consider implementation of organized population-based cervical screening programmes taking into account the current European Guidelines, including the supplements, and the Council Recommendation (see Rec. 2.2 and 2.3). In addition to these general aspects, problems are discussed that are commonly encountered in implementing cervical cancer screening programmes in EU Member States with population-based programme policies, in those with opportunistic programmes, or in Member States in Central and Eastern Europe, and solutions are suggested that have proven to be effective in successful European screening programmes. The recommendations in the supplement are focussed on strategies to optimize screening attendance, including invitations, reminders and self-sampling. For evaluation and monitoring, the supplement also provides key performance indicators specifically related to HPV primary screening; and for the first time, European quality standards are introduced for key performance indicators (coverage by invitation, coverage by examination; and rate of participation or uptake) (see Rec. 2.15 - 2.17).

In the text more detailed advice is provided on the steps that programme management should take in navigating the protracted process of establishing an organized, population-based screening programme, including a checklist for planning, feasibility testing, piloting, monitoring and evaluation (see Sect. 2.7). This guidance illustrates and supplements the recommendations in Annex 1 dealing with the determinants of successful implementation of cancer screening programmes (Lynge et al 2012; von Karsa et al. 2013a; see also Anttila et al. 2015b and von Karsa et al. 2014).

Implementation of vaccination against human papillomavirus in Europe

The third of the present supplements (De Vuyst et al. 2015) summarizes the evidence base for HPV vaccination using the currently licensed bivalent and quadrivalent vaccines in the EU.[14] Over 90 publications are cited and nine main recommendations and conclusions are provided to promote effective implementation of this tool for cervical cancer control in the EU. Clinical trials have shown the current prophylactic HPV vaccines to be safe and highly effective against persistent vaccine-related HPV infections and anogenital precancerous lesions among women who were not infected by these types at the time of vaccination (ECDC 2012; WHO 2009a; WHO 2014a; see also EMA 2014a; EMA 2014b). The use of HPV vaccines in pre-adolescent girls and young women for the primary prevention of cervical cancer and some other HPV-related diseases has been endorsed by the European Medicines Agency (EMA) in 2006 (quadrivalent HPV 6/11/16/18 vaccine)[15] and 2007 (bivalent HPV 16/18 vaccine),[16] and in a position paper by the World Health Organization (WHO) in 2009 and 2014 (WHO 2009b; WHO 2014b). Since then, 21 of the 28 Member States of the European Union plus Norway and Iceland have introduced national HPV vaccination programmes. Recently, WHO updated its HPV vaccines position paper to recommend a two-dose regimen with increased flexibility in the interval between doses (WHO 2014b). EMA has also granted marketing authorizations for bivalent and quadrivalent vaccines in the EU for a two-dose schedule administered by injection at a 6-month interval for girls aged 9-14 and 9-13 years, respectively. If the respective vaccines are administered at

[14] The 9-valent vaccine that was recommended by the European Medicines Agency (EMA) in March 2015 for the prevention of diseases caused by nine types of human papillomavirus (HPV) was not considered in the preparation of the present supplement because at the time of writing and editing it was not licensed for use in the EU. See (accessed 28/05/2015): http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2015/03/WC500184898.pdf

[15] See summary of product characteristics, accessed 10/04/2015: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000703/WC500021142.pdf

[16] See summary of product characteristics, accessed 10/04/2015: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000721/WC500024632.pdf

an older age, the three-dose schedule should be used (EMA 2014a, EMA 2014b). Some EU countries, such as Belgium, France, Italy and the UK, have already implemented a 2-dose HPV vaccination schedule.

The primary target group for routine vaccination is girls at an age before debut of sexual activity, usually 12 to 13 years. Targeting older girls and young women with catch-up vaccination at the start of a routine vaccination programme can accelerate the impact of the vaccination programme, as clinical trials have shown satisfactory immune response and efficacy against infection in women aged 15 to 26 years being HPV 16 and 18 DNA negative. The question whether boys should also be included in the HPV vaccination target population is currently under debate and is the subject of ongoing research. Vaccination of boys could contribute to herd immunity and offer protection against other HPV-related cancers and genital warts in the vaccinated subjects. Moreover, mathematical modelling studies indicate that vaccinating boys would be cost-effective if vaccine coverage in girls is lower than 30%–50%, as is the case in a number of EU Member States, or if vaccine cost is substantially diminished, i.e., is halved.

Clinical trials and post-licensure studies have shown that the current vaccines are safe, and efforts are still on-going to monitor rare events like auto-immune diseases, or possible adverse effects in special groups such as women who have been inadvertently vaccinated during pregnancy. An important measure in process-monitoring of HPV vaccination is the assessment of vaccine coverage data by year of birth and number of administered doses. In addition, individual vaccination records should be retained, to permit linkage of HPV-related disease incidence with individual vaccination status in the future.

A measurable early indicator of the impact of vaccination will be the prevalence of HPV infections in young vaccinated women. Indirect evidence of population level impact of the HPV vaccines has already been provided through the demonstration of a decrease in the prevalence of HPV, the incidence of high-grade cervical abnormalities, and the incidence of genital warts soon after the introduction of vaccination programmes. However, long-term monitoring of end-point indicators is essential to assure that programmes attain their expected impact. This will require careful assessment of changes in the epidemiology of severe precancerous lesions and cancers over decades through linkage between screening and cancer registries irrespective of early indicator studies.

As of early 2014, seven EU countries had not yet initiated HPV vaccination campaigns, all of them new Member States (Estonia, Hungary, Lithuania, Poland, Slovakia, Cyprus and Croatia). HPV vaccination is perceived as being too expensive by many new Member States, but vaccine prices for vaccination campaigns have decreased considerably in recent years, and modelling studies have shown that cost-effectiveness of HPV vaccination tends to be largest in countries with the highest cervical cancer burden, as is the case in most of these countries.

In most of the EU Member States with HPV vaccination campaigns, the vaccine is offered free of charge, predominantly through organized, population-based programmes distributing the vaccine at schools or public health centres. The success in terms of coverage of the target groups has been highly variable, ranging from <30% to 80% and over. At the lower end of the range, in France and Luxemburg, the programmes rely on opportunistic vaccination. The highest rates of 80% and above are in countries or regions with population-based vaccination programmes (Denmark, Malta, Portugal, Sweden, the United Kingdom and the Flemish community in Belgium). Most of the countries choose routine target groups that include ages in the range 11 to 13 years. Organized school-based programmes usually provide the best coverage and more equitable access to HPV vaccines, followed by organized programmes through health-care centres and through general practitioners. Opportunistic programmes usually achieve low or ill-defined levels of coverage. Vaccination campaigns targeting adolescents pose specific challenges, compared to those targeting younger children aged 10–13 years.

Given the current variation in HPV vaccination coverage in the EU, the importance of an organized, population-based approach to vaccine delivery and the need for adaptation of existing vaccine delivery

infrastructure to the special requirements of HPV vaccination are common to all EU countries (see Rec. 3.1 in Suppl. 3). Higher vaccination coverage is a reasonable goal in many EU Member States. HPV vaccination programmes should aim at a minimum coverage of 70% and preferably >80% (see Rec 3.7). Effective monitoring and evaluation will be key to improving the coverage and effectiveness of vaccination programmes across the EU. Organized, population-based HPV vaccination programmes should have systematic register-based monitoring of coverage and safety. Long-term evaluation of vaccine safety and effectiveness is recommended in all countries. Appropriate legal frameworks must be developed, taking funding and organizational resources into account (see Rec 3.3). Every effort should be made to record individual vaccination status to ensure that it will be known for future cohorts reaching the target age for screening (see Rec. 3.8).

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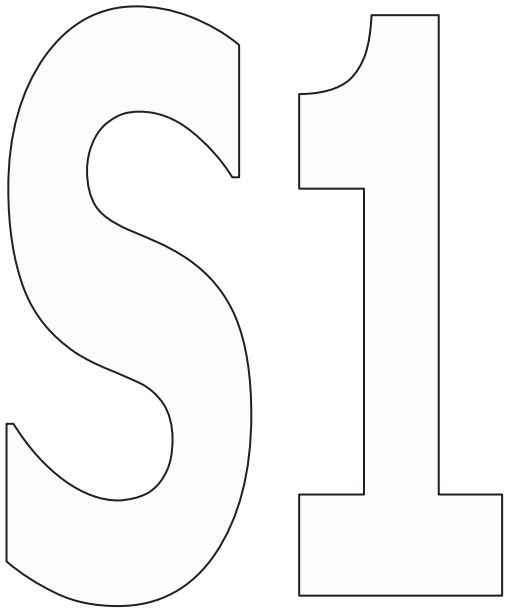

Screening for cervical cancer with primary testing for human papillomavirus

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Recommendations and conclusions[17]

Suitability of HPV primary testing for use in cervical cancer screening programmes

1.1 Primary testing for oncogenic HPV[18] can be used in an organized, population-based programme for cervical cancer screening **(I-A)** provided the other recommendations in this supplement are followed **(VI-A).** Primary testing for oncogenic HPV outside an organized population-based programme is not recommended (see also Suppl. 2, Rec. 2.1) **(VI-E).**[Sect 1.2.1.3; 1.2.3]

Avoidance of co-testing (HPV and cytology primary testing) at any given age

1.2 Only one primary test (either cytology or testing for oncogenic HPV) should be used at any given age in cervical cancer screening (see also Rec. 1.3 - 1.7) **(II-A).**[Sect 1.3.1]

Age at which to start HPV primary testing in cervical cancer screening programmes

1.3 Routine HPV primary screening can begin at age 35 years or above (see also Rec. 1.1) **(I-A).**[Sect 1.3.2.1]

1.4 Routine HPV primary screening should not begin under age 30 years **(I-E).**[Sect 1.3.2.1]

1.5 The available evidence is insufficient to recommend for or against beginning routine HPV primary screening in the age range 30 - 34 years **(VI).**[Sect 1.3.2.1]

Age at which to stop HPV primary testing in cervical cancer screening programmes

1.6 In the absence of sufficient evidence on the optimal age at which to stop screening, HPV primary screening could stop at the upper age limit recommended for cytology primary screening (60 or 65 years), provided a woman has had a recent negative test **(VI-B).**[Sect 1.3.2.2]

Cervical screening using cytology primary testing outside the age range of HPV primary testing

1.7 Cervical screening based on cytology primary testing conducted outside the age range of HPV primary testing should follow the guidance provided for cytology-based screening in the second edition of the European guidelines for quality assurance in cervical cancer screening, and in Supplement 2 (see also Rec 1.9, 1.10, 1.22 and 1.34) **(VI-A).** [Sect 1.3.2.1]

Screening interval after a negative HPV primary test

1.8 The screening interval for women with a negative HPV primary test result should be at least 5 years **(I-A)** and may be extended up to 10 years depending on the age and screening history **(III-C).**[Sect 1.3.3]

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[17] **Sect** (superscript) after each recommendation in the list refers the reader to the section/s of the supplement/s dealing with the respective recommendation.

Rec (superscript) throughout the supplement refers to the number of the recommendation dealt with in the preceding text.

[18] See IARC (2012) and footnote no. 13 on page XV.

Management of women without an adequate HPV primary test result

1.9 Some women attending cervical cancer screening may prefer not to be tested for HPV. If a woman declines HPV primary testing, cytology can be performed (see also Rec 1.7) **(VI-C)**.[Sect 1.3.4]

1.10 Non-attenders and women with a technically inadequate HPV test result should be invited to have a new sample taken **(VI-A)**; alternatively cytology testing without additional sample taking may be performed if technically feasible and preferred by the woman (see also Suppl. 2, Rec. 2.9-2.11) (**VI-B**).[Sect 1.3.4; 2.4]

Management of women after a positive HPV primary test

1.11 Cervical screening programmes using HPV primary testing must adopt specific policies on triage, referral and repeat testing of women with positive primary test results, taking into account the guidance in Rec. 1.12 – 1.31). The policies must include guidance on when women with positive HPV test results should be invited to return to routine screening **(VI-A).** [Sect 1.3.5]

1.12 Screening programmes should carefully monitor management of HPV-positive women. Monitoring should include compliance of individual women with further follow-up of positive primary test results, as well as results of triage, referral, colposcopies, biopsies, and treatment of pre-cancers **(VI-A).**[Sect 1.3.5]

1.13 Triage, referral and repeat testing policies (see Rec. 1.11) should be regularly reviewed and, if necessary, revised taking into account the results of monitoring (see Rec. 1.12) and the available evidence **(VI-A).**[Sect 1.3.5]

Secondary testing

- **Cytology triage**

1.14 Women testing positive for oncogenic HPV at primary screening should be tested without delay for cervical cytology (cytology triage) **(I-A).**[Sect 1.4.1.1] The cytology test should preferably use the specimen collected during the HPV screening visit **(VI-A).**[Sect 1.4.1.1]

1.15 Direct referral to colposcopy of all HPV-positive women is not recommended **(I-D).**[Sect 1.4.1.1]

1.16 Depending on the result of cytology triage, HPV-positive women should be referred to repeat testing, or to colposcopy (see Rec. 1.18 - 1.21) **(I-A)**.[Sect 1.4.1.1]

1.17 Quality assurance of laboratories and professional practice in the provision of cytology, colposcopy and histopathology services used in cytology triage in HPV primary screening should comply with the recommendations in Chap. 3 - 6 of the European Guidelines, second edition (see also Rec. 1.35) **(VI-B)**.[Sect 1.4.1.1]

- **Referral of women with pre-invasive or more severe cytology at triage**

1.18 Women with ASC-H (atypical squamous cells, high-grade squamous lesion cannot be excluded), HSIL (high grade squamous intraepithelial lesion), AIS (adenocarcinoma in situ) or a more severe finding at cytology triage should be referred to colposcopy without further observation or testing **(III-A).**[Sect 1.4.1.2]

- **Referral of women with minor cytological abnormalities at initial triage**

1.19 Women with ASC-US (atypical squamous cells of undetermined significance), AGC (atypical glandular cells), or LSIL (low grade squamous intraepithelial lesion) at triage after an initial HPV primary test in a screening episode may be followed up by retesting, preferably after 6 - 12 months, or referred directly to colposcopy (see Rec. 1.22 - 1.31) **(VI-C).**[Sect 1.4.1.2]

- **Referral of women with negative cytology at initial triage**

1.20 Women who have negative cytology (negative for epithelial abnormality) at triage after a positive initial HPV primary test in a screening episode should be followed up by re-testing after an interval shorter than the regular screening interval, but after at least 6 - 12 months (see also Sect. 1.4.1 and Rec 1.23 and 1.24) **(VI-A).**[Sect 1.4.1.2]

1.21 Direct referral to colposcopy of women with negative cytology at triage is not recommended **(I-D).**[Sect 1.4.1.2]

Management of women at repeat testing

1.22 The prevalence of HPV and the quality and organization of cytology screening affect the efficiency, effectiveness and appropriateness of management of women at repeat testing. These factors should be taken into account in the regular review of management protocols for repeat testing (see also Rec. 1.13) **(VI-A).** [Sect 1.5.3]

- **Type and interval of repeat testing**

1.23 Cytology repeat testing after at least 6 - 12 months is an acceptable alternative to HPV repeat testing (see also Chap. 6, Sect. 6.3.1 in the European Guidelines, second edition) **(III-B).**[Sect 1.5.1]

1.24 Women who were HPV-positive and cytology normal (negative for epithelial abnormality) in primary screening may be managed by HPV retesting with or without cytological triage, and after an interval of preferably at least 12 months **(III-B).**[Sect 1.5.1]

- **Protocols using HPV testing with cytology triage in repeat testing**

1.25 Women should be referred to colposcopy if cytology triage of a positive repeat HPV test yields ASC-US **(VI-B)** or more severe cytology **(VI-A)**.[Sect 1.5.3]

1.26 Women who have negative cytology triage (negative for epithelial abnormality) of a positive repeat HPV test) may be managed by one of the following options (see also Rec. 1.11-1.13) **(VI-B).**[Sect 1.5.3]

- Referral to second repeat testing after at least 12 months
- Referral to colposcopy
- Return to routine screening

1.27 Women who have a negative repeat HPV test should return to routine screening **(III-A).** Cytology triage is not needed for these women **(III-E).**[Sect 1.5.3]

- **Protocols using cytology testing alone in repeat testing**

1.28 Women with ASC-US or more severe cytology at repeat testing should be referred to colposcopy **(VI-B).**[Sect 1.5.3]

1.29 Women with normal cytology at repeat testing should return to routine screening **(III-A).**[Sect 1.5.3]

- **Protocols using HPV testing alone in repeat testing**

1.30 Women who have a negative repeat HPV test should return to routine screening **(II-A).** [Sect 1.5.3]

1.31 Women who have a positive repeat HPV test should be referred to colposcopy **(II-C).**[Sect 1.5.3]

Self-sampling in screening programmes using HPV primary testing

1.32 The clinical accuracy of HPV primary testing on self-collected samples taken for cervical screening is sufficient to conduct organized, population-based pilot programmes for women who have not attended screening despite a personal invitation and a personal reminder (see also Rec. 1.33 and Suppl. 2, Rec. 2.8 - 2.13) **(III).**[Sect 1.7]

Selection of HPV tests suitable for primary cervical cancer screening

1.33 Cervical cancer screening programmes should adopt an HPV primary test for use only if it has been validated by demonstrating reproducible, consistently high sensitivity for CIN2+ and CIN3+ lesions, and only minimal detection of clinically irrelevant, transient HPV infections **(VI-A).**[Sect 1.2.1.3; 1.6]

Implementation of HPV primary testing in cervical cancer screening programmes

1.34 HPV primary screening programmes should follow the guidance in the European Guidelines, that is relevant to any cervical screening programme irrespective of the method of primary testing used. The relevant guidance includes the recommendations on programme organization, planning, monitoring and evaluation (see current Suppl. 2, and second edition, Chap. 2); communication; and quality assurance of the entire screening process including sampling, histopathologic interpretation and classification of cervical tissue; and management of detected lesions (see second edition, Appendix 1 and Chap. 3 - 6) **(VI-A).**[Sect 1.2.3]

1.35 Like cervical cytology testing, HPV testing should be performed only on samples processed and analysed in qualified laboratories, accredited by authorized accreditation bodies and in compliance with international standards. The laboratory should perform a minimum of 10,000 tests per year (see also Rec. 1.34) **(VI-A).**[Sect 1.6]

1.36 Any decision to implement HPV primary testing in cervical cancer screening should take into account health economic factors, and whether correct use of the test as specified in the instructions of the manufacturer and in accordance with the recommendations in this supplement can be organized **(VI-B).**[Sect 1.2.1.3; 1.3.2.1]

- Health economic factors to consider in planning and subsequent steps in programme implementation include the prevalence of HPV infections; the burden of repeat testing, colposcopies, and CIN treatments resulting from HPV testing; and the quality and impact of existing cytology screening programmes.
- Assessments should be conducted to determine the optimal target age groups and screening intervals based on the chosen test and management protocols.
- The feasibility and sustainability of the programme should be assured through adequate resourcing and coordination, including coordinated planning, feasibility and pilot studies, and quality-controlled rollout across a country or region (see Suppl. 2 and Annex 1).

1.1 Introduction

Most cervical cancer cases in a population may be prevented by effective treatment of precancerous lesions detected in cervical screening by cytology primary testing (IARC 2005). For over a decade, detection of the etiologic agent human papillomavirus (HPV) in cervical samples has been investigated as an alternative method of primary cervical screening in cross-sectional studies, cohort studies, and randomized controlled intervention trials.

Evaluation of the utility and suitability of the new method for cervical cancer screening requires assessment of the relevant evidence by answering clearly defined questions about test performance, and feasibility and efficacy of the screening process (Appendix 1). A first step is to assess whether HPV primary testing has greater accuracy than cytology in identifying cervical cancer precursor lesions in cross-sectional analysis. Greater sensitivity for the detection of cervical cancer and its immediate precursors may imply increased safety. Specificity and positive predictive values (PPVs) are also important, as lower specificity and lower PPV imply that such screening will result in increased numbers of unnecessary colposcopies, treatments, and adverse effects (see Sect. 1.2.1).

Provided that cross-sectional assessment of primary test performance is promising, the next step is to evaluate longitudinal outcomes, preferably in studies with active intervention as a result of the test. Lower incidence of invasive cervical cancer after HPV primary screening than after cytology primary screening provides direct evidence of improved efficacy of the new method. However, invasive cervical cancer is rare, particularly in settings with effective screening programmes. Earlier, additional evidence of improved efficacy is provided by reduced detection of the immediate cervical cancer precursor, grade 3 cervical intraepithelial neoplasia (CIN3), after initial HPV screening (see Sect. 1.2.2).

Randomized controlled trials (RCTs) provide the highest level of evidence of efficacy and various determinants of screening impact. Since 2004, reports from six European RCTs have compared HPV and cytology primary screening (Bulkmans et al. 2004; Bulkmans et al. 2007; Kitchener et al. 2009b; Kotaniemi-Talonen et al. 2005; Leinonen et al. 2009; Naucler et al. 2007; Naucler et al. 2009; Rijkaart et al. 2012; Ronco et al. 2006a; Ronco et al. 2006b; Ronco et al. 2008; Ronco et al. 2010). In a Canadian RCT (CCCaST) (Mayrand et al. 2007), HPV and cytology primary testing were performed in combination (co-testing), and the order of sampling was randomly assigned. In a trial conducted in India, HPV primary screening was compared with cytology primary screening (Sankaranarayanan et al. 2005). Four RCTs have published the results of the first two screening rounds (Bulkmans et al. 2007; Kitchener et al. 2009b; Naucler et al. 2007; Ronco et al. 2010).

The chief characteristics of the RCTs are summarized in Table 1.1. The main findings are also presented in a systematic review (Arbyn et al. 2012) conducted during the preparation of the present supplements to the second edition of the European guidelines for quality assurance in cervical cancer screening (European Guidelines) (Arbyn et al. 2008a). Differences in protocols are mainly related to (1) the use of stand-alone HPV testing vs. co-testing all women for HPV and cytology and (2) referring all HPV positive women to colposcopy or conducting triage, in particular by cytology. The different HPV screening protocols used in the trials have been assessed by comparing the results obtained for efficacy, overdiagnosis, and referral to colposcopy, as well as PPV of colposcopy. Given the low incidence of invasive cervical cancer in well-screened women, the efficacy of cervical cancer screening was first examined by determining rates of CIN grade 3 or more severe neoplasia (CIN3+) detected at the second screening round; and the relative impact of different screening protocols was assessed by determining the ratio between the detection rates obtained using HPV primary testing versus cytology primary testing (see Sect. 1.2). The direct effect on cancer incidence was subsequently evaluated in a pooled analysis (Ronco et al. 2014).

Table 1.1. Randomized controlled trials comparing HPV versus cytology primary testing in cervical cancer screening

Study and country (references)	Participants	Primary screening test(s) in intervention arm	Management of test-positive women in intervention arm	Primary screening test in control arm
POBASCAM (The Netherlands) (Bulkmans et al. 2004; Rijkaart et al. 2012)	Randomized: N_{int} = 22 420 N_{cont} = 22 518 Eligible at baseline: N_{int} = 21 996 N_{cont} = 22 106 Age: 29-61 years Second round: N_{int} = 19 579 N_{cont} = 19 731 Age: 29–56 years at baseline	Conventional cytology + HPV	Cytology moderate dyskaryosis or more severe: refer to colposcopy. Borderline or mild dyskaryosis: repeat at 6 and 18 months; colposcopy at 6 months if cytology borderline or more severe and HPV+ or cytology moderate dyskaryosis or more severe; colposcopy at 18 months if still HPV+. Normal cytology: repeat at 6 and 18 months; colposcopy at 6 months if cytology moderate dyskaryosis or more severe; colposcopy at 18 months if still HPV+.	Conventional cytology
(Finland) (Anttila et al. 2010; Kotaniemi-Talonen et al. 2005; Leinonen et al. 2009)	Randomized: N_{int} = 54 207 N_{cont} = 54 218 Age 25–65 years Baseline: N_{int} = 33 100 N_{cont} = 35 475	HPV alone	Refer to colposcopy if cytology Pap III or more severe. Otherwise, 'intensified' screening, ie, repeat testing after 12-24 months. During the intensified screening in the HPV arm, women were referred for colposcopy after repeated borderline findings at cytological triage or after three consecutive positive HPV test results even if cytology was normal.	Conventional cytology
(India) (Sankaranarayanan et al. 2005; Sankaranarayanan et al. 2009)	N_{HPV} = 34 126 N_{cytol} = 32 058 N_{cont} = 31 488 Age 30–59 years	HPV alone	Refer to colposcopy	Conventional cytology; no screening

ARTISTIC (UK) (Kitchener et al. 2006; Kitchener et al. 2011)	Baseline: N_{int} = 1838 N_{cont} = 6124 Second round: N_{int} = 11 862 N_{cont} = 3928 Third round: N_{int} = 6665 N_{cont} = 2208 Age 20–64 years	Liquid-based cytology + HPV	If abnormal cytology, manage accordingly. If negative cytology, new HPV at 12 months. Colposcopy offered if still HPV+ (again at 24 months if refused at 12 and still HPV+).	LBC
NTCC[19] phase 1 (Italy) (Ronco et al. 2006a; Ronco et al. 2008; Ronco & Segnan 2007)	Baseline: N_{int} = 6002 N_{cont} = 5808 Age 25–34 years	LBC + HPV	Refer to colposcopy if cytology ASC-US+. If normal cytology, repeat both tests after 1 year and refer to colposcopy if still HPV+ or cytology ASC-US+	Conventional cytology
NTCC[19] phase 1 (Italy) (Ronco et al. 2006b; Ronco et al. 2008; Ronco & Segnan 2007)	Baseline: N_{cont} = 16 658 N_{int} = 16 706 Age 35–60 years	LBC + HPV	Refer to colposcopy	Conventional cytology
NTCC[19] phase 2 (Italy) (Ronco et al. 2008; Ronco et al. 2010; Ronco & Segnan 2007)	Baseline: N_{int} = 6937 N_{cont} = 6788 Age 25–34 years	HPV alone	Refer to colposcopy	Conventional cytology

[19] Note that in some meta-analyses the NTCC phases 1 and 2 are counted as separate trials.

Table 1.1. Randomized controlled trials comparing HPV versus cytology primary testing in cervical cancer screening, cnt'd

NTCC[20] phase 2 (Italy) (Ronco et al. 2008; Ronco et al. 2010; Ronco & Segnan 2007)	Baseline: N_{int} = 17 724 N_{cont} = 17 747 Age 35–60 years	HPV alone	Refer to colposcopy	Conventional cytology
Swedescreen (Sweden) (Naucler et al. 2007; Naucler et al. 2009)	Baseline: N_{int} = 6257 N_{cont} = 6270 Age: 32–38 years	Conventional cytology + HPV	Immediate referral to colposcopy if cytology abnormal. Otherwise, repeat HPV and cytology after 12 months. Referral to colposcopy if persistent infection with the same HPV type.	Conventional cytology
(Mayrand et al. 2007) (Canada)	Randomized: $N_{focus\ on\ HPV}$ = 5059 $N_{focus\ on\ Pap}$ = 5059 Age 30–69 years Baseline: $N_{focus\ on\ HPV}$ = 4957 $N_{focus\ on\ Pap}$ = 5020	HPV + Conventional cytology	Participants were referred for colposcopy if they had a positive Pap test (defined as ASC-US or more severe) or a positive HPV screening test or if they were randomly selected from among women with a negative index test: 706 of 4575 Pap-/HPV- and 664 of 4600 HPV-/Pap-.	Conventional cytology + HPV

ASC-US+, atypical squamous cells of undetermined significance or more severe; HPV, human papillomavirus; LBC, liquid-based cytology.

[20] See footnote no. 19 on page 11.

Another key question is whether HPV primary screening increases the number of interventions resulting from overdiagnosis of precursor lesions, ie detection of lesions that in the absence of screening would have spontaneously regressed, or would not have progressed to cancer. Overdiagnosed lesions cannot be individually identified but their number can be assessed in randomized trials by comparing the detection of precursor lesions in the HPV arm versus the cytology arm over two (or more) screening rounds. RCTs in which all women are tested for HPV at round 2 are more appropriate for evaluating overdiagnosis. If all women are tested for cytology at the second round then more than two screening rounds are more informative for assessing overdiagnosis (Ronco & Segnan 2007) (see Sect. 1.2.2.3).

Once a decision has been made to use HPV primary testing in cervical cancer screening, the next question is how to assess which test to use. There are more than 150 HPV tests currently available, with varying degrees of documentation. To identify HPV assays that might be considered to be acceptable for primary cervical cancer screening, equivalency criteria have been defined based on the relative cross-sectional accuracy for grade 2 CIN or more severe neoplasia (CIN2+) compared with validated assays (Meijer et al. 2009) (see Sect. 1.6).

As HPV prevalence is strongly age-dependent and the longitudinal performance of HPV primary testing is different from that of cytology, the recommended age range and intervals for HPV primary cervical screening are likely to differ from that of cytology primary screening. Systematic assessment of both beneficial and negative effects of starting and stopping HPV primary screening at various ages, and screening in various intervals is therefore of paramount importance (see Sect. 1.3.2).

As pointed out in the second edition of the European Guidelines, all of the steps in the screening process affect the overall impact and the balance between benefit and harm of cervical cancer screening. The present supplement therefore also provides guidance on the management of women after the result of the primary screening test is determined. This includes management of women lacking an adequate HPV primary test result as well those requiring management due to a positive primary test result. The latter group of women includes those for whom repeat testing is an appropriate approach, ie after normal cytology at triage of a positive HPV primary test (see Sect. 1.3.4, 1.3.5, 1.4 and 1.5).

A new option in the design of cervical screening programmes, when HPV primary screening is considered, is the use of self-collected samples; this may simplify logistics and enable new strategies for outreach to women to increase participation in organized screening programmes. In the absence of longitudinal evidence for equivalent or better sensitivity and specificity of detection of CIN3+ using self-collected samples, application of this sampling method must be planned and evaluated carefully, and should be limited to women not reached by clinician-based sampling (see Sect. 1.7).

It should also be considered that while effectiveness is essential, it is not the only criterion for recommending implementation of new, or modification of existing screening programmes. Health economic factors should also be taken into account to ensure that the expected benefits, and an appropriate balance between benefit and harm can be achieved with the available resources. Despite the wide variation in the cost of screening and medical procedures across the EU, the results and conclusions of cost-effectiveness studies conducted in a given setting can provide insight that will help decision-makers and professionals in other settings to plan and implement effective programmes (Sect. 1.8).

This supplement to the second edition of the European guidelines for quality assurance in cervical cancer screening (Arbyn et al. 2008a) has been developed to inform European policymakers and public health specialists, and any other interested parties about the critical issues that should be considered in weighing the potential benefit and harm of cervical screening programmes based on HPV primary testing. It is not the intention of the authors and editors to promote recent research findings before they have been demonstrated to be of proven benefit in clinical practice. The supplement therefore focuses on the use of primary testing for HPV DNA in cervical cancer screening with cytology triage. As far as possible the authors and editors have attempted to achieve an equit-

able balance that is applicable across a wide spectrum of cultural and economic healthcare settings in the EU. As with any standards and recommendations, these should be continuously reviewed in the light of future experience.

Thirty-six recommendations and conclusions, graded according to the strength of the respective recommendation or conclusion, along with the supporting evidence, are presented at the beginning of the supplement and explained in the body of the text. Some statements of advisory character considered by the authors and editors to be good practice but not sufficiently important to warrant formal grading are included in the text. Following these recommendations should enable decision-makers in EU Member States to ensure that comprehensive efforts to control cervical cancer make appropriate use of HPV primary testing when establishing cervical screening programmes or improving existing programmes.

1.2 Evidence on accuracy and outcome of HPV primary screening

1.2.1 Cross-sectional accuracy

Data on the cross-sectional accuracy of HPV primary testing are available from two types of studies: (1) cross-sectional studies in which women were offered co-testing with both cervical cytology (conventional or liquid-based) and HPV DNA assay, and (2) randomized clinical trials where women were assigned to cytology, HPV testing, or co-testing.

In the assessment of sensitivity and specificity, three study approaches were distinguished (Arbyn et al. 2009a): (1) all cases were verified with a reference standard (assessment of CIN2+ using histopathology of colposcopy-directed biopsies), (2) only screening-test-positive cases were verified and the assumption was made that none of the women who were negative for all tests had underlying CIN2+, and (3) a random sample of women who were negative for all tests underwent additional verification. For the evaluation of relative sensitivity, the ratio of sensitivities and the ratio of the detection rates of CIN2+ were considered.

Meta-analyses on the cross-sectional accuracy of HPV-based and cytology-based screening have concluded that HPV primary screening has higher sensitivity than cytology primary screening in detecting precancerous cervical lesions (CIN2+ and CIN3+) **(I)**. However, HPV testing is generally less specific, leading to increased rates of positive test results **(I)** particularly in younger women (Arbyn et al. 2012; Cuzick et al. 2008a; Koliopoulos et al. 2007; Ronco et al. 2008).

Overall, the sensitivity of the commonly used HPV test Hybrid Capture 2™ (HC2), at standard "cut-off" conditions (≥1 relative light units [RLU]), for finding underlying CIN2+ was 90% (95% confidence interval [CI], 88–93%); see Table 1.2. The heterogeneity in the sensitivity was very large in studies conducted in developing countries (probably due to quality variations in colposcopy and histological verification of CIN2+) (Arbyn et al. 2006). The inter-study variation was substantially reduced in studies conducted in industrialized countries.

In European and North American studies, which are the most relevant for European guidelines, the pooled sensitivity to detect CIN2+ was 96% (95% CI, 95–98%), whereas the pooled specificity was 91% (95% CI, 90–93%); see Table 1.2. The accuracy values of HC2 for CIN3+ were similar to those

for CIN2+. Overall, 10% (95% CI, 8–12%) of the screened population was HPV-positive with the HC2 test targeting high-risk HPV (hrHPV); 1.5% (95% CI, 1.1–1.9%) of the population had CIN2+, and 1.1% (95% CI, 0.8–1.3%) had CIN3+. The diagnostic odds ratio did not vary significantly by completeness of reference standard verification, indicating that verification bias was limited..

1.2.1.1 Cross-sectional accuracy of HPV testing relative to cytology

In 11 European and North American screening studies, the sensitivity of HC2 was on average 37% (95% CI, 22–54%) and 43% (95% CI, 15–77%) higher than that of cytology at the lowest cytological cut-off (atypical squamous cells of undetermined significance or more severe [ASC-US+]) for the detection of CIN2+ and CIN3+, respectively; see Table 1.3. When all pooled studies were considered, the relative sensitivity of HPV testing was higher when compared with cytology at a cut-off of low-grade squamous intraepithelial lesion or more severe (LSIL+).

The specificity of HC2 for excluding CIN2+ was significantly lower than that of cytology, at a ratio of 0.97 (95% CI, 0.96–0.98) and 0.92 (95% CI, 0.90–0.94) when considering the cut-offs ASC-US+ and LSIL+, respectively. GP5+/6+ polymerase chain reaction (PCR) was also more sensitive and less specific than cytology for detecting CIN2+, respectively (ratios: 1.33; 95% CI, 1.13–1.55 and 0.94; 95% CI, 0.85–1.03) (Arbyn et al. 2012).

The combination of cytology with HC2 had a sensitivity that was 42% (95% CI, 36–48%) and 33% (95% CI, 29–37%) higher for the detection of CIN2+ and CIN3+, respectively, than cytology alone (at cut-off ASC-US+), whereas the specificities were 6% (95% CI, 6–7%) and 8% (95% CI, 7–9%) lower, respectively. Adding cytology to the HC2 test increased the average sensitivity by 5 percentage points (95% CI, 4–7%) and 2 percentage points (95% CI, 1–3%) for CIN2+ and CIN3+, respectively, compared with HPV testing alone, but this resulted in a significant loss of specificity (ratios: 0.95; 95% CI, 0.94–0.96 and 0.93; 95% CI, 0.92–0.95) (Arbyn et al. 2012).

1.2.1.2 Relative accuracy of cervical screening using HPV primary testing alone or in combination with cytology primary testing

Baseline results from eight randomized studies compared the accuracy of detecting CIN2+ in cervical screening using hrHPV assays, cytology, or the combination of both (for study characteristics see Table 1.1). Figure 1.1 shows the relative sensitivity for detection of CIN2+ as the detection rate ratio [DRR] of HPV versus cytology primary screening in the eight trials, grouped by cytology method and by developing versus industrialized countries. The results from the industrialized countries showed substantially higher sensitivity of HPV primary testing for detection of CIN2+ than screening using conventional (combined DR ratio of 1.39; 95% CI, 1.23–1.57, p for inter-study heterogeneity = 0.57); the results were significant overall and in three of the six respective trials, all of which had consistent results. The sensitivity clearly appeared to be lower in the trial conducted in India (Sankaranarayanan et al. 2005) and possibly only slightly higher in the ARTISTIC trial (that used liquid-based cytology [LBC]) (Kitchener et al. 2009b). Plausible reasons that have been suggested for the latter findings include misclassification of CIN2+ in the Indian trial, overdiagnosis of lesions detected by LBC (Arbyn et al. 2009b), and loss of a large proportion of HPV-positive women to follow-up in the ARTISTIC trial (Sasieni, Castanon & Cuzick 2009).

Seven of the eight randomized studies also reported on detection of CIN3+. The results from the industrialized countries also showed substantially higher sensitivity of an hrHPV assay compared to

Table 1.2. Summary of meta-analyses of HPV versus cytology primary cervical screening. Sensitivity and specificity (pooled estimates), p-value for inter-study heterogeneity, and range (minimum and maximum observed value) for detection of histologically confirmed CIN2+ or CIN3+; pooled test positivity rate; and prevalence of CIN.

				Sensitivity		Specificity		Test positivity rate	Prevalence
Test	**Test cut-off**	**Outcome**	**Number of studies**	**Pooled estimate (95% CI)**	**Range (%)**	**Pooled estimate (95% CI)**	**Range (%)**	**Pooled estimates (95% CI)**	
HC2	1 pg/mL	CIN2+	31	90.4 (88.0–92.8)	50–100	88.5 (87.0–90.0)	61–95	13.2 (11.4–14.9)	2.2 (1.8–2.6)
		CIN2+	14*	96.3 (94.5–98.1)	69–100	91.4 (89.8–92.9)	86–96	9.9 (8.1–11.8)	1.5 (1.1–1.9)
		CIN3+	22	95.3 (93.3–97.3)	62–100	89.0 (87.2–90.8)	82–95	N.A.	1.1 (0.8–1.3)
HC2 & cytology	1 pg/mL or ASC-US+	CIN2+	13	94.2 (90.8–97.6)	63–100	87.7 (85.0–90.3)	69–94	13.8 (10.9–16.8)	1.3 (1.0–1.6)
		CIN2+	8*	99.8 (99.0–100)	69–100	88.8 (85.5–92.1)	80–93	12.5 (8.7–16.2)	0.7 (0.5–0.9)
PCR	+signal	CIN2+	3	94.5 (94.2–96.9)	94–100	94.8 (93.3–96.3)	86–96	8.0 (5.6–10.4)	2.4 (1.0–3.7)

ASC-US+, atypical squamous cells of undetermined significance or more severe; CI, confidence interval; CIN, cervical intraepithelial neoplasia; HC2, Hybrid Capture 2; PCR, polymerase chain reaction.

* Restricted to studies conducted in North America or Europe.

Source: Table 6 in Chapter 3, Sect. 3.8, European Guidelines, second edition, (Arbyn et al. 2008a), updated with data from Table 1 in: (Arbyn et al. 2012)

conventional cytology (combined DRR of 1.28; 95% CI, 1.09–1.51, p for inter-study heterogeneity = 0.012); the results were significant overall and in one of the five respective trials, all of which had consistent results. In the study with a significant result (NTCC phase 2) the increase in sensitivity for CIN3+ was substantial with a DR ratio of 2.06 (95% CI, 1.16–3.68) (Ronco et al. 2008).

In all of the trials that had an experimental arm with combined HPV and cytology primary screening, adding cytology to hrHPV primary testing yielded only a minor and statistically insignificant increase in sensitivity as reflected in the pooled DR ratios of 1.06 (95% CI, 0.97–1.16) and 1.04 (95% CI, 0.92–1.17) for CIN2+ and CIN3+, respectively (Figure 1.2).

1.2.1.3 Harms of HPV primary screening

Potential significant harms of HPV primary screening include markedly increased rates of positive test results **(I)** and colposcopy referrals at the first HPV screen **(I)** (Bulkmans et al. 2007; Kitchener et al. 2009b; Kitchener et al. 2011; Rijkaart et al. 2012; Ronco et al. 2006b; Ronco et al. 2010). These risks are particularly pronounced among women younger than 35 years. (see Sect. 1.3.2.1). However, the positive predictive value of colposcopy referral was similar for cytology or HPV primary screening in the randomized trials that used cytology triage to manage women with a positive HPV primary test (for further information see Sect. 1.4). These are key reasons for the recommendations in this supplement dealing with the age range and interval for HPV primary screening (see Rec 1.3 - 1.6 and 1.8) and management of women after a positive HPV primary test (see Rec. 1.11 - 1.31). To ensure that cervical cancer screening programmes based on HPV primary testing achieve an appropriate balance between benefit and harm, HPV primary screening is only recommended when used in an organized, population-based programme (see also Suppl. 2, Rec. 2.1) **(VI-E)** and provided the other recommendations in this supplement are followed (see also Sect. 1.2.3) **(VI-A).**[Rec 1.1] These include the need to ensure the correct use of the test as specified in the instructions of the manufacturer and in accordance with the other recommendations in this Supplement **(VI-B).**[Rec 1.36] The latter recommendations include selection only of those HPV primary tests for use in a programme that have been validated by demonstrating reproducible, consistently high sensitivity for CIN2+ and CIN3+ lesions, and only minimal detection of clinically irrelevant, transient HPV **(VI-A)**[Rec 1.33] or performance of HPV testing only on samples processed and analysed in qualified laboratories accredited by authorized accreditation bodies and in compliance with international standards **(VI-A).**[Rec 1.35]

Table 1.3. Relative accuracy of HPV versus cytology primary screening, and of co-testing versus screening with one test alone. Sensitivity and specificity for detection of histologically confirmed CIN2+ or CIN3+.

Comparison	Outcome	Relative sensitivity (95% CI)		Range	Relative specificity (95% CI)		Range	No. of studies
HC2 vs cyto (ASC-US+)	CIN2+	1.23	(1.15–1.31)	0.91–2.93	0.97	(0.96–0.98)	0.86–1.10	28 / 25†
HC2 vs cyto (ASC-US+)**		1.37	(1.22–1.54)	1.06–2.25	0.97	(0.96–0.98)	0.93–1.00	12 / 10†
HC2 vs cyto (LSIL+)		1.40	(1.27–1.54)	1.09–2.37	0.92	(0.90–0.94)	0.67–1.03	20 / 19†
HC2 vs cyto (ASC-US/LSIL+)		1.27	(1.18–1.36)	0.91–2.93	0.96	(0.94–0.97)	0.67–1.10	33 / 30†
PCR vs cyto (ASC-US+)		1.25	(1.08–1.45)	0.75–3.57	0.97	(0.94–1.00)	0.86–1.08	9 / 7†
PCR vs cyto (LSIL+)		1.61	(0.84–3.09)	0.82–5.10	0.92	(0.89–0.95)	0.89–1.00	3
HC2 vs cyto (ASC-US+)	CIN3+	1.27	(1.12–1.44)	0.97–2.63	0.97	(0.96–0.99)	0.88–1.10	20 / 18†
HC2 vs cyto (ASC-US+)**		1.43	(1.15–1.77)	1.01–2.12	0.97	(0.96–0.98)	0.93–1.00	8 / 6†
HC2 vs cyto (LSIL+)		1.36	(1.21–1.53)	0.97–2.32	0.93	(0.91–0.96)	0.84–1.03	13 / 12†
Cyto (ASC+) & HC2 vs Cyto (ASC-US+)	CIN2+	1.42	(1.36–1.48)	1.06–2.30	0.94	(0.93–0.94)	0.89–0.96	13
Cyto (ASC+) & HC2 vs Cyto (ASC-US+)	CIN3+	1.33	(1.29–1.37)	1.02–2.18	0.92	(0.91–0.93)	0.85–0.96	10/9
Cyto (ASC-US+) & HC2 vs HC2$	CIN2+	1.05	(1.04–1.07)	1.00–1.19	0.95	(0.94–0.96)	0.81–0.99	10
Cyto (ASC-US+) & HC2 vs HC2	CIN3+	1.02	(1.01–1.03)	1.04–1.04	0.93	(0.92–0.95)	0.81–0.99	6

ASC-US+, atypical squamous cells of undetermined significance or more severe; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia of grade 2 or more severe; CIN3+, cervical intraepithelial neoplasia of grade 3 or more severe; cyto, cytology; HC2, Hybrid Capture 2; LSIL+, low-grade squamous intraepithelial lesion or more severe; PCR, polymerase chain reaction.

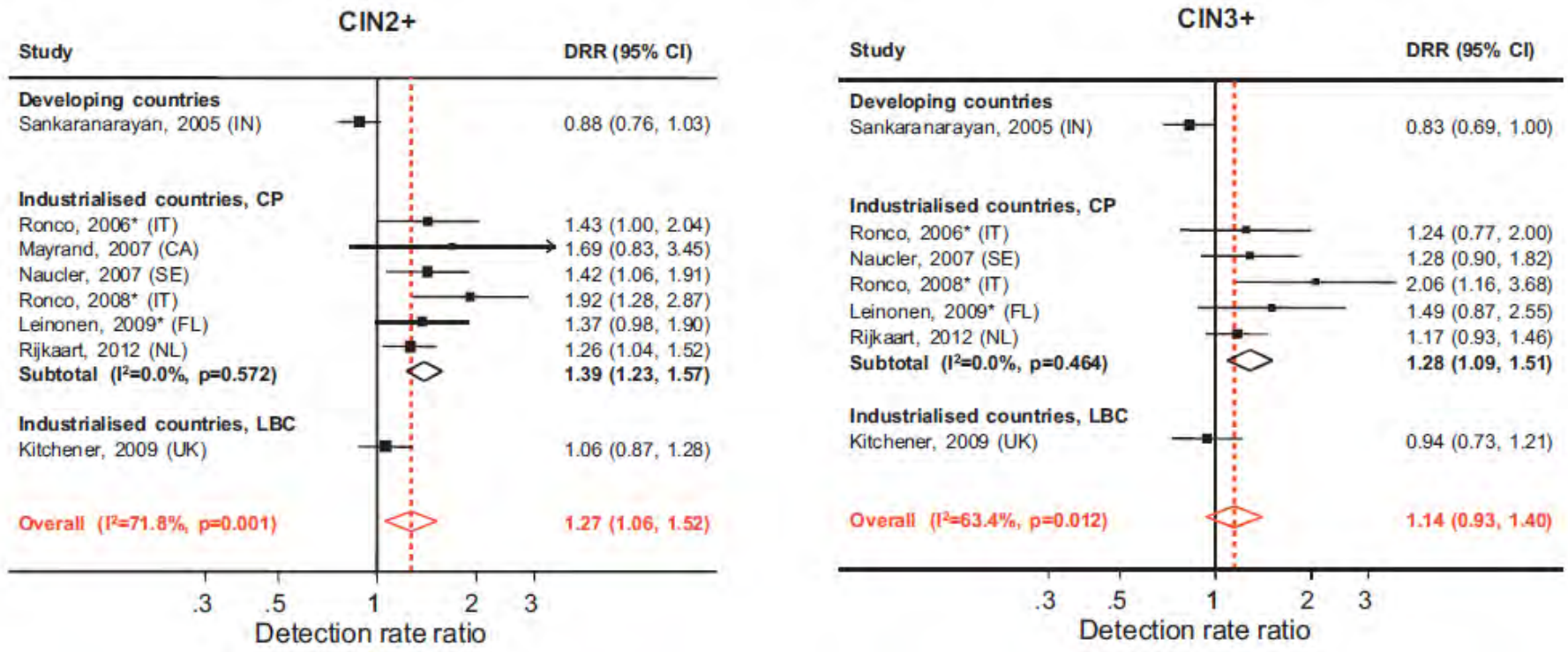
† The meta-analysis of relative sensitivity (first no.) includes randomized controlled trials (RCTs) with a control arm where only cytology was used; the meta-analysis of relative specificity (second no.) does not include these RCTs.

** Restricted to studies conducted in North America or Europe.

$ Exclusion of (Sankaranarayanan et al. 2005), for explanation see text.

Source: Modified from Table 3 in: (Arbyn et al. 2012)

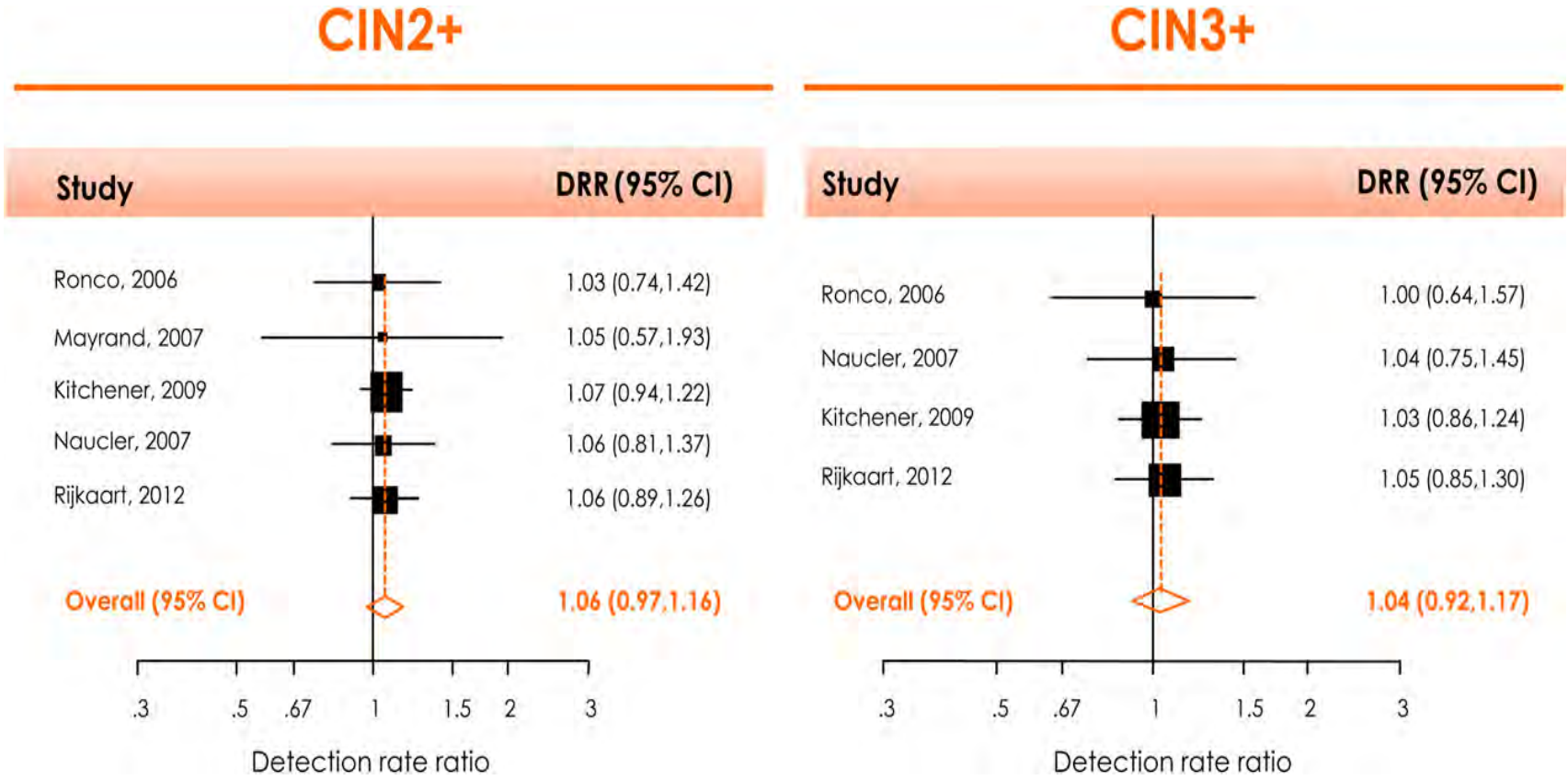
Figure 1.1. Meta-analysis of randomized trial results for detection of CIN2+, and CIN3+.
Relative detection rate of CIN2+ (left) and CIN3+ (right) identified by hrHPV testing versus cytology. Studies are grouped by type of cytology used in the control group (conventional [CP] or liquid-based cytology [LBC]), and by industrialized versus developing countries.



*Restricted to women older than 35 years. p = test for inter-study heterogeneity; I^2 = the percentage of total variation across studies due to heterogeneity.
CI, confidence interval; CIN, cervical intraepithelial neoplasia; DRR, detection rate ratio
CA, Canada; FL, Finland; IT, Italy; NL, Netherlands; SE, Sweden; UK, United Kingdom

Source: (Arbyn et al. 2013)

Figure 1.2. Relative sensitivity of HPV primary testing in combination with cytology versus HPV primary testing alone.
Relative detection rate of CIN2+ (left) and CIN3+ (right) observed in the second screening round among women who were HPV negative versus cytology negative at enrolment.



CI, confidence interval; CIN, cervical intraepithelial neoplasia; DRR, detection rate ratio.

Source: (Arbyn et al. 2012)

1.2.2 Longitudinal outcomes of HPV primary screening in randomized controlled trials

1.2.2.1 Reduction in CIN3+ and cancer incidence

- **Outcomes in the second round of cervical screening**

Results of the second screening round have been published for four RCTs investigating HPV primary screening: despite different protocols for the management of screen-positive women, a remarkably consistent reduction in the incidence of CIN3+ lesions was found among women who had HPV primary screening versus those who had cytology primary screening at round 1 (pooled DRR of 0.43; 95% CI, 0.33–0.56); see Figure 1.3. The results were significant overall and in each of the four studies when analysis of the Italian data was restricted to women older than 35 years. Moreover, in the Italian trials, no cancer cases were found at round 2 among women who had HPV primary screening at round 1, whereas 9 cases were observed among women who had cytology primary screening at round 1 ($p = 0.004$) (Ronco et al. 2010). Since similar numbers of invasive cancer cases were detected in the HPV and cytology arms in the first round, the reduction at round 2 results from more effective prevention, as opposed to earlier diagnosis, of invasive cancers by HPV primary testing.

Compared with cytology, HPV primary screening results in reduced incidence of CIN2 and CIN3 at the second screening rounds **(I)** (Arbyn et al. 2012; Kitchener et al. 2009b; Kitchener et al. 2011; Naucler et al. 2009; Rijkaart et al. 2012; Ronco et al. 2010) showing that HPV based screening allows earlier detection of persistent CIN2 and CIN3 than cytology.

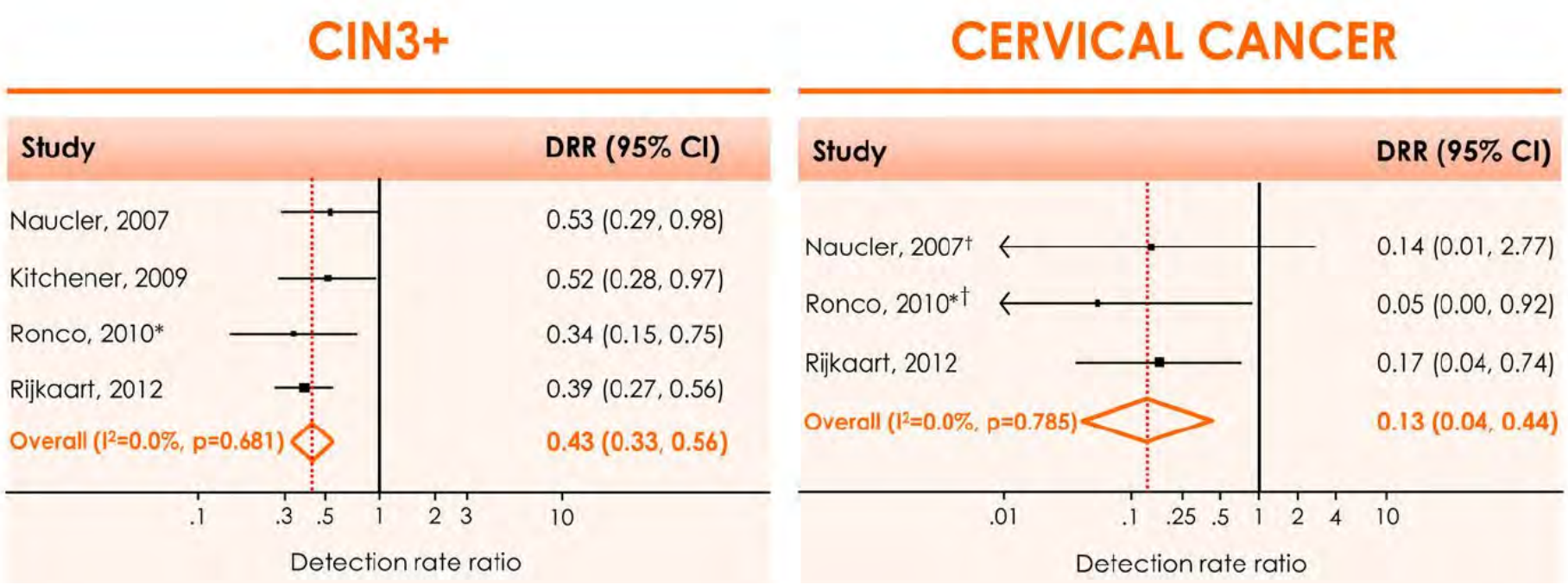
- **Outcomes after the initial screen (two or more rounds of follow-up)**

Based on a joint analysis of four European randomized trials with data for two or more screening rounds, the DRR of cervical cancers for HPV versus cytology primary screening, starting from the initial screen, was 0.60 (95% CI, 0.40–0.89); for the cumulative detection rates see Figure 1.4. There was no evidence of heterogeneity between studies ($p=0.52$). HPV primary screening, compared with cytology primary screening, provides greater protection against invasive cervical cancer **(I)**. In women with a negative screening test at entry, the DRR was 0.30 (95% CI, 0.15–0.60). Rate ratios did not differ by cancer stage (microinvasive carcinoma, 0.58 (95% CI, 0.34–1.01); fully invasive carcinoma, 0.56 (95% CI, 0.31–1.00)), but were lower for adenocarcinoma (0.31; 95% CI, 0.14–0.69) than for squamous cell carcinoma (0.78; 95% CI, 0.49–1.25). The DRR was lowest for women aged 30–34 years at recruitment (0.36; 95% CI, 0.14–0.94). Among women aged 35–49 years at recruitment, the rate ratio was 0.64 (95% CI, 0.37–1.10), and for women aged ≥50 years it was 0.68 (95% CI, 0.30–1.52).

- **Outcomes in a single-screen study**

A trial conducted in India trial did not involve subsequent screening rounds but used passive follow-up through routine cancer registration after a once-in-a-lifetime screening. Reduction in the incidence of advanced cervical cancer (stage II+) and of mortality from cervical cancer was observed in women in the HC2-screening arm compared with the control arm in which no screening was offered: hazard ratios of 0.47 (95% CI, 0.32–0.69) and 0.52 (95% CI, 0.33–0.83), respectively. The reported results demonstrate protection from HPV primary screening against advanced invasive cancers and cervical cancer mortality compared with an unscreened population **(II)** (Sankaranarayanan et al. 2009). The study arms in which primary screening by cytology or VIA (visual inspection of the cervix after application of acetic acid) were employed showed no significant reductions compared to the control arm with an unscreened population.

Figure 1.3. Meta-analysis of the main outcomes from randomized trials comparing HPV and cytology primary cervical cancer screening. Relative detection rate of CIN3+ (left) and cervical cancer (right) observed in the second screening round among women who were HPV-negative versus cytology-negative at enrolment.



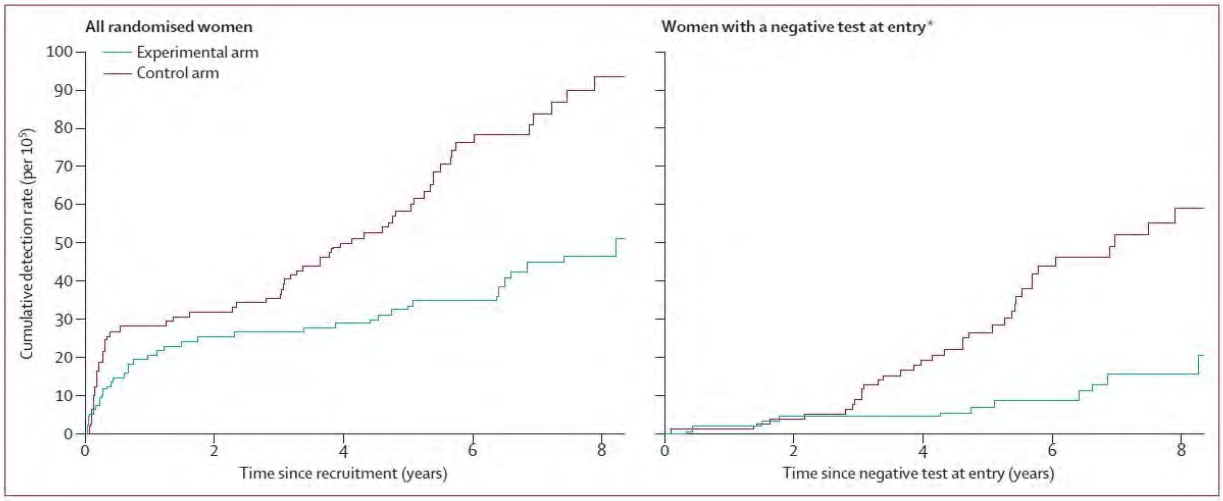
*Restricted to women older than 35 years. †continuity correction (+.5 in each cell because of zero cancer cases among HPV-negative women).

CIN, cervical intraepithelial neoplasia; CI, confidence interval; DRR, detection rate ratio;

I^2 = percentage of total variation across studies due to heterogeneity; p = test for inter-study heterogeneity

Source: (Arbyn et al. 2012)

Figure 1.4. Cumulative detection of invasive cervical carcinoma.



*Observations are censored 2.5 years after CIN2 or CIN3 detection, if any

Source: Figure 2 in: (Ronco et al. 2014)

1.2.2.2 Positive test results, repeat tests, and colposcopy referrals

As Swedescreen and NTCC used HPV testing just at the first screening round, they did not provide data on referral to colposcopy with HPV primary screening at subsequent rounds. In POBASCAM (Bulkmans et al. 2007) the referral rate in the intervention arm at round two (1.0%) was much lower than that at round 1 in the intervention (2.3%) and also in the control arm (1.3% at round 1 and 1.5% at round 2). In ARTISTIC referral to colposcopy also strongly decreased in the HPV arm at round 2. This however happened also in the cytology arm, so that the ratio between arms was unchanged (Kitchener et al. 2009a). The pooled analysis of four European trials reported an increase in the rate ratio of women who had a biopsy (all studies, 1.35; 95% CI, 1.30–1.40). However there was significant heterogeneity between studies ($p < 0.0001$). When considering only studies which used triage[21] the biopsy rate was similar with HPV and cytology (ratio 1.02; 95%CI 0.97-1.07) with no heterogeneity between studies ($p=0.236$) (Ronco et al. 2014). Compared with cytology, the biopsy rate is increased with direct referral **(II)** (NTCC) but not with cytological triage **(I**) (Swedescreen, ARTISTIC, POBASCAM*). No other potentially harmful effects of screening were reported in the joint analysis.

1.2.2.3 Overdiagnosis of precancerous lesions

The only randomized trial that employed HPV testing for all women at the second screening round, POBASCAM, did not observe any significant difference between the study arms in the overall detection of CIN2+ and CIN3+ over the first two rounds combined (Bulkmans et al. 2007; Rijkaart et al. 2012).

[21] In the pooled analysis, cytological triage of HPV-positive women was defined as immediate referral to colposcopy if cytology was positive, and invitation to follow-up HPV testing if cytology was negative, followed by referral to colposcopy if infection persisted

The remaining RCTs used cytology primary testing in the second round. The Swedescreen study found no difference concerning the overall detection of CIN3+ (the ratio of the HPV group vs the cytology group was 1.04; p = 0.20) but found some excess of CIN2 in the HPV arm (ratio, 1.56; p = 0.04) (Naucler et al. 2007). In the ARTISTIC study, the ratio was 1.18 (95% CI, 0.90–1.55) for CIN2 and 0.85 (95% CI, 0.67–1.08) for CIN3+ (Kitchener et al. 2009a). The NTCC study found larger excesses than the ARTISTIC study in the HPV group. Among women aged 35–60 years at recruitment, the HPV versus cytology ratio was 1.65 (95% CI, 1.21–2.26) for CIN3 and 1.68 (95% CI, 1.25–2.26) for CIN2. The increase was larger among younger women (age 25–34 years at recruitment). The HPV versus cytology ratio was 2.14 (95% CI, 1.28–3.59) for CIN3 in phase 2, but 0.99 (95% CI, 0.61–1.65) in phase 1 which did not show earlier detection of CIN3. For CIN2, the ratio was 3.11 (95% CI, 2.20–4.39) for both phases pooled, with no significant differences between phase 1 (with cytology triage) and phase 2 (with direct referral). The Finnish trial, which has a 5-year screening interval, has not yet reported results of the second round. In the first round, the cumulative DR ratios for CIN2 by HPV versus cytology were 1.6 and 1.5 among women aged 25–34 and ≥35 years at randomization, respectively (Leinonen et al. 2012), and the DR ratio for CIN3 was 1.5 (Malila et al. 2013).

All these excesses could, in principle, be explained either by overdiagnosis or by large gains in lead time (earlier diagnosis) with HPV versus cytology. Therefore, the difference between the Swedescreen and NTCC results could be explained either by greater overdiagnosis with direct referral (used in NTCC) than with triage based on repeat cytology and type-specific persistence (used in Swedescreen) or by larger lead-time gain with direct referral than with cytological triage or, plausibly, by both. The same can be said for the age effect observed in NTCC. However, it appears very implausible that the extremely large ratio (>3) observed for CIN2 incidence among women aged <35 years in NTCC can be entirely explained by gains in lead time. It strongly suggests that HPV primary screening in younger women leads to substantial overdiagnosis of regressive CIN2.

The above evidence suggests overdiagnosis of non-progressive CIN2+ **(II)** and, to a lesser extent, CIN3+ **(II)** lesions, although the evidence is not consistent (Naucler et al. 2007; Rijkaart et al. 2012; Ronco et al. 2010). Among women aged ≥35 years, HPV primary screening entails only a limited increase in overdiagnosis of non-progressive lesions compared with cytology primary screening, but it may lead to considerable overdiagnosis of regressive CIN2 in younger women.

1.2.3 Conclusions

Achievable benefits of HPV primary screening compared to cytology primary screening include: higher sensitivity in detecting precancerous cervical lesions; increased protection against cervical cancer and reduced burden of CIN2 and CIN3, reflecting earlier detection of persistent pre-cancerous lesions. Protection against advanced invasive cancers and cervical cancer mortality is also improved compared with an unscreened population.

Potential harms of HPV primary screening include: significantly increased positive test rates, colposcopy referrals and biopsies, and overdiagnosis of non-progressive CIN2+ lesions. These risks are particularly pronounced among women in the younger age groups commonly targeted by screening programmes (25-29 and 30-34 years, see also Sect. 1.3.2.1). These potential harms can be greatly reduced or avoided if appropriate screening policies are applied. For example, with cytological triage the PPV of colposcopy referral is similar to that of cytology primary screening (see section 1.4.1), referral to colposcopy decreases after the first HPV screening round and the biopsy rate is similar to that with cytology primary screening**.**

The above evidence demonstrates that HPV primary screening can achieve greater benefit than cytology screening provided effective protocols and procedures are adopted to maximize the impact and minimize the potential harm of HPV primary screening (see rec. 1.2 - 1.36). Appropriate screening organization and policy are crucial to ensuring that any cervical screening programme successfully implements the requisite protocols and procedures, irrespective of the type of screening method applied (Anttila et al. 2008; see also Suppl. 2). HPV screening programmes should therefore also follow the guidance in the European Guidelines that is relevant to any cervical screening programme **(VI-A).**[Rec 1.34] Hence, primary testing for oncogenic HPV can be used in an organized, population-based cervical cancer screening programme **(I-A)**, provided the other recommendations in this supplement are followed **(VI-A).**[Rec 1.1]

1.3 Screening policies with HPV primary screening

1.3.1 HPV primary testing alone or in combination with cytology primary testing

In primary screening, no RCTs have compared co-testing all women for HPV and cytology with testing for HPV alone. In the RCTs that published the results of the first two screening rounds (Swedescreen, POBASCAM, ARTISTIC, and NTCC) HPV was used as the sole primary screening test only in phase 2 of NTCC. In the other studies, HPV testing was used in combination with cytology, i.e. all women in the experimental group were also tested for cytology and referred to colposcopy if cytology was abnormal, even in the presence of a negative HPV test. In ARTISTIC and phase 1 of NTCC, HPV testing was used in combination with LBC in the experimental arms, whereas in Swedescreen and POBASCAM HPV testing was used in combination with conventional cytology. HPV testing was also used as the only primary screening test in the Finnish trial, which has not yet published results from the second screening round.

In the NTCC study, among women 35-60 years at recruitment, the ratios for detection of CIN2 or CIN3 between the experimental and the control (cytology) arms at screening round 1 were similar and significantly increased in phase 1 that used co-testing (1.94; 95% CI, 1.40–2.68) and phase 2, using HPV testing only (2.13; 95% CI, 1.50–3.03) (p for heterogeneity = 0.70). At screening round 2, the DRR (experimental vs control) was similarly reduced in phase 1 (0.74; 95% CI, 0.34–1.62) and phase 2 (0.30; 95% CI, 0.11–0.81), without evidence of heterogeneity between phases (p = 0.15), but the reduction in phase 1 was not significant (Ronco et al. 2010).

The lack of trial evidence of greater protection against chronic HPV infection, by co-testing (HPV and cytology) versus HPV primary testing alone is in agreement with the high sensitivity of HPV testing for CIN (96%) observed in co-testing studies conducted in Europe and North America: HPV testing in combination with cytology is minimally more sensitive but less specific for CIN2+/CIN3+ **(III)** (Arbyn et al. 2012); see Sect. 1.2.1). The very high sensitivity is reflected in the only limited increase in detection of CIN2+ that can be achieved by co-testing for HPV, and cytology (ratio, 1.05; 95% CI, 1.04–1.07) (Table 1.3). In addition, within the experimental arms of RCTs that used co-testing, the relative sensitivity of combined HPV and cytology versus HPV alone was close to 1.0 (Figure 1.3).

Finally, a very similar long-term low-risk period was observed after being negative for HPV only versus being negative for both HPV and cytology (Arbyn et al. 2012; Dillner et al. 2008).

Systematic co-testing results in higher costs than HPV testing alone, and it also results in higher referral rates to colposcopy and in lower PPVs. In NTCC, baseline referral rates in phase 1 were 737/22466 = 3.2% in the control (cytology) group versus 2500/22708 = 11% in the group where co-testing with HPV was applied, i.e. a 3.4-fold increase (Ronco et al. 2006b; Ronco et al. 2010). The relative PPV of colposcopy referral for CIN2+ in the co-testing versus the cytology arm among women older than 35 years was only 0.34 (95% CI, 0.21–0.54) (phase 1) (Ronco et al. 2006b) while it was 0.80 (95% CI, 0.55–1.18) for HPV testing alone (phase 2) (Ronco et al. 2008) (p for heterogeneity = 0.0074).

In the RCTs that employed cytological triage (see Table 1.1), the PPV for CIN2+ among referred women was similar to that of HPV primary screening alone (47%; 95% CI, 40–54%) and cytology primary screening alone (49%; 95% CI, 40–58%) in POBASCAM (Bulkmans et al. 2007), a study that used co-testing. However, in the Finnish trial, a study that used only HPV primary testing with cytology triage, the PPV for CIN2+ among referred women was even better with HPV primary screening than with cytology primary screening (the relative PPV for CIN2+ in the intervention vs control arm was 1.34; 95% CI, 1.04–1.72) (Leinonen et al. 2009).

In conclusion, among women ≥35 years, the available evidence from RCTs does not indicate that co-testing all women (cytology and HPV) is more protective than HPV primary testing alone. Systematic co-testing entails higher costs, higher referral rates to colposcopy, and a lower PPV for CIN2+ detection among referred women **(II)**, particularly if triage is not used for HPV-positive women. Hence, to avoid unnecessary harm, only one primary test (cytology or testing for oncogenic HPV) should be used at any given age in cervical cancer screening (see also Rec. 1.3 - 1.7) **(II-A)**.[Rec 1.2]

1.3.2 Age range

Overall, the available trial data did not allow establishment of the most appropriate age range for HPV primary screening. This resulted in part from the variability in the age ranges of studies showing earlier detection of persistent CIN2+ and CIN3+ in HPV primary screening than in cytology primary screening: 25-34 years (Ronco et al. 2010), 32-38 years (Naucler et al. 2007) and 29-56 years (Bulkmans et al. 2007). This limited the possibility of comparing data at younger age. The following recommendations should be reviewed when more age-specific data become available.

1.3.2.1 Age to start HPV primary screening

In European countries, the prevalence of HPV infection is higher at younger ages and decreases with increasing age (De Vuyst et al. 2009). Both the gain in sensitivity and the loss in specificity of HPV versus cytology primary testing are greater in younger women and decrease with increasing age. In a pooled analysis of studies conducted in Europe and North America, (Cuzick et al. 2006a) the sensitivities for CIN2+ of HPV and cytology primary testing were 97% and 49%, respectively, for women younger than 35 years; and 98% and 79%, respectively, for women older than 50 years. The specificities for <CIN2 of HPV and cytology were 86% and 95%, respectively, for women younger than 35; and 94% and 98%, respectively, for women older than 50. Loss of specificity with HPV versus cytology primary testing is very large at young ages.

Lower effectiveness of cytology primary screening at younger ages than at older ages was observed in a case–control study in England (Sasieni, Castanon & Cuzick 2009) but not in Sweden (Andrae et al. 2008).

Among RCTs, Swedescreen and POBASCAM included only women aged at least 30 years; the latter trial was conducted in the setting of a population-based screening programme that starts at age 30. The Finnish trial also recruited women mainly from age 30, although women from age 25 were included in some municipalities. No significant overall interaction by age of the relative cross-sectional sensitivity (HPV with cytological triage vs cytology) or of PPV for CIN of any grade was observed. However, the relative sensitivity and PPV for CIN3+ in women aged 25–34 years were 0.88 (95% CI, 0.38–2.02) and 0.70 (95% CI, 0.30–1.64), respectively, versus 1.22 (95% CI, 0.78–1.92) and 1.22 (95% CI, 0.78–1.92), respectively, for the entire population aged 25–60 years (Leinonen et al. 2009).

The ARTISTIC study recruited women from age 20 years. A subgroup analysis of women older than 30 years did not result in any additional significant findings compared to those found for the entire population (Kitchener et al. 2009b).

In NTCC, greater sensitivity and greater protection from HPV compared with cytology primary screening was observed in the age range 25–34 years, only with direct referral to colposcopy of all HPV-positive women. More remarkably, the cumulative detection of CIN2 over the first two screening rounds was 3.11 times higher (95% CI, 2.20–4.39 in the HPV arm compared with the cytology arm. Although part of this excess could be due to a lead-time gain of more than 3 years over cytology, the excess is very large; it suggests clinically significant overdiagnosis of regressive or non-progressive lesions by HPV testing at this age. There was no evidence of heterogeneity (p = 0.60) between phase 1 (HPV and cytology co-testing with 'cytological triage') and phase 2 (HPV alone with direct referral). By comparison, the CIN2 detection ratio was only 1.68 (95% CI, 1.25–2.26) in women aged 35–60 years (Ronco et al. 2010).

The pooled data analysis of four European randomized HPV screening trials reported a significant reduction in cervical cancers (including microinvasive and fully invasive cases) in the HPV screening group already in the age range 30–34 years at enrolment (Ronco et al. 2014).

The potential harm reflected in elevated referral rates after HPV primary testing can be expected to decrease with decreasing prevalence of HPV infection in women above age 35 years, but is not negligible. Therefore, it is important to consider age-specific HPV prevalence in deciding the screening policy of HPV primary screening **(VI-B).**[Rec 1.36]

In conclusion, HPV primary screening has been shown to be more effective than cytology primary screening in reducing cervical cancer incidence from the age of 30 years **(I)** (Ronco et al. 2014)**.** For women younger than 35 years, however, there is evidence from RCTs of increased referral to colposcopy or repeat testing at the first round of HPV primary screening **(I)** (Rijkaart et al. 2012; Ronco et al. 2006a; Ronco et al. 2008). Overdiagnosis due to HPV primary screening in young women may be considerable. One RCT found a large excess of CIN2 in the experimental arm with direct referral to colposcopy of all HPV-positive women younger than 35 and especially at age 25–29 years (Ronco et al. 2010) **(II)**. Unnecessary treatment of regressive lesions is of particular concern because excisional treatment of cervical lesions is associated with increased risk of pregnancy-related morbidity (Arbyn et al. 2008b; Kyrgiou et al. 2006) and mortality (Arbyn et al. 2008b). This problem is particularly relevant at younger ages as the probability of a subsequent pregnancy is high.

A pooled analysis of individual data from RCTs will be useful for better defining the starting age for HPV primary screening. Based on the above evidence, beginning HPV primary testing for cervical cancer screening at age 35 years or above can be recommended (see also Rec. 1.4 and 1.5) **(I-A).**[Rec 1.3] HPV primary screening should not begin under age 30 years **(I-E)**.[Rec 1.4] Evidence is insufficient to recommend for or against HPV primary testing in the age range 30–34 years **(VI)**.[Rec 1.5] Research on markers of progression is needed to develop HPV primary screening strategies at this age.

Any decision on when to start screening women will have to weigh up benefits and harms and should take local conditions into account (see also Suppl. 2 and Annex 1 and 2). The second edition of the European Guidelines recommends beginning cytology-based screening before the peak of incidence in cervical cancer in the female population and not before age 20 or later than age 30 years. It should also be considered that the incidence of cervical cancer in women under age 25 years is very low, posing a significant challenge to achieving a favourable balance between harm and benefit below age 25 years. In a setting where cytology primary screening is currently offered to women from age 20, 25 or 30, policy makers might decide to introduce HPV primary screening beginning at age 35 or possibly 30 years (see Rec. 1.3 - 1.5) and continue previously established cytology-based screening programmes starting in the age range 20-30 years until evidence shows that the harms of screening in the younger age ranges outweigh the benefits. By contrast, where cytology primary screening is not already offered to women under age 30 or 35, priority could be given initially to implementing HPV primary screening starting at age 35, provided the recommendations in the European Guidelines (second edition and present supplements) are followed.

Cervical screening based on cytology primary testing conducted outside the age range covered by HPV primary testing should follow the guidance provided for cytology-based screening in the European Guidelines (second edition and Suppl. 2) (see also Rec 1.9, 1.10, 1.22 and 1.34) **(VI-A).**[Rec 1.7]

1.3.2.2 Age to stop HPV primary screening

HPV primary screening provides longer protection than cytology primary screening. The interval between a negative HPV test and a new CIN2+ lesion is the result of the time needed (a) to acquire a new infection and (b) to progress from infection to CIN2+. Theoretically, screening could be stopped in an HPV-negative woman when the risk of acquiring a new infection ceases. Prevalence of infection by oncogenic HPV types strongly decreases with age up to about age 45 but remains constant after that (De Vuyst et al. 2009). A recent analysis of two RCTs in the Netherlands and Italy showed that the incidence of HPV infections decreases with age but remains non negligible up to 60 years (Veldhujizen et al. 2015).

Little additional evidence is available on which a recommendation on the upper age limit for HPV primary screening could be based. Data from one RCT suggest a greater relative reduction of CIN2 and CIN3 incidence at the second screening round at age 50–60 than at age 35–49 (Ronco et al. 2010). Among women aged 50–60 years, no CIN3 was detected during round 2 in the HPV group among 12 572 women compared with 5 women in the cytology group (Ronco 2010) **(II),** suggesting that there is a potential for longer screening intervals with HPV at older ages, but this is not sufficient to support an earlier age of stopping screening with HPV primary screening than with cytology primary screening. No publications of HPV screening trials were retrieved that have reported cervical cancer incidence or mortality in women over age 64 years. Such studies are needed to improve screening policies.

In conclusion, in the absence of sufficient evidence on the optimal age at which to stop HPV primary testing in cervical cancer screening, HPV primary testing could stop at the upper age limit recommended for cytology screening (60 or 65 years), provided a woman has had a recent negative test **(II-A).**[Rec 1.6]

1.3.3 Screening interval for HPV primary screening

A number of studies have shown that the period of low risk after a negative HPV test is longer than after a negative cytology result (Table 1.4). The first study was based on the Portland cohort (Sherman et al. 2003), in which no action was taken on the result of the HPV test. After 10 years of follow-up of cytologically negative women, those who were also HPV-negative had a much lower rate of CIN3 than those who were HPV-positive. A follow-up paper (Khan et al. 2005) demonstrated further that the risk for CIN3 was particularly high for HPV 16 and to some extent HPV 18 (but only after 2–3 years of follow-up). The incidence for other hrHPV types was lower, but still higher than in HPV-negative women. The Hammersmith study was the first to demonstrate that this was true even after HPV-positive women were referred to colposcopy (Cuzick et al. 2008a). In that study, the risk of developing CIN2+ at 1, 5, and 9 years after a normal cytology result was 0.33%, 0.83%, and 2.20%, respectively, whereas it was 0.19%, 0.42%, and 1.88%, respectively, after a negative HPV test. This was further substantiated in a joint analysis of several European cohorts (Dillner et al. 2008) where the cumulative incidence rate of CIN3+ after 6 years was considerably lower among women negative for HPV at baseline (0.27%; 95% CI, 0.12–0.45%) than among women with negative cytology results (0.97%; 95% CI, 0.53–1.34%). By comparison, the cumulative incidence rate for women with negative cytology results at the most commonly recommended screening interval in Europe (3 years) was 0.51% (95% CI, 0.23–0.77%). In a subsequent study in a two-sample cohort (HART), the cumulative incidence of CIN2+ at 3, 5, and 8 years after a negative HPV test was 0.12%, 0.25%, and 0.61%, respectively; and 0.28%, 0.48%, and 1.04%, respectively, after a normal cytology result (Mesher et al. 2010). Therefore, there is evidence suggesting that the cumulative incidence of CIN2+ 5 years after a negative HPV test is lower than the cumulative incidence 3 years after a normal cytology result **(III)**. In a German co-testing cohort of 4236 women who were HPV-negative and had normal cytology at baseline, no case of CIN2+ was detected during the 5-year follow-up (Petry et al. 2013).

In all four RCTs that published data on the second screening round, detection of CIN3 in round 2 after HPV primary screening in round 1 was approximately half that after cytology primary screening in round 1 (see Section 1.3.1 and Figure 1.3). In the Swedescreen and NTCC trials, which both employed 3-year intervals, and cytology primary testing for all women at round 2, the cumulative detection of CIN3 was higher in HPV-screened women than in cytology-screened women. This suggests that the lead-time gain with HPV testing over cytology could be greater than 3 years for some cases; however, overdiagnosis of regressive lesions is another possible explanation. Therefore, further follow-up is needed to clarify the extent of lead-time gain with HPV over cytology primary testing. The 13-year follow-up results of the Swedescreen study showed that during the first six years of follow-up, the cumulative incidence of CIN3+ was greater in the intervention arm, reflecting that women persistently positive for HPV and with negative cytology had been referred to colposcopy, resulting in additional cases of CIN3+ detected. After six years of follow-up, however, the CIN3+ rates did not differ, suggesting that the additional CIN3+ cases detected were more likely reflecting early diagnosis rather than overdiagnosis. The 5-year cumulative incidence of CIN3+ among women who were HPV-negative at baseline was similar to the 3-year cumulative incidence of women who were cytology negative at baseline (Elfström et al. 2014). In POBASCAM, which used 5-year intervals, the detection rate ratio of CIN2+ at round 2 was also approximately 0.5 after HPV, versus cytology primary screening; these findings also indicate that the interval can be safely extended beyond 5 years. Data from this study do not permit investigation of longer lead times, however, due to HPV primary testing of all women at round 2. After the baseline screen but before the second HPV testing at 5 years, there were 11 CIN3+ cases among the 18 942 HPV-negative women in the intervention group (risk, 0.06%) and 12 CIN3+ cases among the 19 373 women with normal cytology at baseline in the control group (risk, 0.06%) (Rijkaart et al. 2012). A model based on POBASCAM results predicted a lower number of invasive cancers with HPV primary screening at 6-year and at 7.5-year intervals than with cytology at 5-year intervals (Berkhof et al. 2010; Rijkaart et al. 2012). The Finnish study, which has a 5-year screening interval, reported results after a maximum follow-up time of 5 years. Among the 18 095 women with a

negative HPV test at baseline, the cumulative incidence of CIN3+ was 2 (0.01%), whereas among the 18 096 women with normal cytology at baseline it was 7 (0.04%) (Anttila et al. 2010).

In conclusion, prolonged intervals for HPV primary screening would reduce costs and, more importantly, would reduce the probability of unnecessary colposcopy and treatment with attendant side-effects. Randomized studies comparing women with a negative HPV primary screening test to women with normal cytology primary testing reported equal or decreased CIN3+ incidence in the HPV arms over a follow-up time of up to 5 years (Leinonen et al. 2012; Rijkaart et al. 2012). The screening interval for women with negative HPV primary screening results should therefore be at least 5 years **(I-A).**[Rec 1.8] This recommendation is consistent with the results of the pooled analysis of European randomised trials (Ronco et al. 2014); the cumulative incidence of invasive cancer within 5.5 years after a negative HPV primary test (8.7 per 10^5; 95% CI 3.3-18.6) was approximately half the cumulative incidence of invasive cancer within 3.5 years after a negative cytology (<ASC-US) primary test (15.4 per 10^5; 95% CI 7.9-27.0).

Additional evidence from non-randomized co-testing studies indicates that even 6–10 years after a negative HPV primary test, the cumulative CIN3+ incidence rate is lower than after a normal cytology screen with a 3-year or 5-year follow-up period (Dillner et al. 2008; Khan et al. 2005; Schiffman et al. 2011). However, some of these studies had exclusion criteria and additional management during follow-up that differed from usual European cytology primary screening programmes. This evidence suggests that the interval for HPV primary screening may be extended up to a maximum of 6 - 10 years provided age and screening history are taken into account **(III-C)**.[Rec 1.8] For example, women aged 40 years with a history of two consecutive negative HPV tests and no cervical disease could be re-invited at the age of 50 years. Further studies with long-term follow-up could provide additional statistical precision for refining the recommended screening interval for HPV primary screening.

Table 1.4. Longitudinal CIN2+ and CIN3+ risks after a negative HPV primary test compared with the risks after a negative cytology primary test.

Study (reference)	Design	Findings
Hammersmith (Cuzick et al. 2008b)	2-sample cohort (n=2516)	CIN2+ at 5 years 0.42% (HPV neg) vs 0.83% (cyt neg), p = 0.07
European overview (Dillner et al. 2008)	7 cohorts (n=24 295)	CIN3+ at 6 years 0.27% (HPV neg) vs 0.97% (cyt neg), p < 0.0001
HART (Mesher et al. 2010)	2-sample cohort (n=8868)	CIN2+ at 5 years 0.23% (HPV neg) vs 0.48% (cyt neg)
Portland Kaiser cohort study (Khan et al. 2005)	2-sample cohort (n=13 229); age at enrolment ≥30 years	CIN3+ at 10 years 0.5% (95% CI, 0.3–0.8) HPV neg vs 0.8% (95% CI, 0.5–1.0) cyt neg

1.3.4 Management of women without an adequate HPV primary test result

For a number of reasons, some women invited to attend HPV primary screening programmes will not have an adequate HPV test result within a reasonable period of time. Programmes should have policies in place to deal with these foreseeable situations. For example, some women attending cervical cancer screening may prefer not to be tested for HPV, but may accept cytology primary testing. If a woman declines HPV primary testing, cytology may be performed **(VI-C)**.[Rec 1.9] An adequate test

result may not be available because a women has not responded to an invitation within the time period specified in a programme's fail-safe policies, or because the result of an HPV test was technically inadequate. Non-attenders and screened women with a technically inadequate HPV primary test result should be invited to have a new sample taken or to have cytology testing without additional sample taking if technically feasible and preferred by the woman (see also Suppl. 2, Rec 2.9 - 2.11). **(VI-B).**[Rec 1.10]

1.3.5 Management of women with an adequate HPV primary test result

If an HPV primary test used in cervical cancer screening programmes conducted according to the recommendations in this supplement is negative, women will be invited to attend the next round of screening (see Rec. 1.8). If the HPV primary test is positive, programme policies for subsequent clinical management must take into account the potential significant harms mentioned in Sect. 1.2.1.3 and described in greater detail in Sect. 1.4, particularly the potential for markedly increased rates of positive test results and colposcopy referrals compared to cytology primary testing. The different strategies for managing women with positive HPV screening tests employed by the randomized trials are shown in Table 1.1. and explained in Sect. 1.4 (cytology triage) and Sect. 1.5 (repeat testing after baseline cytology triage). The experience in the trials demonstrates the importance of avoiding unnecessary interventions in cervical screening programmes using HPV primary testing. This can be achieved by adopting specific policies on triage, referral and repeat-testing of women with positive primary test results, taking into account the recommendations explained in sections 1.4 and 1.5 (see also Rec. 1.11 - 1.31). The policies must include guidance on when women with positive HPV test results should be invited to return to routine screening. (**VI-A**).[Rec 1.11] Furthermore, to ensure that the services provided achieve an appropriate balance between benefit and harm, screening programmes should carefully monitor management of HPV-positive women. Monitoring should include compliance of individual women with further follow-up of positive primary test results, as well as results of triage, referral, colposcopies, biopsies, and treatment of precancers **(VI-A).**[Rec 1.12]

Current management protocols for women with a positive HPV primary test result vary between countries, and there is insufficient evidence to recommend a single approach for all settings. The current diversity is reflected in the management options explained in greater detail in sections 1.4 and 1.5. The method of repeat testing and the management protocols for repeat testing and referral during the entire screening round should be selected by the programme when planning for HPV primary testing. The respective decisions and programme planning should take into account the prevalence of HPV in the target population and the quality and organization of cytology screening in the region served by the programme. An overriding aim is to avoid increasing the overall burden of testing, colposcopy referral, and CIN treatment in the screening programme as a result of repeat testing, and to maintain an appropriate balance in relation to the outcome (see also Sect. 1.8; and Suppl. 2).

More insight into quality criteria determining the balance between benefit and harm in the management of women with a positive HPV primary test may become available in the future as evidence accumulates on the various protocols currently in use. Clinical experience suggests that the interval between two primary screening tests, differences in local conditions under which relevant trials have been conducted, and numerous other factors such as the interval of HPV repeat testing, the criteria for referral to colposcopy (e.g. persistent HPV at initial or subsequent repeat testing), or the criteria used in cytological interpretation are likely to impact on the efficiency and effectiveness of the management of HPV-positive women in any screening programme. Such factors should therefore be taken into account in optimization studies and in planning the management protocols used in a screening programme. For the same reasons, programme policies on triage, referral and repeat testing (see Rec.

1.11) should be regularly reviewed and revised, if necessary, taking into account the results of monitoring (see Rec. 1.12) and the available evidence **(VI-A).**[Rec 1.13]

1.4 Triage of women with a positive HPV primary test

HPV testing is more sensitive but less specific than cytology for detecting CIN2+ (see Sect. 1.2). This is the rationale for triaging HPV-positive women before referring them to colposcopy. Different methods have been proposed and studied, providing different levels of evidence. The studies that can provide evidence on this subject include:

- RCTs that compare HPV primary testing in combination with triage by a given method, to cytology screening, or to other HPV primary screening strategies.
- Studies evaluating the accuracy for detecting histology-proven CIN2+ of potential triage tests in unselected HPV-positive women who undergo complete colposcopy verification. For comparison of two triage strategies, at least all women positive to either should have been referred to colposcopy. The relevant accuracy is:
    - Cross-sectional. This is relevant for the decision of referring women to colposcopy and the interval before test repeat.
    - Longitudinal, to assess the risk of CIN2, CIN3, and cancer over time. This is relevant to determine the long-term safety and the frequency of test repeats.

1.4.1 Cytological triage

Cytological triage is defined as testing HPV-positive women for cytology and referring directly to colposcopy those women who show relevant cytological abnormalities (ASC-US+ or LSIL+). In trials, HPV-positive but cytology-negative women have typically been re-tested for HPV after 6–12 months and referred to colposcopy if the HPV infection persisted. This approach was based on knowledge that only persistent infections are relevant for the development of CIN2+ and cancer. In the HART study (Cuzick et al. 2003), women aged 30–60 years who were positive for HPV and had normal cytology, as well as all women with borderline cytology, were randomly assigned to immediate colposcopy or to have cytology, HPV testing, and colposcopy after 1 year. No CIN2+ was detected in the 111 women who were cytology-negative and HPV-negative at repeat (at baseline 61 of these were HPV-positive cytology normal, 55 HPV-negative cytology borderline, and 7 HPV-positive cytology borderline), whereas 9 cases of CIN2+ were detected among the 142 women who were HPV-positive or had borderline or more severe cytology or both at repeat.

Various RCTs that compared HPV with cytology primary screening and generated longitudinal data also employed cytological triage for HPV-positive women, although using various protocols (see Table 1.1 and below in this section); one trial (NTCC) directly referred all HPV-positive women to colposcopy, except in phase 1 among women aged 25–34 years. Therefore, the effectiveness and

costs of cytological triage compared to direct referral of all HPV-positive women can be studied by comparing the results of the different RCTs.

Reduction in CIN3 in the intervention versus control arm at round 2 can be considered as an intermediate end-point for protection against cancer (Arbyn et al. 2009a). It should be noted that when the results in younger women (age 25–34) are excluded from the NTCC trial, the size of this relative reduction is very similar in NTCC and in the other trials, i.e. always approximately 0.5, with no evidence of heterogeneity between studies (p = 0.68; see Figure 1.3). This suggests that protection with direct referral is similar to that with cytological triage, at least from age 35 years onward. From the same age onward, the cross-sectional relative sensitivity of HPV primary screening versus screening by conventional cytology was similar in RCTs that used direct referral and those that applied cytological triage (see Figures 1.1 and 1.2). The Finnish trial that has published data only on the first screening round showed an increase in sensitivity similar to that of the other trials (Arbyn et al. 2012; Leinonen et al. 2009) see Figure 1.1), suggesting similar protection.

In the pooled analysis of four randomised HPV screening trials there was no evidence of heterogeneity of the relative cancer incidence in the HPV testing vs. the cytology arm between the three studies that used cytological triage (ARTISTIC, POBASCAM, and SWEDESCREEN) and the study that referred all HPV-positive women directly to colposcopy (NTCC) (Ronco et al. 2014). However, there were clear differences between the trials regarding rates and PPV of colposcopy referral, and the biopsy rate.

Considering the studies in which HPV was the only primary screening test, the relative PPV for CIN2+ compared to cytology was 0.80 (95% CI, 0.55–1.80) in NTCC phase 2 (age 35–60 years), which used direct referral (Ronco et al. 2008); compared with 1.34 (95% CI, 1.04–1.72) in the Finnish trial (age 25-65), which used cytological triage (Leinonen et al. 2009). Co-testing with cytology and HPV as primary screening tests yielded even larger differences. In NTCC phase 1, for women aged 35–60, the relative PPV for CIN2+ of HPV versus cytology was 0.34 (95% CI, 0.21–0.54). In Swedescreen, the PPV for CIN2+ computed within the intervention arm relative to cytology was 0.90 (95% CI, 0.70–1.16) for HPV alone as the primary test (with cytological triage and re-testing for type-specific HPV persistence)(Naucler et al. 2009). In POBASCAM, the PPV of colposcopy referral for CIN2+ was also similar in the intervention versus the control arms: 47% (95% CI, 40–54%) versus 49% (95% CI, 40–58%), respectively (Bulkmans et al. 2007). A POBASCAM trial sub-study compared different triage strategies in HPV-positive women. Baseline cytology triage, followed by repeat cytology screening at 6 months for women with negative baseline cytology had an estimated negative predictive value for CIN3+ of 98.5% and the highest estimated PPV (34.0%) plus the lowest referral rate (44.8%). Follow-up time was 48 months (Dijkstra et al. 2014). In the pooled analysis of four randomised trials there was a strong increase in the biopsy rate in the only study that used direct referral (ratio 2.29; 95% CI 2.09-2.39). Conversely, the referral rate was similar in the HPV and cytology arms of the three studies that used cytological triage (ratio 1.02; 95%CI 0.97-1.07) (Ronco et al. 2014).

1.4.1.1 Performance of cytological triage in primary HPV testing

The above evidence indicates that HPV primary testing with cytological triage provides greater protection against invasive cervical cancer than cytology primary testing alone (Ronco et al. 2014) **(I)**. HPV primary testing with cytological triage at the first screening round increases the referral rate to colposcopy compared with stand-alone cytology primary testing (Bulkmans et al. 2007; Kitchener et al. 2009b; Kitchener et al. 2011) **(I);** but the PPV is similar to or better than with cytology primary screening alone **(I)**. At age 35 or above, the present evidence does not show that direct referral of all HPV-positive women to colposcopy provides higher protection than cytological triage, while there is clear evidence that cytological triage entails a lower rate of referral to colposcopy and a higher PPV **(I)** (Bulkmans et al. 2007; Naucler et al. 2009; Rijkaart et al. 2012; Ronco et al. 2006b; Ronco et al. 2008), and a lower rate of biopsy (Ronco et al. 2014). Therefore, women testing positive for onco-

genic HPV at primary screening should be tested without delay for cervical cytology (cytology triage) **(I-A)**; to avoid recall, the cytology test should preferably use the specimen collected during the HPV screening visit **(VI-A).**[Rec 1.14] Direct referral to colposcopy of all HPV-positive women is not recommended **(I-D)**.[Rec 1.15] Instead, they should be referred to repeat testing or to colposcopy as indicated by the cytology result (see Rec. 1.18 – 1.21) **(I-A)**. [Rec 1.16] High quality laboratories and practices in the provision of cytology, histopathology and colposcopy services are required to achieve the potential benefit of cytology triage of women testing positive for oncogenic HPV at primary screening; hence the respective recommendations in Chap. 3-6 of the second edition of the European Guidelines should be followed (see also Rec. 1.35) **(VI-B)**.[Rec 1.17]

The evidence is less coherent at younger ages (see also Sect. 1.2.2.1 and Rec. 1.3 - 1.5). In women under 35 years, the NTCC study found a statistically significant heterogeneity between phase 1 (double testing with triage) and phase 2 (stand-alone HPV with direct referral) in the detection ratio of CIN3 in the experimental vs control arms at both rounds 1 and 2 (Ronco et al. 2010). Greater sensitivity for CIN3+ and greater reduction of CIN3+ at round 2 compared to cytology was observed only with direct referral. Irrespective of the observed variation in sensitivity of HPV testing in younger women, overdiagnosis of regressive lesions remains a common problem and suggests that better triage algorithms are needed for HPV primary screening in younger women.

Different protocols for managing HPV-positive women by cytological triage were used in the trials that demonstrated a protective effect of HPV primary screening. This suggests that the differences between the various management protocols used in the trials were not critical for protection against precancerous lesions. However, the potential impact of differences in management protocols on screening performance and outcome has not been investigated. In addition, differences in the local conditions under which the trials were conducted preclude firm conclusions about the implications of using different protocols based on the available results of the RCTs. As explained in Sect. 1.3.5, current management protocols for women with a positive HPV primary test result vary between countries, and there is insufficient evidence to recommend a single approach for all settings. However, the minimum guidelines provided in this Supplement should be followed (see Rec. 1.11 - 1.31).

1.4.1.2 Referral after cytological triage in primary HPV testing

Management was different in different RCTs (see Table 1.1). Concerning the three trials that showed increased protection, in Swedescreen, all hrHPV-positive women with abnormal cytology were directly referred to colposcopy while women with normal cytology were re-invited for further testing. In ARTISTIC, all women with abnormal cytology were managed according to the then-standard English protocols, which entail repeat cytology for borderline (equivalent to ASC-US) and mild (equivalent to LSIL) dyskaryosis. In POBASCAM, women with borderline and mild dyskaryosis were re-invited for repeat testing. In this group, 34% (95% CI, 29–39%) of women had CIN2+ detected during such follow-up (Berkhof et al. 2006). In the only trial on stand-alone HPV testing with cytology triage in the protocol, for which no data on the second round are available, HPV-positive women with low-grade squamous cell lesions or a more severe finding in the immediate cytology were referred to colposcopy while intensified screening (repeat testing) was recommended for HPV-positive women with borderline or normal cytology (Anttila et al. 2010).

In conclusion, all trials that used cytological triage did not refer HPV positive and cytology-negative women for colposcopy; instead these women were retested for oncogenic HPV at intervals shorter than the respective screening interval (Anttila et al. 2010; Ronco et al. 2014). As screening with cytological triage in these trials reduced the risk of subsequent high grade CIN and cervical cancer, there is also evidence that this practice of repeat testing was effective**.** Therefore women who have negative cytology (negative for epithelial abnormality) at triage after a positive initial HPV primary test in a screening episode should be followed up by re-testing after an interval shorter than the regular

screening interval **(I-A)**, but after at least 6 - 12 months (see also Sect. 1.4.1 and Rec. 1.23 and 1.24) **(VI-A).**[Rec 1.20] Direct referral to colposcopy of these women is not recommended **(I-D).** [Rec 1.21]

Whereas women with HSIL/ASC-H cytology were referred to colposcopy by all trials, there were differences between trials regarding HPV positive women with ASC-US, and LSIL cytology. A reasonable criterion for choosing which groups to refer to immediate colposcopy is the probability that referred women carry a high-grade lesion, i.e. the PPV. The PPV of women with LSIL/ASCUS cytology was high in POBASCAM (Berkhof et al. 2006); but the PPV of ASC-US cytology is known to vary markedly between and within European countries. There is a high probability that an HPV-positive woman with high grade cytology harbours a high grade CIN **(III)** (Katki et al. 2013)**.** Given the elevated risk of invasive cervical cancer from ASC-H, HSIL or AIS,, women with these results or a more severe finding at cytology triage should be referred to colposcopy without further observation or testing **(III-A).**[Rec 1.18] Given the expected lower probability that women with minor cytological abnormalities will harbour high grade CIN, women with ASC-US, AGC or LSIL at triage after an initial HPV primary test in a screening episode may be either followed up by retesting, preferably after 6 - 12 months, or by direct referral to colposcopy (see Rec 1.22 - 1.31) **(VI-C)**.[Rec 1.19] Currently available evidence is insufficient to recommend one alternative over the other for women with minor cytological abnormalities.

1.4.1.3 Other triaging options for HPV positive women

Several additional methods have been described that have potential for use in triaging HPV positive women to increase the specificity for detection of cervical (pre)cancerous lesions. These include DNA genotyping for HPV 16 or HPV 16/18, HPV mRNA testing, and/or detection of other non-HPV biomarkers.

There are consistent findings that women infected with HPV 16 have much higher risks for high-grade CIN and cancer than those infected with other so-called high-risk types. One suggestion is that women with infection by the most high-risk types (such as HPV 16 or 18) could be referred immediately to colposcopy, and others recalled at regular screening intervals (Castle et al. 2011b; Wright, Jr. et al. 2011). In the Finnish population-based trial, genotyping for HPV 16 more successfully identified women with CIN3+ than cytology triage at the threshold of LSIL+ (Leinonen et al. 2013).

Higher viral load for HPV 16 has been shown to be associated with CIN2+ risk. In the NTCC randomized trial, higher HC2 cut-off for detection of HPV DNA (a proxy of high viral load) had little effect on sensitivity for CIN2+, but PPV relative to cytology increased (Ronco et al. 2006b).

Whereas HPV DNA tests detect the presence or absence of HPV virus genomes, HPV RNA tests are designed to detect the expression (mRNA) of genes that are related to cancer development. Overexpression of HPV E6 and E7 viral genes is required for malignant transformation. Detection of mRNA of E6 and E7 genes may allow a distinction between transient infections and those that will progress to cancer (Cuzick et al. 2012).

Immunostaining for molecular markers of proliferation or regulation of the cell cycle, such as standardized detection of p16-INK4A overexpression with or without other markers (such as Ki-67), has been shown to be very sensitive for determining the severity of dysplasia (Carozzi et al. 2008; Petry et al. 2011).

Evaluation of longitudinal performance of these and other triaging markers is clearly a necessity. Since PPV is a prevalence-dependent measure, comparative evaluation of PPV for the most promising markers should be performed using the same samples. Initial findings are available for p16 (Carozzi et al. Lancet Oncology 2013). Although currently available data are not yet sufficient to recommend meth-

ods other than cytology for triaging HPV positive women (see also Rec. 1.13), a review of the emerging evidence and an update of the current recommendations is likely to be required in the near future.

1.5 Repeat testing

As discussed in Sect. 1.4, cytology triage should be performed without delay for all women testing positive for oncogenic HPV at primary screening (see Rec. 1.14). To reduce the risk of undetected, persistent HPV infection, women who test negative at cytology triage should be followed up by re-testing (see Sect. 1.4.1.2 and Rec. 1.20).

1.5.1 Interval for repeat testing

The interval for repeat testing after a negative triage test must be long enough to allow regression of a sufficient proportion of infections. After 12 months, 70% of a group of young women with an incident HPV infection were no longer infected, and by 24 months only 9% were HPV-positive (Ho et al. 1998). In another study about 60% of LSILs in young women regressed within 1 year and about 90% within 3 years (Moscicki et al. 2004). However, the longer the interval, the smaller the lead-time gain compared with cytology. On the other hand, prolonged intervals increase the probability that lesions prevalent at baseline or occurring during the interval will progress to cancer. Hence the optimal interval also depends on the cross-sectional and longitudinal sensitivity of the triage test. In all RCTs that provided results of 2 rounds, the interval was typically 12 months (6 months in POBASCAM). In all of the trials, cytology interpretation was blind to HPV status. In the only trial that used stand-alone HPV testing with cytological triage, sensitivity was higher in the HPV arm even considering only immediate referral (Kotaniemi-Talonen 2005) showing that cytology 'informed of HPV positivity' is more sensitive than 'HPV-blind' cytology. Hence there is evidence that a longer interval (at least 12 months) for repeat testing than that used in some of the trials is appropriate with stand-alone HPV primary testing. Women who are HPV-positive and cytology normal (negative for epithelial abnormality) in primary screening may therefore be followed up by HPV retesting, with or without cytological triage, and after an interval of preferably at least 12 months **(III-B).** [Rec 1.24] For these women, cytology repeat testing after at least 6 - 12 months is an acceptable alternative to HPV repeat testing (see also Sect. 6.3.1 in Chap. 6 of the second edition of the European Guidelines) (**III-B**).[Rec 1.23] It should be kept in mind that referral of women with persistent HPV infection irrespective of the result of cytology triage yields higher sensitivity of cervical precancerous lesions than referral based on repeat cytology only, but also entails higher referral to colposcopy and lower PPV (Dijkstra et al. 2014).

1.5.2 Type and mode of repeat test

Protocols for repeat testing after baseline triage can be distinguished according to the type of HPV test used, eg, type-specific or general hrHPV assay, and whether cytology co-testing is performed.

- **Type-specific versus hrHPV repeat testing**

Swedescreen used type-specific repeat testing, whereas POBASCAM and phase 1 of NTCC (women aged 25–34 years) used a general hrHPV assay. An analysis of the Guanacaste (Costa Rica) cohort showed that the subsequent risk of CIN2+ is similar with either approach, with the exception of HPV 16 and possibly HPV 18 (Castle et al. 2009).

- **HPV repeat testing alone or co-testing with cytology**

Repeat testing for HPV alone was used in Swedescreen (type-specific persistence), whereas NTCC (phase 1, women aged 25–34 years) and POBASCAM employed cytology co-testing. In NTCC, no CIN2+ was detected by cytology alone at repeat examination, but referral to colposcopy was increased (Ronco et al. 2006a).

Although the RCTs were not designed to assess which of these options is preferable, the overall results with respect to reduced incidence of CIN3+ in the second round of these RCTs are similar and suggest that the impact of HPV primary screening was not critically dependent on the option used.

If an HPV-positive woman tests HPV-negative in the repeat test, the risk of CIN2+ and CIN3+ is greatly reduced; hence further follow-up is unnecessary. In an analysis of the Guanacaste cohort, the subsequent cumulative risk of CIN2+ at 3 years was 1.17% (95% CI, –0.15% to 2.50%) among women who tested HPV-positive at baseline and negative after 1 year. In contrast, the risk was 17.0% (95% CI, 12.05–22.03%) and the cumulative incidence of CIN3+ at 3 years was above 10% among those who tested positive on both occasions (Castle et al. 2009). The 4-year cumulative incidence rate of CIN3+ for women who had a past HPV positive and Pap-negative result was 5.08% (95% CI, 4.01–6.15), compared with 1.12% (95% CI, 0.63–1.60) among women who were HPV-negative at the 1-year repeat testing (Castle et al. 2011a).

In the HPV screening trials, non-negligible loss to follow-up, varying from 20% to 40%, was observed (Bulkmans et al. 2007; Kitchener et al. 2009b; Naucler et al. 2007; Ronco et al. 2006a). Therefore, the number of repeat testing visits after HPV testing should be limited.

1.5.3 Management protocols for repeat testing

As explained in Sect. 1.3.5, current management protocols for women with a positive HPV primary test vary between countries, and there is insufficient evidence to recommend a single approach for all settings. Various approaches to repeat testing can be adopted, however, based on the previous experience in the randomized screening trials. They can be broken down into protocols that use:

- HPV testing alone
- HPV and cytology co-testing
- Cytology testing alone

Since the prevalence of HPV and the quality and organization of cytology screening affect the efficiency and effectiveness of management of women at repeat testing, these factors should be taken into account in the regular review and revision, if necessary, of repeat testing protocols (see also Rec. 1.11, 1.12 and 1.22 - 1.30) **(VI-A).** [Rec 1.22]

Based on the available evidence, the following algorithms can be recommended:

- **Women with a negative HPV repeat test**

The low risk of invasive cancer and pre-invasive lesions persists longer in women who have had a negative HPV test than in those with negative cytology (see Sect. 1.3.4). Furthermore, the risk of CIN2+ is very low in those women for whom the HPV test result is negative in the repeat test, i.e. HPV has not persisted (see Sect. 1.5.2). Therefore, in screening programmes that use HPV testing alone in repeat testing after baseline triage, women who have a negative repeat HPV test at follow-up should return to routine screening **(II-A).**[Rec 1.30] The same holds in programmes using HPV re-testing with cytology triage **(III-A)**; triage is not needed when the HPV repeat test is negative **(III-E).** [Rec 1.27]

- **Women with a positive HPV repeat test**

Conversely, given the elevated risk of invasive cervical cancer in women with a positive HPV test (Sect. 1.2.1), women who have a positive HPV repeat test in programmes that use only HPV repeat testing after baseline triage should be referred to colposcopy **(II-C).**[Rec 1.31] For the same reason, women should be referred to colposcopy if cytology triage of a positive repeat HPV test yields ASC-US **(VI-B)** or more severe cytology **(VI-A).**[Rec 1.25]

In the absence of evidence on the best option for management of women with negative cytology triage (negative for epithelial abnormality) of a positive repeat HPV test, programmes may adopt one of the following algorithms **(VI-B).**[Rec 1.26]

- Referral to second repeat testing after at least 12 months
- Referral to colposcopy. This may be the best option when HPV prevalence is moderate or low and when the PPV of referral to colposcopy of HPV-positive/cytology-negative women is reasonable, such as in women near the upper end of the eligible age range or women who have only attended screening irregularly.
- Return to routine screening. This may be an option in well-established programmes with highly accurate and reliable cytology services 'informed of HPV positivity' (see also Sect. 1.5.1).

- **Women in programmes using only cytology in repeat testing**

Given the relatively low risk of women for cervical cancer precursor lesions 3 or 5 years after a previous negative cytology test (Cuzick et al. 2008a; Mesher et al. 2010) (see Sect. 1.2.3) women with normal cytology at repeat testing using stand-alone cytology should return to routine screening (see also Sect. 6.5 in Chap. 6 in the second edition of the European Guidelines) **(III-A).**[Rec 1.29] Women with ASC-US or more severe cytology at repeat testing should be referred to colposcopy (see Chap. 6 in the second edition) **(VI-B).**[Rec 1.28]

1.6 Minimum requirements for HPV test systems in primary cervical cancer screening

Given the probability that many women targeted for cervical screening will develop and clear transient HPV infections, HPV primary screening test systems must yield results that are informative about the risk of having or developing cervical neoplastic lesions. Two different HPV tests, the HC2 and

GP5+/6+ PCR assays, have been studied thus far in a number of large longitudinal randomized clinical trials for detecting CIN2+/CIN3+ in comparison with cytology. Primary screening with these tests has resulted in reduced incidence of CIN3+ (see Figures 1.1 and 1.3) (Bulkmans et al. 2007; Leinonen et al. 2009; Mayrand et al. 2007; Naucler et al. 2007; Ronco et al. 2010) and cervical cancer (see Figure 1.4) (Ronco et al. 2014) in the subsequent round. In addition, sufficient evidence is available from the trials and other studies for programmes to achieve an appropriate balance between benefit and harm by adhering to minimum standards in the management of women with positive HPV primary tests (Sect. 1.4 and 1.5). Both of the above assays detect DNA of the hrHPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. In addition, the type HPV 66 is targeted by GP5+/6+ PCR-enzyme immunoassay (PCR-EIA) and detected by HC2 through cross-hybridization.

Various available HPV detection methods differ in their clinical performance for the detection of HPV-related premalignant disease (Snijders, van den Brule & Meijer 2003). Due to the time and other resources required for the previously conducted, large prospective trials, studies on a similar scale are unlikely to be feasible or desirable to verify the suitability of other HPV tests for primary cervical cancer screening. Moreover, the longitudinal results of HPV DNA tests depend on the natural history of HPV infection and related CIN, and because these parameters do not depend on the type of HPV test, assessment of the cross-sectional clinical accuracy can be used to evaluate and compare the performance of various HPV DNA tests. Hence, relevant criteria for HPV test performance have been formulated and translated into a validation procedure by an international consortium (Meijer et al. 2009).

The reported validation criteria are based on the performance of the above two HPV test methods, HC2 and GP5+/6+ PCR; they can be used to assess the suitability of new candidate HPV DNA tests with a corresponding or better clinical sensitivity for primary screening without conducting lengthy prospective trials. The rationale behind this approach is that a validated HPV test should display an acceptable balance between clinical sensitivity and clinical specificity (Snijders, van den Brule & Meijer 2003), i.e. high sensitivity for CIN2+/CIN3+ lesions and at the same time as little detection of – generally transient – HPV infections not associated with CIN2+/CIN3+ lesions as possible. Low clinical sensitivity will result in too many missed CIN2+/CIN3+ lesions (false negatives), whereas low clinical specificity will lead to detection of unacceptably high numbers of transient, clinically irrelevant hrHPV infections (false positives). The consequence of the latter would be too many unwanted negative effects (anxiety, repetitive and confirmatory tests, as well as unnecessary treatment) in the generally healthy population, and unnecessarily high costs of the screening programme. Therefore, before new tests are used for cervical cancer screening, their non-inferiority should be demonstrated compared to those HPV tests with proven efficacy in large clinical trials.

It must be recognized that clinical performance depends not only on the intrinsic characteristics of a test, but also on extrinsic factors, such as the procedures and performance of the laboratory in which samples are processed and analysed. Hence, like cervical cytology testing, HPV testing should be performed only on samples processed and analysed in qualified laboratories, accredited by authorized accreditation bodies and in compliance with international standards (see also Rec. 1.34) **(VI-A).**[Rec 1.35] For example, HPV laboratories should have facilities enabling separation of key work tasks (to prevent contamination), complying with good laboratory practice (GLP) and participating in external proficiency panel testing schemes (Eklund et al. 2014; Ferguson et al. 2006; World Health Organization 2009) (see also Suppl. 2).

Unlike the GP5+/6+ PCR, the HC2 assay is widely and commercially available and is approved by the United States Food and Drug Administration. Therefore the HPV DNA test requirements summarized below have been formulated relative to HC2, at the cut-off of 1 RLU in women aged ≥30 years (Meijer et al. 2009). This age was chosen since transient HPV infections are particularly common in younger women, resulting in a relatively low clinical specificity for HPV tests (Cuzick et al. 2006b).

1. Given HC2 clinical sensitivity values for CIN2+ of 95% or more, the candidate test system should have a clinical sensitivity for CIN2+ not less than 90% of the HC2 test in women aged ≥30 years.

This will result in a negative predictive value of the hrHPV test that is sufficiently high to allow extension of current screening intervals for women with negative primary cytology test results.

2. The candidate test system should have a clinical specificity for CIN2+ not less than 98% of that of the HC2 test in women aged ≥30 years. The higher limit on the minimum clinical specificity takes into account reported levels that vary between 85% and 95% (average, 92%; see Table 1.2 and Arbyn et al. 2006), dependent on the geographical region and age. This test criterion is crucial to minimizing unnecessary and excessive follow-up of women testing positive for HPV at screening who will not have or develop clinically meaningful disease.

3. The candidate HPV test system should be robust and display high intra-laboratory reproducibility and inter-laboratory agreement. Taking into account that HC2 and GP5+/6+ PCR have revealed inter-laboratory agreement of at least 92%, candidate tests should demonstrate at least 87% inter-laboratory agreement with HC2.

Based on the test requirements summarized above, a validation strategy for candidate HPV DNA assays has been proposed (Meijer et al. 2009). It involves a clinical equivalence analysis of the candidate assay relative to a clinically validated reference HPV test (HC2); it could be performed, however, with a different test equivalent to HC2. The samples for the non-inferiority testing of sensitivity and specificity for CIN2+, as well as assay reproducibility analysis, must originate from a population-based screening cohort. Power calculations suggest that at least 60 samples should be analysed in order to assess whether a candidate test has a sensitivity for CIN2+ not less than 90% of that of HC; samples should be obtained from a representative group of women with histologically confirmed CIN2+ detected by HC2, either combined or not combined with cytology, and/or the candidate HPV test. In addition, assessment of non-inferiority of the clinical specificity for CIN2+ of a candidate test compared with HC2 requires analysis of at least 800 cervical samples. These should be from women aged ≥30 years in the population-based screening cohort who did not have histologically confirmed CIN2+. Reliable assessment of the intra-laboratory reproducibility in time, and inter-laboratory agreement should be performed by evaluation of at least 500 cervical samples, 30% of which should score HPV-positive by a clinically validated reference test.

It should be noted that criteria based on simple cross-sectional accuracy as outlined above are inadequate for validation of non-DNA-based HPV tests for primary screening (eg HPV viral oncogene mRNA tests, or tests using other biomarkers); such markers measure events that may be subsequent in time to infection detectable with HPV DNA. For example, an HPV infection might not be associated with overexpression of viral oncogenes until later in the process of carcinogenesis. Hence the low-risk period that defines the appropriate screening interval after a negative HPV DNA test may be irrelevant in primary screening using non-HPV DNA tests. Additional, longitudinal data would therefore be required to assess the suitability for primary screening of tests that target molecules other than HPV DNA. It should also be recognized that HPV testing validation studies have produced valuable new information on type-specific HPV prevalence in screening populations and sometimes raised concerns about high age-adjusted test positivity rates and inter-assay disagreement (Goldman et al. 2013; Preisler et al. 2013; Rebolj et al. 2013; Rebolj et al. 2014). A high proportion of women that are HC2-positive but HPV-negative in genotyping (Sargent et al. 2008; Gillio-Tos at al. 2013; Leinonen et al. 2013) suggests that HPV genotyping may be useful for validation of results in HPV screening.

In conclusion, due to differences in clinical performance between different methods of HPV detection, cervical cancer screening programmes should adopt an HPV primary test for use only if it has been validated by demonstrating reproducible, consistently high sensitivity for CIN2+ and CIN3+ lesions, and only minimal detection of clinically irrelevant, transient HPV infections **(VI-A).**[Rec 1.33] As pointed out elsewhere in this supplement, clinical validation is a necessary but not a sufficient criterion for adopting an HPV primary test for use in cervical cancer screening. Additional aspects must be taken into account such as laboratory quality assurance (see Rec. 1.35) and health economic factors, and whether correct use of the test as specified in the instructions of the manufacturer and in accordance with the other recommendations in the Supplement can be organized (see Rec. 1.36).

1.7 Self-sampling for HPV testing

Cervical specimens collected by health-care professionals provide the cellular material for conventional smears or LBC samples used in cervical cancer screening. Collection of cervical material for HPV testing through vaginal self-sampling has potential to improve overall participation in cervical screening programmes in developed countries **(I)** (Bais et al. 2007; Gök et al. 2010; Lindell et al. 2012; Virtanen et al. 2011) and in developing regions, self-sampling may facilitate access to cervical screening (Holanda, Jr. et al. 2006; Qiao et al. 2008) (see Supp. 2, Sect. Section 2.4.3).

- **Cytology testing on self-collected samples**

Vaginal self-sampling does not provide material suitable for accurate cervical cytological assessment because of lower specimen quality, ie, low cellularity (Garcia et al. 2003); poor concordance with cytology on conventional cervical smears obtained by physician sampling (Brink et al. 2006; Budge et al. 2005); and much lower sensitivities for high-grade lesions. However, the specificity of cytology on self-collected samples for high-grade CIN was high in two studies (Brink et al. 2006; Budge et al. 2005).

- **hrHPV detection in self-collected versus physician-collected samples**

Numerous studies have evaluated the diagnostic accuracy of HPV testing to predict CIN2+ using self-collected samples. In concordance analysis between HPV detection in self-collected versus physician-collected samples, the range of HPV positivity varied considerably across studies, most likely reflecting differences in sampling devices, HPV tests, and possibly also study populations. Many studies reported hrHPV results separately, whereas others combined results for hrHPV and low-risk HPV. One of the larger studies performed with hrHPV (HC2), (Wright, Jr. et al. 2000) (n=1415) found moderate agreement (kappa=0.45) between results using self-collected vaginal swabs, and physician-collected cervical brushes. Data from numerous studies on HPV detection in self-taken versus physician-taken samples were collected in systematic reviews and meta-analyses published by (Ogilvie et al. 2005) and by (Petignat et al. 2007). The concordance for hrHPV positivity was good. A similarly good concordance has been found in other studies that compared hrHPV testing in self-sampling with physician sampling (Brink et al. 2006; Daponte et al. 2006; Tamalet et al. 2010).

Conversely, studies that separately evaluated low-risk HPV invariably reported an increased low-risk HPV detection rate in self-sampled specimens (Petignat et al. 2007). These findings most likely reflect the observation that low-risk HPV infections tend to affect vaginal mucosa more commonly than cervical mucosa (Castle et al. 2007). In commonly used self-sampling methods (cotton and Dacron swab, brush), only vaginal material is sampled, and this may have affected the outcome of some studies that used the hrHPV HC2 method. The HC2 test is known to show some cross-reactivity with low-risk HPV types (Castle et al. 2002). The higher hrHPV test positivity rate in self-collected compared to physician-collected samples observed in some HC2 studies is consistent with the possibility that some vaginal low-risk HPV infections may have been detected (Gök et al. 2010; Hillemanns et al. 1999; Holanda, Jr. et al. 2006; Khanna et al. 2007).

In some studies a higher hrHPV detection rate was found in the physician-collected cervical samples (Baldwin et al. 2005; Lorenzato et al. 2002; Nobbenhuis et al. 2002). Possible reasons for this include the type of self-sampling device (swab, brush, tampon, or lavage) and the device used for physician sampling (cone-shaped brush, Cytobrush, Dacron swab, or Cervex-Brush), which probably influence the cervical cell yield, and the different hrHPV detection methods, which all have their specific features in terms of analytical sensitivity and specificity for hrHPV detection.

- **Comparison of detection of CIN2+by hrHPV testing in self-collected samples versus cytology on physician-collected samples**

Collectively, the data summarized in Table 1.5 indicate that hrHPV testing on self-samples in primary screening is as sensitive for CIN2+, as cytology on physician-obtained cervical samples, although less specific, especially when LSIL or more severe is used as the test cut-off (Arbyn et al. 2014). The observed lower specificity of hrHPV tests on self-collected samples can probably be improved if assays are used that do not show cross-reactivity with low-risk HPV types. The sensitivity of HPV testing on self-samples can be improved by choosing an appropriate test showing sufficient sensitivity.

Table 1.5. Detection of CIN2+ in self-taken and clinician-taken samples. Absolute sensitivity and specificity for the detection of CIN2+ by HPV testing on self-samples, and HPV and cytology testing on clinician-taken samples in primary screening

Test and sample type	Test cut-off	Number of studies	Sensitivity in % (95% CI)	Specificity in % (95% CI)
HPV self-taken	defined by manufacturer	14	76 (69–82)	86 (84–90)
HPV clinician-taken	defined by manufacturer	14	91 (87-94)	88 (85-91)
cytology clinician-taken	ASC-US or more severe	12	83 (75–89)	91 (87–94)
	LSIL or more severe	8	71 (66–76)	97 (97–98)

Source: (Arbyn et al. 2014)

- **Comparison between HPV detection on self-collected versus physician-collected samples for detecting high-grade CIN or cervical cancer**

A recent meta-analysis of cross-sectional data (Arbyn et al. 2014) reported that the absolute accuracy (in particular the specificity) of HPV testing in self-taken and in clinician-taken samples varied by setting (screening or follow-up). However, the relative sensitivity and specificity of HPV testing on self-taken compared to clinician-collected samples was similar across settings, allowing pooling. The reported findings of lower cross-sectional sensitivity and specificity in self-taken samples were robust over different influential factors (setting, developed and developing countries, choice of self-sampler, study design and study quality characteristics based on the QUADAS-2 checklist (Whiting et al. 2011). No obvious collection-device effects in the relative sensitivity of HPV testing on self-samples versus clinician-taken samples were detected, but the included studies did not address comparisons between different sampling devices, and because of the variability in study design and settings, the authors drew no strong conclusions about the influence of devices for self-sampling on the accuracy estimates (Arbyn et al., 2014).

Fourteen studies were included that employed HC2; the pooled relative sensitivity and specificity for detection of CIN2+ were significantly reduced in self-taken versus clinician-taken samples: 0.85 (0.81-0.90) and 0.96 (0.93-0.98), respectively. Five studies were included in the meta-analysis that employed PCR GP5+/6+ tests validated according the method described in Sect. 1.6; the pooled PCR GP5+/6+ data did not reveal statistically significant differences in sensitivity and specificity between self-taken and clinician-taken samples: 0.95 (0.89-1.01) and 1.11 (0.95.-1.29), respectively.

The meta-analysis did not report cross-sectional accuracy to detect cervical cancer. A self-sampling study performed with a cotton tip swab revealed that a substantial number of cervical cancers were missed compared with physician sampling (Lorenzato et al. 2002).

- **Conclusions**

Self-sampling of cervicovaginal material may permit development of effective tools to increase acceptability and coverage of cervical screening programmes, especially in women who do not currently attend screening (see also Suppl. 2, Section 2.4.3).

Sensitivity of HPV testing for cervical pre-cancerous lesions and cancer using self-collected cervicovaginal samples is similar to that of conventional cytology or LBC testing on clinician-collected samples, but specificity is frequently reduced (Arbyn et al. 2014). Due to the lower sensitivity of HPV testing on self-collected versus clinician-collected samples and because of the heterogeneity in results between studies, self-sampling should not be the primary option for women participating in cervical cancer screening. The clinical accuracy of HPV testing on self-collected samples for cervical screening is sufficient, however, to conduct organized, population-based pilot programmes for women who have not attended screening despite a personal invitation and a personal reminder (see also Rec. 1.33 and Suppl. 2, Rec 2.8-13) **(III).**[Rec 1.32]

Because of differences in cross-sectional test performance in detecting CIN2+ using self-collected samples, programmes that use self-samples in well-planned and controlled pilot implementation projects must be particularly careful when selecting the test to use for such pilots.

Further research is needed to identify the tests, devices and protocols best suited to self-sampling in cervical cancer screening programmes. The longitudinal safety and effectiveness of HPV testing on self-samples should be monitored and evaluated using linkage of screening, pathology and cancer registries.

1.8 Cost-effectiveness of HPV versus cytology for primary cervical cancer screening

A number of cost-effectiveness analyses (CEAs) of HPV primary screening have evaluated protocols with Pap and HPV testing combined, and a few studies have evaluated HPV testing alone. Published results include cost and effect estimates, and incremental cost-effectiveness ratios (ICERs) based on comparison with Pap screening programmes. Conclusions of published CEAs are heterogeneous: three analyses show favourability of HPV primary screening over a conventional cytology setting (Berkhof et al. 2010; Kim, Wright & Goldie 2005; Mittendorf et al. 2003); one analysis is favourable over LBC but unfavourable over screening with conventional cytology in another setting (Sherlaw-Johnson & Philips 2004); another published CEA comes to opposite conclusions: favourability of HPV primary screening in a conventional setting but not in an LBC setting (Goldie, Kim & Wright 2004); and another CEA is unfavourable for HPV primary screening compared to screening in a conventional setting (Mandelblatt et al. 2002). Key determinants of cost-effectiveness are the quality of cytology screening and the prevalence of HPV infections relative to the risk level for cervical cancer, and the costs of HPV testing relative to those of cytology. When hrHPV prevalence is high, the specificity of testing for CIN2+ decreases, but PPV does not decrease (Giorgi-Rossi, Franceschi & Ronco 2012). The cost is influenced by many local factors, such as quality assurance procedures, the scale of laboratory facilities, and labour costs.

Since key determinants vary between countries, favoured primary screening and triage tests may also differ between countries. To recognize the situations in Europe in which HPV primary screening is favoured over cytology screening, many of the scenarios that would correspond to the cervical cancer

screening situation of various European countries have been analysed from the perspective of cost-effectiveness (de Kok et al. 2012). Cervical cancer risk, HPV prevalence, previous screening, test characteristics of cytological and HPV testing, and costs per test were varied among different scenarios. Various HPV and cytology triage schedules, as well as screening age ranges and intervals were includeed in the analysis. Whereas HPV primary screening would be favourable in many of the analysed scenarios corresponding to the current cervical cancer screening situation in various European countries, primary cytology screening would be favourable in countries with a relatively high prevalence of HPV and high HPV testing costs. These analyses illustrate the importance of organizing HPV primary screening in a manner that minimizes the costs of testing. This can be achieved by analysing HPV tests in large-scale laboratories to maximize economy-of-scale effects (i.e. lower unit costs of high-volume laboratories). In addition, organized, population-based screening programmes are also more likely than opportunistic programmes to be able to take advantage of competition in the marketplace to negotiate favourable prices for laboratory services.

From the perspective of cost-effectiveness, HPV primary screening was preferred in many of the scenarios that would correspond to the current cost, frequency and coverage of cervical cancer screening programmes in various European countries; but implementing HPV screening in situations where screening is not well organized involves risks that may be unacceptable. Uncontrolled, frequent screening in part of the target population, especially at a young age, will decrease programme specificity, given that every screening round adds to false-positive results and screening at a young age detects numerous transient infections and abnormalities that will later regress. Uneven population coverage of HPV screening combined with frequent screening at a young age, may erode the balance between benefit and harm (such as possible adverse pregnancy outcomes after excisional treatment of precancerous lesions, and higher costs).

In conclusion, any decision to implement HPV primary testing in cervical cancer screening should take into account health economic factors, and whether correct use of the test as specified in the instructions of the manufacturer and in accordance with the recommendations in this supplement can be organized **(VI-B).**[Rec 1.36] Health economic factors to consider in planning and subsequent steps in programme implementation include the prevalence of HPV infections; the burden of repeat testing, colposcopies, and CIN treatments resulting from HPV testing; and the quality and impact of existing cytology screening programmes (see also Sect. 1.2.1.3 and 1.2.3). Assessments should be conducted to determine the optimal target age groups and screening intervals based on the chosen test and management protocols (see Sect. 1.3.2.1 and 1.3.2.2). The feasibility and sustainability of the programme should be assured through adequate resourcing, coordinated planning, feasibility and pilot studies, and quality-controlled rollout across a country or region (see Annex 1 and Suppl. 2).

1.9 Conclusions

- **Suitability of HPV primary testing for use in cervical cancer screening programmes**

Cervical screening using primary testing for the DNA of oncogenic HPV types has been shown to be more efficacious than cytology primary screening in preventing invasive cervical cancer (Ronco et al. 2014). Appropriate screening policy and programme organization are essential to achieving an appropriate balance between benefit and harm of any screening programme. These principles are particularly important in HPV primary screening, in order to avoid substantial increase in the number of women with positive test results and additional colposcopies and treatment of no additional benefit to participating women. Following the recommendations in the present supplement will enable pro-

grammes to achieve the potential benefit of HPV primary testing in cervical cancer screening while minimizing the risks (see Rec. 1.1).

- **Avoidance of co-testing (HPV and cytology primary testing) at any given age**

Among women 35 years of age and above, co-testing (cytology and HPV) is not more protective than HPV primary testing alone. Systematic co-testing entails higher costs, higher referral rates to colposcopy, and a lower PPV for CIN2+ detection among referred women, particularly if triage is not used for HPV-positive women. Hence, to avoid unnecessary harm, only one primary test (cytology or testing for oncogenic HPV) should be used at any given age in cervical cancer screening (see also Rec. 1.3 - 1.7) **(II-A)**.[Rec 1.2]

- **Starting age for HPV primary testing in cervical cancer screening programmes**

While sufficient evidence is available to begin HPV primary screening at age 35 years or above, if the other recommendations in the present supplement are taken into account **(I-A),**[Sect 1.3.2.1] there is also clear evidence that the specificity of HPV testing is very low in younger women. In addition, below 30 years HPV primary screening leads to overdiagnosis of CIN2 that would have regressed spontaneously. Routine HPV primary screening should therefore not begin under age 30 years **(I-E).**[Rect 1.4] Some overdiagnosis is also likely in women aged 30–34 years, but this may be outweighed by increased detection of progressive lesions and greater protection against invasive cancer. Sufficient evidence is not yet available to recommend for or against beginning routine HPV primary screening in the age range 30 - 34 years **(VI).**[Sect 1.3.2.1]

- **Stopping age for HPV primary testing in cervical cancer screening programmes**

In the absence of sufficient evidence on the optimal age at which to stop HPV primary screening, HPV primary testing could stop at the upper age limit recommended for cytology screening (60 or 65 years) provided a woman has had a recent negative test **(II-A).**[Rec 1.6]

- **Screening interval after a negative HPV primary test**

Longer intervals for HPV primary screening than for cytology-based screening reduce costs and, more importantly, reduce the probability of unnecessary colposcopy and treatment with attendant side-effects. There is good evidence from randomized trials that the low-risk period is longer after a negative HPV test than after normal cytology. The screening interval for women with negative HPV primary screening results should therefore be at least 5 years **(I-A).**[Rec 1.8] Additional evidence from non-randomized studies suggests that the interval for HPV primary screening may be extended up to a maximum of 6 - 10 years provided age and screening history are taken into account **(III-C)**. [Rec 1.8]

- **Cervical screening using cytology primary testing outside the age range of HPV primary testing**

The European Guidelines recommend that invitation to cervical cancer screening begins between 20 and 30 years of age (Arbyn et al. 2008a). The only primary screening test currently recommended by the EU for cervical cancer screening in women under 35 years of age is cytology (Annex 2). Cervical screening based on cytology conducted outside the age range for HPV primary testing should follow the guidance provided for cytology-based screening in the European Guidelines (Suppl. 2 and second edition) (see also Rec 1.9, 1.10, 1.22 and 1.34) **(VI-A).**[Rec 1.7]

- **Secondary testing (triage)**

To control the considerable potential for overdiagnosis and overtreatment in HPV primary screening, particularly in women under 35 years, cervical screening programmes using HPV primary testing must adopt specific policies for management through triage, referral and repeat testing of women with a

positive HPV primary test result. The policies should take into account Rec. 1.12 - 1.31 and must include guidance on when women with positive HPV test results should be invited to return to routine screening. **(VI-A).**[Rec 1.11] There is negligible additional benefit of direct referral of all HPV-positive women to colposcopy, versus cytological triage (testing HPV-positive women for cytology and referring directly to colposcopy those women who show cytological abnormalities, while the remaining women are re-tested after some time and referred to colposcopy if the infection persists). There is clear evidence, however, that cytological triage, as defined above, leads to a PPV of colposcopy referral similar to or better than that of cytology testing alone**.** Therefore, women testing positive for oncogenic HPV at primary screening should be tested without delay for cervical cytology (cytology triage) **(I-A).**[Rec 1.14] Direct referral to colposcopy of all HPV-positive women is not recommended **(I-D).**[Rec 1.15] To avoid loss to follow-up and ensure efficient use of resources, the cytology triage test should preferably use sampling material collected during the HPV screening visit **(VI-A).**[Rect 1.14] Depending on the result of cytology triage, HPV-positive women should be referred to repeat testing , or to colposcopy (see Rec. 1.18 - 1.21) **(I-A)**.[Rect 1.16]

Other methods of triaging HPV-positive women are under study. Current evidence is not sufficient for recommendation of their use in routine practice.

- **Secondary testing (repeat testing)**

Current management protocols for triage and repeat testing vary between countries, and there is insufficient evidence to recommend a single approach for all settings, apart from the current emphasis on cytology triage for hrHPV DNA primary testing. The current diversity is reflected in the management options explained in greater detail in sections 1.4 and 1.5. The method of repeat testing and the management protocols for repeat testing and referral during the entire screening round should be selected by the programme when planning for HPV primary testing. The respective decisions and programme planning should take into account the prevalence of HPV in the target population and the quality and organization of cytology screening in the region served by the programme.

Clinical experience suggests that the interval between two primary screening tests, differences in local conditions under which relevant trials have been conducted, and numerous other factors such as the interval of HPV repeat testing, the criteria for referral to colposcopy (e.g. persistent HPV at initial or subsequent repeat testing), or the criteria used in cytological interpretation are likely to affect the efficiency and effectiveness of the management of HPV-positive women in any screening programme. Such factors should therefore be taken into account in optimization studies and in planning the management protocols used in a screening programme.

There is evidence that the longer the interval to the repeat test, the better is the specificity and the fewer are the adverse effects. The interval for HPV repeat testing should therefore be shorter than the regular screening interval, but not less than 12 months (see Rec. 1.24). There is also evidence that cytology informed of HPV positivity is more sensitive than "blind" cytology. Due to the lower risk of undetected CIN that may progress to cancer prior to repeat testing, inviting HPV positive cytology negative women to retesting after two years may be an option.

More insight into quality criteria determining the balance between benefit and harm in the management of women with a positive HPV primary test may become available in the future as evidence accumulates on the various protocols currently in use. For the same reasons, programme policies on triage, referral and repeat testing should be regularly reviewed and revised, if necessary, taking into account the results of monitoring (see Rec. 1.11) and the available evidence **(VI-A).**[Rec 1.12]

- **Quality assurance of laboratory and professional services**

The present supplement devotes considerable attention to key policies in organization of HPV primary screening. In the implementation of HPV primary screening it is also important to keep the entire screening process in mind, including the attendant laboratory, colposcopy, cytopathology and histo-

pathology services. Quality assurance of the respective services used in cytology triage in HPV primary screening should comply with the recommendations in Chap. 3 - 6 of the European Guidelines **(VI-B)**.[Rec 1.17] Like cervical cytology testing, HPV testing should be performed only on samples processed and analysed in qualified laboratories, accredited by authorized accreditation bodies and in compliance with international standards (see also Rec. 1.34) **(VI-A).**[Rec 1.35]

- **Self-sampling**

Self-sampling of cervicovaginal material may permit development of effective tools to increase acceptability and coverage of cervical screening programmes, especially in women who do not currently attend screening (see also Suppl. 2, Section 2.4.3).

Sensitivity of HPV testing for cervical pre-cancerous lesions and cancer using self-collected cervicovaginal samples is similar to that of conventional cytology or LBC testing on clinician-collected samples, but specificity is frequently reduced (Section 1.7). Due to the lower sensitivity of HPV testing on self-collected versus clinician-collected samples and because of the heterogeneity in results between studies, self-sampling should not be the primary option for women participating in cervical cancer screening. The clinical accuracy of HPV testing on self-collected samples for cervical screening is sufficient, however, to conduct organized, population-based pilot programmes for women who have not attended screening despite a personal invitation and a personal reminder (see also Rec. 1.33 and Suppl. 2, Rec 2.8-13) **(III).**[Rec 1.32]

- **Choice and validation of HPV tests**

Cervical cancer screening programmes should adopt an HPV primary test for use only if it has been validated by demonstrating reproducible, consistently high sensitivity for CIN2+ and CIN3+ lesions, and minimal detection of clinically irrelevant, transient HPV infections **(VI A).**[Rec 1.33] International guidelines for determining whether other HPV DNA test systems are non-inferior have been formulated for tests targeting the same molecule as the tests used in the RCTs (HPV DNA). Programmes should require vendors to show non-inferiority of test performance in the laboratory that will be performing the testing and with samples from the population to be tested. A cross-sectional clinical accuracy study is not sufficient to validate non-DNA-based HPV tests for screening purposes since the low-risk period after a negative HPV DNA test (which defines the appropriate screening interval) cannot be automatically applied to tests targeting other molecules. Therefore, longitudinal data are needed before the latter can be considered clinically validated for screening.

- **Decision-making on implementation of HPV primary testing in cervical cancer screening programmes**

While most of the recommendations in the present supplement focus on the opportunities and the challenges of HPV primary screening that set it apart from cytology-based screening; decision-makers, programme managers and professionals should also be aware of the guidance in the second edition (Arbyn et al. 2008a) and Suppl. 2 that is relevant to any cervical screening programme irrespective of the method of primary testing used (see Rec. 1.34). Of prime importance in this regard are the recommendations on programme organization, planning, monitoring and evaluation (see Suppl. 2, and Chap. 2 in the second edition); communication; and quality assurance of the entire screening process including sampling, histopathologic interpretation and classification of cervical tissue; and management of detected lesions (see Chap. 3 – 6 in the second edition) **(VI-A).**[Rec 1.34]

Any decision to implement HPV primary testing in cervical cancer screening should also take into account health economic factors, and whether correct use of the test as specified in the instructions of the manufacturer and in accordance with the recommendations in this supplement can be organized. Health economic factors to consider in planning and subsequent steps in programme implementation include the prevalence of HPV infections; the burden of repeat testing, colposcopies, and CIN treatments resulting from HPV testing; and the quality and impact of existing cytology screening pro-

grammes. Assessments should be conducted to determine the optimal target age groups and screening intervals based on the chosen test and management protocols. The feasibility and sustainability of the programme should be assured through adequate resourcing and coordination, including coordinated planning, feasibility and pilot studies, and quality-controlled rollout across a country or region (see Suppl. 2 and Annex 1) **(VI-B).**[Rec 1.36]

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Appendix 1

Evidence Assessment: Clinical Questions, PICOS formulations and conclusions

Clinical question 1

What is the accuracy of HPV-based screening in identifying cervical cancer and high-grade cervical cancer precursors (CIN2+, CIN3+/AIS+)

P: asymptomatic women participating in cervical cancer screening

I1: testing for presence of nucleic acids of hrHPV

I2: testing for presence of nucleic acids of hrHPV in combination with cervical cytology

C1: cytological screening alone (versus I1) or combination of cervical cytology and testing for hrHPV (versus I1)

C2: HPV-based screening alone (versus I2)

O: - absolute accuracy (sensitivity, specificity, PVs, referral rate, absolute risk of disease) from complete diagnostic accuracy studies

- relative sensitivity, relative PPV, relative referral rate from incomplete studies and RCTs. Triage/repeat testing procedures applied to ascertain outcome should be taken into account.

S: - cross-sectional studies with complete design

- cross-sectional studies with incomplete design, with or without correction for verification bias

- RCTs (baseline results)

Results: Cross-sectional data from a very large number of double testing studies found higher sensitivity of HPV testing alone than cytology for CIN2, CIN3 or invasive cancer aggregated (CIN2+) and for CIN3 or invasive cancer aggregated (CIN3+). The overall relative sensitivity of combined HC2 and cytology vs. stand-alone was 1.05 (95% CI 1.04-1.07) for CIN2+ and 1.02 (95% CI 1.01-1.03) for CIN3+ (Arbyn et al. 2012). Five European RCTs out of six found higher sensitivity of HPV testing alone, with cytology triage or co-testing with cytology than cytology alone for CIN2+ and for CIN3+. Numbers were sparse in the six double-testing studies and five European trials that reported separate data on invasive cancers and there was no significant difference between the sensitivity of HPV vs cytology (Leinonen et al. 2012; Ronco et al. 2014).

Several double testing studies have consistently shown lower specificity of HPV testing than cytology for the absence of CIN2+ and CIN3+. The overall relative specificity of combined HC2 and cytology vs. stand-alone was 0.95 (95% CI 0.94-0.96) for absence of CIN2+ and 0.93 (95% CI 0.92-0.95) for absence of CIN3+ (Arbyn et al. 2012).

The relative PPV vs cytology was significantly lower than that of cytology both for CIN2+ and CIN3+ in the RCT that used co-testing with direct referral (Ronco et al. 2006a) and non-significantly lower than cytology both for CIN2+ and CIN3+ in the RCT that used stand-alone HPV with direct referral (Ronco et al. 2008). In the RCTs that used cytological triage PPV was not significantly lower and sometimes higher than with cytology (Leinonen et al. 2009).

HPV-based screening resulted in significantly increased rates of positive screening test results and colposcopy referrals (I) (Bulkmans et al. 2007; Kitchener et al. 2009b; Kitchener et al. 2011; Rijkaart et al. 2012; Ronco et al. 2006b; Ronco et al. 2010).

Conclusion: HPV-based primary screening has a higher sensitivity and lower specificity than cytology-based screening in detecting precancerous cervical lesions in cross-sectional studies (I), and no difference in detecting invasive cancer (I).

Clinical question 2

What is the reduction in the burden of CIN3/AIS+ and cervical cancer incidence and mortality among women screened by hrHPV testing, cytology, or the combination of both?

P: asymptomatic women participating in cervical cancer screening

I1: testing for presence of nucleic acids of HR-HPV

I2: testing for presence of nucleic acids of HR-HPV in combination with cervical cytology

C1: cytological screening alone (versus I1) or combination of cervical cytology and testing for HR-HPV (versus I1)

C2: HPV-based screening alone (versus I2)

O: detection rate of, CIN3/AIS, and invasive cervical cancer and mortality from cervical cancer after recruitment, taking information from the subsequent screening rounds into account; ratios of detection rates. Triage/follow-up procedures applied to ascertain outcome should be taken into account.

S: RCTs (second and further screening rounds); cohort studies with follow-up according to initial screening test results, including studies with registry linkages (screening, follow-up, cancer)

Results: 4 European RCTs showed a reduction of CIN3+ at the second screening round in the arm that used HPV alone in one trial or in co-testing for primary screening compared to the arm that used cytology (Kitchener et al. 2011; Naucler et al. 2007; Rijkaart et al. 2012; Ronco et al. 2010). Two RCTs reported a significant reduction of invasive cancers at round 2 in the HPV vs in the cytology arm (Rijkaart et al. 2012; Ronco et al. 2010), and a joint analysis that included 4 European trials reported a rate ratio for HPV screening versus cytology of 0.60 (95% CI, 0.40–0.89) (Ronco et al. 2014).

In a cluster randomized single screen RCT in India, HPV testing was associated with a significant decline in the rate of advanced cervical cancers and deaths from cervical cancer in comparison with the unscreened control group. No significant reductions in the numbers of advanced cancers or deaths were observed in the cytology-testing group or in the VIA (visual inspection with acetic acid) group, as compared with the control group (Sankaranarayanan et al. 2009).

Conclusion: HPV-based primary screening alone or in co-testing reduces CIN3+ (I) and invasive cervical cancer (I) in comparison with cytology-based screening. HPV-based primary screening reduces cervical cancer mortality in comparison with no screening (II).

Clinical question 3

What is the amount of overdiagnosis (diagnosis of regressive lesions) associated with HPV-based, cytology-based, and combined (HPV and cytology) screening?

P: asymptomatic women participating in cervical cancer screening

I1: testing for presence of nucleic acids of hrHPV

I2: testing for presence of nucleic acids of hrHPV in combination with cervical cytology

C1: cytological screening alone (versus I1) or combination of cervical cytology and testing for hrHPV (versus I1)

C2: HPV-based screening alone (versus I2)

O (clinical question 2): detection rate of, CIN3/AIS, and invasive cervical cancer and mortality from cervical cancer after recruitment, taking information from the subsequent screening rounds into account; ratios of detection rates. Triage/follow-up procedures applied to ascertain outcome should be taken into account. Primary test applied in round 2 taken into account (if HPV is used in all women then any difference is due to over-diagnosis); otherwise lead time gain due to >1 screening round is a possible alternative explanation).

O (clinical question 3): sum of cumulative CIN2 and CIN3 detected over time (for instance, first and second [and further] screening rounds together)

S: RCTs (second and further screening rounds); cohort studies with follow-up according to initial screening test results, including studies with registry linkages (screening, follow-up, cancer)

Results: No increase in the cumulative detection of CIN2+ and CIN3+ over 2 rounds was observed in POBASCAM (HPV testing in both arms at round 2). The HPV vs. cytology arm ratio was 1.08 (0.94-1.24) for CIN2+ and 0.96 (0.81-1.14) for CIN3+. Significantly increased cumulative detection rates of both CIN2 and CIN3 were observed in NTCC that used cytology in both arms at round 2. Ratios were (1.77, 95%CI 1.18-2.67) and (1.61, 1.05-2.47) respectively for women aged 35-60 years, with a larger effect in CIN2 among women aged 25-34 years (2.81, 1.69-4.66). Even higher rates were observed in the second phase of the trial when HPV was used as a stand-alone test (3.38, 2.11-5.43) and (2.14, 1.28-3.59) for women aged 25-34 years (Ronco et al. 2010). An increase in the cumulative detection rate of CIN2 over the first 2 rounds was observed also in the Swedescreen trial that also applied cytology in both arms at round 2. Ratios were (1.56, 95% CI not reported) (Naucler et al. 2007). In ARTISTIC (testing at round 2 performed as in round 1, at round 3 cytology in both arms), over three screening rounds, there was no significant difference in CIN2+ (OR: 1.06, 95%CI 0.89 - 1.26, p = 0.5) or CIN3+ (OR: 0.90, 95%CI 0.72 - 1.14, p = 0.4) rates between the trial arms (Kitchener et al. 2014). There were no trials comparing systematically HPV stand-alone to co-testing with HPV and cytology. The only trial with HPV stand-alone (NTCC phase 2) had cytology as the comparison. However, the decrease in CIN2+ and CIN3+ in round 2 as well as excess in the cumulative incidence of CIN2+ and CIN3+ over 2 rounds was larger in the HPV stand-alone, compared with other trials.

Conclusion: Data are consistent with overdiagnosis of regressive/non-progressive CIN2 (I) and to a lesser extent CIN3 (II) but lead time gain due to >1 screening round is a possible alternative explanation. The excess is larger at younger age.

Clinical question 4a

What are the relative beneficial effects of HPV screening with and without cytological triage? Do they have similar sensitivity?

P: women from an unselected primary screening population

I: screening by HPV testing with cytological triage, separately for stand-alone HPV testing and for HPV + cytology as the primary test

C: screening by HPV testing, direct referral of all HPV-positives

O: detection of CIN2 and CIN3 within the completion of a screening round (up to test repeat and related colposcopy)

S: RCTs

and

P: women from an unselected primary screening population

I: screening by HPV testing (a) with cytological triage or (b) with direct referral to colposcopy of all HPV-positives, separately for stand-alone HPV testing with triage and for HPV + cytology with triage

C: screening by cytology, with or without HPV triage of borderline cytology, or no screening

O: detection of CIN2 and CIN3 within the completion of a screening round. The I/C ratio in type (a) studies should be compared with the same ratio in type (b) studies.

S: RCTs

Results: At round 1 of the European RCTs, the relative **CIN2+** detection rates of HPV-based screening vs stand-alone cytology were significantly higher in co-testing : 1.51 (1.13-2.02) (Naucler et al. 2007), 1.25 (1.05-1.50) (Rijkaart et al. 2012), except in the UK trial: 1.14 (0.94-1.38) (Kitchener et al. 2009b), and significantly higher in stand-alone HPV testing with cytology triage: 1.44 (1.02-2.02)

(Kotaniemi-Talonen et al. 2008). The rate was still higher with direct referral (2.13 (1.50-3.03) (Ronco et al. 2010). The relative **CIN3+** detection rates of HPV-based screening vs stand-alone cytology were significantly higher in all European RCTs except in the Swedish study 1.31 (0.92-1.87) (Naucler et al. 2007), the Finnish study (RR for CIN3 1.10, 95%CI 0.57-2.12) (Kotaniemi-Talonen et al. 2008), ARTISTIC (OR 0.97, p>0.2) (Kitchener et al. 2009b) and NTCC phase 1 age 25-34 (Ronco et al. 2006a).

Conclusion: HPV-based primary screening in co-testing with cytological triage is more sensitive than cytology-based screening (I). HPV-based primary screening with cytological triage is more sensitive than cytology (II).

Clinical question 4b

What are the relative beneficial effects of HPV screening with and without cytological triage in terms of earlier detection of persistent CIN2+ and CIN3+?

P: women from an unselected primary screening population

I: screening by HPV testing (a) with cytological triage or (b) with direct referral to colposcopy of all HPV-positives, separately for stand-alone HPV testing with triage and for HPV + cytology with triage

C: screening by cytology, with or without HPV triage of borderline cytology

O: detection of CIN2 and CIN3 at the second screening round and beyond. The I/C ratio in type (a) studies should be compared with the same ratio in type (b) studies.

S: RCTs with at least two screening rounds

Results: At round 2 of the European RCTs, the relative **CIN2+** detection rates of HPV-based screening vs stand-alone cytology were significantly lower in all RCTs with data available (0.58, 0.36–0.96 for Swedescreen, (Naucler et al. 2007); 0.63, 0.42–0.96 for ARTISTIC, Kitchener et al. 2009a and 0.42, 0.23-0.74 for NTCC among women aged 35-60 years and 0.55, 0.31-0.99 for NTCC among women aged 25-34, (Ronco et al. 2010). Also the relative **CIN3+** detection rates were lower in HPV-based screening in all RCTs with data available (0.53, 0.29–0.98 for Swedescreen, (Naucler et al. 2007); 0.53, 0.30–0.96 for ARTISTIC, (Kitchener et al. 2009b); 0.73, 0.55-0.96 for POBASCAM, (Rijkaart et al. 2012), except NTCC phase 1 among women aged 25-34 years (1.00, 0.38-2.67, (Ronco et al. 2010). In women aged 35 or more years there was no evidence of heterogeneity between studies regarding the relative detection of CIN3+(P=0.681).

Conclusion: HPV-based primary screening results in earlier detection of persistent CIN2 and CIN3 (I) than screening by cytology. There is no evidence that HPV with direct referral provides greater gain (in comparison to cytology) in lead time of pre-cancerous lesions than HPV with cytological triage.

Clinical question 4c

What are the relative negative effects (false positives and colposcopy referral) of HPV screening with and without cytological triage?

P: women from an unselected primary screening population

I: screening by HPV testing with cytological triage, separately for stand-alone HPV testing and for HPV + cytology as the primary test

C: screening by HPV testing, direct referral of all HPV-positives

O: PPV and referral to colposcopy within the completion of a screening round

S: RCTs
and

P: women from an unselected primary screening population

I: screening by HPV testing (a) with cytological triage or (b) with direct referral to colposcopy of all HPV–positives, separately for stand-alone HPV testing with triage and for HPV + cytology with triage
C: screening by cytology, with or without HPV triage of borderline cytology
O: PPV and referral to colposcopy within the completion of a screening round. The I/C ratio in type (a) studies should be compared with the same ratio in type (b) studies.
S: RCTs

Results: 2 RCTs reported colposcopy referral rates of HPV testing with cytology triage vs cytology. In the first round of POBASCAM the rate was 2.3% (2.0–2.7) vs 1.3% (1.1–1.6) (Bulkmans et al. 2007). ARTISTIC reported a colposcopy rate of 6.8% for the group whose HPV test result was revealed vs 5.2% for the group whose HPV test result was concealed an there was a statistically significant difference in the proportions of women attending colposcopy ($p < 0.0001$ for both round 1 and the full trial), mainly because the protocol for the revealed arm recommended that women who remained HPV positive after defined periods of time should be assessed by colposcopy. (Kitchener et al. 2009b). No data was available from RCTs that used stand-alone HPV. In NTCC baseline results, after direct referral of HPV-positives the relative risk of colposcopy referral was very high, 3.55 (95% CI 3.22-3.91) (Ronco et al. 2006a), whereas in the Finnish RCT with cytology triage the relative risk of colposcopy referral in the HPV arm was 1.23 (95% CI 1.02–1.48) (Kotaniemi-Talonen et al. 2008).

Conclusion: HPV-based primary screening without cytological triage results in more frequent false positive test results than cytology-based screening (II). HPV-based primary screening with cytological triage increases the referral rate to colposcopy, compared to cytology-based screening (I). HPV-based primary screening without cytological triage increases the referral rate to colposcopy, compared to cytology-based screening (II).

Clinical question 5a

What are the beneficial effects (reduction in cancer incidence, reduction in interval cancers including next screening round) of starting HPV screening at the age of 20/25/30/35/40?

P: women from an unselected primary screening population

I: screening by HPV testing

C: screening by cytology

O: cervical cancer incidence

S: RCTs with at least two screening rounds

Separately for age groups 20–24, 25–29, 30–34, 35–39, and 40+ whenever available.

Results: Invasive cancer incidence for separate age groups was reported in the joint analysis of four European RCTs. After a median follow-up time of 6.5 years, there was no significant difference between the HPV- and cytology screening groups among women who were younger than 30 years, 35-49 years of age or 50 years or older. In the age group 30-34 years at enrolment, 5 cancers were detected in the HPV group and 15 cancers in the cytology group, rate ratio 0.36 (0.14-0.94) (Ronco et al. 2014).

Conclusion: Starting HPV primary screening at the age of 30-34 years prevents more invasive cervical cancers than starting cytology primary screening at the same age (II).

Clinical question 5b

What are the beneficial effects (does it allow earlier diagnosis of persistent CIN2 and CIN3 than cytology?) of starting HPV screening at the age of 20/25/30/35/40?

P: women from an unselected primary screening population

I: screening by HPV testing

C: screening by cytology

O: relative reduction of CIN2 and CIN3 during the second screening round

S: RCTs with at least two screening rounds

Separately for age groups 20–24, 25–29, 30–34, 35–39, and 40+ whenever available.

Results: Data from 3 European RCTs were considered. NTCC reported relative CIN2 and CIN3 detection rates for age groups 25-29, 30-34 and 35-60 years: 0.50 (0.15-1.68) for CIN2; 1.00 (0.25-4.00) (phase 1) and 0.51 (0.09-2.79) (phase 2) for CIN3 at age 25-29 years; 0.58 (0.17-1.97) for CIN2; 2.00 (0.37-10.91) (phase 1) and 0.00 (phase 2) for CIN3 at age 30-34 years; 0.54 (0.23-1.28) for CIN2 and 0.48 (0.21-1.11) for CIN3 at age 35-60 years. Among women aged 25-34 (median 30) years who were referred to colposcopy only if cytological abnormalities were present or HPV infection persisted for at least 1 year, no decrease in the detection of CIN3 was observed for the HPV versus cytology group in the second round, whereas direct referral of all HPV-positive women led to a large decrease in detection of CIN3 (RR 0.20, 0.04-0.93) vs. the cytology group) in the second round. POBASCAM showed a CIN3+ reduction in the 2nd round but no numerical data were reported. In the Swedescreen study that recruited only women aged 32-38 years, a significant reduction of both CIN2+ (0.58, 0.36-0.96) and CIN3+ (0.53, 0.29-0.98) was observed in the HPV arm in the second screening round.

Conclusion: Starting HPV-based primary screening at the age of 25-29 years results in earlier detection of persistent CIN2+ and CIN3+ than cytology-based screening (II) (Ronco et al. 2010). Starting HPV-based primary screening at the age of 30-38 results in earlier detection of persistent CIN2+ and CIN3+ than cytology-based screening (I) (Bulkmans et al. 2007; Naucler et al. 2007; Ronco et al. 2010).

Clinical question 6a

What are the negative effects of starting HPV screening at the age of 20/25/30/35/40 in terms of false-positive rate?

P: women from an unselected primary screening population

I: screening by HPV testing

C: screening by cytology

O: colposcopy referral rate, false-positive rate (as measured by PPV for CIN2+ and CIN3+)

S: RCTs or cross-sectional diagnostic accuracy

Results: 3 European RCTs reported higher **colposcopy referral rates** in HPV-based screening vs cytology-based screening. In POBASCAM the colposcopy referral rates for women who started screening at the age of 29-33 years and 35-46 years were 4.8% vs 4.0% (RR 1.17) and 2.7% vs 2.4% (RR 1.12), respectively. The corresponding rates in the NTCC trial for women who started screening at the age of 25-34 years with and without cytology screening were 11.6% vs 4.08% (RR 2.8) and 13% vs 5% (RR 2.6), respectively and for women aged 35-60 years 10.6% vs 1.71% (RR 6.19) and 5.8% vs 2.4% (RR 2.4), respectively. In the Finnish study, women younger than 35 years were referred more often in the HPV DNA screening vs the conventional screening arm (RR = 1.27, 95% CI = 1.01 - 1.60). The rates for age groups 25-29, 30-35, 35-39 and 40-44 were 3.5% vs 3.5% (RR 1.0), 2.5% vs 1.7% (RR 1.5), 1.9% vs 1.7% (RR 1.1) and 1.26% vs 1.3% (RR 0.94), respectively (Leinonen et al. 2009).

Two European RCTs reported PPVs for CIN2+ and CIN3+ for separate age groups. In NTCC the relative PPVs for age group 25-34 years were 0.55 (0.37-0.82) and 0.24 (0.13-0.45) with cytology triage and 0.89 (0.55-1.44) and 0.66 (0.31-1.40) without cytology triage. For the age group 35-60 years the corresponding figures were 0.40 (0.23-0.66) and 0.34 (0.21-0.54) with cytology triage and 0.80 (0.55-1.18) and 0.86 (0.49-1.52) without cytology triage. In the Finnish study the relative PPVs for age group 25-34 years were 1.01 (0.69-1.49) and 0.70 (0.30-1.64) with cytology triage and 0.17

(0.11-0.24) and 0.12 (0.05-0.28) without cytology triage; for age group 35-44 years 1.54 (1.00-2.36) and 1.81 (0.84-3.89) with cytology triage and 0.31 (0.21-0.48) and 0.36 (0.17-0.78) without cytology triage (Leinonen et al. 2009).

Conclusion: HPV-based primary screening results in more frequent false positive test results and colposcopy referrals than cytology-based screening among women aged 25-34 years (I) (Leinonen et al. 2009; Ronco et al. 2006b), more frequent false positive test results among women 35-60 years (I) (Leinonen et al. 2009; Ronco et al. 2006a) and more colposcopy referrals than cytology-based screening among women aged 35-60 years (II) (Ronco et al. 2006a).

Clinical question 6b

What are the negative effects of starting HPV screening at the age of 20/25/30/35/40 in terms of overdiagnosis?

P: women from an unselected primary screening population

I: screening by HPV testing

C: screening by cytology

O: overdiagnosis as measured by relative cumulative incidence of CIN2+ and CIN3+ up to the second screening round and beyond

S: RCTs with at least two screening rounds

Results: NTCC reported data separately for women aged 25-34 and 35.60 years at recruitment. The former group was further split in ages 25-29 and 30-34. Starting HPV screening at age 25-29 years resulted in an about four-fold cumulative CIN2 and 2-fold cumulative CIN3 detection rate compared to cytology-based screening. Starting HPV screening at age 30-34 years resulted in an almost three-fold cumulative CIN2 and 2-fold cumulative CIN3 detection rate compared to cytology-based screening. Starting screening at age 35-60 years resulted in a 60-70% increase in cumulative incidence of both CIN2 and CIN3 in comparison with cytology-based screening (1.68 (95%CI 1.25-2.26) and 1.65 (1.21-2.26) respectively) (Ronco et al. 2010). POBASCAM data were reported separately for ages 29-33 and 34-56. The cumulative detection of CIN2+ and CIN3+ over the first two screening rounds was similar in the two arms in both age groups. In Swedescreen, starting HPV-screening at age 32-38 years resulted in point estimates of relative cumulative incidence of CIN2, CIN2+ and CIN3+ of 1.56, 1.17 and 1.04 respectively. The data were not reported by the authors, they were calculated using results available in the publication (Naucler et al. 2009).

Conclusion: See clinical question 3. In one study the excess in cumulative detection of CIN2+ was very large below age 35 and particularly below age 30, suggesting that the increase in overdiagnosis could be marked at such ages.

Clinical question 7a

What are the beneficial effects (reduction in cancer incidence, reduction in interval cancers including next screening round) of continuing HPV screening at the age of 60/65/70?

P: women from an unselected primary screening population

I: screening by HPV testing

C: screening by cytology

O: cervical cancer incidence

S: RCTs with at least two screening rounds

Separately for age groups 50–59, 60–64, and 65–70 whenever available.

Results: In a pooled analysis of 3 large European RCTs, after a median follow-up of 6.5 years, there was no significant difference in cervical cancer incidence between the HPV- and cytology primary groups among women screened at the age of 50 or above (Ronco et al. 2014). However, there was no evidence of heterogeneity between age groups in the effect of HPV screening. Data on the effect of HPV- vs. cytology primary screening on invasive cancers at the age of 60 years are sparse. No HPV screening studies have reported cervical cancer incidence among women screened at the age of 65 years or older.

Conclusion: It is not known whether continuing HPV screening at the age of 60/65/70 years reduces cervical cancer incidence.

Clinical question 7b

What are the beneficial effects (does it allow earlier diagnosis of persistent CIN2 and CIN3 than cytology?) of continuing HPV screening at the age of 60/65/70?

P: women from an unselected primary screening population

I: screening by HPV testing

C: screening by cytology

O: relative reduction of CIN2 and CIN3 during the subsequent screening round

S: RCTs with at least two screening rounds

Separately for age groups 50–59, 60–64, and 65–70 whenever available.

Results: In one RCT, there were no cases of CIN3 at the second screening round among women aged 50–60 in the HPV group vs 5 cases in the cytology group, while the ratio was 0.67 among women aged 35-49 years (Ronco et al. 2010). No HPV screening studies have reported comparative results of older age groups.

Conclusion: HPV-based primary screening may allow earlier detection of CIN3 than cytology-based screening among women aged 50-60 years in comparison with younger women (II). The benefit for older age groups is not known.

Clinical question 8a

What are the negative effects of continuing HPV screening at the age of 60/65/70 in terms of false-positive rate?

P: women from an unselected primary screening population

I: screening by HPV testing

C: screening by cytology

O: colposcopy referral rate, false-positive rate (as measured by PPV for CIN2+ and CIN3+)

S: RCTs or cross-sectional diagnostic accuracy

Results: False positive rate comparisons for ages 60/65/70 years have not been reported. Only one RCT reported colposcopy referral rates among women aged 60 years and above. In comparison with screening by cytology, the relative colposcopy referral rate point estimates among women screened by HPV testing with cytology triage were 0.92 among women aged 60-64 years and 0.6 among women aged 65 years or older. Absolute referral rates were also lower in the older age group (Leinonen et al. 2009).

Conclusion: It is not known whether continuing HPV screening at the age of 60/65/70 increases false-positive rates. Continuing HPV primary screening after the age of 65 years does not increase relative or absolute colposcopy referral rate (II).

Clinical question 8b

What are the negative effects of continuing HPV screening at the age of 60/65/70 in terms of overdiagnosis?

P: women from an unselected primary screening population

I: screening by HPV testing

C: screening by cytology

O: overdiagnosis as measured by relative cumulative incidence of CIN2+ and CIN3+ up to the second screening round and beyond

S: RCTs with at least two screening rounds

Results: Overdiagnosis comparisons for ages 60/65/70 years have not been reported.

Conclusions: It is not known whether continuing HPV screening at the age of 60/65/70 results in overdiagnosis.

Clinical question 9

What are the best time intervals for offering cervical HPV screening?

P: women from an unselected primary screening population

I: negative HPV test

C: normal cytology

O: cumulative incidence of cervical cancer, CIN3+, and CIN2+ after I and C at different intervals (at 3, 5, 6, and 7 years)

S: RCTs or double testing studies with follow-up

Results: The five European RCTs (Anttila et al. 2010; Bulkmans et al. 2007; Kitchener et al. 2009b; Naucler et al. 2007; Ronco 2010) utilised 3- or 5-year screening intervals. A pooled analysis of four of them reported a cumulative incidence of invasive cervical carcinoma in women with negative entry tests of 4.6 per 10^5 (95% CI 1.1–12.1) and 8.7 per 10^5 (3.3–18.6) at 3.5 and 5.5 years, respectively, in the experimental arm and 15.4 per 10^5 (7.9–27.0) and 36.0 per 10^5 (23.2–53.5), respectively, in the control arm (Ronco et al. 2014). The risk of CIN3+ was about the same at five years for women who tested negative for HPV at screening as at three years after a negative cytology screening test result (Elfström et al. 2014).

Conclusion: The optimal time interval for offering HPV primary screening is at least 5 years (I).

Clinical question 10

Is a self-collected vaginal sample as accurate as a cervical sample taken by a clinician?

P: women attending cervical cancer screening or women referred for repeat cytology testing because of previous cytological lesions or with gynaecological symptoms; or mixed population (to be separated by setting)

I: self-sampling of vaginal cells (stratified by sampling device)

C: cervical cell sample taken by a clinician

O: sensitivity, specificity for CIN2+ (only in studies with complete verification)

Relative sensitivity (detection rate ratio) in studies where only test-positives were verified, PPV, relative PPV, approximated specificity

S: cross-sectional studies with virological co-test outcomes with histologically verified outcomes

Results: Fourteen primary screening studies compared HPV self-sampling to HPV testing based on clinician-collected samples to detect CIN2+ (Belinson et al. 2001; Belinson et al. 2012; Girianelli et al. 2006; Guan et al. 2013; Holanda, Jr. et al. 2006; Longatto-Filho et al. 2008; Nieves et al. 2013; Qiao et al. 2008; Salmerón et al. 2003; Szarewski et al. 2007; Wright, Jr. et al. 2000; Zhao et al. 2012). HPV testing from the self-collected samples versus clinician-collected samples had a consistently lower sensitivity and specificity. HPV testing on self-samples detected 76% (95% CI 69–82) of CIN2 or worse. The pooled absolute specificity to exclude CIN2 or worse was 86% (95% CI 83–89) (Arbyn et al. 2014).

Conclusion: HPV self-sampling is less sensitive and less specific than clinician-collected sampling in detecting CIN2+ lesions (III).

S2

Organization of cytology-based and HPV-based cervical cancer screening

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Recommendations[22]

Organization of cytology-based and HPV-based cervical cancer screening

2.1 Irrespective of the method of primary testing (cytology or HPV assay) cervical cancer screening should always be performed in an organized, population-based screening programme with comprehensive quality assurance covering all steps in the screening process (see also Suppl. 1, Rec. 1.34 and Annex 1 and 2) **(VI-A).**[Sect 2.3]

2.2 If organized, population-based cervical screening programmes do not currently exist in a country or region, decision-makers should review the relevant policy on cervical cancer screening taking into account the Council Recommendation on Cancer Screening (Annex 2), the European Guidelines for quality assurance in cervical cancer screening, second edition, and the present Supplements (see also Annex 1) **(VI-A).**[Sect 2.3]

2.3 In countries or regions in which population-based cervical screening programmes using cytology primary testing are currently established, decision-makers should consider whether implementation of HPV primary testing in existing programmes would improve the balance between harm and benefit, and if so, integrate the change into the comprehensive cancer control programme (see also Suppl. 1, Rec. 1.1 and 1.36) **(VI-A).**[Sect 2.3]

Quality-assured process of screening programme implementation

2.4 If a decision is made to implement HPV primary testing in an existing population-based cervical screening programme, comprehensive planning, feasibility testing and pilot programmes should be conducted prior to routine implementation to ensure that an appropriate balance between harm and benefit is achieved in the transition to HPV primary screening, including effective and efficient use of resources (see also Annex 1) **(VI-A).**[Sect 2.3.1]

2.5 If a decision is made to implement a population-based cervical screening programme in a country or region previously lacking such a programme, special attention must be paid not only to selecting the method of primary testing (cytology or HPV testing), but also to testing and developing the capacity for a population-based approach to programme implementation including building up comprehensive quality assurance (see also Rec. 2.4 and Annex 1 and 2) **(VI-A).**[Sect 2.3.2]

2.6 The introduction of new population-based screening programmes should be coordinated by a unit with a comprehensive mandate and sufficient autonomy and resources to ensure that the European quality assurance guidelines are followed and that international experts familiar with the process and determinants of successful programme implementation can be consulted (see also Annex 1) **(VI-A).**[Sect 2.3.3]

[22] **Sect** (superscript) after each recommendation in the list refers the reader to the section/s of the Supplements dealing with the respective recommendation.

Rec (superscript) throughout the supplement refers to the number of the recommendation dealt with in the preceding text.

Population-based approach to cervical cancer screening

- **Avoiding financial barriers to participating in screening**

2.7 Screening should be free of charge or subject to only a limited charge for women who attend, regardless of whether cytological or HPV screening is offered **(I-A).**[Sect 2.4.1]

- **Personal invitation letters**

2.8 Personal invitation letters to participate in screening should include a scheduled appointment (date, time and place) and instructions about how to change the appointment if necessary **(I-A).**[Sect 2.4.2]

- **Personal reminders**

2.9 Women who do not attend screening should receive a personal reminder **(I-A).** The reminder should be sent by letter and should include a scheduled appointment (date, time and place) and instructions about how to change the appointment if necessary **(II-A).**[Sect 2.4.3]

2.10 A second personal invitation reminder should be sent if there is no response to an initial reminder **(I-B).**[Sect 2.4.3]

2.11 Personal invitation reminders may also be delivered by telephone call, provided women who are not reached by telephone are sent a reminder letter **(I-B).**[Sect 2.4.3]

- **Self-sampling**

2.12 Piloting self-sampling for women who did not participate in primary HPV screening despite a personal invitation and a personal reminder is recommended, provided it is conducted in an organized, population-based screening programme with careful monitoring and evaluation of the aimed performance and outcomes (see Rec. 2.8 – 2.11 and Suppl. 1, Rec. 1.32 and 1.36) **(I-A).**[Sect 2.4.4]

2.13 Prior to rollout towards national implementation, a self-sampling pilot project should demonstrate successful results compared to clinician-based sampling (positivity rate, positive predictive value of a positive test result, and cost-effectiveness). The pilot should also demonstrate that key organizational problems, such as the appropriate screening interval and compliance with invitation and management protocols for women with positive test results, have been adequately resolved **(III-D).**[Sect 2.4.4]

Monitoring cervical cancer screening performance

2.14 Monitoring of population-based cervical screening programmes should include the performance parameters defined in the European guidelines for quality assurance in cervical cancer screening (Suppl. 2, and Chap. 2 and 7 of the second edition) **(VI-A).**[Sect 2.6]

2.15 Programmes should achieve an invitation coverage of 95% (acceptable level) **(III-A)**; >95% is desirable **(III-A).**[Sect 2.6.1]

2.16 Programmes should achieve an examination coverage of 70% (acceptable level) **(III-A)**; >85% is desirable **(VI-A)**.[Sect 2.6.1]

2.17 Programmes should achieve a participation rate of 70% (acceptable level) **(III-A)**, >85% is desirable **(VI-A).**[Sect 2.6.1]

2.1 Introduction

The Council Recommendation on Cancer Screening (Council of the European Union 2003) (Annex 2) and the second edition of the European Guidelines for quality assurance in cervical cancer screening (Arbyn et al. 2008) provide recommendations on the most effective and appropriate approach for screening to reduce cervical cancer incidence and mortality. Despite agreement across the EU on the importance of these European recommendations, population-based cervical screening programmes have yet to be established or fully implemented in several EU Member States. Moreover, additional evidence on the suitability of novel cervical screening methods has emerged since publication of the second edition of the European Guidelines in 2008. In particular, human papillomavirus (HPV) primary testing has been evaluated in large randomized trials (see Suppl. 1, Table 1), providing sufficient evidence for new initiatives in the EU member states to implement and improve cervical cancer screening programmes. At the same time, vaccination against the oncogenic HPV types (hrHPV) that are responsible for a large proportion of cervical cancer incidence has been integrated into the cancer control programmes of many EU member states (see Suppl. 3). These developments underline the importance of establishing and improving population-based cervical cancer screening programmes in the EU, taking into account the new developments.

The graded recommendations printed at the front of the present supplement and the additional guidance provided in the main text focus on strategies to improve the population basis that is crucial to effective monitoring, evaluation and other aspects of quality assurance of any cervical cancer screening programme, irrespective of the method of primary testing. A new set of key performance indicators particularly relevant to primary HPV screening is also provided in the present supplement; and the process by which effective implementation of new population-based screening programmes, or improvements in existing programmes can be assured is highlighted (see also Annex 1 in the current Supplements volume). The issues covered are deemed by the authors and editors to be particularly relevant to the new EU Member States from Central and Eastern Europe, many of which have not yet established fully functional population-based cervical screening programmes despite resident populations with the highest cervical cancer incidence and mortality rates in the EU (Ferlay et al. 2013; Anttila et al. 2013). The guidance provided in the present Supplement is also highly relevant to current initiatives in 'old' EU member states, some of which, like France and Germany, are currently navigating the transition from opportunistic to population-based cervical cancer screening programmes and are considering whether to integrate HPV primary testing into the statutory screening programme (Republic of France 2014, Seifert & Klug 2014) or, like England, Finland, Italy, Sweden and the Netherlands are in the process of integrating HPV primary testing into existing population-based screening programmes previously based solely on cytology (see also Public Health England 2015). Many of the graded recommendations in the present supplement are applicable to cervical screening employing any evidence-based test and are therefore complementary to the recommendations in Supplement 1 dealing with quality assurance of screening based on HPV primary testing.

2.2 Defining evidence-based policies

Several fundamental issues must be considered when organizing population-based cervical screening programmes, including programmes using new evidence-based screening methods (Table 2.1). The key issues include the availability and accuracy of the necessary epidemiological data on which the

decision to begin screening is based; the definition of screening methods and policies based on relevant information on the health-economic and quality-of-life aspects; and the establishment of the legal framework for the overall population-based activity, including monitoring and regular linkage with relevant data sources. The availability of essential demographic data to identify the target population and establish a reliable invitation system must be carefully assessed; and the availability and accessibility of quality-assured primary testing, diagnostic and treatment services must be verified (Anttila et al. 2008). A careful planning period should precede the introduction of a new or modified screening programme. During this period, the feasibility of the above and other aspects essential to comprehensive quality assurance of the entire screening process should be carefully examined, in order to make any necessary modifications and improvements prior to large scale implementation (see Annex 1) (Lynge et al. 2012; von Karsa et al. 2013). New programmes and modifications of existing programmes should be introduced gradually, to permit demonstration of sufficient quality and efficiency to ensure that the balance between benefit and harm of routine screening services is appropriate (von Karsa 2014b).

The evidence-based recommendations and other guidance in the present supplement are relevant to current efforts in the EU member states to integrate HPV primary testing into population-based cervical screening programmes. Practical experience in the implementation of efficacious HPV primary screening is only available from a limited number of trials (Ronco et al. 2014); at the same time there is evidence of adverse effects of unnecessarily intensive screening policies (such as an excess of diagnosis of cervical intraepithelial neoplasia [CIN], and false-positive test results) (see Suppl. 1, Sect. 1.2). Furthermore, current management protocols for women with a positive HPV primary test result vary between countries, and there is insufficient evidence to recommend a single approach for all settings (see Suppl. 1, Sect 1.3.5). Therefore, when planning implementation of HPV-based screening, careful attention must be paid to monitoring and evaluation of the service, and to ensuring an adequate balance between effectiveness, costs, and adverse effects (see Annex 1 and Suppl. 1, Rec. 1.34 and 1.36). For the same reasons, like cervical screening based on cytology, HPV primary screening is only recommended in organized, population-based programmes (see Suppl. 1, Rec 1.1).

Table 2.1. Key steps in developing policies for population-based cervical screening programmes using a novel test

1. A consensus-building and planning period to carefully examine the evidence and feasibility of all programme components. For novel methods of primary testing for cervical abnormalities, both the pre and post-HPV-vaccination era should be taken into account.
2. Assuring the availability and accuracy of the epidemiological data in the target population to assess the burden of HPV-related disease.
3. Definition of screening methods and policies based on information about relevant resources, economic aspects, and quality-of-life issues.
4. Establishment of the legal framework for the population-based activity, including regular linkage of individual screening data with data from other relevant sources for quality assurance and continuous quality improvement, including monitoring and evaluation.
5. Establishment of an effective invitation system.
6. Quality assessments of available services, and systems planned and developed for quality-assured primary testing, rapid diagnostic referral and treatment of women with detected lesions.
7. Inclusion of all organizational elements in the planning process and piloting and gradual introduction of a new programme or a modification of an existing programme to ensure that adequate performance and quality of all components is demonstrated prior to full national or regional roll-out.

2.3 Organization of screening

Key elements of organized, population-based screening programmes include (see also Annex 1; Arbyn et al. 2008; Anttila et al. 2013; von Karsa et al. 2014a):

- A defined screening policy, including screening test, interval, and target population
- An autonomous, accountable team responsible for programme coordination and provision and quality of the screening services
- A call–recall system for inviting all eligible women to attend screening and for recall of women to repeat examinations or to additional examinations to assess abnormalities detected in screening
- Effective and appropriate detection, diagnosis and treatment services
    - Primary testing
    - Secondary testing and referral for colposcopy
    - Diagnostic confirmation
    - Treatment services
    - Post-treatment follow-up
- Quality assurance of all steps in the screening process and in all phases of programme implementation
- Centralized data systems to include: list of target population, data on performed screenings, management recommendations, assessment, and final diagnosis
- Regular monitoring based on the centralized data systems
- Screening databases linked to population, cancer, mortality, and vaccination databases and to other relevant registers in health services. These results should be used to prepare regular evaluation reports of the screening programme outcome. The reports should be made available as early as possible to stakeholders and to screened populations.

In accordance with the Council Recommendation on cancer screening (Annex 2) and the second edition of the European Guidelines and its supplements, and irrespective of the method of primary testing (cytology or hrHPV assay) cervical cancer screening should always be performed in an organized, population-based screening programme with comprehensive quality assurance covering all steps in the screening process **(VI-A).**[Rec 2.1] The population-based approach is recommended because it provides the organisational framework for effective quality assurance, and for improving the equity and accessibility of screening programmes through personal invitation of each eligible woman in the target population to attend screening (von Karsa et al. 2008).

If organized, population-based cervical screening programmes do not currently exist in a country or region, decision-makers should review the existing policy on cervical cancer screening taking into account the Council Recommendation on Cancer Screening (Annex 2), the European Guidelines for quality assurance in cervical cancer screening, second edition, and the present supplements **(VI-A).**[Rec 2.2] In countries or regions in which population-based cervical screening programmes using cytology primary testing are currently established, decision-makers should consider whether introduction of HPV primary testing in existing programmes would improve the balance between harm and benefit, taking into account the recommendations in Supplement 1, and, if so, integrate the change into the comprehensive cancer control programme (see also Suppl. 1, Rec. 1.1 and 1.36) **(VI-A).**[Rec 2.3] Irrespective of whether or not cervical screening programmes are already implemented in a country, preparation and planning for introduction or improvement of any cervical screening pro-

gramme should include a careful assessment of the economic aspects of HPV-based and cytological screening and of possible future HPV vaccinations (see Suppl. 1, Rec. 1.36; and Suppl. 3).

Effective, population-based organization is crucial in HPV primary screening because of the risk of high costs and adverse effects due to the potential for overdiagnosis and overtreatment in the absence of appropriate policies and protocols (see also Suppl. 1, Sect.1.2, Rec. 1.1 and 1.34). Non-population-based, ie opportunistic screening lacks the organizational infrastructure for effective quality assurance including strict monitoring and evaluation of the screening process and rapid response to any detected need for improvement of the service (Anttila et al. 2015). If an organized programme is not yet operational, or if an existing programme is being modified to introduce HPV primary screening, a careful planning phase and piloting is recommended to demonstrate satisfactory performance of all of the above-mentioned programme elements (see also Sect. 2.2 and Annex 1). Pilot studies or programmes can be randomized or non-randomized, depending on the programme or modification of a programme that is being introduced (Anttila et al. 2008). Randomized health-services studies (Hakama, Malila & Dillner 2012) or large-scale randomized controlled trials (RCTs) with relevant outcome analyses may also be conducted to obtain information otherwise obtained through piloting. In addition to organizational aspects, such as changes in laboratory systems, integration of screening services within existing health care services, legal issues, data sources, and registers, pilots can also provide information relevant to validity issues in the diagnostic and clinical service, information relevant to acceptance, health behaviour, and the effect of the screening programme on quality of life in the target population. Of prime importance is the availability and sustainability of adequate human, financial, and technical resources to ensure that the programme achieves an appropriate balance between benefit and harm (Annex 1) (Lynge et al. 2012, von Karsa et al. 2013).

It is also important to consider both the advantages and the potential problems of basing cervical cancer screening programmes on primary testing for HPV rather than cytology testing, including, for example the conversion of substantial capacity for cytology services in existing programmes. If, as is recommended in Suppl. 1, Rec. 1.36, health economic factors are taken into account in decision making, and adequate measures are taken to assure correct use of an HPV primary test in cervical cancer screening programmes, most scenarios for cervical cancer screening under the conditions expected in the EU member states will favour population-based programmes based on HPV primary testing (see Suppl. 1, Sect. 1.8). In HPV-based programmes, the volume of cytology testing and cytopathology resources required for effective cervical screening programmes will be substantially reduced because cytology will only be required in management of women with a positive HPV primary test (see Suppl. 1, Rec. 1.14 and 1.24). The significantly lower requisite capacity for high quality cytopathology laboratories for cervical screening based on HPV primary testing may be decisive in overcoming barriers to successful implementation of population-based programmes in countries or regions currently lacking sufficient capacity for cytology primary testing.

If a decision is made to move to HPV primary screening in a setting with an established cytology-based programme, cytology will move from being a primary test to being part of the diagnostic work-up, and therefore the type and volume of work will change: for example, a much higher proportion of slides will show abnormalities. In addition, it is important that cytologists do not lose specificity despite awareness that slides are from HPV-positive women ('HPV-informed' cytology). Cytopathologists and pathologists interpreting slides from HPV-positive women will require special training, appropriate quality control, and careful monitoring of the predictive value of cytology triage. The cost per participating woman of HPV testing need not exceed that of conventional cytological screening, especially when the cost of cytological screening is higher than in low-resource settings.

The quality assurance and organization of HPV testing facilities also requires attention (see also Suppl. 1, Rec. 1.35). Due to greater automation in laboratory processing and reading than in cytology screening, HPV testing can yield highly reproducible results with substantial economies of scale. Laboratory size and volume are also relevant for quality and the requisite centralization of facilities will

generally result in fewer laboratories compared with cytology-based screening. The respective consequences must be taken into account in the organization of services.

Any cervical screening programme based on HPV primary testing requires a clear protocol for management of HPV-positive women (see Suppl. 1, Rec. 1.11-1.13). This is particularly important with HPV screening in order to avoid high costs and a high level of adverse effects. Protocols must also cover the different situations in which the HPV test is positive but the cytology test or colposcopy is negative (see Suppl. 1, Rec. 1.16, 1.20, 1.21, 1.23, 1.24, 1.28). It is advisable that the frequency of referral for management (triage, repeat tests, colposcopy, biopsy) does not increase substantially with HPV-based screening compared with conventional screening. If conventional screening has never been evaluated and it has occurred with very short intervals, the cumulative burden of recommendations and assessments with organized HPV screening should decrease. Several new triage procedures, such as molecular markers and HPV genotyping, are currently being evaluated, but the available evidence is not sufficient for them to be recommended. Therefore, it is important that protocols for management of women with positive HPV tests are regularly reviewed (see Suppl. 1. Rec. 1.22). It should be kept in mind that an organized, population-based programme provides the organizational framework for successful implementation of updated evidence-based management protocols, and that new protocols should not be adopted until they have been validated (von Karsa et al. 2014a).

Policy makers should also be aware that the experience in Europe shows that successful implementation of population-based cancer screening programmes requires long-term political commitment, and sustainable resources (Annex 1) (Lynge et al. 2012). In a fully established programme, the proportion of the expenditure devoted to quality assurance should be no less than 10–20%, depending on the scale of the programme (von Karsa et al 2013). In the initial years, this proportion may be substantially higher due to the low volume of screening examinations compared with the situation after complete rollout of a nationwide programme. When resource limitations are a particularly strong barrier to programme implementation (eg, in several countries in Central and Eastern Europe, see Sect. 2.3.3) programme planning and management should focus on what is essential and sustainable, keeping in mind that quality-assured programme implementation involves phased rollout, generally over a number of years, therefore avoiding a sharp rise in expenditure. If, despite geographically phased rollout, adequate resources are not available to invite all the age groups in the target population at the intended screening interval, the age range, and hence the number of lifetime tests, should be limited initially. Subsequent assessments should be used to learn how the available resources can be used in the most cost-effective manner. Otherwise, the lack of adequate resources is likely to result in inferior quality and coverage, with unacceptable consequences for the balance between benefit and harm, and for cost-effectiveness.

2.3.1 Screening in EU countries with organized, population-based programmes

Countries that have already established well-organized, population-based screening programmes with comprehensive quality assurance as recommended in the second edition of the European Guidelines are well-prepared to follow through on the essential policies and organization of cervical cancer screening mentioned above (see Anttila et al. 2009). Despite this favourable situation, implementation of HPV primary screening in these countries also requires adequate development of all of the elements of organized, population-based screening (see Sect. 2.2) and all of the key policies mentioned above and in Suppl. 1 (see Rec. 1.1 – 1.36; Sect. 1.3 – 1.5, 1.7 and 1.8).

In addition, any country implementing organized, population-based HPV primary screening should take action to discourage non-organized screening activities in asymptomatic women, in order to minimize the potential adverse effects and to optimize cost-effectiveness (Anttila et al. 2008). Oppor-

tunistic screening is associated with underuse of screening capacity in a sizeable proportion of the target population, and too intensive screening in the rest of the population. Unnecessary screening in some women will increase adverse health effects and will have a negative impact on cost-effectiveness, in addition to promoting inequity due to lack of coverage of other women in the target population (Arbyn et al. 2008; see also Anttila et al. 2013). The potential for negative effects of opportunistic screening that is not controlled by the quality assurance of an organized programme is pronounced with HPV primary screening (see Suppl. 1, Sect. 1.2). To avoid side-effects that would result from unnecessarily aggressive management of HPV-positive women, it is also essential to include management of women with positive test results, and diagnostic work-up within the scope of services organized by a population-based screening programme. Decision-makers and responsible authorities should ensure that adequate resources are provided for the sustainability of appropriate diagnostic services for symptomatic women.

For the above reasons, if a decision is made to implement HPV primary testing in an existing population-based cervical screening programme, comprehensive planning, feasibility testing and pilot programmes should be conducted prior to routine implementation to ensure that an appropriate balance between harm and benefit is achieved in the transition to HPV primary screening, including effective and efficient use of resources (see also Annex 1) **(VI-A).**[Rec 2.4] The responsible coordinator preparing a pilot programme should identify and highlight the changes in organization required, among other things, for the conversion from a cytology-based system and for optimal organization of HPV primary testing. Pilot projects also provide the opportunity to clarify the costs of routine implementation. In countries in which significant volumes of screening tests are performed outside organized, population-based programmes (e.g. in Finland or parts of Italy) the capacity should be redirected to more cost-effective use in organized, population-based screening.

2.3.2 Screening in EU countries with opportunistic policies

If a decision is made to implement a population-based cervical screening programme in a country or region previously lacking such a programme, comprehensive, planning, feasibility testing and piloting must not only take into account the selected method of primary testing (cytology or HPV testing). Special attention must also be paid to testing and developing the capacity for a population-based approach to programme implementation including building up comprehensive quality assurance for all steps in the screening process and for coordination, training, monitoring and supervision, and evaluation of the programme (see also Annex 1 and 2) **(VI-A).**[Rec 2.5] Although the same principles of comprehensive quality assurance described in the Council Recommendation (Annex 2) and the second Guidelines edition apply in any setting, implementing a population-based screening programme for the first time in any country requires significant effort over a period of up to several years due to the lack of population-based infrastructure for programme monitoring, evaluation and management, and the lack of experience in the complex process of coordinating other aspects of programme implementation (see Annex 1) (von Karsa et al. 2008, see also Anttila et al. 2013).

The capacity for testing and treatment in the health care system is usually sufficient, and in a number of countries there is even excess capacity reflecting inefficient use of available resources (Anttila et al. 2009). However, if the testing and diagnostic services used in the screening programme are not well organized, then cervical screening can substantially increase overall costs and adverse effects, particularly if screening is based on HPV primary testing. Under such conditions, achievement of the intended impact of screening would be unlikely. Of prime importance is not only the planning and piloting of the invitation system and the information provided to ensure that all eligible women are able to make an informed decision about participation. Considerable attention must also be paid to organization and quality assurance of laboratory and other diagnostic services, including mandatory

protocols for sample-taking, testing, and triage procedures, and for management of HPV-positive women, including systematic fail-safe mechanisms to ensure that all women with positive test results are followed up (see Suppl. 1, Rec 1.34 and 1.35). Systems for comprehensive registration, monitoring, and evaluation must also be developed and tested and modified, if necessary to achieve optimal performance. All related services, including those that occur outside the planned programme, should be reviewed in terms of adherence of the medical professionals and the screened population to the recommended screening policies and professional guidelines. Nationwide rollout of a population-based screening programme should not begin until piloting has demonstrated that screening performed according to the adopted programme policies achieves key targets of quality and efficiency and is accepted by the population (see Annex 1) (see also von Karsa et al. 2012 and von Karsa et al. 2014b).

2.3.3 Screening in Central and Eastern Europe

Pilot programmes in the 'new' member states that acceded to the EU after 2003 have often encountered barriers in organizing screening. For example, understanding of the concept of screening has been limited in the population and among medical professionals (Todorova et al. 2009; Valerianova et al. 2010), attendance has been low (eg only 15–40%) (Anttila & Ronco 2009; Kivistik et al. 2011; Nicula et al. 2009), and performance suboptimal (Ronco et al. 2009). Systematic quality assurance, including the responsibilities of the professionals involved, may be poorly defined if not lacking throughout the complex screening process (Anttila et al. 2013). In many new EU member states, a substantial but ill-defined amount of opportunistic screening is conducted (Veerus et al. 2010) and linkage between screening participation and outcome is generally not available (Anttila et al. 2010). Consequently, the impact of large numbers of samples taken outside the organized, population-based programme has not been evaluated. Moreover, in many cases the same professionals participating in the programme also take samples outside the programme. But they do not inform women adequately about the opportunities and risks of participating in the screening programme; nor do they take into account the full screening history and relevant management protocols. A special problem is that in some settings very large numbers of cervical samples are taken for cytological analysis, but the methods used for processing the slides are neither validated nor recommended by the European guidelines. (von Karsa et al. 2012). The substantial shortcomings prevent or severely limit any impact of these extensive efforts on the burden of cervical cancer in the population, as reflected in the high rates of cervical cancer incidence and mortality in these countries, despite consumption of considerable health resources (Anttila et al. 2009, see also Anttila et al. 2013).

Some new EU member states have sufficient, or even excess capacity for delivering screening services (Anttila & Ronco 2009), whereas others lack capacity. For the former group of countries, the challenges to improve the conventional programmes and to introduce novel tests are the same as described above for countries with organized, population-based programmes based on cytology (Sect. 2.3.1). Due, however, to lack of experience and infrastructure for population-based screening, dedicated coordination of efforts to develop viable pilot projects for population-based cancer screening frequently lacks adequate, sustainable support (Anttila et al. 2013). The experience in the new EU member states therefore demonstrates the importance of a lesson learned in the cancer screening networks originally established in the Europe Against Cancer programme: the introduction of new population-based screening programmes should be coordinated by a unit with a comprehensive mandate and sufficient autonomy and resources to ensure that the European quality assurance guidelines are followed and that international experts familiar with the process and determinants of successful programme implementation can be consulted (see Annex 1) (**VI-A**).[Rec 2.6]

2.3.4 HPV vaccination and screening programmes

The evidence on which the current European recommendations for quality assurance in cervical cancer screening are based was obtained in populations that have not been immunized *en masse* with preventive HPV vaccines, i.e. populations from the pre-vaccination era. HPV vaccines are already in general use in several EU member states (see Suppl. 3). Vaccination of young cohorts that have not been infected with HPV will have an important impact on the future burden of HPV infections and corresponding disease, and therefore also on the performance and impact of cervical screening programmes (Franco et al. 2006; Kiviat, Hawes & Feng 2008; Lynge et al. 2009; Meijer et al. 2008; Ronco & Giorgi-Rossi 2008). Direct evidence of the cost and effectiveness of different screening protocols in vaccinated women is currently lacking, however, making this subject a high research priority. Mathematical modelling can provide relevant information, and randomized controlled screening trials conducted among vaccinated women are also likely to be informative.

Based on current knowledge, even in countries where mass vaccination of young cohorts is implemented, effective screening will need to continue for both vaccinated and unvaccinated women (Arbyn et al. 2010; Bosch et al. 2008; Lynge et al. 2009). Screening of women inoculated with the currently available bivalent or quadrivalent vaccines will be necessary because of the vaccines' incomplete protection against cervical cancer (see Suppl. 3). Due to unavailability of sufficient evidence, the present supplements do not include recommendations tailored to the needs of vaccinated women. This topic should be addressed in future editions of the European Guidelines. Given the potential of linkage between screening and vaccination data to reduce the requisite future volume of cervical cancer screening, register-based data collection on vaccinations, and development of procedures to permit linkage of screening and vaccination data in the management of screening programmes should not be delayed (Anttila et al. 2015). This capacity should be used to reduce harm by avoiding unnecessary screening examinations and may also be used to improve primary prevention of cervical cancer through more effective monitoring of HPV vaccination.

2.3.5 Screening of HIV-positive women

Cytopathological and histopathological lesions of the cervix are 5–6 times more common among HIV-positive than among HIV-negative women (Holmes et al. 2009; Russomano et al. 2008). Of HIV-positive women, 15–20% have CIN lesions. In addition, the prevalence of vulvovaginal dysplasia is 5–7 times higher in this group than in the female population as a whole (Chiasson et al. 1997; Ellerbrock et al. 2000).

In HIV-positive women, histopathological changes progress and recur after treatment more often than among other patients. CIN lesions recur in 40–60% of HIV-positive women irrespective of the treatment methods used. Antiviral medication increases the spontaneous regression of CIN lesions among HIV-positive women and improves the permanent effects of treatment (Heard et al. 2002; Holcomb et al. 1999; Lima et al. 2009; Russomano et al. 2008; Spitzer 1999; Wright, Jr. et al. 1994).

HIV-positive women should have primary cervical screening and repeat testing at shorter intervals than the general female population. In the case of routine screening, experts currently recommend bi-annual cytology during the first year after HIV diagnosis and, if the results are normal, subsequent annual screening (Kaplan et al. 2009). One study including 1534 HIV-positive women reported that a 2-yearly screening interval would be safe and that no benefit resulted from an initial routine screening by colposcopy (Kitchener et al. 2007). It should also be noted that even mild cytopathological changes

often indicate CIN lesions in HIV-positive patients; hence these women should have colposcopy even if only one cervical smear indicates the presence of an abnormality (Kaplan et al. 2009; Spitzer 1999; Wright, Jr. et al. 1996).

Experts recommend similar use of HPV testing in HIV-negative and HIV-positive women. Similar protocols can also be used for management of CIN lesions in HIV positive women. It is very important to take the likelihood of compliance with management recommendations into account (Massad et al. 2004). Colposcopic examinations for HIV-positive women should be centralized in units with special expertise in the treatment of HIV infections.

2.4 Strategies to optimize coverage and participation

Coverage of cervical cancer screening has been reported to vary from 10% to 79% in EU Member States, reflecting not only differences in key factors that impact directly on uptake, such as type of organisation, communication, and methods of invitation, but also differences in the status of programme implementation, eg: piloting, rollout ongoing, or rollout complete (Anttila et al. 2009). Differences in uptake have been related to age/birth cohorts, and the difficulty of reaching women in less advantaged socioeconomic groups, immigrants, and other specific population groups (Lancuck, Patnick & Vessey 2008; Lancucki et al. 2010; Rodvall et al. 2005). The more recent studies describe a declining trend in uptake by younger women. These figures indicate in broad terms variations in the perceptions and understanding of screening that influence the level of acceptance by the target population, decision-makers, and medical professionals. The variations also relate to different models of service provision, and to differences in the type, sample taker, and earlier patterns of use of screening services, as well as the availability of screening outside official programmes. The number of lifetime screens offered also may have an effect on uptake. It should be kept in mind that most studies examining methods to improve coverage have involved cytological screening programmes. Findings are not available that would shed light on the question of whether participation in a routine HPV screening programme may depend on the same factors that affect conventional programmes, but it is plausible to assume both types of programme are similar in this regard. An important difference is the opportunity to increase screening participation and coverage through appropriate integration of self-sampling into the process of HPV primary testing (see Sect. 2.4.4).

Irrespective of any strategies adopted to ensure that cervical cancer screening is fully accessible to all eligible women (for key strategies see Sect. 2.4.1-2.4.3) good knowledge of and strong support for a screening programme by the health care providers in the area served by the programme is of prime importance. By providing balanced information to women and encouraging them to consider the information provided about attending screening and adhering to relevant policies on follow-up and treatment in the event that abnormalities are detected, local health care providers can help to ensure that many women can make an informed decision. That is key to promoting high compliance throughout the entire screening process.

2.4.1 Reduction or elimination of participation fee

Financial incentives for patients are effective in improving use of preventive services such as screening (Stone et al. 2002). Financial interventions such as reducing patient payments or co-payments are effective in increasing participation in cervical screening. Hence, screening should be free of charge or subject to only a limited charge for women who attend, regardless of whether cytological or HPV screening is offered **(I-A).**[Rec 2.7]

2.4.2 Personal invitation letter with appointment time, date and place

A personal letter of invitation is the recommended method for increasing attendance and coverage of cervical screening **(I)** (Black, Yamada & Mann 2002; Buehler & Parsons 1997; Pierce et al. 1989; Segnan et al. 1998; Torres-Mejia et al. 2000). Invitation letters that contain a scheduled appointment (date, time, and place) are more effective than invitations with open appointments **(I)** (Everett et al. 2011, Jepson et al. 2000, Giorgi-Rossi et al. 2012, see also Camilloni et al. 2013). Coordination of information campaigns and tailored information in the invitation letter are helpful. Personal invitation letters to participate in screening should therefore include an appointment (date, time and place) and instructions on how to change the appointment if necessary **(I-A).**[Rec 2.8]

Using a personalized invitation from the woman's primary health care provider increases compliance with screening in settings that rely predominantly on GPs as the point of contact for outpatient services **(II)** (Bowman et al. 1995, de Nooijer et al. 2005). However, the overall participation rates reported in the retrieved studies were limited (<50%).

2.4.3 Personal reminder

Overall, reminders to non-attending women appear to be effective at increasing screening participation and hence also coverage (Kupets & Covens 2001, Stone et al. 2002, Yabroff, Mangan & Mandelblatt 2003) **(I)**. Both telephone reminders, and reminder letters are effective (Stone et al. 2002, Yabroff, Mangan & Mandelblatt 2003; Everett et al. 2011; Acera et al. 2014) **(I)** and reminder letters with a scheduled appointment are likely to be more effective than open reminder letters (Wilson & Leeming 1987) (see also sect. 2.4.2) **(II).**[Rec 2.9] For women who are invited but do not attend, one reminder letter (Burack et al. 1998; Eaker et al. 2004; Hermens et al. 2000; Kupets & Covens 2001) or a reminder by telephone (Eaker et al. 2004; Broberg et al. 2013) has been recommended. Two reminders, first by letter and then by telephone are also an option (Eaker et al. 2004). Attendance after a reminder letter was at 16% (increase in overall coverage, 9.2%; 95% confidence interval [CI], 7.9–10.9%, compared with those who did not receive a reminder). Attendance after a telephone reminder was available from a sample of non-attenders: 41% (gain in coverage, 31.4%; 95% CI, 26.9–35.9%). The cumulative attendance after these two interventions was reported at approximately 50% among those who had not attended after the initial invitation letter (Eaker et al. 2004). Increased attendance based on this strategy has been demonstrated also in a trial in the USA (Vogt et al. 2003) **(I)**. In addition, among those who attended in the telephone-reminder arm, the

frequency of cytological abnormalities and precancerous lesions was increased, indicating a good response in a population at higher than normal risk (Eaker et al. 2004).

Three other RCTs have also evaluated the effect of telephone reminder versus invitation by a letter only or with a reminder by letter (Vogt et al. 2003; Oscarsson et al. 2007, Heranney 2011); and a review has been published by Giorgi Rossi et al. (2012). Based on the three first trials, Giorgi-Rossi concluded that the trials have shown a positive effect of a telephone reminder in the uptake of cervical screening (Giorgi Rossi et al. 2012; see also Camilloni et al. 2013). However, in the French RCT the uptake after a telephone reminder was only modest, 6.3% (95% CI: 5.6–7.0%) at 8 months, and not statistically significantly different from that following a reminder letter (Heranney et al. 2011). There are examples, however, of programmes where this reminder strategy has not worked well (Stein et al. 2005; Haguenoer et al. 2014) indicating that a programme needs to tailor its overall strategy to an acceptable level of attendance and coverage with the help of appropriate studies to determine the reasons for low attendance, and to test effective interventions.

In conclusion, personal reminder letters with a scheduled appointment (date, time and place) and instructions on how to change the appointment, if necessary, should be sent to non-attending women **(I-A).**[Rec 2.9] A second personal invitation reminder should be sent if there is no response to an initial reminder **(I-B).**[Rec 2.10] Personal invitation reminders may also be delivered by telephone call, provided women who are not reached by telephone are sent a reminder letter **(I-B).**[Rec 2.11] However, telephone reminders may require more resources than other strategies; hence more investigations on this topic are needed. Programmes may also consider other e-based mailing methods for reminders and primary invitation than letters, for example, via mobile phones. Pilot studies should be conducted prior to adoption of new invitation and reminder methods to ensure their feasibility and effectiveness.

2.4.4 Self-sampling

There is sufficient evidence from randomized studies that offering self-sampling for HPV testing is an effective method to increase attendance and coverage of screening compared with standard recall letters to non-responders, re-inviting them to attend for clinician-based sampling (Pap test) **(I)** (Giorgi Rossi et al. 2011; Gök et al. 2010 and 2012; Piana et al. 2011; Szarewski et al. 2011; Virtanen et al. 2011; Wikström et al. 2011; Broberg et al. 2014; Haguenoer et al. 2014; Cadman et al. 2014). However, the possibility of selection bias and survey instrument measurement error may have led to overestimation of women's favourable opinions about self-sampling. No data are available yet on the impact on further prevention of cervical cancers by means of self-sampling versus other strategies to increase participation and coverage. A self-sampling option may increase screening coverage, but anxieties of women about screening must still be addressed **(V)** (Giorgi Rossi et al. 2014; Virtanen et al. 2014).

In a trial in the Netherlands, a self-sampling invitation as a second reminder increased participation by approximately 27% among women who had not attended after receiving a primary invitation and a reminder letter (Gök et al. 2010). The control group, although small, received a second reminder letter; attendance was increased by 16% among them ($p < 0.001$). Self-sampling also reached women with increased risk of precancerous lesions. In the study, self-sampling responders who had not participated in the previous invitational round of screening had an increased risk of detected CIN2 and CIN3+, compared to self-sampling among women who had been screened in the previous round (Gök et al. 2010).

Previous experience in trials also demonstrates that the number of women with missing information about further assessment and treatment is a potential problem that should be clarified before routine

implementation of self-sampling (Haguenor et al. 2014 and Cadman et al. 2014). Restricting self-sampling to organized, population-based screening programmes with comprehensive quality assurance will help to minimize adverse effects and avoid potential excessive cost increases. Hence, self-sampling outside organized population-based screening programmes is not recommended.

As explained in Suppl. 1, Sect. 1.7, the sensitivity of HPV testing on self-collected samples taken for cervical screening is lower than on clinician-collected samples. For this reason, and also because of the heterogeneity in results between studies, self-sampling should not be the primary option for women participating in cervical cancer screening. The clinical accuracy of HPV testing performed on self-samples taken to obtain material for HPV primary screening is sufficient, however, to conduct organized, population-based pilot programmes for women who have not attended screening despite a personal invitation and a personal reminder (see also Rec 2.8-2.13 and Suppl. 1, Rec 1.32).

To improve participation and coverage, piloting self-sampling for women who did not participate in primary HPV screening despite a personal invitation and a personal reminder is recommended, provided it is conducted in an organized, population-based screening programme with careful monitoring and evaluation of the aimed performance and outcomes (see Suppl. 1, Rec. 1.32 and 1.36) (**I-A**).[Rec 2.12] Prior to rollout towards national implementation, a self-sampling pilot project should demonstrate successful results compared to clinician-based sampling (positivity rate, positive predictive value of a positive test result, and cost-effectiveness); the pilot should also demonstrate that key organizational problems, such as the appropriate screening interval and compliance with invitation and management protocols for women with positive test results, have been adequately resolved (**III-D**).[Rec 2.13]

2.5 Communication

Recommendations on awareness, communication and dissemination of information about cervical cancer screening have been published in the second Guidelines edition (Giordano et al. 2008). A key challenge for screening programmes implementing HPV primary testing will be developing ways of communicating accurate information about benefits and the associated risks that help women to understand the relevant and interrelated issues of cervical cancer prevention and control through screening and vaccination. Appendix 2, Sect. 1.2.4 of the second edition includes key messages about cervical cancer and HPV that explain, among other things: the causal role of HPV in cervical cancer, the common sexual transmission of HPV, possible uses of HPV testing in cervical cancer screening, and the importance of continuing cervical cancer screening after introduction of HPV vaccination. Updated guidance including information about HPV vaccination, HPV testing and the implications of positive or negative test results is a priority for future updates of the European Guidelines. A recent example of information designed to inform women and the general public about HPV primary screening is available on the website of the NHS Cervical Cancer Screening Programme in England (Public Health England 2015).

2.6 Evaluation and monitoring

Principles of information systems, and the importance of continuous evaluation and monitoring of cervical cancer screening, have been described previously (Anttila et al. 2008; IARC 2005; Ronco, von Karsa & Anttila 2008). These principles of quality assurance apply equally to screening based on cytology or HPV primary testing. Evaluation and monitoring should cover all services in the screening process, including clinical services that that are not directly managed by the programme (Anttila et al. 2008). HPV primary screening can markedly increase rates of referral for repeat testing or diagnostic work-up, unless appropriate protocols are adhered to; monitoring is therefore particularly important to control human and financial costs.

As indicated in Sect. 2.3 and in the second Guidelines edition, evaluation requires outcome information reflected in cervical cancer incidence and mortality, as well as process information. The latter includes information about performance of screening tests and the treatment burden, not only in the screened population, but also the entire target population (ie including women examined outside the programme and non-attenders). In addition, studies on behavioural aspects, quality of life, and potential harms should be systematically conducted. Population-based cervical screening programmes should therefore be monitored using performance parameters defined in the European Guidelines (current Suppl. 2, and Chap. 2 and 7 of the second edition) **(VI-A).**[Rec 2.14]

The design of data input formats and tables for monitoring HPV primary screening (cf A and B Tables in Chap. 2 of the second edition) depends greatly on how HPV testing is integrated into a screening programme, and on the protocols adopted. Given the current diversity in the development of HPV primary screening protocols, and management protocols for women with a positive HPV primary test result (see Suppl. 1, Sect. 1.3-1.5) and the rapid evolution of relevant knowledge, further work is required to develop standard monitoring tables and data input formats for HPV primary screening programmes. In the meantime, the tables in the second edition of the European Guidelines can serve as examples that may be adapted to the conditions in pilot studies and in the preparation of rollout of successfully piloted HPV primary screening programmes. Some of the current A and B tables are generic and can already be applied to screening based on HPV primary testing without or with only minimum modification. These include the following tables; they may also be used separately for programmes piloting or implementing HPV primary screening in middle aged or older women, and cytology-based screening in younger women (see Suppl. 1, Rec. 1.2 - 1.7):

Table A1 Definition of the target population

Table A2 Mode of invitation

Table B1 Invitations, coverage by invitation, and status of target population in the cervical cancer screening programme in the year _____

Table B5. Number of women referred for colposcopy in the cervical cancer screening programme in the year _____

Note: for HPV primary testing: the breakdown by cytology applies to the result of the triage test. Women can also be referred as a result of the overall "cytology triage" process but without having abnormal cytology. For example, those who are positive at 1-year HPV test repeat. Also indicate no. of women referred without cytology triage, if any.

Table B6. Compliance with referral for colposcopy in the cervical cancer screening programme in the year _____

Note: for HPV primary testing: the breakdown by cytology applies to the result of the triage test. Women can also be referred as a result of the overall "cytology triage" process but without having abnormal cytology. For example, those who are positive at 1-year HPV test repeat. Also indicate no. of women referred without cytology triage, if any.

Table B7. Cytological and histological results of women who had colposcopy in the cervical cancer screening programme in the year _____

Note: for HPV primary testing: the breakdown by cytology applies to the result of the triage test. Women can also be referred as a result of the overall "cytology triage" process but without having abnormal cytology. For example, those who are positive at 1-year HPV test repeat. Also indicate no. of women referred without cytology triage, if any. Compute PPV broken down by reason of referral.

Table B8. Women with histologically confirmed CIN or invasive cancer by age group in the cervical cancer screening programme in the year _____

Table B9. Treatment performed for CIN/Invasive Cancer in the cervical cancer screening programme in the year _____

2.6.1 Key performance indicators

Performance indicators using standard definitions must be used to continuously measure the quality of the screening process and to assess its potential longer-term impact. The second Guidelines edition (Chap. 7) recommended three groups of performance parameters for monitoring population-based cervical screening programmes):

- screening intensity
- screening test performance
- diagnostic assessment, treatment, and post-treatment follow-up.

Some parameters require adaptation to changes in the screening protocol. An outline is presented here of the parameters that should be changed when primary HPV testing is used in cervical screening. A review is recommended after more experience has accumulated in practical implementation.

If HPV primary screening and cytology-based screening are implemented for women in different age ranges, the respective indicators that are specific to HPV and cytology screening should always be calculated separately. The other indicators should be calculated jointly, and separately, to monitor performance overall, as well as in the respective programmes.

Due to limited available information from screening programmes in Europe, achievable and desirable benchmarks are only provided for three of the following indicators (coverage by invitation, coverage by examination, and participation rate).

- **Screening intensity**

The same parameters defined in the second edition, for cervical cancer screening based on cytology (see Chap. 7 and parameters 1-6 below) can be used for HPV primary screening, taking into account that different tests are referred to. The recommended interval with cytological screening is 3–5 years. Since prolonged screening intervals are appropriate with HPV testing, the authors have assumed an

interval of 5 or 7 years for HPV primary screening; intervals up to a maximum of 10 years would be compatible with the recommendations in Suppl. 1 (see Rec. 1.8):

1. Programme extension
2. Coverage of the target population by invitation
3. Coverage of the target population by smear tests / HPV primary tests
4. Compliance with invitation (participation rate)
5. Smear consumption / HPV primary test consumption
6. Incidence of invasive cancer in unscreened and underscreened women in a given interval (3.5 or 5.5 years for cytology-based screening; and 5.5 or 7.5 years for HPV primary screening)

European benchmarks: Note that for three parameters (coverage of the target population by invitation, coverage by examination; and compliance with invitation [participation rate]) European standards are now recommended in order to maximize the impact of screening: The feasibility of the benchmarks has been demonstrated in screening programmes in the EU (Anttila et al. 2009).

- Programmes should achieve an invitation coverage of 95% (acceptable level) **(III-A)**; >95% is desirable **(III-A)**.[Rec 2.15]

For calculation of invitation coverage, the number in the numerator is the number of women invited during a given time frame. The number in the denominator is the number of women in the target population during a given time frame.

- Programmes should achieve an examination coverage of 70% (acceptable level) **(III-A)**; >85% is desirable **(VI-A)**.[Rec 2.16]

For calculation of examination coverage, the number in the numerator is the number of women examined during a given time frame. The number in the denominator is the number of women in the target population during a given time frame.

- Programmes should achieve a minimum participation rate of 70% (acceptable level) **(III-A)**, >85% is desirable **(VI-A)**. [Rec 2.17]

For calculation of the participation rate, also referred to as 'compliance with invitation' in the second edition, the number in the denominator is the number of eligible women invited during a given time frame. The number in the numerator is the number of women invited and screened by primary testing during a given time frame. It should be noted, however, that some women who attend screening and require management due to a positive test result may not comply with the entire management protocol and therefore the entire screening episode may not be completed despite failsafe procedures. Programmes should monitor and regularly review such cases to minimize dropouts.

In countries or programmes that only invite non-attenders, invitation coverage and participation rate should be calculated twice (one rate with only those women actually sent an invitation included in the respective calculations, and the other rate with the number invited including those actually invited as well as those not invited because they attended without receiving a prior invitation sent by the programme).

In countries with programmes based on different tests (eg cytology and HPV primary testing). The benchmarks should be calculated separately for the different test types. Additional joint calculations for overall results should be performed with annual data adjusted to the length of the respective screening interval in order to obtain comparable data.

- **Screening test performance**

The key parameters for monitoring HPV screening test performance (see 7-14 below) are conceptually the same as those recommended for cytology (see second edition, Chap. 7):

- o proportion of women positive at the primary screening test
- o rate of referral for triage testing
- o referral rate for colposcopy
- o positive predictive value of referral for colposcopy
- o test specificity
- o detection rate of CIN (particularly of CIN2 and CIN3)
- o incidence of cancers that are detected in women after a normal primary test result

The latter parameters require linkage with cancer registries. Parameters 7-9 and 14 have been adapted below to the situation where HPV testing is the primary screening test. The main difficulty in defining the parameters relates to the adoption of different management protocols for women with positive screening tests, in various programmes (see Suppl. 1, Rec. 1.14-1.31). The modified parameters recommended here and defined in detail in Sect. 2.6.2 assume that HPV is the only screening test and that cytology triage is performed, as recommended in Suppl. 1. Cytology triage means that HPV-positive women are tested for cytology, referred to colposcopy if cytology is abnormal, and invited to repeat testing (HPV test alone or with cytology triage) after some time, if cytology is normal. For the definition of the following parameters, it is assumed that the cytology triage conducted for all HPV-positive women is performed as a reflux test on a liquid-based sample, or a conventional smear is taken together with a sample for HPV testing; and the conventional smear is interpreted if the HPV test is positive.

7. Distribution of screened women by the results of cytology / HPV primary test result
8. Referral rate for repeat cytology / repeat HPV primary testing
9. Compliance with referral for repeat cytology / HPV primary testing
10. Referral rate for colposcopy in cytology-based / HPV-based screening
11. Positive predictive value of referral for colposcopy after cytology / HPV primary testing
12. Test specificity
13. Detection rate by histological diagnosis
14. Cancer incidence after normal cytology / normal HPV primary test

- **Diagnostic assessment, treatment, and post-treatment follow-up**

The definitions for these aspects of the parameters remain the same as in the second edition. The incidence of invasive cancers should be computed for all:

- o invited women
- o women who participated in screening
- o women who tested negative for HPV
- o women who tested positive for HPV

For HPV primary screening, calculation of compliance to referral for colposcopy should differentiate between women referred directly and those referred after retesting (see Sect. 2.6.2).

15. Compliance to referral for colposcopy in cytology-based / HPV-based screening
16. Treatment of high-grade intraepithelial lesions
17. Proportion (%) of women hysterectomised on screen-detected intraepithelial lesions
18. Proportion (%) of women treated on CIN1
19. Incidence of invasive cancer after abnormal cytology
20. Proportion of women with cytology negative for SIL, 6 months after treatment

In conclusion, population-based cervical screening programmes should be monitored using performance parameters defined in the European Guidelines (current Suppl. 2, and Chap. 2 and 7 of the second edition) **(VI-A).**[Rec 2.14]

2.6.2 Definition of key performance parameters

The following key performance indicators are specifically related to primary HPV screening. The numbering corresponds to the numbering of the analogous key performance indicators in Chap. 7 of the second edition of the European Guidelines. For the key performance indicators that are essentially the same regardless of the screening test used, see Sect. 2.6.1.

7 Distribution of screened women by HPV test result

- Calculate overall and separately for subgroups of women:
  a. for the regular screening interval and shorter time periods
  b. attending initial or subsequent screening round, by method (primary cytology or HPV screening)

$$\frac{\text{N screened women positive for HPV}}{\text{N screened women}}$$

8 Referral rate for repeat testing

- Calculate separately for initial and subsequent screening
- Triage: of hrHPV+ women: % hrHPV+ women who have received the recommended triage test. Note: repeat testing will be needed for those who are hrHPV+ but triage–.

$$\frac{\text{N screened women advised to repeat test at shorter than regular interval}}{\text{N screened women}}$$

Distribution of triage test results

9 Compliance with referral for repeat testing

- Calculate separately for initial and subsequent screening

$$\frac{\text{N women screened following recommendation for repeat}}{\text{N women recommended for repeat testing}}$$

10 Referral rate for colposcopy

- Calculate separately:
  a. for women referred immediately (screen+, triage+) and for those referred after re-testing (screen+, triage–, report missing value if repeat not performed)
  b. for initial and subsequent screening

$$\frac{\text{N screened women referred for colposcopy}}{\text{N screened women}}$$

11 Positive predictive value of referral for colposcopy

- If the number of women for whom colposcopy was performed is not known, estimate PPV of colposcopy by calculating PPV of referral to colposcopy using the number of women referred.

- Calculate overall and separately by:
  a. women referred immediately or after test repeat
  b. histology (CIN1+, CIN2+, CIN3/AIS+, invasive cancer)
  c. initial and subsequent screening

$$\frac{\text{N screened women who had colposcopy with histologically confirmed CIN}}{\text{N screened women who had colposcopy}}$$

15 Compliance with referral for colposcopy

- Calculate separately:
  a. by different intervals after referral (3 months/6 months)
  b. for women referred immediately and for those referred after re-testing

$$\frac{\text{N screened women actually undergoing colposcopy}}{\text{N screened women referred for colposcopy}}$$

2.7 Checklist for key tasks in implementation and improvement of population-based cervical screening programmes

Screening programmes generate a very large volume of health services. Approximately 110 million women in the EU are in the age range 30-60 years which corresponds to the minimum target age for cervical cancer screening recommended in the second Guidelines edition. If women outside the minimum age range who are targeted by existing programmes are considered, then the total population targeted in the EU is approximately 150 million. Given the very large number of women involved, even small improvements in the quality, effectiveness and efficiency of the services provided can have a substantial impact on the overall balance between benefit and harm and the requisite resources (von Karsa et al. 2008; see also Commission of the European Communities 2008).

The graded recommendations provided in the present supplement underline universal principles and standards of quality assurance that should be followed in implementing cervical cancer screening programmes based on HPV or cytology primary testing. Given the complexity of the screening process, the present recommendations cannot cover all essential aspects. Of great importance are not only the careful consideration of the content of the other supplements and the previously published second edition. Successful implementation of any cervical cancer screening programme also requires a coordinated, comprehensive approach to the overall process of programme planning and management. To ensure that appropriate steps are taken at the appropriate time, programme management must not only be aware of the organizational issues described in Sect. 2.3; additionally relevant clinical, scientific and managerial issues are outlined below in checklist format. Programme coordinators are encouraged to modify and expand the list to take into account the conditions in their countries or regions.

Checklist for key tasks in implementation and improvement of population-based cervical screening programmes

Indicate the status in the brackets [ ] using the following code, or a similar approach:

R-N: reviewed, not relevant	R-R: reviewed, relevant
P-O: planning ongoing	P-C: planning completed
F-O: feasibility testing ongoing	F-C: feasibility testing completed
P-O: piloting ongoing	P-C: piloting completed

1. [ ] Definition and adoption of the standard organizational model for implementing cervical cancer screening (conventional cytology-based and/or HPV primary screening) in the programme (see current Annex 1 and Sect. 2.3; see also Chap. 2 in the second Guidelines edition).
    a. [ ] Coordinator appointed with appropriate mandate and oversight to manage the process of planning and quality-assured implementation of the programme
    b. [ ] Autonomous team with appropriate, sustainable budget provided for the coordinator
    c. [ ] Legal framework established for the smooth functioning of the coordination team.
    d. [ ] Legal framework established for quality-assured programme implementation
        i. [ ] Programme coordination and oversight
        ii. [ ] Studies to test feasibility
        iii. [ ] Pilot studies / programmes

iv. [ ] Rollout phase

v. [ ] Routine implementation

vi. [ ] Quality assurance including training, documentation, cancer and screening registration, technical aspects, accreditation, monitoring and evaluation

2. [ ] Definition and adoption of the same model as in 1. across the country for cytology and HPV (if applicable) primary screening.

3. [ ] Policies and legally binding agreements, official regulations or legislation defined and adopted to demonstrate appropriate integration of all related health-care services (e.g. tests and treatments that may have been performed earlier outside the programme) into the services managed or provided directly by the programme (ie the programme has the mandate, authority and appropriate budget to manage these):

   a. [ ] Who defines and who provides the requisite data to invite the eligible women?

   b. [ ] Who takes the samples?

   c. [ ] Who analyses the samples?

   d. [ ] Who informs women about the results?

   e. [ ] Who recommends clinical management / makes referrals?

   f. [ ] Who coordinates further clinical management?

   g. [ ] Who performs colposcopic / histologic diagnosis, treatment / management?

4. [ ] Special planning for integrating primary HPV testing into the screening programme (if applicable). These are important topics from the organizational viewpoint, but also in relation to efficacy and adverse effect outcomes from longitudinal studies (see Suppl. 1, Sect. 1.2.2 and 1.8).

   a. [ ] Process of triaging women with a positive screening test result

      i. [ ] triage methods

      ii. [ ] management procedure for women with a negative triage test

   b. [ ] Interval for re-testing

   c. [ ] Criteria, based on re-testing results, for:

      i. [ ] colposcopy referral

      ii. [ ] return to a normal screening interval

      iii. [ ] follow-up after treatment

5. [ ] Benchmarks for the respective test (cytology or HPV) defined, taking into account local and national conditions; and adopted for planning, feasibility testing, and piloting to test implementation under routine conditions throughout the screening process that includes: 1) information for women and professionals, 2) invitation, 3) performing the screening examination/test, 4) management of screen positives (ie triage, repeat testing and referral to colposcopy), 5) treatment and treatment follow-up (see below):

   a. [ ] Sect. 2.6 defines 3 benchmarks with acceptable/desirable levels: 1) coverage by invitation (95%/>95%), 2) coverage by examination (70%/>85%) and participation rate (70%/>85%). Are these benchmarks adopted for the programme?

   b. [ ] Other benchmarks defined and adopted for the screening process, in addition to those in 5.a. (for example, documentation of training, or laboratory accreditation/re-accreditation).

c. [ ] Benchmarks defined and adopted for adherence of the medical practitioners and other staff to the EU guidelines (Suppl. 1 and 2, and second edition).

d. [ ] Other benchmarks defined and adopted in addition to those in 5.c. for adherence of the medical practitioners and other staff to national / regional guidelines.

e. [ ] Benchmarks defined and adopted to demonstrate appropriate perceptions and understanding by the invited / participating women and the medical professionals and staff in addition to achievement of appropriate coverage and participation as indicated in 5.a. (eg proficiency testing).

f. [ ] Benchmarks defined and adopted to demonstrate that overuse of testing can be / has been avoided (eg opportunistic/spontaneous testing or testing at shorter intervals or younger ages than recommended by the programme).[23]

g. [ ] Benchmarks defined and adopted to demonstrate successful fail-safe mechanisms to ensure that women with positive tests are managed, and if necessary diagnosed and treated adequately.

h. [ ] Benchmarks defined and adopted to demonstrate that women who drop out of the screening process (management of screen positives, diagnosis and treatment) are dealt with adequately (see also 5.g.).

i. [ ] Benchmarks defined and adopted to demonstrate that the programme policies for management of screening positives, diagnosis and treatment are adhered to by the health-care professionals involved (see also 3., 4., and 5.d.).

6. [ ] Continuous monitoring of performance, and evaluation (see also 7.) of:

a. [ ] test validity prior to selection

b. [ ] technical and clinical test performance

c. [ ] impacts on cervical cancer incidence and mortality outcomes

d. [ ] possible adverse effects

e. [ ] changes in 6.a. – 6.d. resulting from introduction of HPV primary testing, if appliable

f. [ ] changes in 6.a. – 6.e. due to introduction of HPV vaccination.

7. [ ] Additional research needed on organizational and public health aspects, eg:

a. [ ] self-sampling and other strategies to increase coverage:

b. [ ] inclusion of 7.a. in outcome and health-economic evaluations

c. [ ] studies on individual acceptance of invitation and recall

d. [ ] continuous evaluation of effectiveness.

e. [ ] evaluations of possible synergies and possible future integrations between screening and HPV vaccinations, eg, studies on:

i. [ ] HPV vaccination in women of screening age who tested HPV-negative (prophylactic) or HPV-positive (therapeutic and prophylactic).

ii. [ ] screening policies among birth cohorts vaccinated en masse at a young age before contracting HPV.

iii. [ ] how to follow the needs of sceening in birth cohorts not vaccinated en masse or only partially vaccinated.

[23] Note that testing at shorter intervals or younger ages than recommended by the programme may account for a large proportion of overuse of tests during a round of screening (Antilla et al. 2009).

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Appendix 1

Evidence Assessment:

Clinical Questions, PICOS formulations and conclusions

Clinical question 1

Does an invitation letter increase screening attendance and/or coverage?

(a.1) Whether place, time, and date for the visit was given in the invitation letter

(a.2) Whether place, time, and date was not given in the invitation letter

P: women of screening age

I: invitation letter (place, time, and date)

C: compared with (a) standard cytology programmes with same interventions; (b) no intervention (i.e. if no invitations done)

O: attendance rate; coverage; smear consumption/use; referral rate; detection rate of CIN2+ lesions; hrHPV positivity

S: case–control, RCT, pilot studies (all studies)

Results: 3 systematic reviews (Everett et al. 2011; Jepson et al. 2000; and Giorgi Rossi et al. 2012) were considered: The Cochrane review (Everett et al. 2011) included a meta-analysis of 12 RCTs (99651 women) showing significantly higher uptake of screening for women who received an invitation letter than women who received usual care or no invitation (RR= 1.44, 95% CI: 1.24 to 1.67). A meta-analysis of 4 RCTs assessing 2998 women found that women who received letters with an open invitation had significantly higher uptake of cervical screening than women in the control group (RR= 1.61, 95% CI: 1.15 to 2.26). Another meta-analysis of 4 RCTs (2342 women) showed significantly higher uptake of screening among women who received a telephone invitation than in the control group (RR=2.16, 95% CI: 1.70 to 2.74). A meta-analysis of two trials assessing 1899 participants found that women who received telephone invitations had a significantly higher uptake of screening than women who were sent invitation letters (RR = 1.32, 95% CI: 1.15 to 1.53). A meta-analysis of four trials assessing 4706 participants found that women who were sent letters with a scheduled appointment had a significantly higher uptake than women who received a letter with an open invitation to make an appointment (RR= 1.57, 95% CI 1.43 to 1.72) (Everett et al. 2011). No significant difference between face to face invitations and invitation letters in the coverage of cervical screening found in a small trial that assessed 123 participants (Hunt et al. 1998).

The systematic review by Jepson et al. (2000) included 22 relevant studies (16 of them included in Everett et al. 2011) for appointment letter, telephone calls, a reminder letter and physician reminder. Five RCTs evaluated giving or offering appointments for screening versus a control group, or another appointment strategy. The scheduled appointment versus control, the open appointment versus usual care (physician recommendation) and scheduled appointments versus open or flexible appointments had statistically significant results (RR ranged from to 1.48 to 2.13). 15 studies invited women by letter (versus no intervention or usual care) to attend for Pap smear. Five showed a significant effect of the intervention, three showed no effect and for other seven studies RRs were not calculated. One RCT found that an open appointment at a health clinic was less effective than a letter from a GP in increasing the uptake of Pap smears.

The systematic review by Giorgi Rossi et al. (2012) (see also Camillioni et al. 2013) is an update of Jepson et al. (2000) and includes seven studies for appointment and invitation letter in organized cervical screenings which were already included in the other two reviews. Comparing invitation letter with telephone call, the pooled analysis of four RCTs assessing 5237 women found heterogeneous results: women who received telephone invitations had a non- significantly higher uptake (+8%) than women who were sent invitation letters (letter vs phone: RR = 0.92, 95% CI: 0.68 to 1.23); in two studies the telephone call was more effective and in another two the invitation letter. A pooled analysis of 3 trials found that women who received an letter with a scheduled appointment to attend a

cervical screening programme had 56% increased uptake (95% CI 43-69) compared with women with an open invitation (Giorgi Rossi et al. 2012). A longer invitation letter versus standard letter showed no effect on uptake (RR = 1.02, 95% CI: 0.94 to 1.10) (Segnan et al. 1998).

Conclusion: A letter of invitation to screening is effective at increasing attendance and coverage of cervical screening, and invitation letters with scheduled appointments are more effective than invitations with open appointments **(I)**.

Clinical question 2

Does a reminder letter increase screening attendance and/or coverage?

(b.1) Whether place, time, and date for the visit was given in the reminder letter

(b.2) Whether place, time, and date was not given in the reminder letter

P: women of screening age

I: reminder letter (place, time, and date)

C: compared with (a) standard cytology programmes with same interventions (with invitation letter); (b) no intervention (i.e. if no invitations done)

O: attendance rate; coverage; smear consumption/use; referral rate; detection rate of CIN2+ lesions; hrHPV positivity

S: case–control, RCT, pilot studies (all studies)

Clinical question 3

Does a telephone reminder increase screening attendance and/or coverage?

P: women of screening age
I: telephone reminder (place, time, and date)
C: compared with (a) standard cytology programmes with same interventions (with invitation letter only); (b) with invitation letter and reminder letter; (c) after invitation letter and one reminder letter (as the second reminder); and (d) no intervention (i.e. if no invitations done)
O: attendance rate; coverage; smear consumption/use; referral rate; detection rate of CIN2+ lesions; hrHPV positivity
S: case–control, RCT, pilot studies (all studies)

Results for clinical questions 2 AND 3: In ithe UK, women aged 45-65 with no previous smears were randomized either to receive an open invitation with two similar reminders (n=125, 122 analyzed), or a letter with a pre-assigned appointment with two similar reminders (n=125, 118 analyzed). Participation rate in the group with pre-assigned appointments in letters increased from 36% after primary invitation to 44% after second invitation and 47% with the third letter. In the group with open invitations, participation increase from 21% to 28% to 32%, respectively. (Wilson & Leeming, 1987). In another randomized study from the UK, Stein et al. investigated women who had not been screened in the previous 15 years despite the automated call-recall system, and found that a letter from the public health doctor (13/285 attended) was more likely to encourage women to obtain a cervical smear, than either a telephone call (4/285), a letter from a celebrity (5/285) or taking no additional action (4/285); although this difference was not statistically significant. (Stein et al., 2005).

In Iceland where 89.3% of eligible women had attended screening during the previous 5 years, women who had never attended screening were allocated to receive a GP invitation letter, and women who had attended but not during the preceding 5 years received a usual reminder from the Cancer Society. The respective uptakes were 10% and 11% (Bergmann et al. 1996).

In Italy, during the first round shortly after the introduction of the organized screening programme, attendance rates after primary invitation varied between 11.1 and 32.6%, depending on mode of invitation. A postal reminder was associated with a 6.6% absolute increase in compliance (Segnan et al. 1998).

14 RCTs were included in three reviews (Kupets & Covens 2001; Tseng et al. 2001; Yabroff, Mangan & Mandelblatt 2003). A meta-analysis of 10 RCTs showed that women who received a reminder letter to attend for cervical screening were significantly more likely to attend (OR = 1.64, 95% CI: 1.49 to 1.80) than those who received routine care (Tseng et al. 2001).

The systematic review of Kupets & Covens (2001) included 4 North American RCTs assessing mailed patient reminders: only one study reported a significant attendance increase of 10.4% (95%CI 7.6-13.2) (Somkin et al. 1997). A meta-analysis by Yabroff, Mangan & Mandelblatt (2003) reported the results of 4 RCTs (including Somkin et al. 1997) showing that both letter reminders and telephone reminders were effective at increasing cervical screening uptake in comparison with active controls: from 10.1% (95%CI 7.2-13.0) with letter reminder to 18.8% (95%CI 15.8-21.8) with telephone reminder (Binstock et al. 1997). A meta-analysis of 16 studies showed that patient reminders increased the use of cervical cytology screening services: adjusted OR 1.74 (95% CI: 1.58–1.92). It was not possible to rule out possible overlap of studies included in other reviews (Stone et al. 2002).

In Oregon, a telephone reminder following an invitation letter for women who had not attended for screening within 6 weeks was more effective than a reminder letter (OR 4.07, 95%CI 2.67-6.20), while attendance was not significantly higher following a letter reminder compared to usual care (OR = 1.37, 95% CI: 0.89-2.12) (Vogt et al. 2003). This study was included in a recent HTA report with two other RCTs. Eaker et al. (2004) compared the reminder letter to non-attenders with no reminder letter, and the results showed a higher uptake (RR=2.46, 95% CI: 2.15-2.81). The three RCTs evaluated also the effect of telephone reminder versus only letter invitation (Eaker et al. 2004; Oscarsson et al. 2007) or letter reminder and the pooled effect was RR= 2.52, 95% CI: 1.44-4.41. All showed a positive effect of telephone reminder in the uptake of cervical screening (Giorgi Rossi et al. 2012; Camilloni et al. 2013). A more recent Swedish study randomized 8,000 women with no record of participation in screening in 6-8 years to a telephone reminder arm or a control group. Participation during the following 12 months was significantly higher with a telephone reminder than in the control group: 718 (18.0%) versus 422 (10.6%; RR 1.70, CI 1.52–1.90) (Broberg et al., 2013).

In a cluster RCT within a local Danish cervical screening programme, 117129 women aged 23-59 years were randomized to receive the standard invitation letter at 3-year interval or two interventions if non attending screening for the last 5 years: a special personal letter signed by the individual GP and their GP received a visit from a collegue who facilitated quality enhancements of the screening programme. The targeted invitation decreased the proportion of women not participating for the last 5 years by 0.87% (95% CI 0.57% to 1.16%), and increased the coverage rate by 1.97% (95% CI 0.03% to 3.91%) during a period of 9 months (Jensen et al. 2009).

In a French RCT, 10662 women aged 25-65 years who had not had a smear test 1 year after the first invitation had been sent and no smear within the previous 3 years, were randomly allocated to receive either a new letter with a reply coupon, or a telephone call. Uptake at 8 months was 6.3% (95% CI: 5.6–7.0%) for telephone calls and 5.8% (95% CI: 5.2–6.4%) for letters. The difference was not significant (Heranney et al. 2011). In another trial, 6000 unscreened women aged 30–65 years, living in a French region covered by a screening programme, who had not responded to an initial invitation to have a Pap smear were equally randomised to three groups: ‘no intervention’; ‘recall’ (women received a letter to have a Pap smear); and ‘self-sampling’ (women received a self-sampling kit to return to a centralised virology laboratory for PCR-based HPV testing). There was no appreciable difference in uptake after 12 months among non-attendees who were randomized to receive a reminder letter (11.7%) and a control group with no intervention (9.9%; OR 1.20, CI 0.98-1.47) (Haguenoer et al. 2014; results by self-sampling are dealt in the PICOS 4 on the Clinical question 4 below).

Within the Finnish cervical screening programme, reminder letters increased participation from 72.6% (95% CI 72.1, 73.1) to 79.2% (95% CI 78.8, 79.7). Reminder letters with scheduled appointments resulted in higher increase than open invitations (10 vs 6%). Screening of original non-attendees increased the yield of CIN3+ lesions by 24% (Virtanen et al. 2014).

Despite evidence suggesting that the use of letter or physician reminders may have an impact on cervical screening uptake in young women aged 35 years or younger, a recent systematic review found insufficient evidence to conclusively determine which interventions are effective (Albrow et al. 2014).

In a Spanish RCT among women aged 60-70 years with no record of cervical cytology over the last 3 years, a personalized letter signed by the patient's primary care physician and professionals from the corresponding Public Health Center, with a pre-assigned date for the screening visit, increased coverage from 51.2% to 76.0%; the same invitation letter plus an informative leaflet on the prevailing reasons for screening cervical cancer increased coverage from 47.4% to 79.0%; and the same invitation plus leaflet, complemented by a telephone reminder call 3 days prior to the appointment date indicated in the invitation letter increased coverage from 44.5% to 74.6% (Acera et al. 2014).

A systematic review of studies assessing the efficacy of interventions to increase participation in organised population-based screening programs found an effect on participation of reminder letter in addition to invitation letter vs invitation letter alone, RR 1.71 (95%CI 1.60, 1.83). The effect on participation of telephone reminder in addition to invitation letter vs invitation letter and reminder letter was found in four studies out of five, the largest study (Heranney et al. 2011) showing a modest, non-significant effect (Camilloni et al. 2013).

Conclusions for clinical questions 2 and 3: Reminders by letter or telephone call to non-attenders are effective at increasing attendance and coverage of screening **(I)**.

A telephone reminder is associated with the largest increase in the uptake of cervical cancer screening, but reminder letters by mail will be necessary for women without a telephone **(I)**.

Reminder letters with a scheduled appointment are likely to be more effective than open reminder letters **(II).**

Clinical question 4

Does an HPV test with self-sampling increase screening attendance and/or coverage?

P: women of screening age

I: self-sampling

C: compared with (a) standard cytology programmes with same interventions (with invitation letter only); (b) with invitation letter and reminder letter; (c) with invitation letter and telephone reminder; (d) after invitation letter and reminder letter (as the second reminder); (e) after invitation and telephone reminder (as the second reminder); and (f) no intervention (i.e. if no invitations done)

O: attendance rate; coverage; smear consumption/use; referral rate; detection rate of CIN2+ lesions; hrHPV positivity

S: case–control, RCT, pilot studies (all studies)

Results: In the Italian RCT, a random sample of 2480 non-responder women aged 35–64 years, was randomly split into four arms: two control groups received standard recall letters to perform either Pap-test (first group) or human papillomavirus (HPV) test (second group) at the clinic. A third arm was sent letters offering a self-sampler for HPV testing, to be requested by phone, whereas a fourth group was directly sent the self-samplers home. Compliance with standard recall was 13.9%. Offering HPV test at the clinic had a non-significant effect on compliance, relative risk (RR)=1.08; 95% CI=0.82–1.41. Self-sampler at request had the poorest performance, 8.7%, RR=0.62; 95% CI=0.45–0.86, whereas direct mailing of the self-sampler registered the highest compliance: 19.6%, RR=1.41; 95% CI¼1.10–1.82. This effect on compliance was observed only in urban areas, Florence and Rome, RR=1.69; 95% CI=1.24–2.30, but not in Abruzzo, RR=0.95; 95% CI=0.61–1.50, a prevalently rural area (Giorgi Rossi et al. 2011).

In RCTs performed in France and the Netherlands, respectively, 9334 women not having had a Pap test performed after a first individual invitation, and 26409 non-attending women after the first

invitation and reminder invitation were allocated to receive either a new reminder letter for regular cytology screening or an HPV self-sampling kit at home. In both studies, the response rate in the group who received the self-sampling kit was significantly increased compared to the group who received reminder invitation for Pap test. French: 26.4% vs 7.2%, p < 0.001 (Piana et al. 2011); Dutch: 30.8% vs 6.5%; p < 0.001 (Gök et al. 2012). Response rates in the English study were considerably lower: 10.2% in the self-sampling group and 4.5% in the cytology group (Szarewski et al. 2011).

In the RCT performed in Finland, 8699 women non-attendees after the primary invitation were randomized to receive either an HPV self-sampling kit by mail or an extra invitation. 25% of non-attendees after the reminder letter also received the self-sampling kit as a third intervention. Total attendance increased from 65% to 76% by self-sampling. Combining the interventions (reminder letter and then self-sampling) increased total attendance from 63% to 78% (Virtanen et al. 2011).

In the Swedish RCT, 4060 women aged 39-60 years who had not attended the organised Pap-smear screening for 6 years or more were randomised to self-sample vaginal fluid at home or invited to a midwife reception for cervical smear. The participation rate was 39% in the self-sampling group and 9% in the conventional cytology group (P<0.001). The odds ratio for offering self-sampling and HPV testing instead of Pap-smear screening for detection of CIN2–3 was 5.42 (95% CI: 1.30–31.8) (Wikström et al. 2011).

In another Swedish population-based, randomized trial of the effectiveness and cost-effectiveness of different interventions aimed at increasing participation in the cervical cancer screening program in western Sweden, 8,800 women aged 30-62 were randomly selected among women without a registered Pap smear in the two latest screening rounds. These women were randomized 1:5:5 to one of three arms: 800 were offered a high-risk HPV self-sampling-test; 4,000 were randomized to a telephone call (reported previously, see PICOS to the clinical question 3 above); and 4,000 constituted a control group (standard screening invitation routine). Results were based on intention-to-treat analysis and cost-effectiveness was calculated as marginal cost per cancer case prevented. The endpoint was the frequency of testing. The total response rate in the self-sampling arm was 24.5% and was significantly higher than in the telephone arm (18%, RR 1.36, 95% CI 1.19-1.57) and the control group (10.6%, RR 2.33, 95% CI 2.00-2.71). All nine self-sampled women who tested positive for high-risk HPV attended for a cervical smear and colposcopy. From the health-care sector perspective, the intervention will most likely lead to no additional cost. The authors concluded that offering a self-sample for HPV testing as an alternative to Pap smears increases participation among long-term non-attendees, and that offering various screening options can be a successful method for increasing participation in this group (Broberg et al. 2014).

In a RCT performed in the UK, 6000 non-attenders were sent an HPV self-sample kit (intervention) or a further invitation for cytology screening (comparator). 8% returned a self-sample and 5% attended for cytology, compared with 6% attending for cytology, relative risk 2.25 (95% CI 1.90-2.65). Of those testing hrHPV positive (13%), 59% subsequently attended cytology screening. Persistent non-responders to invitations for cervical screening were significantly more likely to respond to a postal invitation to return a self-collected sample for HPV testing than a further invitation for cytology screening. However, just over half followed up on this positive HPV result (Cadman et al. 2014).

In a French RCT, 6000 non-responders aged 30–65 years, were equally randomised to three groups: ‘no intervention’; ‘recall’, women received a letter to have a Pap smear; and ‘self-sampling’, women received a self-sampling kit for PCR-based HPV testing. Participation was higher in the ‘self-sampling’ than in the ‘no intervention’ group (22.5% vs 9.9%, P<0.0001; OR 2.64) and ‘recall’ group (11.7%, P<0.0001; OR 2.20). In the ‘self-sampling’ group, 320 used the self-sampling kit; for 44 of these women with positive HR-HPV test results, 40 had the recommended triage Pap smear. The incremental cost-effectiveness ratio per extra screened woman was 77.8€ and 63.2€ for the ‘recall’ and ‘self-sampling’ groups, respectively, relative to the ‘no intervention’ group. Offering an in-home, return-mail kit for vaginal self-sampling with a dry swab was more effective and cost-effective than a recall letter in increasing participation in cervical cancer screening (Haguenoer et al. 2014).

Conclusion
Offering self-sampling for HPV testing is an effective way to increase attendance and coverage of screening compared with standard recall letters to non-responders for the Pap test **(I)**.

Clinical question 5

Does invitation via a family doctor increase screening attendance and/or coverage?

P: women of screening age

I: invitation by family doctor endorsement

C: compared with (a) standard cytology programmes with same interventions with invitation by other authorities; and (b) no intervention (i.e. if no invitations done)

O: attendance rate; coverage; smear consumption/use; referral rate; detection rate of CIN2+ lesions; hrHPV positivity

S: case–control, RCT, pilot studies (all studies)

Results: The studies considered were a Cochrane review (Everett et al. 2011), a review published in Health Technology Assessment Database (Jepson et al. 2000) and its update (Giorgi Rossi et al. 2012) which reported data of 3 RCTs.

All three reviews included a large RCT which randomized women to receive /1 a personal invitation letter, signed by the GP, with a prescheduled appointment; 2/ same letter as group 1, signed by the screening program coordinator; 3/ same letter as group 1, signed by the GP, asking the woman to contact the screening centre within 3 weeks to arrange an appointment; 4/ a personal invitation letter with extended text, signed by the GP, with a scheduled appointment. All non-attenders were sent reminder letters. Compliance at 12 months was 36.1%, 30.9%, 22.7% and 36.7%, respectively. In comparison with personal invitation letters signed by the woman's family doctor, with pre-allocated appointments, open invitation and invitation signed by programme coordinator induced significantly inferior compliance, RR=0.85, 95%CI 0.78-0.93; 0.63, 95%CI 0.57-0.69, respectively (Segnan et al. 1998).

The second RCT included in the reviews randomized women who had not been screened within the previous 3 years to receive 1/ a mailed educational pamphlet; 2/ a mailed personalised letter inviting to attend a women's health clinic for a smear; 3/ a mailed personalised letter from the woman's "regular" general practitioner, advising that she should have a Pap smear; 4/ control group with no intervention. The respective self-reported 6-month screening attendance rates were 25.9%, 95%CI 19.2, 32.6; 22.6%, 95%CI 16.2, 29.0; 36.9%, 95%CI 29.8, 44.0; 24.5%, 95%CI 17.7, 31.3. Attendance rate was significantly higher within the group receiving the physician letter (p=0.012) (Bowman et al. 1995).

The third RCT randomized women who had not been screened for at least 15 years to receive a telephone call from a nurse, a letter from a celebrity, a letter from the local cervical screening commissioner or no intervention. 3-month uptakes were 1.4%, 95%CI 0.38–3.6%; 1.8%, 95% CI 0.57–4.0%; 4.6%, 95% CI 2.5–7.7%; 1.8%, 95% CI 0.57–4.0%, respectively. There were no significant differences between groups (Stein et al. 2005).

In the South-Western region of the Dutch national screening programme, women invited by a GP had an attendance rate of 68.6%, which was 7.9% higher (95%CI 7.5-8.3) than among women invited by the local health authority (de Nooijer et al. 2005).

Conclusion: A personalized invitation from the woman's family doctor can increase compliance with screening **(I)**.

Clinical question 6

Does payment affect screening attendance and/or coverage?

P: women of screening age

I: invitation by letter, where attendance is (a.1) free of charge and (a.2) with a minimal payment

C: compared with (a) standard cytology programmes with same interventions with invitation but with a full payment; (b) no intervention (i.e. if no invitations done) and with a full payment; (c) no intervention with a minimal payment; and (d) no intervention but screening attendance free of charge

O: attendance rate; coverage; smear consumption/use; referral rate; detection rate of CIN2+ lesions; hrHPV positivity

S: case–control, RCT, pilot studies (all studies)

Results: One systematic review assessing the impact of different methods to enhance participation rate in cancer screening programs was retrieved. It included 27 studies (RCTs or CCTs) specific on cervical cytology screening, 3 of which assessed the impact of patient financial incentives. The adjusted OR for participation was 2.82 (95% CI: 2.35–3.38). Patients financial incentives (reductions in patient payment or copayment, direct compensation to patients) were rated as the next most effective intervention after reorganization of the delivery of preventive services in their ability to increase participation (Stone et al. 2002). In Japan, 7.8% of women who had not previously participated in cervical screening indicated self-payment as the reason for non-participation. When free coupons for cervical screening were given, 43% of women attending private screening used them. Among 7 motivation categories, the free coupon was the main motivator to attend screening for 4% of women (Kuroki, 2012).

Conclusion: Financial interventions consisting of reductions in patient payments or co-payments are effective at increasing participation in cervical cancer screening **(I)**.

S3

Implementation of vaccination against human papillomavirus in Europe

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Organization of HPV vaccination

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- A population-based programme is likely to achieve higher coverage, less social inequalities in vaccine uptake, and lower vaccination costs per vaccine **(III).**Sect 3.6
- If a country has started implementation with the opportunistic approach, transition to an organized, preferably school-based (or other public-service-based) programme is recommended **(III-A).**Sect 3.6

Target age for HPV vaccination

3.2 The primary target group to consider for routine population-based vaccination is girls at an age before the onset of sexual activity, usually between 10 and 13 years **(I-A).**Sect 3.2.1

- Targeting older girls and young women with catch-up vaccination at the start of a routine vaccination programme can accelerate the impact of the vaccination programme **(I).**Sect 3.2.2

Monitoring and evaluation of HPV vaccination programmes

3.3 Organized, population-based HPV vaccination programmes should have systematic register-based monitoring of coverage and safety. Long-term evaluation of vaccine safety and effectiveness is recommended in all countries. Appropriate legal frameworks must be developed, taking funding and organizational resources into account **(VI-A).**Sect 3.3

- Coordination between vaccine evaluation and cancer control programmes is recommended. It will be critical to assess the impact of the vaccine and its synergies with screening and health education **(VI-A).**Sect 3.3
- Long-term evaluation based on systematic registration of HPV vaccination and linkage studies using relevant healthcare registries should be used to assess vaccine effectiveness and safety in various settings. If a country has the capacity, it is desirable that assessment of vaccine impact include: surveillance for vaccine-related and other oncogenic HPV infections, precancerous lesions, and HPV-related cancers **(VI-A).**Sect 3.3
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[24] **Sect** (superscript) after each recommendation in the list refers the reader to the section/s of the Supplements dealing with the respective recommendation.

Rec (superscript) throughout the supplement refers to the number of the recommendation dealt with in the preceding text.

Planning, piloting, and modifying HPV vaccination programmes

3.5 Planning and modification of vaccination programmes and policies should take into account local conditions, including vaccine and vaccination costs and resources required in monitoring, provision of information, and communication. Pilot studies are recommended to assess how to improve coverage and public awareness **(VI-A).**[Sect 3.6]

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HPV screening and HPV vaccination

3.8 Vaccination status should be known to screening and vaccination registries for women reaching the target screening age (**VI-A**).[Sect 3.3]

3.9 Planning and research on synergies between HPV vaccination and HPV screening is recommended to improve the effectiveness and cost-effectiveness of prevention of HPV-related disease **(VI-A).**[Sect 3.3]

3.1 Introduction

Clinical trials have shown human papillomavirus (HPV) vaccines to be safe and highly effective against anogenital precancerous lesions and persistent infections due to vaccine-related HPV types among women/adolescents who were not infected by these types at the time of vaccination (ECDC 2012; WHO 2009a; WHO 2014a; see also EMA 2014a; EMA 2014b). The use of prophylactic HPV vaccines in pre-adolescent girls and young women for the primary prevention of cervical cancer and some other HPV-related diseases has been endorsed by the European Medicines Agency (EMA) in 2006 (quadrivalent vaccine)[25] and 2007 (bivalent vaccine)[26], and by the World Health Organization in 2009 and 2014 (WHO 2009b; WHO 2014b).[27] Since then, most European countries have taken initiatives to decide on policies about whether and how to introduce national HPV vaccination programmes. Important issues under consideration are the added value of HPV vaccination compared with cervical screening programmes; health-economic aspects of the vaccine; target groups for vaccination; programme organization; and how to monitor the process, safety, and effectiveness of these programmes. Alternative delivery systems had to be explored, as the generally well established vaccination infrastructure for children is less appropriate for reaching the older target group for HPV vaccination. Policies of individual countries may differ, depending on the extent and effectiveness of previously existing cervical screening programmes, the organization of health-care delivery, and other competing health priorities. Much of the evidence for the present recommendations results from the experience with different vaccination programme approaches and the current state of implementation in different European Union (EU) countries.

3.2 Target populations for HPV vaccination

3.2.1 Target age for routine vaccination of young girls

To optimize the impact of the prophylactic vaccines on HPV-associated disease in women, the primary target group to consider for routine vaccination is girls at an age just before the onset of sexual activity (and therefore first probable exposure to HPV). In fact, several studies have confirmed that high rates of HPV infection, especially with HPV 16 and 18, occur during the first few years following the start of sexual activity (IARC 2007). Therefore, most EU countries have targeted girls aged 11–13 years. Lowering the age of vaccination below this age would not prevent many infections and requires

[25] See summary of product characteristics, accessed 10/04/2015: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000703/WC500021142.pdf

[26] See summary of product characteristics, accessed 10/04/2015: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000721/WC500024632.pdf

[27] The 9-valent vaccine that was recommended by the European Medicines Agency (EMA) in March 2015 for the prevention of diseases caused by nine types of HPV was not considered in the preparation of the present supplement because at the time of writing and editing the Supplements it was not licensed for use in the EU. See (accessed 28/05/2015): http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2015/03/WC500184898.pdf

evidence that the vaccine has a long duration of full vaccine efficacy. Younger children, however, have been shown to have a stronger immunogenic response to HPV vaccines. This prompted some countries (e.g. Sweden) to start vaccinating girls at the age of 10 years. Expanding the upper age of the target population above age 13 entails a gradual decrease of the cost-effectiveness of HPV vaccination, as the proportion of young women with a previous or existing infection increases (Tsu, Murray & Franceschi 2012; Westra et al. 2011). In conclusion, the primary target group to consider for routine population-based vaccination is girls at an age before the onset of sexual activity, usually between 10 and 13 years **(I-A).**[Rec 3.2]

Number of doses and interval for vaccination of young girls:

Until recently, all HPV vaccination programmes have implemented a schedule of three intramuscular injections. The second injection is given at 1 month or at 2 months after the first injection (for bivalent and quadrivalent vaccine, respectively) and the third injection at 6 months. Based on new immunogenicity and safety data, the introduction of a 2-dose schedule has been endorsed by the WHO, wherein the second dose is given 6 months after the first one, allowing for a maximum interval of 15 months (WHO 2014b). The 3-dose schedule remains recommended for girls of 15 years or older. By analogy based on immunogenicity data, the same schedules are applicable to boys. EMA has also granted marketing authorizations for bivalent and quadrivalent vaccines in the EU for a two-dose schedule administered by injection at a 6-month interval for girls aged 9-14 and 9-13 years, respectively. If the respective vaccines are administered at an older age, the three-dose schedule should be used (EMA 2014a, EMA 2014b). Some EU Member States, such as Belgium, France, Italy and the UK, have already implemented a 2-dose HPV vaccination schedule.

3.2.2 Catch-up vaccination of young women

Targeting older girls and young women with catch-up vaccination at the start of a routine vaccination programme can accelerate the impact of the vaccination programme through the following mechanisms **(I)**:[Rec 3.2]

- Clinical trials have shown satisfactory immune response and efficacy against new infection in HPV 16 and 18 DNA-negative women aged 15–26 years (Lehtinen et al. 2012; Muñoz et al. 2010) and, based on much smaller trials, in the age group 26–45 years (Muñoz et al. 2009; Schwarz et al. 2011).
- Currently available prophylactic vaccines do not improve the outcome of an infection with HPV vaccine types that are present in the cervix at the time of vaccine administration (Hildesheim et al. 2007). However, for women who were already infected with one of the two oncogenic HPV vaccine types, clinical trials have also shown that the efficacy of the vaccines against the other type remains intact (FUTURE II Study Group 2007; Szarewski et al. 2012). The vaccines also appear to offer protection against vaccine HPV types to which women were exposed previously (as shown by corresponding antibody seropositivity) but that were no longer present in the cervix at the time of first vaccination (DNA-negative women) (Olsson et al. 2009; Szarewski et al. 2012). A recent meta-analysis of RCTs also showed that young women who were vaccinated at the age of 16 or older, both HPV naïve or not, had a 20% and 46% lower risk of developing any CIN2+ and HPV-related CIN2+, respectively, during 4 years after vaccination, compared to those who received placebo (Couto et al. 2014).

Country-specific data such as age at onset of sexual activity, age-specific prevalence of HPV infections, vaccine delivery strategies, and acceptance of vaccination by the target group (and their parents or guardians) can also be useful to determine the optimal age range for routine vaccination and catch-up vaccination.

Although both vaccines appear to be immunogenic and effective in vaccine HPV type-negative women older than 26 years, the risk of new cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3) among these women is low, and significant efficacy of the vaccine against CIN2/3 has not been demonstrated (Castellsague et al. 2011). More data on the impact and health-economic aspects of vaccinating women older than 26 years are, however, warranted before conclusions can be drawn from a public health perspective. This applies also to possible synergies between vaccination and screening.

3.2.3 Vaccination of boys

The question of whether boys should also be included in the HPV vaccination target population is a topic of current debate. National advisory committees of the USA, Canada, and Australia have issued recommendations to include vaccination of boys in the routine vaccination schedules (CDC 2011b; NACI 2012; PBAC 2011). Variable fractions of anal, penile, and oropharyngeal cancers, as well as genital warts, are caused by HPV types included in the bivalent and/or quadrivalent vaccine (Arbyn et al. 2012). Both vaccines are immunogenic in males, and clinical trials have shown high efficacy of the quadrivalent vaccine in males against persistent infection with HPV 16 and 18, vaccine type-related genital warts, and the few anal intraepithelial lesions that were observed in the trials (Giuliano et al. 2011; Palefsky et al. 2011). The quadrivalent vaccine is licensed in boys aged 9 years or older for the prevention of genital warts, precancerous lesions of the anus and anal cancer (EMA 2014b). Vaccination of males is expected not only to induce direct benefits to the vaccinated person but also to reduce the circulation of HPV and the risk of HPV infections in unvaccinated women and men (herd immunity). However, studies on health-economic aspects showed that the inclusion of boys in an HPV vaccination programme would not be cost-effective at the vaccine prices included in the evaluation, and would be worth considering only if vaccine coverage in girls is lower than 30–50% (Brisson et al. 2011; Taira, Neukermans & Sanders 2004). In high-income countries, increasing vaccination coverage among girls is still the most cost-effective option for decreasing HPV 16/18 infection. If this is not achievable, then vaccinating boys is justifiable if vaccine cost has at least halved since the introduction of the programme, because this option would almost double the number of vaccinees (Baussano et al. 2014). Lower cost-effectiveness in males is also driven by the lower HPV-related cancer burden in men compared with women, with the possible exception of countries in which the incidence of cervical cancer has been greatly reduced by screening and the incidence of HPV-associated oropharyngeal cancer is very high.

Further studies are also needed to assess the relevance of male vaccination in specific populations, eg in HIV-positive men, or men who have sex with men, who have a high burden of anal cancer and, in contrast to men who have sex with women, would receive little protection from vaccination of girls.

3.3 Quality assurance – safety and programme monitoring

Clinical trials have shown HPV vaccines to be safe and effective (ECDC 2012; WHO 2008; WHO 2009a; WHO 2014a; see also EMA 2014a; EMA 2014b)[28]. Three randomized controlled trials investigated the

[28] See also footnotes no. 25 - 27 on page 115.

safety and reactogenicity of HPV vaccines in young adolescent females. Compared with recipients of placebo in the quadrivalent vaccine studies (Block et al. 2010; Reisinger et al. 2007) or of control combined hepatitis A and B vaccine in the bivalent vaccine study (Pedersen et al. 2012), HPV vaccine recipients were more likely to have local injection-site reactions, but were not significantly more likely to experience serious or systemic adverse events. These findings are consistent with large safety studies in older adolescent girls and women (WHO 2008). The short (2–3 years) post-marketing surveillance periods of these vaccines do not permit final assessments of possible rare or long-term adverse effects.

However, like for all medicines, it is important to continue *safety monitoring* for HPV vaccines in general use on a larger scale. Safety monitoring can make use of existing systems and/or involve the development of specific safety monitoring systems. WHO recommends that all countries should monitor and investigate adverse events after immunization, through sustainable systems (WHO 2010) **(VI-A)**.[Rec 3.3] Safety monitoring is mostly done through routine pharmacovigilance systems that capture adverse events after the administration of medicines and vaccines. For example, in the United Kingdom adverse events after HPV immunization are monitored through the established *Yellow Card Scheme* whereby health-care professionals and the public report suspected adverse events (MHRA 2012). Such systems have not revealed any serious health risks associated with HPV vaccination after administration of many millions of doses of HPV vaccines in the USA (Slade et al. 2009), Australia (TGA 2011), or the United Kingdom (MHRA 2012). Post-licensure studies using routinely collected health-care data, by vaccine manufacturers or health-care providers, can compare adverse events in vaccinated versus un-vaccinated individuals or cohorts and hence enable the study of any excess of rare adverse events like auto-immune diseases. The outcomes of post-licensure studies have also been reassuring (Chao et al. 2012; Gee et al. 2011; WHO 2009a; WHO 2014a). Where feasible and if resources allow, additional safety monitoring may be valuable. For example, in some settings pregnancy outcomes after inadvertent vaccination during pregnancy have been investigated (Dana et al. 2009; HPA 2010).

The population-level impact of a vaccine can be interpreted only if the extent and manner of its use in the population are known. An important measure in *process monitoring* of HPV vaccination is therefore the assessment of vaccine coverage achieved for the target population in a country or region. WHO recommends collecting coverage data by year of birth and number of administered doses by single year of age (WHO 2014b; WHO 2010) **(VI-A)**.[Rec 3.3] In addition to monitoring population-level coverage, individual vaccination records should be retained to ensure that vaccination status is known for women reaching the target screening age (**VI-A**),[Rec 3.8] and any existing practical and legal barriers to record keeping should be dealt with. This is important because future cervical screening of women who had access to HPV vaccination will likely benefit from knowledge of vaccination status. Any efforts to determine vaccine effectiveness against cervical cancer end-points in countries with less-than-optimal vaccine uptake will require individual-level data on vaccination status for many years after immunization. Australia has implemented such a registry including individual vaccination data (IAP 2013). This registry enables the monitoring of coverage data, but it can also be used to issue reminders in the case of incomplete vaccination courses. The registry will also make it possible to link the occurrence of HPV-related diseases in screening or cancer registries with individual vaccination status, in order to evaluate the impact of HPV vaccination in the future.

Although it will take more than two decades before it is possible to monitor the impact of HPV vaccination on reducing the number of cervical cancer cases, earlier measurable indicators of the impact of vaccination will be the prevalence of cervical precancerous lesions, genital warts, and HPV infections (WHO 2010). If possible, sentinel surveillance of the impact of vaccination on precancerous lesions should be organized **(VI-A)**.[Rec 3.3] Early monitoring will need to focus on young women, and it will ideally include the ascertainment of HPV type-specific genital infection and vaccination status in population samples. Surveys could be specifically conducted as population-based studies or also make use of specimens from sexually transmitted infection testing. Separate assessment of vaccine effectiveness against vaccine types and non-vaccine types (i.e. cross-protection or type replacement) will

be of value. Studies from the USA and Australia comparing the presence of HPV in similar groups of young women before and after vaccination have already found significant decreases in the prevalence of vaccine-related HPV types over time (32% to 13%, USA; 29% to 7%, Australia) (Kahn et al. 2012; Tabrizi et al. 2012). Both studies also showed herd protection among women who were not vaccinated. A similar significant decrease in incidence of high-grade cervical lesions among women younger than 18 years was found in Victoria, Australia, 3 years after vaccination (incidence, 0.42%) compared with before vaccination (0.80%) (Brotherton et al. 2011). In countries or regions where the quadrivalent vaccine is in use, incidence of genital warts (clinical manifestations of HPV 6 or HPV 11 infection) could also be used as an early indicator of the impact of HPV immunization on HPV infections. Ecological data on the impact of the quadrivalent vaccination programme in Australia and Denmark have reported a rapid decline in genital wart diagnoses in birth cohorts of women targeted by the programme (Baandrup et al. 2013; Donovan et al. 2011) and men who have sex with women (Donovan et al. 2011).

Monitoring and long-term evaluation of changes in the epidemiology of severe precancerous lesions and cancers (end-point indicators) will remain important irrespective of early indicator studies. Coordination between vaccine evaluation and cancer control programmes is recommended. It will be critical to assess the impact of the vaccine and its synergies with screening and health education **(VI-A).**[Rec 3.3] In countries with established screening programmes, cervical screening data can be used to generate these end-point indicators. Such monitoring will require linkage of screening and cancer registries with records of individual vaccination status and screening histories **(VI-A)**.[Rec 3.3] Such conditions are met in Nordic countries (Denmark, Finland, Norway, and Sweden), where vaccine manufacturers have rolled out Phase IV studies to monitor long-term incidence of precancerous lesions and cervical cancer after HPV vaccination (Bonanni et al. 2010; Lehtinen et al. 2006; Arnheim-Dahlström BMJ 2013). HPV typing of precancerous lesions and cervical cancers will also be necessary for effective monitoring and evaluation (ECDC 2008).

In conclusion, organized, population-based HPV vaccination programmes should have systematic register-based monitoring, including safety, coverage, and long-term evaluation. Appropriate legal frameworks must be developed, taking the need for adequate funding and organizational resources into account **(VI-A).**[Rec 3.3] Also, planning and research on synergies between HPV vaccination and HPV screening is recommended to improve the effectiveness and cost-effectiveness of prevention of HPV-related disease **(VI-A).**[Rec 3.9]

3.4 Vaccination programme models – current policies

In EU Member States, HPV vaccination programmes are implemented in substantially different ways. This section describes three widely-used models – organized school-based programmes, organized public-health-institution-based programmes, and opportunistic vaccination programmes. The corresponding settings, achieved coverage, and foreseeable problems are illustrated by the approaches taken in three large EU Member States.

3.4.1 Organized school-based model (United Kingdom)

In the United Kingdom, the expert advisory body on vaccinations and immunization, the Joint Committee on Vaccination and Immunisation (JCVI), stated that HPV immunization would be delivered most efficiently through schools (JCVI 2008). Since 2008, nearly all areas in the United Kingdom have consequently delivered HPV vaccination through school-based programmes to the routine cohort of 12–13-year-old girls. Since September 2014, the number of doses of HPV vaccine that the girls will receive has been reduced from three to two, given at least six months apart. A mixed model including delivery through schools and primary care (general practitioners) was used for older girls up to age 18 years (catch-up cohort). HPV immunization is free for all girls up to age 18 years.

Annual data for the first 3 years of the HPV immunization programme show that a high uptake has been achieved. In England by 2010/2011, 66% of 12–20-year-old girls were fully (3-dose) vaccinated (White & Das 2012). In the routine cohorts, 3-dose coverage within 1 year after the start of the programme was 80% in 2008/2009, 76% in 2009/2010, and 84% in 2010/2011 (Sheridan et al. 2010; Sheridan & White 2011; White & Das 2012). The majority of these inoculations were delivered to the routine cohorts through schools; in 2010/2011, for example, 89% were delivered through schools and 9% through primary care (White & Das 2012).

Coverage (3-dose) achieved in England in catch-up cohorts ranged from 32% to 69% during the first year of the programme (Sheridan et al. 2010; Sheridan & White 2011; White & Das 2012). Similarly to the routine cohorts, the majority of inoculations in catch-up cohorts were delivered through schools; for example, 90% of doses delivered to 15–16-year-old girls in 2009/2010 were delivered through schools and 8% through primary care (Sheridan & White 2011). Coverage decreased with increasing target age and was highest in those catch-up cohorts who were still attending compulsory education (up to age 15 years). Vaccine delivery among 16–17-year-old girls (outside compulsory education) made greater use of primary care (52% of doses). Areas in which 60% or more of vaccines were delivered through primary care generally achieved lower uptake than areas in which vaccines were predominantly delivered through schools. In 16–17-year-old girls in 2009/2010, only 13% (n=10/78) of areas with a predominantly primary-care model achieved 3-dose coverage of 50% or more, compared with 58% (n=36/62) of areas with a predominantly school-based programme (Sheridan & White 2011).

As for all immunizations in England and other parts of the United Kingdom, individual HPV vaccination history is documented in primary-care records irrespective of the place at which the vaccine was administered (Chief Medical Officer 2008). As recommended by the JCVI, surveillance and monitoring of the impact of HPV immunization is under way (JCVI 2008).

3.4.2 Organized public-health-institution-based model (Italy)

In Italy, HPV vaccine has been delivered free of charge to 11-year-old girls since March 2007. Since 2008, parents of girls in the 11-year-old birth cohort have been sent individual letters of invitation in all Italian administrative regions. Some regions also implemented free catch-up vaccination of older cohorts (up to age 16, 18, or 25 years), and almost all regions offered the vaccine at a reduced price to women younger than 26 years. The aim was to achieve 95% coverage within the first 5 years after the start of the programme.

The introduction of the programme was prepared for by training health professionals involved in vaccination and screening. Teaching tools were designed at the national level and delivered by regions through local courses. Vaccinations were mostly administered in public health centres that usually

administer paediatric vaccines and also had previous experience in delivering hepatitis B virus vaccination to 11-year-old girls and boys. Office-based general practitioners provided only a small proportion of the inoculations for the 11-year-old girls, but a larger proportion for the catch-up cohorts.

Vaccination registration with individual identifiers is mandatory, but not all public health centre providers have electronic registries, and other providers seldom comply with the mandatory reporting to public health services. Some regions are implementing an integrated information system for vaccination and screening programmes in order to monitor the effectiveness of both and eventually permit the application of different screening protocols for vaccinated and non-vaccinated women.

The nationwide coverage for the 1997 birth cohort as of 30 June 2012 was 71% for the first dose and 66% for the third dose, with wide variability between regions (range, 25–89%) (Giambi 2012). Data are less variable for younger cohorts (first-dose coverage, 69% and 62% for girls born in 1998 and 2000, respectively) (Giambi 2012).

In the 1990s, a similar strategy yielded about 95% hepatitis B virus vaccination coverage for 11-year-old boys and girls. The achievements with HPV vaccine have been less satisfactory to date, which may be due to several factors. Hepatitis B virus vaccination was mandatory by law, targeted both sexes, and faced less opposition by the anti-vaccine groups than HPV vaccination. In addition, HPV vaccination has not been uniformly endorsed by paediatricians and gynaecologists. Moreover, the price of the HPV vaccine was high in Italy, and in some regions public providers struggled to guarantee timely distribution and avoid wastage. Other limitations of HPV vaccination programmes in Italy included geographical disparities in vaccine provision and in the adequacy of infrastructure (clinics and registries) and poor information on vaccine delivery outside of the targeted age cohort(s) and outside the public health sector.

3.4.3 Reimbursed opportunistic model (France)

HPV vaccination was included in the French national immunization schedule in 2007, and it currently targets 11-to-14-year-old, pre-adolescent girls. A catch-up for older girls and young women up to age 20 years is also recommended.

Given the lack of national or regional HPV vaccination campaigns in France, girls in the targeted cohorts or their parents have to take the initiative to obtain vaccination. Similarly to other childhood vaccines, HPV vaccines are mainly administered by office-based general practitioners and paediatricians. For children up to age 6 years, maternal and child health clinics perform an estimated 15% of vaccinations. Public vaccination centres offer free vaccination for older children and adults. They are managed by local district authorities, hospitals, or nongovernmental organizations. Decisions about the organization of clinics and the type of vaccines offered are made by local district authorities, leading to heterogeneity in the availability and accessibility of the vaccines in the public sector. HPV vaccinations performed in the office-based sector are reimbursed by the social security scheme at 65% (70% for the clinician's consultation) for the recommended routine or catch-up target populations. However, >90% of the population are covered by private health insurance that reimburses the remaining portion. There is no registration of vaccination status of the targeted population outside of the vaccination centre or practitioner's office where it was administered. An evaluation performed on the National Drug Reimbursement Database has shown that of girls who were aged 14 years in 2007 and 2008, only 33% and 23%, respectively, had received the 3-dose HPV vaccination by the end of 2009 (Fagot et al. 2011).

In conclusion, the HPV vaccine delivery system in France has advantages and limitations similar to the delivery of other vaccines in the country. Vaccines are widely accessible because any medical practi-

tioner can prescribe and administer them, and a very high proportion of the target population can obtain them at no expense. However, the lack of active identification, invitation, and follow-up of the target population is a substantial impediment to achieving high coverage, and to monitoring HPV vaccine use. It should also be noted that HPV vaccination is not uniformly endorsed by paediatricians and gynaecologists in France, and it has only recently been decided to make a transition from the predominantly opportunistic cervical screening programmes in the country to a population-based approach (Republic of France 2014).

3.5 State of HPV vaccination implementation in Europe

Most European countries have national vaccination committees that provide vaccination policy recommendations to the national health authorities. The committees and advisory groups are composed of a diverse group of paediatricians, epidemiologists, and other experts. In some countries, decisions about vaccination schedules are made at a subnational level (e.g. Austria, Germany, and Spain); in others, differences in the implementation of a vaccination strategy may exist at a subnational level (e.g. Belgium, Ireland, Italy, and the United Kingdom).

To ascertain the state of implementation of HPV vaccination in the 28 EU Member States as well as Norway and Iceland, we updated a 2009 survey on HPV vaccination that was conducted in a project (VENICE 2) funded through the European Centre for Disease Prevention and Control (ECDC) (Dorleans et al. 2010) and a 2012 review by the ECDC (ECDC 2012). The survey explored, among other information, the status of introduction of HPV vaccination in these European countries, the respective target populations, the main modalities of implementation, and, when relevant, the coverage achieved.

The main results are summarized in Table 3.1. As of early 2014, five countries had not yet formulated a recommendation about HPV vaccination, all of them new Member States that acceded to the EU after 2003 (Croatia, Cyprus, Estonia, Hungary, and Lithuania). Two countries had issued recommendations but had not yet integrated HPV vaccination into the national immunization schedule (Poland and Slovakia). The remaining 21 EU Member States as well as Norway and Iceland have started vaccination campaigns between 2007 and 2013. Table 3.1 shows a substantial heterogeneity in the target populations for both routine and catch-up vaccination strategies across EU countries. For routine vaccination, 14 countries have chosen age 12 years (±1 year), and the other countries have chosen age 11, 13, or 14 years or an age range between 11 and 15 years. Ten countries planned national catch-up campaigns, and one (Italy) had catch-up campaigns in some regions. The chosen age ranges for catch-up vaccination were more heterogeneous than those for routine vaccination and usually started for girls that were 1 year older than the upper limit of the routine vaccination group, except for Italy and Portugal, where there was a gap of at least 2 and 3 years, respectively. The upper age limit was mostly between 16 and 18 years, but it was 20 in France and 24 in Romania.

Vaccination is offered free of charge to adolescent girls and young women in the target age groups in most EU countries (18), is partially reimbursed in Belgium and France, and is paid for completely out-of-pocket in Austria.

Coverage data are currently available for 13 countries, and comparability between countries is limited due to the use of different definitions, such as cumulative coverage by birth cohort or coverage during a certain period of time. Keeping this caveat in mind, however, coverage for 3-dose vaccination of girls in routine cohorts was generally suboptimal across Europe. It was low in Luxembourg (17%) and

France (29%), medium in Italy, the Netherlands, Norway, and Slovenia (range, 55–66%), and high in Belgium, Denmark, Malta, Spain, the United Kingdom, and Portugal (range, 77–88%). Information on catch-up vaccination is more limited than for routine vaccination. The highest coverage for catch-up vaccination was 81%, in Denmark, and this coverage ranged between 29% and 69% in 6 other countries.

In conclusion, there is a need to improve coverage of HPV vaccination in the EU. HPV vaccination programmes should aim for a minimum coverage of 70% and preferably >80% **(III-A).**[Rec 3.7] The reported 3-dose coverage of primary vaccination in a population-based vaccination programme should reach 70% within the first 12 months **(III-A)**; the same coverage target applies for programmes using a 2-dose schedule **(VI-A)**.[Rec 3.7] In addition, standard definitions and parameters for coverage of vaccination should be developed and used in vaccination monitoring **(VI-A).**[Rec 3.4] Age at primary vaccination, age at catch-up vaccination, number of doses, time between doses, and duration of follow-up since offering primary vaccination should be included in the definitions and performance parameters **(VI-A).**[Rec 3.4]

3.6 Determinants of success for HPV vaccination programmes

The determinants of a high uptake of HPV vaccination programmes are multi-factorial. They include programme characteristics (opportunistic vs organized); cost of the vaccine and vaccination campaigns; quality of advocacy and communication to the public; awareness and acceptance by the target population and their parents; endorsement by the medical community and other stakeholders; and, in some instances, the presence of anti-vaccine ideology and activities. The sustainability of the health budget required for successful implementation of HPV vaccination for prevention of cancer may depend on collective negotiations with the commercial sector (see for example, van de Vooren, Curto & Garattini 2014). Decision-makers, policy-makers and programme managers should therefore be aware of the wide range of prices for HPV vaccines in the EU and the potential to reduce the overall costs of HPV vaccination programmes by appropriate tendering, and negotiating vaccine prices that are comparable to the low prices obtained in some EU Member States **(VI-A).**[Rec 3.6]

There are no randomized studies comparing coverage levels by different approaches of HPV vaccination campaigns. Indirect evidence for the comparison of effectiveness of different programmatic approaches can be drawn from comparing the coverage obtained by different delivery systems in industrialized countries across the world. Coverage achieved by opportunistic programmes in Europe usually has not exceeded 40% (in France, Luxembourg, and Sweden before 2012), although in a regional programme in Belgium coverage reached 60–70% in certain birth cohorts (Arbyn et al. 2012) (Table 3.1). In general, organized school-based programmes have yielded high coverage levels, reaching 3-dose vaccination in >70% of routine target groups (United Kingdom, 80%; Belgium, 83%; Australia, 73% (IAP 2013)), although less satisfactory coverage has also been reported (Norway, 63%; Slovenia, 55%). Substantial success has also been noted in some countries with organized programmes through public health centres (Italy, 65%; Portugal, 81%) or general practitioners (Denmark, 79%).

The organized school-based approach has also been shown to ensure a more equitable distribution of at least routine vaccination among more deprived sections of the population. Coverage among 12-year-old girls in the most deprived local areas in the United Kingdom reached 83% in 2008–2009,

Table 3.1: Overview of implementation of HPV vaccination in countries of the European Union, Iceland, and Norway

Country	Start date of routine HPV vaccination (No: no campaign)	Campaign: organized/ opportunistic	Target age for routine vaccination	Age range for catch-up vaccination	Cost: free (F) / % cost reimbursed for routine and catch-up group	Coverage monitoring system in place? (Y/N)	Coverage of routine population (3 doses) (reporting year) C: birth cohort	Coverage of catch-up population (3 doses) (reporting year) C: birth cohort	Source
Austria	2006	Opportunistic	>9[a]	-	0%	N	-	-	-
Belgium	2007	Opportunistic/organized (school-based)[b]	12–13	14–18	90%	Y	Opportunistic: (2009) C1995: 37% School-based (2011) C1998: 83%	Opportunistic: (2009) C1992: 69%	(Lefevere et al. 2011) ((ZG) Vlaams Agentschap Zorg en Gezondheid 2013) (Arbyn et al. 2012)
Bulgaria	2012	Organized (through health centres or primary-care providers)	12	-	F for routine; catch-up is opportunistic and not free of charge	-	-	-	(Poljak et al. 2013; Seme et al. 2013)
Croatia	No	-	-	-	-	-	-	-	(Seme et al. 2013)
Cyprus	No	-	-	-	-	-	-	-	
Czech Republic	2012	Organized (through health centres, paediatricians)	12–14 13–14	-	Covered by general health insurance for routine	Y	-	-	(Poljak et al. 2013; Seme et al. 2013)

Country	Start date of routine HPV vaccination (No: no campaign)	Campaign: organized/ opportunistic	Target age for routine vaccination	Age range for catch-up vaccination	Cost: free (F) / % cost reimbursed for routine and catch-up group	Coverage monitoring system in place? (Y/N)	Coverage of routine population (3 doses) (reporting year) C: birth cohort	Coverage of catch-up population (3 doses) (reporting year) C: birth cohort	Source
Denmark	2009	Organized (through general practitioners)	12	13–17	F	Y	(2009) C1996: 79%	(2009) 81%	(Sander et al. 2012) (SSI - Statens Serum Institut 2013)
Estonia	No	-	-	-	-	-	-	-	-
Finland	2013	Organized (school-based)	11–12	13–15	F	Y	-	-	(Mannonen & Waller 2013)
France	2007	Opportunistic	11-14	15–20	65%	Y	(2008) C1994: 29%	-	(Fagot et al. 2011)
Germany	2007	Opportunistic	12–17	-	F	N	-	-	
Greece	2008	Opportunistic/ organized	12–15	-	F	N	-	-	
Hungary	No	-	-	-	-	-	-	-	
Iceland	2011	Organized (school-based)	12	13	F	Y	-	-	
Ireland	2010	Organized (school-based)	12–13	-	F	Y	-	-	
Italy	2007–2008	Organized (through public health centres)	11	14/15/16/17/24[c]	F	Y	(2011) C1997: 66%	-	(Giambi 2012)

Country	Start date of routine HPV vaccination (No: no campaign)	Campaign: organized/ opportunistic	Target age for routine vaccination	Age range for catch-up vaccination	Cost: free (F) / % cost reimbursed for routine and catch-up group	Coverage monitoring system in place? (Y/N)	Coverage of routine population (3 doses) (reporting year) C: birth cohort	Coverage of catch-up population (3 doses) (reporting year) C: birth cohort	Source
Latvia	2010	Organized (through public health centres)	12	-	F	Y	(2012) 53%	-	(Seme et al. 2013)
Lithuania	No	-	-	-	-	-	-	-	
Luxembourg	2008	Opportunistic	12–13	14–18	F	Y	(2009) 17%[d]	(2009) 29%[d]	(Dorleans et al. 2010)
Malta	2013	Organized (through health centres)	12	-	F	Y	(2013) 88%	-	(Farrugia Sant'Angelo, 2014)
Netherlands	2009	Organized (through public health centres)	12	13–16	F	Y	(2012) C1997: 56%	(2012) 58%	(van Lier et al. 2012)
Norway	2009	Organized (school-based)	12	-	F	Y	(2011) C1997: 63%	N/A	(Sander et al. 2012)
Poland	No	-	-	-	-	-	-	-	
Portugal	2008	Organized (through health centres)	13	17	F	Y	(2009) 81%[d]	(2009) 56%[d]	(Dorleans et al. 2010)
Romania	2009	Organized (school-based)	12	13–24	F	Y	-	-	-
Slovakia	No	-	-	-	-	-	-	-	-

Country	Start date of routine HPV vaccination (No: no campaign)	Campaign: organized/ opportunistic	Target age for routine vaccination	Age range for catch-up vaccination	Cost: free (F) / % cost reimbursed for routine and catch-up group	Coverage monitoring system in place? (Y/N)	Coverage of routine population (3 doses) (reporting year) C: birth cohort	Coverage of catch-up population (3 doses) (reporting year) C: birth cohort	Source
Slovenia	2009	Organized (school-based)	11–12	-	F	Y	(2011)[e] 55%	-	(ECDC 2012)
Spain	2008	Organized (through public health centres/school-based)	11–14[f]	-	F	Y	(2009)[g] 77%	-	(Limia & Pachon 2011)
Sweden	2012	Organized (school-based)	10–12	13–18[h]	F	Y	(2013)[i] C2000–C2001: 82%	57%	(Folkhälsomyndigheten 2014)
United Kingdom	2008	Organized (school-based)	12–13	14–17	F	Y	80%[d]	32%[d]	(Dorleans et al. 2010)

[a] Before onset of sexual activity, without upper age limit; boys also included.

[b] Varies by region: organized, school-based since 2010 in the Flemish community and since 2012 in the French community; also, a national opportunistic system is in place for girls aged 12–18 years.

[c] Target age depends on the region.

[d] VENICE 2 survey; birth cohorts not specified.

[e] Birth cohort not specified.

[f] Varies by region.

[g] By targeted birth cohort in each region.

[h] Opportunistic, with co-payment.

[i] At least one-dose coverage reported. Cumulative vaccination percentage by birth cohort size in 2013, updated end of March 2014.

compared with a similar 86% in the least deprived areas (Desai et al. 2010). In contrast, for the USA with an opportunistic vaccination approach (coverage, 32% (CDC 2011a)), it was shown that coverage was significantly lower in the relatively poorer states than in the wealthier states. For example, in 2008 the coverage rate for 3 doses among girls aged 13–17 years was 20% in Mississippi, compared with 55% in Rhode Island, a wealthier state (Bach 2010; CDC 2010). Social and geographical disparities in HPV vaccination have been shown to be directly correlated with similar differences in access to cervical screening. This situation is likely to further exacerbate inequalities in mortality from cervical cancer; for example, in 2008 the age-standardized cervical cancer mortality rate in Mississippi was 3.6 per 100 000, compared with 1.8 per 100 000 in Rhode Island (CDC 2009).

Compared with delivery through health centres, however, school-based programmes need logistics and infrastructure (staff, vaccine storage and delivery routes, data handling) that may not be readily available, and careful matching of the school timetable with vaccination sessions. The advantages of school-based programmes are likely to be lower for catch-up vaccination of adolescents who are older than the compulsory age of education than for routine vaccination of young girls.

In conclusion, planning and modification of vaccination programmes and policies should take into account local conditions, including vaccine and vaccination costs and resources required in monitoring, provision of information, and communication. Pilot studies are recommended before and after national roll-out, to assess how to improve coverage and public awareness **(VI-A)**.[Rec 3.5]

HPV vaccination is best implemented through organized, population-based programmes **(III A)**; a population-based programme is likely to achieve higher coverage, less social inequalities in vaccine uptake, and lower vaccination costs per vaccine **(III).**[Rec 3.1] If a country has started implementation with the opportunistic approach, transition to an organized, population-based programme, preferably school-based (or other public-service-based) programme is recommended **(III-A)**.[Rec 3.1]

3.7 Relevant issues for EU countries with high cervical cancer burden and low screening capacity

Several new EU Member States are middle-income countries with high cervical cancer mortality rates due to limited coverage and/or poor performance of cytological screening programmes (Arbyn et al. 2009; Arbyn et al. 2011; Nicula et al. 2009). The decision-making process for the introduction of HPV vaccination in national immunization programmes is complex, especially in these countries, where estimated benefits in terms of prevention of cervical cancer (effectiveness) must be weighed against the still comparatively high cost of the vaccine and the existence of numerous other competing health needs. Although vaccine costs have fallen substantially in recent years, and the recently recommended 2-dose vaccination schedule would be less costly than the 3-dose schedule, HPV vaccination still has a comparatively high cost compared with most routine children's vaccines. Mathematical models have shown, however, that the cost-effectiveness of HPV vaccination tends to be largest in countries with the highest cervical cancer burden. Cost-effectiveness analysis was particularly favourable for Brazil (Goldie et al. 2007) and Lithuania (Vanagas et al. 2010), countries that have elevated age-standardized rates of cervical cancer incidence (24.5 and 21.0 per 100 000, respectively) and mortality (10.9 and 8.3 per 100 000, respectively).

Romania started introducing HPV vaccination in November 2008. HPV vaccines were administered through a school-based programme to girls in the 4th grade of school (average age, 10 years). However, during the first year of implementation only about 2% of the target group received 3-dose vaccination (Seme et al 2013). In 2009, the Ministry of Health of Romania implemented large-scale advocacy and communication activities, and training for medical workers and schoolteachers to rebuild community confidence and interest in HPV vaccination. The Romanian national immunization programme became directly involved in the vaccination campaign of girls aged 10 years and a catch-up programme for girls and young women aged 12–26 years. The vaccination was discontinued at the end of 2011 due to a negative public reaction, lack of proper communication, and consequent low coverage of the target population (less than 5%). The programme was launched for the third time in April 2013 (Seme et al. 2013). Latvia started HPV vaccination, integrated into the national immunization schedule, in 2010. Vaccination coverage for three doses was 60.6% in 2011 and 53.4% in 2012. An EU candidate country, the former Yugoslav Republic of Macedonia, included HPV vaccination in its national immunization programme starting in November 2009. Coverage for three doses increased from 37% for the 2009/2010 school year to 67% for the 2010/2011 school year, and then declined to 65% for the 2011/2012 school year (Seme et al. 2013).

3.8 Discussion

As of early 2014, 21 of 28 EU countries, plus Norway and Iceland, have initiated HPV vaccination campaigns. In most of these countries, HPV vaccine is offered free of charge, predominantly through organized school-based programmes. The success in terms of coverage of the target groups has been highly variable, ranging from <30% in France and Luxembourg to 80% or more (in Belgium, Denmark, Malta, Portugal, Sweden, and the United Kingdom). In other EU countries, coverage is not known and is probably even lower than 30%. Organized, population-based programmes achieved the best coverage, but access to HPV vaccines has been more equitable in school-based programmes than in public-health-centre-based programmes. Opportunistic programmes usually achieved low or ill-defined levels of coverage. Most of the countries chose girls aged between 11 and 13 years as the routine target group. As expected, vaccination campaigns targeting adolescents posed greater challenges compared with paediatric vaccination. All EU countries had to put in place a new delivery infrastructure for HPV vaccine administration, and strengthen community awareness and dissemination of information on HPV and cervical cancer.

It is important to continue to monitor the safety of HPV vaccines at a population level through routine pharmacovigilance systems and/or specific post-licensure studies. Results from both have been reassuring to date. Vaccination coverage of the target populations is an important process monitoring indicator, and is planned in 17 of the 21 EU countries with HPV vaccination campaigns. Considerable time will be required to monitor the impact of the vaccines at the population level. Effects on cervical cancer incidence will typically take two or three decades to be measurable. Early indicators of the impact of HPV immunization are the prevalence of vaccine-targeted HPV 16 and 18 and their associated precancerous lesions in vaccinated populations. Several initiatives have been taken to monitor these indicators, especially in Nordic countries and the United Kingdom. Indirect evidence of the population-level impact of the HPV vaccines has already been provided through demonstration of decreases in the prevalence of HPV, the incidence of high-grade cervical abnormalities, and the incidence of genital warts soon after the introduction of vaccination programmes.

3.9 Conclusions

The available information on HPV vaccine coverage in many different countries supports the superiority of organized programmes versus opportunistic ones. Comparisons across a few countries suggest that the coverage achievable by school-based programmes and those organized by other public service providers can be similar. Examples of low coverage of population-based programmes also exist, for reasons that are not fully explained. Coverage in opportunistic programmes tends to be consistently low, i.e. <40%, and is often ill-reported. In addition to coverage, other aspects including costs of vaccine and vaccine delivery also need to be taken into account.

Vaccines have been licensed for use in girls as young as 10 years (9 years in some countries) to prevent cervical precancers and cancers (WHO 2009b). To optimize the impact of HPV vaccines, the primary target group to consider for routine vaccination is girls at an age just before sexual activity (and therefore exposure to HPV). Lowering the age of vaccination would not prevent many infections and should be avoided until there is evidence that the vaccine can offer long-term protection (ECDC 2012).

For many European countries, information about vaccine coverage is not available. Currently available coverage estimates often apply to programmes of different duration, especially for the catch-up group, and do not always derive from validated register-based sources. As of 2010, 13 countries (Denmark, France, Ireland, Italy, Latvia, Luxembourg, the Netherlands, Norway, Portugal, Romania, Slovenia, Sweden, and the United Kingdom) had reported that there was a national HPV vaccination coverage monitoring system in place for routine immunization. Five of these countries (France, Italy, the Netherlands, Norway, and Sweden) reported the existence of systems in place to follow up on adults/adolescents (ECDC 2012). While it is important to assess coverage, if a country has the capacity it is also desirable to assess intermediate events (e.g. prevalence of oncogenic HPV infections, genital warts, screening tests, and precancerous lesions), possible adverse effects and long-term outcomes. WHO recommends long-term follow-up (e.g. for 10 years) of antibody levels in vaccinated cohorts (WHO 2006).

For adverse events, standard definitions are provided by WHO (WHO 2005). Standards for allowable vaccine wastage rates have also been set by WHO (WHO 2003).

There has been wide variation in the readiness to implement well-functioning vaccination programmes in EU Member States. Countries with limited resources could especially benefit from HPV vaccination, but there are problems in identifying sustainable working models. In the planning and modification of vaccination programmes and policies, appropriate analyses of health-economic aspects need to be included, taking local conditions into account. In addition to HPV vaccination planning, it is essential to include complementary prevention strategies, notably cervical screening.

Support from stakeholders is essential for the success of any vaccination programme. Effective communication to the public and advocacy are essential to reach high acceptance and to favourably affect the perceptions of the vaccine in the targeted population of children, and especially their parents. The most successful methods of communication and implementation of the different programme aspects can be piloted in restricted regions of a country and then rolled out at the national level.

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Appendix 1: Evidence Assessment

Clinical Questions, PICOS components, results and conclusions

Clinical question 1

Is HPV vaccination efficacious and safe?

P: Girls or young women or women HPV negative at time of vaccination (ATP or naive cohort)
I: HPV vaccination
C: Unvaccinated control group
O1: Histologically confirmed cervical Intraepithelial Neoplasia (CIN) grade 2-3, Adenocarcinoma in Situ (AIS), and cervical carcinoma (associated with the HPV types included in the vaccine or not):
O2: Oncogenic HPV (vaccine types or other oncogenic types) persistent cervical infection
O3: Occurrence of short-term and long-term adverse events either proved to be directly related to vaccination or not
S: RCTs, Reviews of RCTs

Results: The latest high-quality systematic review (Lu et al. 2011) was considered for efficacy and safety; the medium-quality review by Malagon et al. (2012) for cross protection and the low-quality review by Verstraeten et al. (2008) for adverse events related to the AS04 adjuvant. In addition, the Costa Rica Vaccine Trial (Herrero et al. 2008, Rodríguez et al. 2013) was considered for efficacy and safety. Reports of the Global Advisory Committee on Vaccine Safety (WHO 2009a, 2014a) were considered for safety. Reports of European Medicine Agency[29] and the World Health Organization (WHO 2009b) were considered for efficacy and safety.
Lu et al. (2011) included 7 trials enrolling 44142 females. Eligible participants were non-pregnant women aged 15 to 44 who had 6 or fewer lifetime sexual partners and no history of abnormal Pap smears. The mean age was approximately 20 years except in one trial it was 34. The trials studied the bivalent vaccine (containing HPV 16 and 18 VLPs) (2 trials); the monovalent (containing HPV 16 VLPs) (1 trial) and quadrivalent vaccine (containing HPV 6, 11, 16 and 18 VLPs) (4 trials). All trials used placebo as the comparator except for two in which all or part of the control group received hepatitis A vaccine, or placebo plus hepatitis B vaccine. The primary endpoint for efficacy was CIN2+. Participants were tested for HPV DNA every 6 months and for cytological abnormality every 6 or 12 months. The length of trials ranged from 26 to 60 months. The results are reported in the tables below.

Efficacy

	CIN 2+ associated with HPV16	CIN 2+ associated with HPV18	**CIN 1+ associated with HPV16**	CIN 1+ associated with HPV18	**CIN 2+ associated with HPV 31/33/45/52/58**
Intention to treat	4 trials 28639 participants, RR=0.47 (95% CI:0.36-0.61)	3 trials, 28053 participants, RR=0.16 (95%CI:0.08-0.34)	4 trials, 21891 participants, RR=0.43 (95% CI:0.33-0.58)	3 trials, 20885 participants, RR=0.22 (95%CI:0.10-0.44)	3 trials, 34476 participants, RR=0.79 (95% CI:0.67-0.92)
Per protocol	3 trials, 22940 participants, RR=0.04 (95% CI:0.01-0.11)	2 trials, 23565 participants, RR=0.10 (95% CI:0.03-0.38)	2 trials, 5240 participants, RR=0.02 (95% CI:0.00-0.11)	1 trial, 4222 participants, RR=0.02 (95%	3 trials, 25011 participants, RR=0.10 (95% CI:0.03-0.38)

[29] See footnotes no. 25 - 27 on page 115.

	Persistent HPV 16 infection ≥ 6 months	**Persistent HPV 18 infection ≥ 6 months**	**Persistent infection with HPV 31,33,45,52 and/or 58 ≥ 6 months**
Intention to treat	2 trials, 11964 participants, RR=0.15 (95% CI:0.10-0.23)	2 trials, 12948 participants, RR=0.24 (95% CI:0.14-0.42)	2 trials, 20524 participants, RR=0.77 (95% CI:0.72-0.83)
Per protocol	3 trials, 14485 participants, RR=0.06 (95% CI:0.04-0.09)	2 trials, 14008 participants, RR=0.05 (95% CI:0.03-0.09)	2 trials, 17372 participants, RR=0.72 (95% CI:0.65-0.79)

In the Costa Rica Vaccine Trial, during the 4-year follow-up among the 2284 women aged 18-25 years with no evidence of previous HPV exposure, 2.5% in the HPV arm and 4.8% in the control arm were diagnosed with HSIL, resulting in relative reduction of 49.2% (95%CI 20.3, 68.1). For ASC-US/LSIL the corresponding figures were 17.2%, 21.0% and 18.1% (95% CI 1.09, 32.2) (Herrero et al. 2008, Rodríguez et al. 2013).

Safety

Pain at injection site was the most frequently reported AE ranging from 83.0 - 93.4% in vaccine groups. Headache and fatigue were the most common vaccine-related systemic AEs observed in approximately 50-60% of all participants. Serious AEs that were judged to be related to injection included bronchospasm, gastroenteritis, headache, hypertension, injection-site pain, decrease in joint movement at injection site, hypersensitivity to injection, chills, headache and fever. Among trials reporting vaccine-related serious AEs, the event rate ranged from 0-0.1%. Overall, No significant differences between experimental and control groups in the incidence of serious adverse events were noted in the trials comparing vaccine vs no vaccine: pooled RR (all studies, 43856 participants): 1.00 (95% CI:0.91-1.09) or injection-related serious adverse events: Pooled RR (all studies, 43856 participants): 1.82 (95% CI:0.79-4.20) (Lu et al. 2011).

Verstraeten et al. 2008 included 18 phase II and phase III clinical trials comparing HPV 16/18 vaccination with and without AS04 adjuvants for the incidence of adverse events of potential autoimmune aetiology.

Pooled RR (AS04/no AS04) of autoimmune events (N=39160)

At least one AE=0.92 (95% CI 0.70-1.22)
Neuroinflammatory overall=0.67 (95% CI 0.006-5.82)
Gastrointestinal overall=0.97 (95% CI 0.37-2.43)
Musculoskeletal overall=1.24 (95% CI 0.62-2.47)
Skin disorders overall=0.92 (95% CI 0.37-2.24)
Thyroid disease overall=0.85 (95% CI 0.57-1.25)
Other overall=0.88 (95% CI 0.28-2.64)

Cross-protective efficacy of the bivalent vaccine (HPV 16 and 18) and quadrivalent vaccine (HPV 6, 11, 16, and 18) against non-vaccine type HPVs

Two clinical trials (FUTURE I and II) of the quadrivalent vaccine and three (PATRICIA, HPV007, and HPV-023) of the bivalent vaccine were included in the review by Malagon et al. 2012. Analysis of the most comparable populations (pooled FUTURE I/II data vs PATRICIA) suggested that cross-protective vaccine efficacy estimates against infections and lesions associated with HPV 31, 33, and 45 were usually higher for the bivalent vaccine than the quadrivalent vaccine.

Persistent infection with HPV 31:

- Bivalent vaccine: relative risk reduction (RRR)=77.1% [95% CI 67.2 to 84.4]
- Quadrivalent vaccine: RRR 46.2% [95%CI 15.3 to 66.4]; p=0.003)

Persistent infection with HPV 45

- Bivalent vaccine: RRR=79.0% [95%CI 61.3 to 89.4]
- Quadrivalent vaccine: RRR=7.8% [95%CI –67.0 to 49.3]; p=0.0003)

CIN grade 2 or more severe lesion associated with HPV 33

- Bivalent vaccine RRR=82.3% [95%CI 53.4 to 94.7]
- Quadrivalent vaccine: RRR=24.0% [95%CI –71.2 to 67.2]; p=0.02)

CIN grade 2 or more severe lesion associated with HPV 45

- Bivalent vaccine: RRR=100% [95%CI 41.7 to 100]
- Quadrivalent vaccine: RRR= –51.9% [95%CI –1717.8 to 82.6]; p=0.04).

Conclusions:

Are HPV vaccines efficacious?

VLP-based prophylactic HPV vaccines are highly efficacious in preventing persistent infection and cervical diseases (CIN1-CIN3 and adenocarcinoma in situ) associated with vaccine HPV types among young female adults. The vaccines are safe and generally well tolerated **(I)**. Questions related to long-term efficacy have yet to be addressed.

Is HPV vaccination safe?

No significant differences between experimental and control groups in the incidence of serious adverse events were noted in the included trials comparing vaccine vs no vaccine **(I**.

Clinical Question 2

At what age is the immune response to vaccination highest?

P: Girls or women at different age range at time of vaccination: 9-11, 12-13 year old girls, or older girls and women
I: HPV vaccination (3 doses)
C: Unvaccinated control group
O: HPV antibodies level
S: RCTs, Reviews of RCTs

Results: An analysis of the combined immunogenicity database of phase 2/3 studies submitted to regulatory agencies, including data from 12343 subjects aged 9-26 years found that age at vaccination was inversely proportional to the vaccine-induced anti-HPV response (Giuliano et al. 2007). 3 prospective trials compared the immune response to vaccination between early adolescent girls and young women (10-14 or 10-15 vs 15-25 or 16-23 years). Both age groups achieved ≥99% seroconversion for HPV 16 and 18, and geometric mean titres (GMT) measured 1 month after the completion of the vaccination regimen were 1.7-2 times as high in the younger age group (Block et al. 2006, Pedersen et al. 2007, Sow et al. 2013).

Conclusion: Immunogenic response to vaccination in early adolescent girls (10-15 years) is non-inferior to that in young women (15–25 years). HPV vaccination during early adolescence is highly immunogenic **(I)**.

Clinical question 3

What are the determinants of successful HPV vaccination programmes?

P: Girls at vaccination target- and catch-up age for HPV vaccination
I: Organised vaccination programmes using
(a) school-based setting,
(b) health institution-based setting and
(c) reimbursement approach (on-demand)
C: Vaccine available at full cost
O: Coverage in target age groups
S: All studies Comparison between countries using different settings as described above.

Results: No studies comparing organized vaccination programmes with vaccination at full cost were available. Three cross sectional surveys assessing coverage of school-based vaccination programmes in adolescents aged 12 to 18 years were considered: two were conducted in Australia (Reeve et al. 2008; Watson et al. 2009) and one in the UK (Brabin et al. 2008). The uptake for the first dose was 70-89%; for the second dose it was similar or lower: 64-88% and for the third dose 55-79%. The UK study reported a significantly lower vaccine uptake in schools with a higher proportion of girls from ethnic minority groups ($P<0.001$ for trend) or girls with entitlement to free school meals ($P=0.029$ for trend). The main reasons for parents refusing initial consent was lack of familiarity with the vaccine and concerns about vaccine safety, especially long term.
Organized vs opportunistic vaccination programmes were compared based on data from national monitoring reports. Coverage was highly variable, ranging from less than 30% to 80% or more. At the lower end of the range the programmes were relying on opportunistic vaccination. The highest rates, of 80% or more, were reported in countries or regions with population-based vaccination programmes providing the vaccine free of charge, either school-based like in the UK (Dorleans et al. 2010) and Sweden (Folkhälsomyndigheten 2014), organized through public health centres as in Portugal (Dorleans et al. 2010), Malta (Farrugia Sant'Angelo 2014) and Belgium (Arbyn et al. 2012) or organized through general practitioners as in Denmark (Sander et al. 2012).

Conclusion: The determinants of successful HPV vaccination programmes in terms of coverage include: population-based programme, free of charge vaccine, either school-based or organized through public health centres or general practitioners. **(V)**.

Annex 1

Successful implementation of population-based cancer screening programmes

Annex 1a

Stockholm statement on successful implementation of population-based cancer screening programmes

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Declarations of interest
C. de Wolf is a self-employed consultant to a non-profit organization working in the public interest (Swiss Cancer Screening Federation) and to various public entities in Switzerland (breast screening programmes in the cantons of Bern, Fribourg and Thurgau) that are engaged in the development, implementation and evaluation of population-based breast screening programmes. All income derived from these sources is paid to him through the Agency for Development and Evaluation of Health Policy, a company registered in Geneva, Switzerland with a value of 20 000 CHF, of which he is the sole proprietor and employee.

An interest of N. Segnan is reported on page 157.

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Acknowledgements
The present statement is based on the results of a workshop held by the European Science Advisory Network for Health (EuSANH) on implementation and quality assurance of cancer screening programmes in Stockholm on 7–9 February 2011. A more detailed report has been published elsewhere and is reproduced in the second part of this annex with permission of Elsevier.

Members of the workshop expert committee were: Ahti Anttila, Finland; Magdalena Bielska-Lasota, Poland; Thomas Davidson, Sweden; Johannes JM van Delden, The Netherlands; Lawrence von Karsa, International Agency for Research on Cancer; Elsebeth Lynge, Denmark; Sue Moss, United Kingdom; Maja Primic Žakelj, Slovenia; Leo van Rossum, The Netherlands; Nereo Segnan, Italy; Sven Törnberg, Sweden; Chris de Wolf, Switzerland.

The workshop was also attended by the following observers: Euzebiusz Dziwinski, European Cancer Patient Coalition; Karl Freese, European Commission; Gunta Lazdane, World Health Organization; and by the following EuSANH representatives: Susanne V Allander, Sweden; Dorine Coenen, The Netherlands; Louise Gunning, The Netherlands; Monica Hultcrantz, Sweden; Måns Rosén, Sweden.

Comments were received from Jose Manuel Baena, Luc Bleyen, Mireille Broeders, Luis Bujanda, José Expósito, Roger Pla Farnós, Xandra Gravenstein, Rosella Hermans, Roland Holland, Harry de Koning, Chris Meijer, Nieves Ascunce Elizaga, Xavier Castells Oliveres, Julietta Patnick, Marina Pollán, Dolores Salas, Hélène Sancho-Garnier, and Jaroslav Volf.

The research leading to these results has received funding from the European Union's Seventh Framework Programme [FP7/2007-2013] under agreement number 229716 for the EuSANH project Improving Science Advice for Health in Europe (EuSANH-ISA) (www.eusanh.eu).

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Note, Annex 1a is a copy of the same annex published in 2013 in the *European guidelines for quality assurance in breast cancer screening and diagnosis, fourth edition – Supplements*. The annex is included in the present Supplements publication because it also applies to cervical cancer screening.

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Stockholm statement on successful implementation of population-based cancer screening programmes

A multidisciplinary group of scientists and professionals experienced in implementation and quality assurance of cancer screening programmes and in development of scientific advice on health policy met at a pan-European workshop in Stockholm from 7 to 9 February 2011. The workshop was organized by the European Science Advisory Network for Health (EuSANH, www.EuSANH.eu). The list of experts attending the workshop is provided in this annex. The experts reviewed the available evidence on implementation and quality assurance of cancer screening programmes with a focus on organization and reduction of barriers to participation. After comprehensive discussion, the experts reached the following, mutually agreed conclusions:[1]

Any policy decision in Europe to implement a cancer screening programme should take into account European Union (EU) recommendations and guidelines based on the available evidence and the experience in Europe in implementing population-based cancer screening programmes. Key references in this regard are the Council Recommendation of 2 December 2003 on cancer screening of the Council of the European Union [1], the European guidelines for quality assurance in breast, cervical and colorectal cancer screening [2–4] and recent reports dealing with the implementation of cancer screening programmes in the EU [5–7]. These references recognize that societal values in addition to professional, technical and scientific standards are of prime importance in any decision to implement cancer screening programmes. Furthermore, there is no doubt that the population-based approach to programme implementation as recommended by the Council of the EU and the European guidelines is more equitable, more effective and more cost-effective than an opportunistic approach. The latter usually leads to overuse of health resources by a portion of the target population with lower cancer risk, and underuse by less advantaged groups with higher cancer risk.

The experience in Europe shows that successful implementation of population-based cancer screening programmes requires long-term political commitment, a comprehensive quality management programme and sustainable resources. In a fully established programme, the proportion of the expenditure devoted to quality assurance should be no less than 10–20%, depending on the scale of the programme. In the initial years, this proportion may be substantially higher due to the low volume of screening examinations compared with the situation after complete rollout of a nationwide programme. This investment is cost-effective and will save lives.

Once the political decision has been taken to establish a population-based cancer screening programme, a competent programme coordinator should receive the mandate to manage the entire process of programme implementation, beginning with a planning phase and followed by feasibility testing, piloting and, depending on the interim results, subsequent gradual rollout of a programme fulfilling the principles and standards recommended in the Council Recommendation [1] and the European guidelines [2–4] and relevant national standards and guidelines. The coordinator should be provided with sufficient organizational and financial resources to effectively manage the screening programme and take further decisions as necessary. These decisions should enable the coordinator

[1] The present statement summarizes key results of the workshop. A more detailed report has been published elsewhere [8] and is reproduced with permission of Elsevier in the second part of this annex.

and the coordination team to establish the screening programme in the respective health services context, taking into account the need for the professional and organizational management to control the quality of the entire screening process, including informing and inviting the target population, performance of the screening test, diagnosis, therapy and subsequent care. The existing expertise in Europe in implementation of population-based cancer screening programmes should be available for exchange of information and experience, such as through the European cancer screening networks and the European guidelines development activities coordinated by the International Agency for Research on Cancer (IARC, www.iarc.fr), and related initiatives such as the European Partnership for Action Against Cancer (EPAAC, www.epaac.eu).

Additional tools, including computerized information systems and accessible registries, are necessary for the management of effective and efficient screening services (e.g. for call and re-call systems and fail-safe procedures in follow-up of participants with abnormal test results). They are also needed to monitor and evaluate the performance and the outcome of the screening programme, e.g. through linkage of individual data on cancer occurrence and morbidity, screening history, diagnosis and treatment.

Furthermore, key performance and quality indicators of the screening process must be recorded and monitored and the results must be analysed and used for quality management processes. Monitoring and evaluation reports must be published regularly to inform the public and decision makers and to permit timely modification of programme policy, if necessary. The experience of EuSANH in developing advice for health policy making, taking into account not only scientific and professional but also societal aspects, could play an important role in this regard in the future.

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Annex 1b

Determinants of successful implementation of population-based cancer screening programmes

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Declarations of interest
Interests of E. Lynge and N. Segnan are reported on page 157.

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Elsebeth Lynge is undertaking a comparative study of new-generation HPV tests, involving collaboration with Roche Diagnostics A/S, Genomica S.A.U., Qiagen Gaithersburg Ltd., and Gen-Probe Inc., and has served as unpaid adviser for Gen-Probe and Norchip. Nereo Segnan participated at an advisory board meeting for Colorectal Cancer Screening in January 2011, as a paid expert, on colorectal cancer blood screening assay, organized by Roche Diagnostics Ltd.

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The research leading to these results has received funding from the European Union's Seventh Framework Programme [FP7/2007-2013] under agreement number 229716 for the EuSANH project Improving Science Advice for Health in Europe (EuSANH-ISA) (www.eusanh.eu).

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Determinants of successful implementation of population-based cancer screening programmes

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ABSTRACT

To facilitate the future implementation of population-based cancer screening programmes in European countries, we summarised the experience gained from existing programmes across Europe. We listed points that citizens, advocacy groups, politicians, health planners, and health professionals should consider when planning, implementing and running population based cancer screening programmes. The list is general and is applicable to breast, cervical and colorectal cancer screening. It is based on evidence presented in the three European Union guidelines on quality assurance in cancer screening and diagnosis, supplemented with other literature and expert experience presented at a European Science Advisory Network for Health workshop. The implementation of a cancer screening programme should be divided into the following seven phases: (1) before planning, (2) planning, (3) feasibility testing, (4) piloting or trial implementation, (5) scaling up from pilot to service, (6) running of full-scale programme, and (7) sustainability. For each phase, a substantial number of specified conditions have to be met. Successful implementation of a cancer screening programme requires societal acceptance and local ownership along with the best evidence-based practise and verification of adequate performance in each phase of implementation.

1. Introduction

Screening and early detection of asymptomatic cases constitute important elements in the control of breast cancer, cervical cancer, and colorectal cancer. In accordance with the 2003 recommendation of the Council of the European Union (EU),[1] many European countries have implemented screening programmes for some or all of these three cancer sites. Additional programmes are currently being planned or established.

In principle, a good screening test should be simple and easy to use. However, the full preventive potential of screening tests will only be realised within a good screening programme, and such a programme is a complex organisation. To facilitate the future implementation of population-based screening programmes in European countries, it is therefore valuable to summarise the experiences gained from existing programmes across Europe. With this aim in mind, an expert group convened in Stockholm on 7–9 February 2011 under the

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auspices of the European Science Advisory Network for Health, and this paper reports on the outcome of this work.

The aim of cancer screening is to reduce the mortality from the disease screened for. When pre-cancer lesions are detected and treated, the incidence of the disease should also be reduced. For cancer screening to achieve its aim, a number of conditions need to be fulfilled. This report sets out the key points that all citizens, advocacy groups, politicians, health planners, and health professionals should consider when planning, implementing and running population-based cancer screening programmes. The following list is based on evidence from the scientific literature and expert experience. A major part of the evidence is reported in the EU guidelines on quality assurance of cancer screening and diagnosis.[2–4]

The list follows the steps in programme implementation; from the societal deliberations about new cancer-control measures to the sustainability of a well-implemented screening programme. Successful implementation of cancer screening encompasses many steps, here these are grouped into: before planning, planning, feasibility, piloting, roll-out (scaling-up from pilot to service and running a full-scale programme) and sustainability. The points are general and are applicable to breast, cervical, and colorectal cancer screening. In a few cases, points have been repeated if they are of prime importance in more that one phase.

2. Determinants

2.1. *Before planning*

The starting point must always be to promote professional and public understanding of the purpose, the benefits and the risks of screening. This implies that one has to organise a societal debate. The next step is to review existing evidence-based recommendations and guidelines taking into account the local setting. During the whole process international exchange of experience is encouraged. Key points at this stage are:

- Review of scientific literature.
- Collection of information on disease incidence, stage distribution, and survival.
- Collection of information on availability and quality of cure offered.
- Understanding the potential role of screening in cancer control.
- Assessment of evidence for adding screening to existing cancer control measures.
- Collection of experience from other countries.
- Building up professional and public understanding of the benefits and risks of screening.
- Political will, commitment, at all relevant levels (EU, Member States and regional).
- Decision on political responsibility for the process.
- Review of existing guidelines.
- Availability of treatments and facilities (both competence and resources).
- Assessment of facilitating factors/barriers for implementation of organised screening.
- Economic impact and cost-effectiveness of the programme.
- Formal decision and allocation of budget.
- Organisation of continuous societal debate and input.

2.2. *Comprehensive planning: feasibility of screening models, professional performance, organisation, financing, and quality assurance (QA)*

After the political decision has been taken to start the process of establishing a population-based cancer screening programme, the first step is comprehensive planning. This should cover the entire multidisciplinary screening process and the organisational aspects and will help to avoid unnecessary delays and costs later on.

The feasibility of screening models should be tested before detailed planning of pilot studies can begin. Planning should include: professional performance, organisational and financial aspects, as well as the scope and content of a comprehensive quality assurance programme. The initial plans should also consider the time frame within which the various issues need to be further developed. Key points at this stage are:

- Creation of professional dedication (understanding).
- Planning of infrastructure.
- Establishing of coordinating office with supervision mandate.
- Ensuring that screening is seen as a process.
- Designation of a process owner with mandate to run and manage the quality of the programme.
- Organisational development (self learning, quality driven).
- A separate coordination budget.
- Multidisciplinary case management.
- Collaboration between screening and treatment systems.
- Appropriate diagnostic assessment of patients.
- An appropriate screening monitoring IT-system with access and possibility to link registers e.g. population-, patient- and cancer registers.
- Comprehensive information system, serving all purposes.
- Development of a quality assurance plan, including technical QA.
- Adoption of approved QA plan.
- Definition of performance parameters and acceptable levels, including standards for health professionals.
- Contracts with health care providers.
- System for auditing, training and re-training.
- Assessment tools to exclude bad performers.
- Consideration of accreditation system or other comprehensive systems for ensuring competent service delivery.

2.3. *Preparation of all components of screening process, including feasibility testing*

Based on the comprehensive planning, the feasibility of the screening services and key components of programme management should be tested in small-scale studies that are designed to yield initial results with a limited amount of

financial, technical, staff and time resources. The study results are taken into account in revising the initial plans, if necessary, prior to initiating pilot studies on a larger scale. Before the piloting phase can begin, the outcome of the feasibility phase should be thoroughly evaluated. Key points at this stage are:

- Scientific and ethical review of feasibility protocol.
- Correct and balanced information on 'benefit and risk'.
- Development of communication strategy.
- Societal input.
- Clearance of data protection and confidentiality issues.
- Creation of formal oversight for screening programmes.
- Scientific publication of feasibility results.

2.4. *Piloting and modification, if necessary, of all screening systems and components, including quality assurance in routine settings*

In England and many other European countries, implementation of breast, cervical and colorectal screening programmes started in pilot areas, and based on this experience the programmes were scaled up to national coverage.[5] In Finland, implementation of the programmes started in randomly selected cohorts, and was gradually extended to all targeted age groups.[6] This allows the outcome to be evaluated as a randomised controlled trial (randomised health policy).[7] The Finnish approach requires a national decision on screening implementation and the availability of a national population register. The approach permits evidence-based modification of the programme before it extends to the entire country.

The pilot implementation model starts with selection of one or a few pilot regions. Supervision and coaching is important in this phase in order to pick up problems in the screening process as soon as possible. The pilot phase also serves as a testing ground for the legal framework. The pilot outcome should be reported in the scientific literature and widely disseminated to health planners, politicians and health professionals. Based on the piloting, the financial implications of the roll out of the programme should be determined. Key points at this stage are:

- Budgeting.
- Ensuring financial commitment.
- Supervision and coaching of screening staff.
- Testing the legal framework.
- Ability to exclude bad performers.
- Scientific publication of outcome.

2.5. *Scaling up from pilot to service screening*

This is the actual implementation of the piloted intervention. All the points above need to be scaled-up to the size of the full programme. Effective communication of the experience gained to date in the implementation process should help to develop societal confidence in the programme. Key points at this stage are:

- Defining and contracting the local, regional and national programme teams, defining responsibilities.
- Setting-up infrastructure for coordination within health care settings.
- Identifying possible obstacles.
- Developing a plan for evaluation.
- Availability of staff (professional skills and numbers).
- Multidisciplinary case management.
- Special training, reference centre.
- Comprehensive information system, covering all steps in the screening process.
- Collaboration between screening, treatment and IT systems.
- Technical quality assurance.
- Reduction of barriers to participation.
- Tools to encourage compliance.
- Advocacy and collaboration with local civil society organisations.
- Population confidence.

2.6. *Running of a full-scale screening programme. Intensive monitoring of programme roll-out for early detection and correction of quality problems*

Maintaining high-quality of the screening service requires continuous supervision and rigorous scientific reporting. Attention must be paid to performance at each step in the screening process from information and invitation to performance of the screening test, assessment of abnormalities, and diagnosis and treatment of lesions detected in screening. Key points at this stage are:

- Supervision of all steps in the screening process.
- Ability to exclude bad performers.
- Testing grounds for new technologies.
- Monitoring the benefits and harms of screening.
- Scientific publication of outcome.

2.7. *Sustainability*

Sustainability is essential to achieve the potential impact of screening on the burden of disease in the population. This requires adequate, continuous financial support for preserving high programme quality. To maintain societal support, adequate communication of programme performance and impact is essential. This requires long-term evaluation in adequately planned studies with high-quality testing, reporting of performance and follow-up of screening outcomes. Key points at this stage are:

- Accurate and accessible communication of screening outcome.
- Population confidence.
- Organisational anchoring.
- Ensuring adequate financial resources and political commitment.

3. Discussion

The importance of screening as a tool for cancer control has been on the EU agenda for more than 20 years. In the European Code Against Cancer from 1989, women were advised to 'have a cervical smear regularly' and 'if possible, [to] undergo mammography at regular intervals above the age of 50'.[8] The need for organisation of screening into population-based programmes was stressed in the first quality assurance guidelines on breast[9] and cervical[10] cancer from 1993, and further developed in the preparatory work for the recommendation on cancer screening of the Council of the EU in 2003.[11] In the Council Recommendation, the EU Member States unanimously agreed on standards and principles for implementation of breast, cervical, and colorectal cancer screening programmes.[1]

However, the actual implementation of population-based screening programmes in the EU is still far from complete. By 2007, opportunistic cervical cancer screening was still the only available option for nearly half of the European target population, and 30% (8% without service and 22% outside groups served) of the women and men in the European target population were not offered colorectal cancer screening,[12] Table 1. The coverage by colorectal cancer screening programmes has, however, improved after 2007. For example, in Italy by the end of 2008, 36% of 50–69 year old men and women were invited to biennial screening with faecal occult blood test, and 1,171,000 persons were screened, attendence rate 47.5%.[13] The programmes in France and England became nationwide in 2009, and roll-out of programmes in the Netherlands and Denmark will start in 2013 and 2014, respectively. Furthermore, the screening activity is not yet standardised across the EU according to the European recommendations. For example by 2009, the lifetime number of recommended screening tests for cervical cancer varied from 6 to 50+ across the EU countries.[14]

Various obstacles in health care systems and in setting political priorities can inhibit the implementation of population-based screening. In 'new' Member States (that acceded to the EU after 2003), lack of resources is a serious problem. Adequate budgeting is a prerequisite for a successful programme as illustrated by recent experience from Poland.[15]

In 'old' Member States, organisation of screening may conflict with a traditional fee-for-service payment system. To decrease the number of opportunistic smears, the Netherlands stopped reimbursement of preventive smears taken outside the organised programme in 1996.[16] In England, target payments were introduced for general practitioners in 1990 to encourage them to include their female patients in the screening programme. There was no payment if the coverage was below 50%, a small payment if the coverage was between 50% and 79%, and a higher payment when the coverage reached 80%.[17]

Several countries have encountered problems with data confidentiality despite the fact that the EU directive on data protection[18] allows for linkage of health services data. The performance indicators listed in the EU guidelines may be used to monitor the programmes. However, it is clear that these indicators can be calculated only if access is provided to the necessary data. For example, calculation of the 'interval cancer rate as proportion of the underlying, expected, breast cancer incidence rate in the absence of screening'[2] requires access to data on all women with a normal screening mammogram and the individual follow-up of each of these women for incident breast cancer, death and emigration. Furthermore, a population-based breast cancer incidence rate for the period prior to initiation of screening must be available. It is encouraging that this indicator has been calculated for several European breast cancer screening programmes.[19]

Evaluation might also require the merging of datasets that have been separate in the past. In Sweden, the responsibility for cervical cancer screening rests with the counties that also keep the respective records. In order to perform a national audit of the screening programme data were retrieved and merged from 30 pathology and cytology laboratories throughout Sweden, and local cytology codes were converted to a common nomenclature.[20] Once national datasets have been established it is also possible to identify regional differences in screening uptake and outcome; a routine practise in the English[21] and Italian[22] programmes. Centralisation of activities also facilitates monitoring. The EU obligation to invite tenders for provision of large scale services has, however, in some cases impeded centralisation such as in the case of cytology services.

Local ownership and appropriate adaptation to the local health care system are important factors for success. In France, widespread opportunistic mammography screening was the norm until the organised programme became nation-

Table 1 – State of cancer screening in 27 Member States of the European Union by 2007 (adapted from von Karsa et al.[12]).

European recommendation* EU Target population	Breast cancer Women, aged 50–69 59 mio	Cervical cancer Women, aged 30–60 109 mio	Colorectal cancer Women and men, aged 50–74 136 mio
Proportion of target population covered by:			
Population-based, rollout complete	41%	22%	0%
Population-based, roll-out ongoing, piloting, planning	50%	29%	43%
Non-population-based	6%	47%	27%
Excluded from the regions and/or age groups offered screening	2%	2%	22%
no service	2%	<1%	8%

* Target ages recommended for breast and colorectal cancer screening recommended by European Union,[1] minimum target age recommended for cervical cancer screening by Arbyn et al.[3]

wide in 2004. The organised screening programme has therefore encompassed some of the features from the opportunistic practise. For example, a screening examination includes a clinical examination, a minimum of two views per breast, and a supplementary view if needed; all undertaken by an accredited radiologist.[23] In England, the organised programme started much earlier, in 1988. A radiographer with special training in mammography takes two views of each breast, and the whole visit lasts about half an hour.[24]

The comparison of performance indicators from different countries serves as a tool to monitor possible consequences of adapting screening programmes to local health care systems. For example, results from selected European breast cancer screening programmes showed that the cancer detection rate divided by the background incidence rate was somewhat higher in Copenhagen, 3.2, where the programme resembles the English set-up, than in Marseille, 2.5, and in Strasbourg, 2.9.[25]

To ensure the sustainability of a screening programme new evidence concerning screening methods should be reviewed regularly and the potential implications for programme policy should be considered, e.g. with regard to new technologies as flexible sigmoidoscopy,[26] or combination of screening with other preventive measures as human papillomavirus (HPV) vaccination.[27] Evidence-based guidelines should therefore be updated regularly.

Broad societal understanding of the benefits and risks of screening is also essential to the sustainability of an effective screening programme. Many of the performance parameters in the European guidelines are designed to provide an early indication of the benefits and risks of screening. However, long-term follow-up is needed to accurately assess both the benefit in reducing cancer specific mortality and the risk of over-diagnosis. The methodological challenges of such long-term studies using observational data[28] make it all the more important to provide sustainable support for accessibility and management of individual data.

Given the large number of individuals attending screening programmes, it is of utmost importance to avoid risks of low-quality screening. To ensure public confidence in the programme, it should be possible to identify and exclude poor performers. This is challenging because no screening service is infallible. A good example is the actions taken in England following identified failures in the cervical cancer screening programme.[29] Where resources are limited, it is better to implement one cancer screening programme at a time, than to start screening for all three cancer sites at once. Prioritisation may be based amongst other things on the number of cases, political will, and the availability of professional expertise and dedication. The detailed lists provided in this paper can serve as a guide to a gradual and successful implementation.

4. Conclusion

Screening programmes must be implemented effectively and operated in accordance with societal values and priorities. Prerequisites for a successful screening programme are societal acceptance, local ownership, and effective coordination along with the best evidence-based practice.

Given the complexity of the implementation process, it is not surprising that 10 or more years are commonly required to establish population-based cancer screening programmes. Effective, sustained coordination is required, beginning early in the process, with a clear vision of the multiple steps involved and adequate resources to provide leadership, develop consensus, and adapt to the evolving needs of the unfolding programme.

Conflict of interest statement

Elsebeth Lynge: Elsebeth Lynge is undertaking a comparative study of new-generation HPV tests, involving collaboration with Roche Diagnostics A/S, Genomica S. A. U., Qiagen Gaithersburg Ltd., and GenProbe Inc., and has served as unpaid advisor for GenProbe and Norchip.

Sven Törnberg: None declared.

Lawrence von Karsa: None declared.

Nereo Segnan: I participated to an advisory board meeting for Colorectal Cancer Screening in January 2011, as a paid expert, on colorectal cancer blood screening assay, organised by the Roche Diagnostics Ltd. I asked and received the formal permission by my employer, the S. Giovanni University Hospital of Turin.

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Annex 2

Council Recommendation of 2 December 2003 on cancer screening (2003/878/EC)

L 327/34 EN Official Journal of the European Union 16.12.2003

COUNCIL RECOMMENDATION
of 2 December 2003
on cancer screening

(2003/878/EC)

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 152(4), second subparagraph, thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the European Parliament,

Whereas:

(1) Article 152 of the Treaty provides that Community action is to complement national policies and be directed towards improving public health, preventing human illness and diseases, and obviating sources of danger to human health. Such action shall cover the fight against the major health scourges, by promoting research into their causes, their transmission and their prevention, as well as health information and education. Community action in the field of public health shall fully respect the responsibilities of the Member States for the organisation and delivery of health services and medical care.

(2) Further development of cancer screening programmes should be implemented in accordance with national law and national and regional responsibilities for the organisation and delivery of health services and medical care.

(3) Cancer is a major disease and cause of death throughout Europe, including the future Member States. An estimated number of 1 580 096 new cancer cases, excluding non-melanoma skin cancer, occurred in the European Union in 1998. Of these, 1,4 % were cervical cancers, 13 % breast cancers, 14 % colorectal cancers and 9 % prostate cancers. Cervical and breast cancer constituted 3 % and 29 %, respectively, of new cancers in women. Prostate cancer constituted 17 % of new cancers in men.

(4) Principles for screening as a tool for the prevention of chronic non-communicable diseases were published by the World Health Organisation in 1968 and by the Council of Europe in 1994. These two documents form, together with the current best practice in each of the cancer screening fields, the basis for the present recommendations.

(5) Additionally, these recommendations are based on the 'Recommendations on cancer screening' of the Advisory Committee on Cancer Prevention together with the experience gathered under the different actions sustained under the Europe against Cancer programme where European collaboration has helped, for example, high quality cancer screening programmes to provide efficient European guidelines of best practice and to protect the population from poor quality screening.

(6) Important factors which have to be assessed before a population-wide implementation is decided upon include, *inter alia*, the frequency and interval of the application of the screening test as well as other national or regional epidemiological specificities.

(7) Screening allows detection of cancers at an early stage of invasiveness or possibly even before they become invasive. Some lesions can then be treated more effectively and the patients can expect to be cured. The main indicator for the effectiveness of screening is a decrease in disease-specific mortality. As in the case of cervical cancer, cancer precursors are detected, a reduction in cervical cancer incidence can be considered a very helpful indicator.

(8) Evidence exists concerning the efficacy of screening for breast cancer and colorectal cancer, derived from randomised trials, and for cervical cancer, derived from observational studies.

(9) Screening is, however, the testing for diseases of people for which no symptoms have been detected. In addition to its beneficial effect on the disease-specific mortality, screening can also have negative side effects for the screened population. Healthcare providers should be aware of all the potential benefits and risks of screening for a given cancer site before embarking on new population-based cancer screening programmes. Furthermore, for the informed public of today, these benefits and risks need to be presented in a way that allows individual citizens to decide on participation in the screening programmes for themselves.

(10) Ethical, legal, social, medical, organisational and economic aspects have to be considered before decisions can be made on the implementation of cancer screening programmes.

(11) Due account should be taken of specific needs of persons who may be at higher cancer risk for particular reasons (e.g. biological, genetic, lifestyle and environmental, including occupational).

(12) The public health benefits and cost efficiency of a screening programme are achieved if the programme is implemented systematically, covering the whole target population and following best-practice guidelines.

(13) The cost-effectiveness of cancer screening depends on several factors such as epidemiology, and healthcare organisation and delivery.

(14) Systematic implementation requires an organisation with a call/recall system and with quality assurance at all levels, and an effective and appropriate diagnostic, treatment and after-care service following evidence-based guidelines.

(15) Centralised data systems, including a list of all categories of persons to be targeted by the screening programme and data on all screening tests, assessment and final diagnoses, are needed to run organised screening programmes.

(16) All procedures for collecting, storing, transmitting and analysing data in the medical registers involved must be in full compliance with the level of protection referred to in Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data [1], as well as in full compliance with the relevant provisions of Member States on the management and processing of health data in accordance with Article 8 of the Directive.

(17) Quality screening includes analysis of the process and outcome of the screening and rapid reporting of these results to the population and screening providers.

(18) This analysis is facilitated if the screening database can be linked to cancer registries and mortality databases.

(19) Adequate training of personnel is a prerequisite for high quality screening.

(20) Specific performance indicators have been established for cancer screening tests. These should be monitored regularly.

(21) Adequate human and financial resources should be available in order to assure the appropriate organisation and quality control in all the Member States.

(22) Action should be taken to ensure equal access to screening taking due account of the possible need to target particular socioeconomic groups.

(23) It is an ethical, legal and social prerequisite that cancer screening should only be offered to fully informed people with no symptoms if the screening is proved to decrease disease-specific mortality, if the benefits and risks are well known, and if the cost-effectiveness of the screening is acceptable.

(24) The screening methods which presently meet these strict prerequisites are listed in the Annex.

(25) No screening test other than those listed in the Annex is scientifically justified to be offered to people with no symptoms in an organised population-based programme before it has been shown in randomised controlled trials to decrease disease-specific mortality in particular.

(26) The screening tests listed in the Annex can only be offered on a population basis in organised screening programmes with quality assurance at all levels, if good information about benefits and risks, adequate resources for screening, follow-up with complementary diagnostic procedures and, if necessary, treatment of those with a positive screening test are available.

(27) The introduction of the recommended screening tests in the Annex, which have demonstrated their efficacy, should be seriously considered, the decision being based on available professional expertise and priority-setting for healthcare resources in each Member State.

(28) Once there is evidence that a new screening test is effective, evaluation of modified tests may be possible using other epidemiologically validated surrogate endpoints if the predictive value of these endpoints is established.

(29) Screening methodologies are subject to ongoing development. The application of recommended screening methodologies should therefore be accompanied by simultaneous assessments of the quality, applicability and cost-effectiveness of new methods if available epidemiological data justify this. In fact, the ongoing work may lead to new methods, which could ultimately replace or complement the tests listed in the Annex or be applicable to other types of cancer.

[1] OJ L 281, 23.11.1995, p. 31.

HEREBY RECOMMENDS THAT MEMBER STATES:

1. Implementation of cancer screening programmes

(a) offer evidence-based cancer screening through a systematic population-based approach with quality assurance at all appropriate levels. The tests which should be considered in this context are listed in the Annex;

(b) implement screening programmes in accordance with European guidelines on best practice where they exist and facilitate the further development of best practice for high quality cancer screening programmes on a national and, where appropriate, regional level;

(c) ensure that the people participating in a screening programme are fully informed about the benefits and risks;

(d) ensure that adequate complementary diagnostic procedures, treatment, psychological support and after-care following evidence-based guidelines of those with a positive screening test are provided for;

(e) make available human and financial resources in order to assure appropriate organisation and quality control;

(f) assess and take decisions on the implementation of a cancer screening programme nationally or regionally depending on the disease burden and the healthcare resources available, the side effects and cost effects of cancer screening, and experience from scientific trials and pilot projects;

(g) set up a systematic call/recall system and quality assurance at all appropriate levels, together with an effective and appropriate diagnostic and treatment and after-care service following evidence-based guidelines;

(h) ensure that due regard is paid to data protection legislation, particularly as it applies to personal health data, prior to implementing cancer screening programmes.

2. Registration and management of screening data

(a) make available centralised data systems needed to run organised screening programmes;

(b) ensure by appropriate means that all persons targeted by the screening programme are invited, by means of a call/recall system, to take part in the programme;

(c) collect, manage and evaluate data on all screening tests, assessment and final diagnoses;

(d) collect, manage and evaluate the data in full accordance with relevant legislation on personal data protection.

3. Monitoring

(a) regularly monitor the process and outcome of organised screening and report these results quickly to the public and the personnel providing the screening;

(b) adhere to the standards defined by the European Network of Cancer Registries in establishing and maintaining the screening databases in full accordance with relevant legislation on personal data protection;

(c) monitor the screening programmes at adequate intervals.

4. Training

adequately train personnel at all levels to ensure that they are able to deliver high quality screening.

5. Compliance

(a) seek a high level of compliance, based on fully informed consent, when organised screening is offered;

(b) take action to ensure equal access to screening taking due account of the possible need to target particular socioeconomic groups.

6. Introduction of novel screening tests taking into account international research results

(a) implement new cancer screening tests in routine healthcare only after they have been evaluated in randomised controlled trials;

(b) run trials, in addition to those on screening-specific parameters and mortality, on subsequent treatment procedures, clinical outcome, side effects, morbidity and quality of life;

(c) assess level of evidence concerning effects of new methods by pooling of trial results from representative settings;

(d) consider the introduction into routine healthcare of potentially promising new screening tests, which are currently being evaluated in randomised controlled trials, once the evidence is conclusive and other relevant aspects, such as cost-effectiveness in the different healthcare systems, have been taken into account;

(e) consider the introduction into routine healthcare of potentially promising new modifications of established screening tests, once the effectiveness of the modification has been successfully evaluated, possibly using other epidemiologically validated surrogate endpoints.

7. Implementation report and follow-up

report to the Commission on the implementation of this Recommendation within three years of its adoption and subsequently at the request of the Commission with a view to contributing to the follow-up of this Recommendation at Community level.

HEREBY INVITES THE COMMISSION:

1. To report on the implementation of cancer screening programmes, on the basis of the information provided by Member States, not later than the end of the fourth year after the date of adoption of this Recommendation, to consider the extent to which the proposed measures are working effectively, and to consider the need for further action.
2. To encourage cooperation between Member States in research and exchange of best practices as regards cancer screening with a view to developing and evaluating new screening methods or improving existing ones.
3. To support European research on cancer screening including the development of new guidelines and the updating of existing guidelines for cancer screening.

Done at Brussels, 2 December 2003.

For the Council

The President

R. MARONI

ANNEX

SCREENING TESTS WHICH FULFIL THE REQUIREMENTS OF THE RECOMMENDATION (*):

— pap smear screening for cervical cancer precursors starting not before the age of 20 and not later than the age of 30;

— mammography screening for breast cancer in women aged 50 to 69 in accordance with European guidelines on quality assurance in mammography;

— faecal occult blood screening for colorectal cancer in men and women aged 50 to 74.

(*) The indicated age ranges are to be understood as maximum ranges; subject to national epidemiological evidence and prioritisation, smaller age ranges may be appropriate.

List of Abbreviations

AGC	atypical glandular cells (according to the terminology of the Bethesda System, version 2001, specify endocervical, endometrial or not otherwise specified) [30]
AIS	adenocarcinoma in situ [30]
ASC-H	atypical squamous cells, high-grade squamous lesion cannot be excluded [30]
ASC-US	atypical squamous cells of undetermined significance (according to the terminology of the Bethesda System, version 2001) [30]
CANCON	European Guide on Quality Improvement in Comprehensive Cancer Control
CDC	Centers for Disease Control
CI	confidence interval
CIN	cervical intra-epithelial neoplasia
DRR	detection rate ratio
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EPAAC	European Partnership for Action Against Cancer
EU	European Union
GLP	good laboratory practice
HC2	Hybrid Capture® 2 High-Risk HPV DNA Test™
HPA	Health Protection Agency
HPV	human papillomavirus
hrHPV	high-risk HPV type
HSIL	high-grade squamous intra-epithelial lesion [30]
IARC	International Agency for Research on Cancer
JCVI	Joint Committee on Vaccination and Immunisation
IAP	Immunise Australia Program

[30] See also Table 2 in Annex 2 of Chap. 3 in the second edition of the European guidelines for quality assurance in cervical cancer screening; and Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, Raab S, Sherman M, Wilbur D, Wright T & Young N for the Forum Group Members and the Bethesda 2001 Workshop (2002) The 2001 Bethesda System: Terminology for Reporting Results of Cervical Cytology. *JAMA. Vol.* 287, no. 16, pp. 2114-2119. doi:10.1001/jama.287.16.2114. Epub 2002 Apr 24.

LBC	liquid-based cytology
LSIL	low-grade squamous intraepithelial lesion[31]
MHRA	Medicines and Healthcare products Regulatory Agency
NACI	National Advisory Committee on Immunization
NPV	negative predictive value
NTCC	New Technologies for Cervical Cancer Screening
PBAC	Pharmaceutical Benefits Advisory Committee
PCR	polymerase chain reaction
PICOS	Population, Intervention, Control, Outcome, Study design
PPV	positive predictive value
RCT	randomized controlled trial
RLU	relative light units
TGA	Therapeutic Goods Administration
WHO	World Health Organization

[31] See footnote no. 30 on page 166.

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European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination

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ABSTRACT

In a project coordinated by the International Agency for Research on Cancer (IARC) 31 experts from 11 European countries and IARC have developed supplements to the current European guidelines for quality assurance in cervical cancer screening. The supplements take into account the potential of primary testing for human papillomavirus (HPV) and vaccination against HPV infection to improve cervical cancer prevention and control and will be published by the European Commission in book format. They include 62 recommendations or conclusions for which the strength of the evidence and the respective recommendations is graded. While acknowledging the available evidence for more efficacious screening using HPV primary testing compared to screening based on cytology, the authors and editors of the supplements emphasize that appropriate policy and programme organization remain essential to achieve an acceptable balance between benefit and harm of any screening or vaccination programme. A summary of the supplements and all of the graded recommendations are presented here in journal format to make key aspects of the updated and expanded guidelines known to a wider professional and scientific community.

Contents

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Background

In the current 28 Member States of the European Union (EU), approximately 34,000 new cases of cervical cancer and 13,000 deaths due to the disease occur annually [17]. Despite significant progress in Europe in recent decades in reducing the burden of cervical cancer, rates of death attributed to the disease are still high in many of the 'new' Member States that joined the EU after 2003: estimates of the annual age-standardized rates per 100,000 women in Hungary (6.9), the Slovak Republic (6.9), Poland (7.4), Latvia (8.2), Bulgaria (8.8) and Lithuania (9.8) are five to seven times higher, and in Romania (14.2) ten times higher than in Finland (1.4) and Malta (1.2), the EU Member States with the lowest rates in 2012. The age-standardized incidence rates of cervical cancer reveal a similar picture. The current 10-fold gradient in the mortality rates of cervical cancer among the EU Member States largely reflects the persistent absence, or inadequate implementation of cervical cancer screening programmes more than 10 years after organized, population-based screening programmes following European quality assurance guidelines were unanimously recommended by the Health Ministers of the EU [10].

Quality assurance aims to ensure that an endeavour leads to the outcome for which it is intended; this is particularly important for complex systems, such as screening programmes designed to lower the burden of cancer in the population [44]. The second edition of the European guidelines for quality assurance in cervical cancer screening [4,5] was published seven years ago. The continuing clear need to improve implementation of cervical cancer screening in the EU underlines the importance of re-emphasizing the European guidelines through the publication of the present supplements to the second edition. The supplements have been developed in a time of transition. Vaccination of girls and possibly also of boys in the future against the human papillomavirus (HPV) types that cause approximately 70% of cervical cancer has become an additional, complementary option of cervical cancer prevention, the main impact of which will emerge in a few decades when currently vaccinated girls are in their thirties and forties. In addition, cytology[1] is no longer the only test suitable for use in cervical cancer screening in the EU. The evidence presented in the first of the present supplements shows that primary testing for oncogenic HPV[2] fulfils the requirements for evidence-based screening tests laid down in the Council Recommendation [10], provided that cervical cancer screening programmes follow the recommendations for quality assurance published in the second edition [4,5] and the present supplements of the European guidelines [2,11,34].

Of particular importance is the recent evidence from the second round of European randomized controlled trials showing a more pronounced effect of cervical screening using HPV primary testing compared to cytology-based screening [35,6]. Given the evidence for improved efficacy of HPV primary screening that is explained in the first supplement, decision-makers, advocates, professionals, and women in the EU are increasingly confronted with the question of whether or not, and if so, how these new developments should be integrated into more successful approaches to control cervical cancer in Europe, both for the individual women affected and for the population as a whole. By focusing on the core topics of primary HPV testing in the first supplement [34], organization of HPV-based and cytology-based screening programmes in the second supplement [2], and implementation of HPV vaccination programmes in the third supplement [11], the joint publication of these supplements aims to provide appropriate answers to these important questions and to lay the foundation for further development of the comprehensive European guidelines in the coming years.

Publication format

The supplements are presented in a joint volume including 62 main recommendations and conclusions for which the strength of the evidence and the respective recommendations is graded according to a defined format. These recommendations are presented at the beginning of each supplement and their annotation indicates the places in the subsequent text where the evidence and the rationale pertaining to each recommendation are explained, including cross-references to other supplements and recommendations. This enables the reader to rapidly review the key content of the supplements and to identify places in the volume likely to be of interest for further reading. In addition, some statements of advisory character are considered to be good practice but not sufficiently important to warrant formal grading are provided in each supplement.

[1] Conventional cervical cytology with Papanicolaou staining (Pap smear) and validated liquid-based cervical cytology (LBC) are evidence-based screening tests that fulfil the requirements of the Council Recommendation on Cancer Screening of 2 December 2003 if performed in accordance with the European guidelines for quality assurance in cervical cancer screening. The applicable items in the Council Recommendation of 2 December 2003 are 1(a) for conventional cervical cytology with Papanicolaou staining (Pap smear) and 1(a) in combination with 6(e) for validated liquid-based cervical cytology (LBC) (see Annex 2 of the Supplements volume [10]). Primary testing for oncogenic HPV with validated assays also fulfils the requirements of the Council Recommendation of 2 December 2003 for evidence-based screening tests, provided the recommendations in Supplements 1 and 2 to the second edition of the European guidelines for quality assurance in cervical cancer screening are followed. The applicable items in the Council Recommendation are 6(c) and 6(e) (see Annex 2 of the Supplements volume [10]).

[2] Oncogenic *HPV* refers to the 13 high-risk HPV types (*hrHPV*): 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. These include the 12 HPV types currently classified as *carcinogenic to humans* and one type (68) classified as *probably carcinogenic to humans* in the IARC monograph series [7,19]. Unless otherwise indicated, the terms *HPV primary testing* and *HPV primary screening* used in this supplement refer to HPV testing conducted with systems based on validated hrHPV DNA assays. Oncogenic HPV also induces other cancers than those of the cervix uteri, such as vulvar, vaginal, anal and oropharyngeal cancers.

Table 1
Screening for cervical cancer with primary testing for human papillomavirus[A]. Recommendations and conclusions. Supplement 1[B].

Suitability of HPV primary testing for use in cervical cancer screening programmes

1.1 Primary testing for oncogenic HPV[C] can be used in an organized, population-based programme for cervical cancer screening (**I-A**) provided the other recommendations in this supplement are followed (**VI-A**). Primary testing for oncogenic HPV outside an organized population-based programme is not recommended (see also Suppl. 2, Rec. 2.1) (**VI-E**).[Sect. 1.2.1.3; 1.2.3]

Avoidance of co-testing (HPV and cytology primary testing) at any given age

1.2 Only one primary test (either cytology or testing for oncogenic HPV) should be used at any given age in cervical cancer screening (see also Rec. 1.3–1.7) (**II-A**).[Sect. 1.3.1]

Age at which to start HPV primary testing in cervical cancer screening programmes

1.3 Routine HPV primary screening can begin at age 35 years or above (see also Rec. 1.1) (**I-A**).[Sect. 1.3.2.1]

1.4 Routine HPV primary screening should not begin under age 30 years (**I-E**).[Sect. 1.3.2.1]

1.5 The available evidence is insufficient to recommend for or against beginning routine HPV primary screening in the age range 30–34 years (**VI**).[Sect. 1.3.2.1]

Age at which to stop HPV primary testing in cervical cancer screening programmes

1.6 In the absence of sufficient evidence on the optimal age at which to stop screening, HPV primary screening could stop at the upper age limit recommended for cytology primary screening (60 or 65 years), provided a woman has had a recent negative test (**VI-B**).[Sect. 1.3.2.2]

Cervical screening using cytology primary testing outside the age range of HPV primary testing

1.7 Cervical screening based on cytology primary testing conducted outside the age range of HPV primary testing should follow the guidance provided for cytology-based screening in the second edition of the European guidelines for quality assurance in cervical cancer screening, and in Supplement. 2 (see also Rec. 1.9, 1.10, 1.22 and 1.34) (**VI-A**). [Sect. 1.3.2.1]

Screening interval after a negative HPV primary test

1.8 The screening interval for women with a negative HPV primary test result should be at least 5 years (**I-A**) and may be extended up to 10 years depending on the age and screening history (**III-C**).[Sect. 1.3.3]

Management of women without an adequate HPV primary test result

1.9 Some women attending cervical cancer screening may prefer not to be tested for HPV. If a woman declines HPV primary testing, cytology can be performed (see also Rec. 1.7) (**VI-C**).[Sect. 1.3.4]

1.10 Non-attenders and women with a technically inadequate HPV test result should be invited to have a new sample taken (**VI-A**); alternatively cytology testing without additional sample taking may be performed if technically feasible and preferred by the woman (see also Suppl. 2, Rec. 2.9–2.11) (**VI-B**).[Sect. 1.3.4; 2.4]

Management of women after a positive HPV primary test

1.11 Cervical screening programmes using HPV primary testing must adopt specific policies on triage, referral and repeat testing of women with positive primary test results, taking into account the guidance in Rec. 1.12–1.31. The policies must include guidance on when women with positive HPV test results should be invited to return to routine screening. (**VI-A**). [Sect. 1.3.5]

1.12 Screening programmes should carefully monitor management of HPV-positive women. Monitoring should include compliance of individual women with further follow-up of positive primary test results, as well as results of triage, referral, colposcopies, biopsies, and treatment of precancers (**VI-A**).[Sect. 1.3.5]

1.13 Triage, referral and repeat testing policies (see Rec. 1.11) should be regularly reviewed and, if necessary, revised taking into account the results of monitoring (see Rec. 1.12) and the available evidence (**VI-A**).[Sect. 1.3.5]

Secondary testing

- **Cytology triage**

1.14 Women testing positive for oncogenic HPV at primary screening should be tested without delay for cervical cytology (cytology triage) (**I-A**).[Sect. 1.4.1.1] The cytology test should preferably use the specimen collected during the HPV screening visit (**VI-A**).[Sect. 1.4.1.1]

1.15 Direct referral to colposcopy of all HPV-positive women is not recommended (**I-D**).[Sect. 1.4.1.1]

1.16 Depending on the result of cytology triage, HPV-positive women should be referred to repeat testing, or to colposcopy (see Rec. 1.18–1.21) (**I-A**).[Sect. 1.4.1.1]

1.17 Quality assurance of laboratories and professional practice in the provision of cytology, colposcopy and histopathology services used in cytology triage in HPV primary screening should comply with the recommendations in Chap. 3–6 of the European Guidelines second edition (see also Rec. 1.35) (**VI-B**).[Sect. 1.4.1.1]

- **Referral of women with pre-invasive or more severe cytology at triage**

1.18 Women with ASC-H (atypical squamous cells, high-grade squamous lesion cannot be excluded), HSIL (high grade squamous intraepithelial lesion), AIS (adenocarcinoma in situ) or a more severe finding at cytology triage should be referred to colposcopy without further observation or testing (**III-A**).[Sect. 1.4.1.2]

- **Referral of women with minor cytological abnormalities at initial triage**

1.19 Women with ASC-US (atypical squamous cells of undetermined significance), AGC (atypical glandular cells), or LSIL (low grade squamous intraepithelial lesion) at triage after an initial HPV primary test in a screening episode may be followed up by retesting, preferably after 6–12 months, or referred directly to colposcopy (see Rec. 1.22–1.31) (**VI-C**).[Sect. 1.4.1.2]

Referral of women with negative cytology at initial triage

1.20 Women who have negative cytology (negative for epithelial abnormality) at triage after a positive initial HPV primary test in a screening episode should be followed up by re-testing after an interval shorter than the regular screening interval, but after at least 6–12 months (see also Sect. 1.4.1 and Rec. 1.23 and 1.24) (**VI-A**).[Sect. 1.4.1.2]

1.21 Direct referral to colposcopy of women with negative cytology at triage is not recommended (**I-D**) [Sect. 1.4.1.2]

Management of women at repeat testing

1.22 The prevalence of HPV and the quality and organization of cytology screening affect the efficiency, effectiveness and appropriateness of management of women at repeat testing. These factors should be taken into account in the regular review of management protocols for repeat testing (see also rec. 1.13) (**VI**). [Sect. 1.4.3]

- **Type and interval of repeat testing**

1.23 Cytology repeat testing after at least 6–12 months is an acceptable alternative to HPV repeat testing (see also Chap. 6, Sect. 6.3.1 in European Guidelines, second edition) (**III-B**). [Sect. 1.5.1]

1.24 Women who were HPV-positive and cytology normal (negative for epithelial abnormality) in primary screening may be managed by HPV retesting with or without cytological triage, and after an interval of preferably at least 12 months (**III-B**).[Sect. 1.5.1]

- **Protocols using HPV testing with cytology triage in repeat testing**

1.25 Women should be referred to colposcopy if cytology triage of a positive repeat HPV test yields ASC-US (**VI-B**) or more severe cytology (**VI-A**).[Sect. 1.5.3]

1.26 Women who have negative cytology triage (negative for epithelial abnormality) of a positive (repeat HPV test) may be managed by one of the following options (see also Rec. 1.11–1.13) (**VI-B**).[Sect. 1.5.3]

  - Referral to second repeat testing after at least 12 months
  - Referral to colposcopy
  - Return to routine screening

1.27 Women who have a negative repeat HPV test should return to routine screening (**III-A**). Cytology triage is not needed for these women (**III-E**).[Sect. 1.5.3]

- **Protocols using cytology testing alone in repeat testing**

1.28 Women with ASC-US or more severe cytology at repeat testing should be referred to colposcopy (**VI-B**).[Sect. 1.5.3]

1.29 Women with normal cytology at repeat testing should return to routine screening (**III-A**).[Sect. 1.5.3]

Table 1 (*continued*)

Suitability of HPV primary testing for use in cervical cancer screening programmes

- **Protocols using HPV testing alone in repeat testing**

1.30 Women who have a negative repeat HPV test should return to routine screening (**II-A**). [Sect. 1.5.3]

1.31 Women who have a positive repeat HPV test should be referred to colposcopy (**II-C**).[Sect. 1.5.3]

Self-sampling in screening programmes using HPV primary testing

1.32 The clinical accuracy of HPV primary testing on self-collected samples taken for cervical screening is sufficient to conduct organized, population-based pilot programmes for women who have not attended screening despite a personal invitation and a personal reminder (see also Rec. 1.33 and Suppl. 2, Rec. 2.8–2.13) (**III**).[Sect. 1.7]

Selection of HPV tests suitable for primary cervical cancer screening

1.33 Cervical cancer screening programmes should adopt an HPV primary test for use only if it has been validated by demonstrating reproducible, consistently high sensitivity for CIN2+ and CIN3+ lesions, and only minimal detection of clinically irrelevant, transient HPV infections (**VI-A**).[Sect. 1.2.1.3; 1.6]

Implementation of HPV primary testing in cervical cancer screening programmes

1.34 HPV primary screening programmes should follow the guidance in the European Guidelines, that is relevant to any cervical screening programme irrespective of the method of primary testing used. The relevant guidance includes the recommendations on programme organization, planning, monitoring and evaluation (see current Suppl. 2, and second edition, Chap. 2); communication; and quality assurance of the entire screening process including sampling, histopathologic interpretation and classification of cervical tissue; and management of detected lesions (see second edition, Appendix 1 and Chap. 3–6) (**VI-A**).[Sect. 1.2.3]

1.35 Like cervical cytology testing, HPV testing should be performed only on samples processed and analysed in qualified laboratories, accredited by authorized accreditation bodies and in compliance with international standards. The laboratory should perform a minimum of 10,000 tests per year (see also Rec. 1.34) (**VI-A**).[Sect. 1.6]

1.36 Any decision to implement HPV primary testing in cervical cancer screening should take into account health economic factors, and whether correct use of the test as specified in the instructions of the manufacturer and in accordance with the recommendations in this supplement can be organized (**VI-B**).[Sect. 1.2.1.3; 1.3.2.1]

- Health economic factors to consider in planning and subsequent steps in programme implementation include the prevalence of HPV infections; the burden of repeat testing, colposcopies, and CIN treatments resulting from HPV testing; and the quality and impact of existing cytology screening programmes.
- Assessments should be conducted to determine the optimal target age groups and screening intervals based on the chosen test and management protocols.
- The feasibility and sustainability of the programme should be assured through adequate resourcing and coordination, including coordinated planning, feasibility and pilot studies, and quality-controlled rollout across a country or region (see Suppl. 2 and Annex 1).

[A] Source: [34].

[B] **Sect.** (superscript) after each recommendation in the list refers the reader to the section/s of the Supplements dealing with the respective recommendation. **Rec.** followed by a number refers to the number of the respective recommendation.

[C] Oncogenic *HPV* refers to the 13 high-risk HPV types (*hrHPV*): 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. These include the 12 HPV types currently classified as *carcinogenic to humans* and one type (68) classified as *probably carcinogenic to humans* in the IARC monograph series [7,19]. Unless otherwise indicated, the terms *HPV primary testing* and *HPV primary screening* used in this supplement refer to HPV testing conducted with systems based on validated hrHPV DNA assays. Oncogenic HPV also induces other cancers than those of the cervix uteri, such as vulvar, vaginal, anal and oropharyngeal cancers.

Methodology

To develop the evidence-based recommendations, the approach used for the European guidelines for quality assurance in colorectal cancer screening and diagnosis [27] was adopted and modified slightly to take into account the different subject matter and time period of the present project. A multidisciplinary group of authors and editors experienced in quality assurance in cervical cancer screening, programme implementation and guideline development collaborated with a 'literature group' consisting of epidemiologists with special expertise in the field of cervical cancer screening and in systematic literature review. Experts in HPV vaccination were also recruited to participate in the project together with the other editors, authors and reviewers. The literature group systematically retrieved, evaluated and synthesized relevant publications dealing with cervical cancer screening according to clinical questions defined by the authors and editors. The clinical questions were subsequently elaborated according to the Patient-Intervention-Comparison-Outcome-Study (PICOS) method [18,30,31] that was modified slightly to take into account the aim of screening to lower the burden of the disease in the population.

Bibliographic searches for most clinical questions were limited to the time period January 2000 to March 2012 and were performed on Medline, and in many cases also on Embase and the Cochrane Library. Priority was given to recent comprehensive reviews. Additional searches were conducted without date restrictions or starting before 2000 if the authors or editors who were experts in the field knew that there were relevant papers published before 2000. Where no observational data were available, outcomes simulated by mathematical models and expert opinion were accepted as the lowest level of evidence. Papers of adequate quality recommended by authors because of their clinical relevance were also included, especially in the time period after March 2012 and up to December 2014 prior to completion of final editing of the draft manuscripts that began in July 2014. Preliminary versions of the draft supplements were repeatedly reviewed and revised through multidisciplinary meetings and discussions in which authors, editors and members of the literature group participated. Prior to finalization and review by the complete group of editors, the draft manuscripts were intensively reviewed by selected editors and/or external experts.

The editorial board was responsible for the final formulation of the supplements and the grading of the evidence and strength of the recommendations. The level of evidence and the strength of each of the graded recommendations are indicated using the slightly modified scales adopted for the European guidelines for quality assurance in colorectal cancer screening [27,41]; see below:

Grading of recommendations and supporting evidence

For the level of evidence:

I. Consistent multiple randomised controlled trials (RCTs) of adequate sample size, or systematic reviews (SRs) of RCTs, taking into account heterogeneity
II. One RCT of adequate sample size, or one or more RCTs with small sample size
III. Prospective cohort studies or SRs of cohort studies; for diagnostic accuracy questions, cross-sectional studies with verification by a reference standard
IV. Retrospective case-control studies or SRs of case-control studies, trend analyses
V. Case series; before/after studies without control group, cross-sectional surveys
VI. Expert opinion

For the strength of the respective recommendation:

A. Intervention strongly recommended for all patients or targeted individuals

B. Intervention recommended
C. Intervention to be considered but with uncertainty about its impact
D. Intervention not recommended
E. Intervention strongly not recommended

Screening for cervical cancer with primary testing for human papillomavirus

The first of the present supplements [34] aims to inform European policy makers and public health specialists, and any other interested parties about the critical issues that should be considered in weighing the potential benefit and harm of cervical screening programmes based on HPV primary testing. It includes 36 graded recommendations dealing with the suitability of HPV primary testing for use in cervical cancer screening. Key messages and topics covered in the supplement include the lack of appropriate benefit from co-testing, and the appropriate target age group and interval for HPV primary testing. Management protocols for women with positive or technically inadequate HPV primary tests, the clinical accuracy of HPV testing using self-collected samples, and the selection of tests suitable for primary screening are also covered; and other policies and professional and scientific standards, such as consideration of health economic issues, are indicated that should be adhered to in the design and implementation of quality-assured cervical cancer screening programmes based on HPV primary testing. It is not the intention of the authors and editors to promote recent research findings before they have been demonstrated to be of proven benefit in clinical practice. The supplement therefore focuses on the use of primary testing for HPV DNA in cervical cancer screening with cytology triage in the EU. As far as possible the authors and editors have attempted to achieve an equitable balance that is applicable across a wide spectrum of cultural and economic healthcare settings in the EU. As with any standards and recommendations, these should be continuously reviewed in the light of future experience.

The scientific justification for the recommendations in the first supplement is provided by over 110 publications cited in the text, including published cross-sectional and longitudinal data from eight randomized clinical trials conducted in Canada, Finland, India, Italy, Sweden, The Netherlands and the United Kingdom [1,8,12,20–24,26,28,29,32,33,35–40]. It should be noted that the efficacy of HPV primary testing in cervical cancer screening has been demonstrated in studies using clinician-based samples. The authors and editors emphasize that currently the clinical accuracy

Table 2
Organization of cytology-based and HPV-based cervical cancer screening[A]. Recommendations and conclusions. Supplement 2[B].

2.1 Irrespective of the method of primary testing (cytology or HPV assay) cervical cancer screening should always be performed in an organized, population-based screening programme with comprehensive quality assurance covering all steps in the screening process (see also Suppl. 1, Rec. 1.34, and Annex 1 and 2) (**VI-A**).[Sect. 2.3]

2.2 If organized, population-based cervical screening programmes do not currently exist in a country or region, decision-makers should review the relevant policy on cervical cancer screening taking into account the Council Recommendation on Cancer Screening (Annex 2), the European Guidelines for quality assurance in cervical cancer screening, second edition, and the present Supplements (see also Annex 1) (**VI-A**).[Sect. 2.3]

2.3 In countries or regions in which population-based cervical screening programmes using cytology primary testing are currently established, decision-makers should consider whether implementation of HPV primary testing in existing programmes would improve the balance between harm and benefit, and if so, integrate the change into the comprehensive cancer control programme (see also Suppl. 1, Rec. 1.1 and 1.36) (**VI-A**).[Sect. 2.3]

Quality-assured process of screening programme implementation

2.4 If a decision is made to implement HPV primary testing in an existing population-based cervical screening programme, comprehensive planning, feasibility testing and pilot programmes should be conducted prior to routine implementation to ensure that an appropriate balance between harm and benefit is achieved in the transition to HPV primary screening, including effective and efficient use of resources (see also Annex 1) (**VI-A**).[Sect. 2.3.1]

2.5 If a decision is made to implement a population-based cervical screening programme in a country or region previously lacking such a programme, special attention must be paid not only to selecting the method of primary testing (cytology or HPV testing), but also to testing and developing the capacity for a population-based approach to programme implementation including building up comprehensive quality assurance (see also Rec. 2.4 and Annex 1 and 2) (**VI-A**).[Sect. 2.3.2]

2.6 The introduction of new population-based screening programmes should be coordinated by a unit with a comprehensive mandate and sufficient autonomy and resources to ensure that the European quality assurance guidelines are followed and that international experts familiar with the process and determinants of successful programme implementation can be consulted (see also Annex 1) (**VI-A**).[Sect. 2.3.3]

Population based approach to cervical cancer screening

- **Avoiding financial barriers to participating in screening**

2.7 Screening should be free of charge or subject to only a limited charge for women who attend, regardless of whether cytological or HPV screening is offered (**I-A**).[Sect. 2.4.1]

- **Personal invitation letters**

2.8 Personal invitation letters to participate in screening should include a scheduled appointment (date, time and place) and instructions about how to change the appointment if necessary (**I-A**).[Sect. 2.4.2]

- **Personal reminders**

2.9 Women who do not attend screening should receive a personal reminder (**I-A**). The reminder should be sent by letter and should include a scheduled appointment (date, time and place) and instructions about how to change the appointment if necessary (**II-A**).[Sect. 2.4.3]

2.10 A second personal invitation reminder should be sent if there is no response to an initial reminder (**I-B**).[Sect. 2.4.3]

2.11 Personal invitation reminders may also be delivered by telephone call, provided women who are not reached by telephone are sent a reminder letter (**I-B**).[Sect. 2.4.3]

- **Self-sampling**

2.12 Piloting self-sampling for women who did not participate in primary HPV screening despite a personal invitation and a personal reminder is recommended, provided it is conducted in an organized, population-based screening programme with careful monitoring and evaluation of the aimed performance and outcomes (see Rec. 2.8–2.11 and Suppl. 1, Rec. 1.32 and 1.36) (**I-A**).[Sect. 2.4.4]

2.13 Prior to rollout towards national implementation, a self-sampling pilot project should demonstrate successful results compared to clinician-based sampling (positivity rate, positive predictive value of a positive test result, and cost-effectiveness). The pilot should also demonstrate that key organizational problems, such as the appropriate screening interval and compliance with invitation and management protocols for women with positive test results, have been adequately resolved (**III-D**).[Sect. 2.4.4]

Monitoring cervical cancer screening performance

2.14 Monitoring of population-based cervical screening programmes should include the performance parameters defined in the European guidelines for quality assurance in cervical cancer screening (Suppl. 2, and Chap. 2 and 7 of the second edition 2) (**VI-A**).[Sect. 2.6]

2.15 Programmes should achieve an invitation coverage of 95% (acceptable level) (**III-A**); >95% is desirable (**III-A**).[Sect. 2.6.1]

2.16 Programmes should achieve an examination coverage of 70% (acceptable level) (**III-A**); >85% is desirable (**VI-A**).[Sect. 2.6.1]

2.17 Programmes should achieve a participation rate of 70% (acceptable level) (**III-A**), >85% is desirable (**VI-A**).[Sect. 2.6.1]

[A] Source: [2].
[B] See footnote B of Table 1.

of HPV primary testing on self-collected samples is sufficient to conduct organized, population-based pilot programmes for women who have not attended screening despite a personal invitation and a personal reminder (Rec. 1.32 in Suppl. 1 [34], see also Table 1). Policy makers and professionals must be aware, however, that HPV testing on self-taken samples is less accurate than on clinician-taken samples. For this reason, self-sampling is not recommended for all women invited to screening (see Sect. 1.7 in [34] and Sect. 2.4.4 and Rec. 2.8–2.13 in Suppl. 2 [2], see also Table 2).

The authors and editors also emphasize that despite the convincing evidence for more efficacious screening using HPV primary testing, appropriate screening policy and programme organization are essential to achieving an acceptable balance between benefit and harm of any screening programme. These principles are particularly important in HPV primary screening, in order to avoid substantial increase in the number of women with positive test results and additional colposcopies and treatment of no additional benefit to participating women. Following the recommendations in the present supplement will enable programmes to achieve the potential benefit of HPV primary testing in cervical cancer screening while minimizing the risks (see Rec. 1.11 in [34], see also Table 1).

While most of the recommendations in the first supplement focus on the opportunities and the challenges of HPV primary screening that set it apart from cytology-based screening; decision-makers, programme managers and professionals should also be aware of the guidance in the previously published volume of the second Guidelines edition [4,5] that is relevant to any cervical screening programme irrespective of the method of primary testing used (see Rec. 1.34). Of prime importance in this regard are also the recommendations on programme organization, planning, monitoring and evaluation in the second supplement. The authors and editors also emphasize the importance of using reliable, validated HPV tests (see Rec. 1.33) in qualified laboratories, accredited by authorized accreditation bodies and in compliance with international standards (see Rec. 1.35) In addition, any decision to implement HPV primary testing in cervical cancer screening should take into account health economic factors, and whether correct use of the test as specified in the instructions of the manufacturer and in accordance with the recommendations in the supplement can be organized (see Rec. 1.36). The authors and editors also point out that sustainability is crucial to the success of any cervical screening programme, and in the first supplement they underline the importance of the respective recommendations in Supplement 2 and in Annex 1 of the Supplements volume.

Organization of cytology-based or HPV-based cervical cancer screening

The second supplement [2] addresses the persisting gap in the EU between knowledge of the potential of population-based cervical screening to reduce the burden of the disease in the population, on the one hand, and the extent to which this knowledge has been translated into effective national programmes to control cervical cancer, on the other hand. As pointed out in the Council Recommendation on cancer screening (Annex 2 of the Supplements volume, see also [10]), the most effective and appropriate way for screening to reduce cervical cancer incidence and mortality is through implementation of population-based programmes according to the European quality assurance guidelines. Despite this knowledge, many old and new Member States of the European Union do not have population-based screening programmes in place or have programmes that are underperforming. The supplement provides 17 recommendations on the policy and organizational issues that are inherent to the use of cytology and HPV testing in screening programmes. First and foremost is recognition of the need to implement HPV primary screening only in organized, population-based programmes (see Rec. 2.1 in Suppl. 2 [2], see also Table 2). This is an important prerequisite for effective quality assurance of any cancer screening programme (see Annex 1 [25,43] and of the Supplements volume) and one that applies particularly to HPV primary screening.

The scientific justification for the recommendations in the second supplement is provided by over 90 publications cited in the text. In light of the evidence that HPV primary screening of appropriate quality can yield better results than cytology-based screening, policy-makers in EU countries or regions with cytology-based population programmes are advised to review current policies and consider whether transition to HPV primary screening would improve the balance between harm and benefit in their programmes. Policy makers in EU countries or regions lacking any population-based cervical screening programme are advised to review current policies and consider implementation of organized population-based cervical screening programmes taking into account the current European guidelines [4,5], including the supplements [2,11,34], and the Council Recommendation [10] (see Rec. 2.2 and 2.3). In addition to these general aspects, problems are discussed that are commonly encountered in implementing cervical cancer screening programmes in EU Member States with population-based programme policies, in those with opportunistic programmes, or in Member States in Central and Eastern Europe, and solutions are suggested that have proven to be effective in successful European screening programmes. The recommendations in the supplement are focussed on strategies to optimize screening attendance, including invitations, reminders and self-sampling. For evaluation and monitoring, the supplement also provides key performance indicators specifically related to HPV primary screening; and for the first time, European quality standards are introduced for key performance indicators (coverage by invitation, coverage by examination; and rate of participation or uptake) (see Rec. 2.15–2.17).

In the text more detailed advice is provided on the steps that programme management should take in navigating the protracted process of establishing an organized, population-based screening programme, including a checklist for planning, feasibility testing, piloting, monitoring and evaluation (see Sect. 2.7). This guidance illustrates and supplements the recommendations in Annex 1 dealing with the determinants of successful implementation of cancer screening programmes [25,43]; see also [3,45].

Implementation of vaccination against human papillomavirus in Europe

The third of the present supplements [11] summarizes the evidence base for HPV vaccination using the currently licensed bivalent and quadrivalent vaccines in the EU.[3] Over 90 publications are cited and nine graded recommendations are provided to promote effective implementation of this tool for cervical cancer control in the EU. Clinical trials have shown the current prophylactic HPV vaccines to be safe and highly effective against persistent vaccine-related HPV infections and anogenital precancerous lesions among women who were not infected by these types at the time of vaccination [13,46,48]; see also [15,16]. The use of HPV vaccines in pre-adolescent girls and young women for the primary prevention of cervical cancer and some other HPV-related diseases has been endorsed by the European

[3] The 9-valent vaccine that was recommended by the European Medicines Agency (EMA) in March 2015 for the prevention of diseases caused by nine types of human papillomavirus (HPV) was not considered in the preparation of the present supplement because at the time of writing and editing the Supplements it was not licensed for use in the EU. See accessed 28/05/2015: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2015/03/WC500184898.pdf.

Table 3
Organization of HPV vaccination[A]. Recommendations and conclusions. Supplement 3[B].

3.1 HPV vaccination is best implemented through organized, population-based programmes (**III-A**).[Sect. 3.6]
- A population-based programme is likely to achieve higher coverage, less social inequalities in vaccine uptake, and lower vaccination costs per vaccine (**III**).[Sect. 3.6]
- If a country has started implementation with the opportunistic approach, transition to an organized, preferably school-based (or other public-service-based) programme is recommended (**III-A**).[Sect. 3.6]

Target age for HPV vaccination

3.2 The primary target group to consider for routine population-based vaccination is girls at an age before the onset of sexual activity, usually between 10 and 13 years (**I-A**).[Sect. 3.2.1]
- Targeting older girls and young women with catch-up vaccination at the start of a routine vaccination programme can accelerate the impact of the vaccination programme (**I**).[Sect. 3.2.2]

Monitoring and evaluation of HPV vaccination programmes

3.3 Organized, population-based HPV vaccination programmes should have systematic register-based monitoring of coverage and safety. Long-term evaluation of vaccine safety and effectiveness is recommended in all countries. Appropriate legal frameworks must be developed, taking funding and organizational resources into account (**VI-A**).[Sect. 3.3]
- Coordination between vaccine evaluation and cancer control programmes is recommended. It will be critical to assess the impact of the vaccine and its synergies with screening and health education (**VI-A**).[Sect. 3.3]
- Long-term evaluation based on systematic registration of HPV vaccination and linkage studies using relevant healthcare registries should be used to assess vaccine effectiveness and safety in various settings. If a country has the capacity, it is desirable that assessment of vaccine impact include: surveillance for vaccine-related and other oncogenic HPV infections, precancerous lesions, and HPV-related cancers (**VI-A**).[Sect. 3.3]
- The minimum set of information for monitoring HPV vaccination should include data on vaccine coverage, monitoring of adverse events following immunization and, if possible, a sentinel surveillance of impact on precancerous lesions (**VI-A**).[Sect. 3.3]

3.4 Standard definitions and parameters for coverage of vaccination should be developed and used in vaccination monitoring (**VI-A**).[Sect. 3.5]
- Age at primary vaccination, age at catch-up vaccination, number of doses by single year of age and time between doses, and duration of follow-up since offering primary vaccination should be included in the definitions and performance parameters (**VI-A**).[Sect. 3.5]

Planning, piloting, and modifying HPV vaccination programmes

3.5 Planning and modification of vaccination programmes and policies should take into account local conditions, including vaccine and vaccination costs and resources required in monitoring, provision of information, and communication. Pilot studies are recommended to assess how to improve coverage and public awareness (**VI-A**).[Sect. 3.6]

Procurement

3.6 Decision-makers should be aware of the wide range of prices for HPV vaccines in the EU and the potential to reduce the overall costs of HPV vaccination programmes by negotiating vaccine prices that are comparable to the low prices obtained in some EU Member States (**VI-A**).[Sect. 3.6]

Coverage target for HPV vaccination programmes

3.7 HPV vaccination programmes should aim for a minimum coverage of 70% and preferably $>80\%$ (**III-A**).[Sect. 3.5]
- The reported 3-dose coverage of primary vaccination in a population-based vaccination programme should reach 70% within the first 12 months (**III-A**). The same coverage target applies for programmes using a 2-dose schedule (**VI-A**).[Sect. 3.5]

HPV screening and HPV vaccination

3.8 Vaccination status should be known to screening and vaccination registries for women reaching the target screening age (**VI-A**).[Sect. 3.3]

3.9 Planning and research on synergies between HPV vaccination and HPV screening is recommended to improve the effectiveness and cost-effectiveness of prevention of HPV-related disease (**VI-A**).[Sect. 3.2]

[A] Source: [11].
[B] See footnote B of Table 1.

Medicines Agency (EMA) in 2006 (quadrivalent HPV 6/11/16/18 vaccine)[4] and 2007 (bivalent HPV 16/18 vaccine),[5] and in a position paper by the World Health Organization (WHO) in 2009 and 2014 [47,49]. Since then, 21 of the 28 Member States of the European Union plus Norway and Iceland have introduced national HPV vaccination programmes. Recently, WHO updated its HPV vaccines position paper to recommend a two-dose regimen with increased flexibility in the interval between doses [49]. EMA has also granted marketing authorizations for bivalent and quadrivalent vaccines in the EU for a two-dose schedule administered by injection at a 6-month interval for girls aged 9–14 and 9–13 years, respectively. If the respective vaccines are administered at an older age, the three-dose schedule should be used [15,16]. Some EU countries, such as Belgium, France, Italy and the UK, have already implemented a 2-dose HPV vaccination schedule.

The primary target group for routine vaccination is girls at an age before debut of sexual activity, usually 12–13 years. Targeting older girls and young women with catch-up vaccination at the start of a routine vaccination programme can accelerate the impact of the vaccination programme, as clinical trials have shown satisfactory immune response and efficacy against infection in women aged 15–26 years being HPV 16 and 18 DNA negative. The question whether boys should also be included in the HPV vaccination target population is currently under debate and is the subject of ongoing research. Vaccination of boys could contribute to herd immunity and offer protection against other HPV-related cancers and genital warts in the vaccinated subjects. Moreover, mathematical modelling studies indicate that vaccinating boys would be cost-effective if vaccine coverage in girls is lower than 30–50%, as is the case in a number of EU Member States, or if vaccine cost is substantially diminished, i.e., is halved.

Clinical trials and post-licensure studies have shown that the current vaccines are safe, and efforts are still on-going to monitor rare events like auto-immune diseases, or possible adverse effects in special groups such as women who have been inadvertently vaccinated while being pregnant. An important measure in process-monitoring of HPV vaccination is the assessment of vaccine coverage data by year of birth and number of administered doses. In addition, individual vaccination records should be retained, to permit linkage of HPV-related disease incidence with individual vaccination status in the future.

A measurable early indicator of the impact of vaccination will be the prevalence of HPV infections in young vaccinated women. Indirect evidence of population level impact of the HPV vaccines has already been provided through the demonstration of a decrease in the prevalence of HPV, the incidence of high-grade cervical abnormalities, and the incidence of genital warts soon after the introduction of vaccination programmes. However, long-term monitoring of end-

[4] See summary of product characteristics, accessed 10/04/2015: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000703/WC500021142.pdf.
[5] See summary of product characteristics, accessed 10/04/2015: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000721/WC500024632.pdf.

point indicators is essential to assure that programmes attain their expected impact. This will require careful assessment of changes in the epidemiology of severe precancerous lesions and cancers over decades through linkage between screening and cancer registries irrespective of early indicator studies.

As of early 2014, seven EU countries had not yet initiated HPV vaccination campaigns, all of them new Member States (Estonia, Hungary, Lithuania, Poland, Slovakia, Cyprus and Croatia). HPV vaccination is perceived as being too expensive by many new Member States, but vaccine prices for vaccination campaigns have decreased considerably in recent years, and modelling studies have shown that cost-effectiveness of HPV vaccination tends to be largest in countries with the highest cervical cancer burden, as is the case in most of these countries.

In most of the EU Member States with HPV vaccination campaigns, the vaccine is offered free of charge, predominantly through organized, population-based programmes distributing the vaccine at schools or public health centres. The success in terms of coverage of the target groups has been highly variable, ranging from $<30\%$ to 80% and over. At the lower end of the range, in France and Luxemburg, the programmes rely on opportunistic vaccination. The highest rates of 80% and above are in countries or regions with population-based vaccination programmes (Denmark, Malta, Portugal, Sweden and the UK and Flemish community in Belgium). Most of the countries choose routine target groups that include ages in the range 11–13 years. Organized school-based programmes usually provide the best coverage and more equitable access to HPV vaccines, followed by organized programmes through health-care centres and through general practitioners. Opportunistic programmes usually achieve low or ill-defined levels of coverage. Vaccination campaigns targeting adolescents pose specific challenges, compared to those targeting younger children aged 10–13 years.

Given the current variation in HPV vaccination coverage in the EU, the importance of an organized, population-based approach to vaccine delivery and the need for adaptation of existing vaccine delivery infrastructure to the special requirements of HPV vaccination are common to all EU countries (see Rec. 3.1 in Suppl. 3 [11], see also Table 3). Higher vaccination coverage is a reasonable goal in many EU Member States. HPV vaccination programmes should aim at a minimum coverage of 70% and preferably $>80\%$ (see Rec. 3.6). Effective monitoring and evaluation will be key to improving the coverage and effectiveness of vaccination programmes across the EU. Organized, population-based HPV vaccination programmes should have systematic register-based monitoring of coverage and safety. Long-term evaluation of vaccine safety and effectiveness is recommended in all countries. Appropriate legal frameworks must be developed, taking funding and organizational resources into account (see Rec. 3.3). Every effort should be made to record individual vaccination status to ensure that it will be known for future cohorts reaching the target age for screening (see Rec. 3.8).

Discussion and conclusions

In an evidence-based process, supplements have been developed that expand the current second edition of the European guidelines for quality insurance in cervical cancer screening [4,5] to cover topics essential to successful implementation of population-based programmes for HPV primary screening and vaccination. In addition to a large package of recommendations graded according to the strength of the recommendations and the supporting evidence, numerous recommendations considered to be good practice by the authors and editors but not of sufficient importance to warrant formal grading are provided in the 200-page Supplements volume that will be published by the European Commission. Neither the Supplements volume nor the previously published volume of the second Guidelines edition should be regarded as a text book or in any way a substitute for practical clinical training and experience, but together they provide important European reference documents that decision makers in EU Member States and other countries should consult to determine whether current policies and prgrammes for cervical cancer prevention and control can be improved before a new and fully revised third edition of the European guidelines becomes available.

The need for further improvement in cervical cancer prevention and control in Europe, particularly in many of the newer EU Member States is the rationale for focusing the present supplements on topics relevant to HPV primary screening and vaccination. The completion of the supplements by a multidisciplinary group of experts in cervical screening, HPV vaccination and quality assurance and their publication by the European Commission has the potential to become a watershed in improvement of cervical cancer prevention and control in Europe. Based on robust evidence the editors of the supplements explain that cytology primary testing is no longer the only method for population-based cervical cancer screening that fulfils the requirements of the Council Recommendation on Cancer Screening of 2 December 2003. HPV primary testing is also an appropriate, evidence-based screening method, provided the recommendations in the supplements are followed in programme implementation.

Recognition of the conformity of cervical cancer screening based on HPV primary testing with the Council Recommendation on Cancer Screening is of prime importance because the first report on cancer screening in the EU documented considerable interest in the EU members states in following through on the Council Recommendation by establishing and improving cancer screening programmes in accordance with European Guidelines for quality assurance [9,42]. Raising awareness for the supplements through publication of the present summary should encourage responsible authorities and programme managers to review current policies to determine whether further improvement in cervical cancer prevention and control may be achieved through modification of existing screening programmes or implementation of new, HPV-based programmes where cervical screening programmes are lacking; and through optimized implementation of HPV vaccination.

The choice of content of the present summary is to some extent arbitrary and cannot in any way be regarded as an alternative to the requirement for reading each supplement as a whole and within the context of the complete second edition of the European quality assurance guidelines [4]. This will be possible when the full Supplements volume is available. It should be kept in mind however, that despite encouraging progress, the availability of the extensive supplements will not provide answers to all of the questions that are relevant to future improvement in cervical cancer prevention and control in Europe. Additional points, such as the potential role of methods other than cytology in triaging women with positive HPV test results and evaluation of new primary tests and vaccines require further attention.

It has recently been pointed out that the variation in Europe in the implementation of cancer screening offers a unique opportunity to learn from best practices in collaboration between cancer registries and screening programmes [3] and in quality assurance [14]. In order to accelerate improvements in cancer control, cancer registries should take co-responsibility with screening and vaccination programmes and registries in promoting continuous improvement of primary and secondary cancer prevention in Europe. Additional sustainable investments are vital to further development of infrastructures and activities for quality assurance, including organization training, evaluation and monitoring in the national settings and also at the pan-European level. This is an important point that is also emphasized in Annex 1 [43] of the Supplements volume and that not only applies to cervical cancer screening but also HPV vaccination [3,14].

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The authors of the present manuscript are the members of the editorial board of the current supplements to the second edition of the European guidelines for quality assurance in cervical cancer screening. J. Dillner served on the editorial board only for issues related to screening, not vaccination.

Competing interests

J. Dillner has received research grants to his university with significant funding from Merck/SPMSD, a manufacturer of HPV vaccines, for monitoring studies on HPV vaccines. He declares no personal remuneration.

L. Dillner is the spouse of J. Dillner who has reported the competing interest listed above.

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Datum 31. Mai 2016

Betreff: Stellungnahme zur

Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

Sehr geehrte Damen und Herren,

bitte finden Sie nachfolgend die Stellungnahme der DGEpi zu o.g. Richtlinienänderung.

Diese Stellungnahme wurde von Prof. Stefanie Klug und Prof Joachim Kieschke erarbeitet.

Im Auftrag der Deutschen Gesellschaft für Epidemiologie

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Deutsche Gesellschaft für Epidemiologie (DGEpi)	
31.05.2016	
Stellungnahme / Änderungsvorschlag	**Begründung**
Optionsmodell ab 30 Jahren im Primärscreening / Frauen ab dem Alter von 30 Jahren soll für die ersten drei Screeningrunden des neuen organisierten Screeninprogrammes in einem Intervall von drei Jahren ein Co-Testing von HPV-Test und Zytologie angeboten werden. Nach Auswertung dieser ersten Phase soll entschieden werden, wie mittelfristig weiter zu verfahren ist.	Von dem vorgeschlagenen Optionsmodell, bei welchem die Frauen ab 30 Jahren wählen sollen zwischen einem jährlichem Zytologie-basiertem Zervixkarzinom-Screening oder einem HPV-basiertem Zervixkarzinom-Screening alle fünf Jahre, wird dringend abgeraten. Gegen ein solches Optionsmodell spricht, dass es nicht mit einer randomisierten Studie vergleichbar ist und auch nicht als solche auswertbar ist. Es wird unkontrollierbare Vermischungen zwischen beiden Optionen geben, die eine vergleichende Auswertung aufgrund der dadurch entstehenden Verzerrungen (Bias) unmöglich machen werden. Am Ende wird viel Zeit verloren gehen, ohne wissenschaftlich brauchbare Erkenntnisse zu generieren. Gegen die Beibehaltung eines einjährigen zytologischen Screenings als Option spricht zum einen, dass sich in der letzten Dekade kaum noch eine Reduktion der Inzidenz des Zervixkarzinoms in Deutschland gezeigt hat und zum anderen, dass es Hinweise auf eine mangelhafte Qualität der Zytologie gibt [1]. Gegen einen alleinigen HPV-Test alle fünf Jahre spricht, dass nach momentaner wissenschaftlicher Evidenz befürchtet werden muss, dass ein alleiniger HPV-Test mehr hochgradige Läsionen übersieht, als ein Co-Testing. Selbst wenn man davon ausgehen möchte, dass ein alleiniger HPV-Test alle fünf Jahre im Rahmen eines sehr gut organisierten qualitätsgesicherten Screeningprogrammes ausreichend ist [2], um die meisten hochgradigen Läsionen zu erkennen, müssen folgende Punkte beachtet werden: In Deutschland sind wir momentan sehr weit von einem sehr gut organisierten qualitätsgesicherten Screeningprogramm entfernt. Zunächst muss sichergestellt werden, dass ein ebensolches in den nächsten Jahren zuverlässig implementiert wird. Dazu gehören folgende Aspekte: - Sicherstellung und Überprüfung der bestmöglichen Qualität bei der Durchführung der HPV-Tests. - Festlegung der/des im Rahmen des organisierten Screeningprogrammes in Deutschland akzeptablen HPV-Test/s, idealerweise durch eine zu implementierende unabhängige ständige Kommission, da sich die erhältlichen HPV-Tests rasch verändern. - Sicherstellung und Überprüfung der bestmöglichen

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	Qualität der durchgeführten Zytologie. - Sicherstellung einer lückenlosen und qualitativ hochwertigen Abklärung von auffälligen Befunden. - Implementierung von unabhängigen Stellen, über die bevölkerungsbezogen die berechtigten Frauen alle drei Jahre zum Screening (Co-Testing) eingeladen werden. - Beauftragung einer unabhängigen Institution zur Evaluation des neuen organisierten, qualitätsgesicherten Programmes (siehe unten). Die wissenschaftlichen Ergebnisse der letzten Jahre deuten darauf hin, dass eine Kombinationsdiagnostik aus HPV-Test und Zytologie der alleinigen Zytologie überlegen ist [3]. Aufgrund der oben genannten Fakten plädiert die DGEpi für eine Übergangsphase von drei Screening-Runden, in der jede Frau ab 30 Jahre alle drei Jahre zu einem Co-Testing von Zytologie und HPV-Test schriftlich eingeladen wird. Nach Auswertung und Evaluation der Ergebnisse dieser Übergangsphase sollen dann mittelfristig die Entscheidungen für die beste Screening-Strategie für Deutschland getroffen werden. Des Weiteren erlaubt diese Übergangsphase die Implementation aller notwendigen Aspekte eines organisierten qualitätsgesicherten Zervixkarzinom-Screeningprogrammes.
Einladungsverfahren / Einladungen sollten ausgehend von Daten der Einwohnermeldeämter über entsprechende zentrale Stellen, nicht über Krankenkassen, versendet werden.	Im Rahmen des Mammographie-Screeningprogrammes werden die Einladungen über zentrale Stellen an die teilnahmeberechtigten Frauen versendet. Dieses Verfahren ist etabliert und empfiehlt sich ebenso für die Nutzung in einem organisierten Zervixkarzinom-Screening. Die zentralen Stellen erhalten von den zuständigen Einwohnermeldeämtern die aktuellen Adressen und somit werden die anspruchsberechtigten Frauen identifiziert. Mit diesem Vorgehen wird jede teilnahmeberechtigte Frau, die nach den Vorgaben vom G-BA zur Teilnahme an der Krebsfrüherkennungsuntersuchung berechtigt ist, mit hoher Sicherheit in allen Screening-Runden eingeladen. Informationen zu Nicht-Teilnahme werden zentral dokumentiert. In Deutschland gibt es hunderte von Krankenkassen, Wechsel zwischen den Kassen werden immer üblicher. Die daraus resultierenden Probleme sind nur schwer oder gar nicht in den Griff zu bekommen. Innerhalb einer randomisierten bevölkerungsbezogenen Kohortenstudie wurden Frauen auf der Grundlage der Daten von Einwohnermeldeämtern bei freier Arzt- und Terminwahl eingeladen [4]. Die Ergebnisse zeigen deutlich, dass Nichtteilnehmerinnen, gerade weniger gebildete Frauen sowie Frauen mit Migrationshintergrund, über die zentralen Einladungsschreiben sehr gut zu einer Teilnahme

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	motiviert werden konnten.
Screeningpopulation / Die Screeningpopulation sollte genauer definiert werden und die Altersgrenze auf 65 Jahre begrenzt werden.	In allen drei Beschlussentwürfen der GKV, KBV und Patientenvertretung wird auf eine Teilnahme von Frauen zwischen 20 und 60 Jahren verwiesen. Die DGEpi rät dazu, die obere Altersgrenze zumindest während der Übergangsphase der ersten drei Screening-Runden auf das vollendete 65. Lebensjahr festzusetzen, wenn keine auffälligen Befunde vorliegen. Nach Auswertung und Evaluation der Übergangsphase können dann die Festlegungen entsprechend angepasst werden. In den europäischen Ländern variiert die obere Altersbegrenzung zwischen 60 und 70 Jahren [5]. In den USA läuft das Screening bis 65 Jahre [6]. Es stellt sich die Frage, inwieweit die Grenze bei 60 Jahren als sinnvoll erscheint, wenn laut RKI die altersspezifische Erkrankungsrate zwischen 60 und 64 Jahren in Deutschland für 2011-2012 höher waren als bei Frauen zwischen 20 und 35 Jahren [7]. Zwar ist anzunehmen, dass die Erkrankungsraten bei den älteren Frauen über 60 Jahre nach Implementation eines organisierten und qualitätsgesicherten Screeningprogrammes zurückgehen werden, aber auch das sollte in der Übergangsphase von 3 Screening-Runden gezeigt werden. Ebenso sollten Subgruppen wie z.B. hysterektomierte Frauen und Frauen mit HPV-Impfung in das Screeningprogramm entsprechend eingeordnet werden, wie es bei der EU-LL sowie bei der US-LL der Fall ist [6;8].
Evaluation, Monitoring und Dokumentation des organisierten Zervixkarzinom-Screenings Beauftragung einer unabhängigen wissenschaftlichen Institution, einen detaillierten Plan zur Evaluation auszuarbeiten. Dabei muss die Machbarkeit der Datenerhebung im Rahmen des Screenings be-rücksichtigt und Aufwand und Nutzen abgewogen werden.	Eine kontinuierliche Evaluation des Zervixkarzinom-Screenings ist von grundlegender Bedeutung. Analysen von konsentierten Endpunkten sowie ein Daten-Abgleich mit Krebsregistern müssen durchgeführt werden [9,10]. Hierbei handelt es sich um eine Grundanforderung, die im Nationalen Krebsplan unter Ziel 3 formuliert ist [11]. Im Entwurf der KBV sind im § 32 des Beschlussentwurfes wichtige Bestandteile für eine erfolgreiche Evaluation enthalten. Allerdings ergeben sich Zweifel, ob die Einbindung der Daten epidemiologischer Krebsregister in der vorgesehenen Form möglich sein wird. So heißt es im § 32 Absatz 2 Satz 4 des KBV Beschlussentwurfes: „Des Weiteren werden, sofern landesrechtliche Bestimmungen eine entsprechende Übermittlung zulassen, von den epidemiologischen Krebsregistern jährlich pseudonymisiert die personenbeziehbaren Angaben zu neu aufgetretenen Zervixkarzinomen (inklusive des Tumorstadiums) und zu Todesfällen aufgrund von Zervixkarzinomen aller anspruchsberechtigten Frauen ab dem vollendeten 20.

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	Lebensjahr an die datenzusammenführende Stelle übermittelt.“ Eine Übermittlung personenbeziehbarer Daten erfordert jedoch nach vielen Landeskrebsregistergesetzen eine Einwilligung der betroffenen Personen [z.B. 12-13]. Damit stehen der routinemäßigen Übermittlung personenbeziehbarer Angaben über Zervixkarzinomfälle von epidemiologischen Krebsregistern an eine datenzusammenführende Stelle landesrechtliche Bestimmungen entgegen. Andererseits wird die Machbarkeit einer datenzusammenführenden Stelle aus der Perspektive des Datenschutzes nicht hinreichend beschrieben. Zudem sind den epidemiologischen Krebsregistern die anspruchsberechtigten Frauen nicht bekannt. Eine dafür erforderliche Datenübermittlung von Kontrollnummern der anspruchsberechtigten Teilnehmerinnen an die Krebsregister ist jedoch nicht vorgesehen. Auch könnte die Übermittlung der Daten von anspruchsberechtigten Nicht-Teilnehmerinnen aus Sicht des Datenschutzes bedenklich erscheinen. Möglichkeiten eines Widerspruchs zu Datenflüssen oder Datenabgleichen werden nicht näher beschrieben. Wir halten in der Konsequenz das vorgeschlagene Verfahren für gegenwärtig praktisch nicht umsetzbar. Eine zielführende Evaluation des Screenings ist dadurch in Frage gestellt. Beim Mammographie-Screening erfolgt ein personenbezogener Abgleich der Teilnehmerinnen mittels Kontrollnummern zur Ermittlung der Intervallkarzinome in den epidemiologischen Krebsregistern; dies ist in den meisten Landeskrebsregistergesetzen mit entsprechenden Regelungen bereits formuliert. Diese Abgleiche in den Landeskrebsregistern würden auch für die Evaluation eines organisierten Zervixkarzinom-Screenings genutzt werden können. Nach Durchführung eines derartigen Abgleichs in den epidemiologischen Krebsregistern mit einer Zusammenführung von Zervixkarzinom-Screening- und Krebsregisterdaten wären auch vergleichende Auswertungen von inzidenten bzw. tödlich verlaufenden Zervixkarzinomerkrankungen unter Teilnehmerinnen und Nicht-Teilnehmerinnen möglich. Die Optionen der Verwendung bzw. Erweiterung eines derartigen Ansatzes, der unter dem Aspekt der Machbarkeit viel erfolgversprechender ist, sollte unbedingt geprüft werden. Aufgrund dieser Bedenken zum § 32 des Beschlussentwurfes der KBV wird von der DGEpi **dringend** empfohlen, eine unabhängige wissenschaftliche Institution mit entsprechender epidemiologisch-methodischer Expertise mit der Planung, Vorbereitung und Durchführung der Evaluation zu beauftragen.

DEUTSCHE GESELLSCHAFT FÜR GYNÄKOLOGIE UND GEBURTSHILFE e.V.

Präsident
Prof. Dr. Diethelm Wallwiener
Ärztlicher Direktor
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25.05.2016

232. Stellungnahme der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (DGGG)

zur Änderung der Krebsfrüherkennungs-Richtlinie (KFE-RL): Zervixkarzinom-Screening

Das seit 1971 existierende Früherkennungsverfahren für das Zervixkarzinom hat wie in vielen anderen Ländern zu einer deutlichen Abnahme von Karzinomfällen und zu einer Reduktion der Sterblichkeit geführt.

Aufgrund der Einführung neuer Technologien wurden diese bewertet und Empfehlungen zur Berücksichtigung einer HPV-basierten Screeningstrategie bei der Umsetzung der gesetzlichen Bestimmungen des Krebsfrüherkennung und Registergesetzes formuliert.

Die Grundannahme ist dabei, dass der HPV-Test einfacher, zuverlässiger, weniger subjektiv und in Kombination mit einer Zytologie-Triage unter Einsatz von Biomarkern zu einer kleineren Zahl von Abklärungsuntersuchungen und längeren Untersuchungsintervallen führt.

Der Evidenzgrad für das bessere Outcome der HPV-Testung (alleine oder in Kombination mit zytologischen Untersuchungen) im Vergleich zur alleinigen Zytologie mit dem Endpunkt CIN 3 ist dabei moderat, für den Endpunkt Invasives Zervixkarzinom sehr niedrig[12].

Die Grundannahme für die Einführung ist die angenommene nahezu 100%ige Positivität für den Nachweis von HPV bei invasiven Befunden[3].

[1] Evidence Review for S3 guideline „Prevention of Cervical Cancer“ Kleijnen Systematic Reviews Ltd.2014
[2] Zusammenstellung: Evidenzberichte und Zusatzmaterialien von M.Arbyn et al. für die Leitliniengruppe Praevention des Zervixkarzinoms Brussels 2014

Die von Walboomer et al. im Jahre 1999 publizierte Studie ging der Frage nach, ob es überhaupt HPV-negative Zervixkarzinome gibt. Mit diversen aufwendigen molekular-biologischen, aber auch histologischen Re-Evaluierungsmethoden wurde versucht, HPV nachzuweisen. Dies gelang in 99,7% der Fälle mit eindeutig histologisch verifizierten Zervixkarzinomen.

In der neueren Literatur findet sich dies jedoch nicht mehr – Es ist davon auszugehen, daß in Europa die HPV-Prävalenz sinkt und ca. 1/Drittel der Zervixpathologien HPV-negativ sind[4]. Wir müssen damit rechnen, daß 18,7% der Fälle von CIN III, 7,8% der Plattenepithelkarzinome und 35,7% der Adenokarzinome HPV-negativ sind.

In unterschiedlichen Analysen variiert der Anteil der HPV-Negativität, aber zeigt darüberhinaus ein Absinken mit zunehmendem Alter. Das impliziert ein deutliches Risiko bei einer Einführung eines neuen Verfahrens, welches sich ausschließlich auf den Nachweis von HPV oder HPV-assoziierten Biomarkern stützt[5].

Daher begrüßt die DGGG ausdrücklich, den vom GBA gewählten Ansatz in Form eines Optionsmodelles, welches sorgfältig dokumentiert und bzgl. patientenrelevanter Endpunkte ausgewertet wird, um im Anschluss basierend auf dem Feldversuch mit einer fundierten Datenlage eine Bewertung treffen zu können. Nur so kann eine Form des Überscreenings vermieden und ein möglicher negativer Einfluss auf die Lebensqualität verhindert werden[6].

Die generelle Frage der Untersuchungsintervalle, sollte aus Sicht der DGGG nochmal überdacht und ein 3-jähriges gegenüber dem gewählten 5-jährigen Intervall für die HPV-Screening-Gruppe abgewogen werden – die Evidenz ist für beide ähnlich, würde aber das Risiko einer Doppel/Paralleluntersuchungen beim kürzeren Intervall vermindern.

Eine Altersbegrenzung wird dabei generell abzulehnen sein, da die Inzidenz des Zervixkarzinoms auch nach dem 65. Lebensalter hoch oder sogar steigend ist. Die jährliche gynäkologische Untersuchung sollte fortgesetzt werden, da diese in der Lage ist, einen Großteil extrazervikaler Neoplasien früh zu entdecken – Beispiele: Vulvakarzinom mit für 2016 prognostizierten 4400 Fällen und einer T1-Entdeckungsrate von ca. 90%[7] und ca. 2000 Fälle von Endometriumkarzinomen, die nur durch die jährliche zytologische Untersuchung identifiziert werden[8].

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[3] Walboomers et al.: Human papillomavirus is a necessary cause of invasive cervical cancer worldwide J Pathol 1999

[4] Anderson et al.: HPV Prevalence and Type-Distribution in Cervical Cancer and Premalignant Lesions of the cervix: A Population-based study from Northern Ireland J Med Virol 2016

[5] Hammer et al.: HPV Genotype distribution in older Danish women undergoing surgery due to cervical cancer Acta Obst Gyn Scand 2015

[6] Naber et al.: The potential harms of primary papillomavirus screening in over-screened women. Cancer Causes Control 2016

[7] RKI – Krebs in Deutschland 10. Ausgabe 2015

[8] Marquardt et al. Jahresstatistik Zervix-Zytologie Frauenarzt 2014

Zu den einzelnen Beschlussentwürfen:

Beschlussentwurf des GKV-SV Stand 26.04.2016

§28 (2) e

Nach der Münchner Nomenklatur III ist ein II-a Befund bewusst von dem unauffälligen I zu unterscheiden – der Hinweis a für Anamnese zielt darauf ab, dass im Vorfeld höhergradige Befunde nachgewiesen wurden und muss zu einer weiteren Kontrolle führen, die dann nach zweimaliger Wiederholung und unauffälligem Befund zur Vergabe von der Gruppe I führen und muss daher der Patientin mitgeteilt werden[9].

§28 (3)

Die vorrätige Abnahme einer Dünnschichtzytologie führt im HPV-basierten Primärscreeningarm zu einer umfassenden Lagerhaltung und -verwaltung. Großpraxen mit bis zu 100 Abstrichentnahmen pro Tag müssen darauf vorbereitet werden. Die Kosten für Probeentnahmematerial der Dünnschicht-Zytologie sind zu berücksichtigen.

§29 1 a

Der Abklärungsalgorithmus für das Primärscreening mittels Zytologie ist aus der Konsultationsfassung der S3 Leitlinie Praevention des Zervixkarzinomes entnommen.

Die Evidenz für dieses Vorgehen ist ein reiner Expertenkonsens. Hier wird vorgeschlagen, daß bei Befunden der Gruppe IIIp, IIIx, IIIe oder IIIg eine Abklärung mittel HPV Test oder p16/Ki67 erfolgen kann.

Verlorengegangen ist bei der Übertragung jedoch der Hinweis, dass bei den Befunden IIIx, IIIe und IIIg eine endometriumspezifische Abklärung zum Ausschluss einer endometrialen Neoplasie zu erfolgen hat und demnach eine Vaginalsonographie, Hysteroskopie und fraktionierte Abrasio sowie Kolposkopie nach sich ziehen muss.

Der Verlust dieser wichtigen Hinweise ist umso mehr nachvollziehbar, da in der Konsultationsfassung die graphische Darstellung des Algorithmus diesen Hinweis im Vorgehen für Frauen über 30 Jahre nicht abbildet, sondern für diese Gruppe der Algorithmus für Frauen zwischen 25 und 30 Jahren Anwendung finden soll.

§30 (4) 1-6

Bei der Einführung wird eine Übergangsregelung für die Implementierung und flächendeckende Umsetzung beider Optionsarme notwendig sein –

[9] Addendeum zur Münchner Nomenklatur III Frauenarzt 2015

Beschlussentwurf des KBV Stand 12.04.2016

§28 (1)

Die Definitionen sollte einheitlich verwandt werden und nicht zum einen von einem jährlichen zytologie-basierten Zervixkarzinomscreening und dann von einer zytologischen Untersuchung zum anderen gesprochen werden, wobei hier eine gynäkologische Untersuchung beschrieben wird.

§33

Die Umsetzung des Feldstudiencharakters hängt unmittelbar von der Erfassung und Dokumentation ab. Die Vollerhebung aller anspruchsberechtigter Frauen ist ein noch nicht abschätzbarer Aufwand und gerade von der Dokumentation eines Over-Screenings zB. kürzere freiwillige Intervalle oder additive Anwendung der Methoden hängt der generelle Erfolg einer Bewertung ab.

Beschlussentwurf der Patientenvertretung Stand 14.04.2016

§28(2)e

siehe GKV-Kommentar

§29 (1) a

siehe GKV-Kommentar

§29 (2) c

Pap IIIc existiert nicht in der Münchner Klassifikation III

§30 (4)

siehe GKV-Kommentar

Die Stellungnahme wurde von

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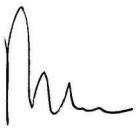
erstellt.

Prof. Dr. Diethelm Wallwiener
Präsident der DGGG e.V.



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Stellungnahme der Deutschen Gesellschaft für Psychosomatische Frauenheilkunde und Geburtshilfe (DGPFG e.V) zur Änderung der Krebsfrüherkennung - Richtlinie: Zervixkarzinom - Screening

Grundsätzlich begrüßen wir eine Änderung des bisherigen Systems der Krebsfrüherkennung mit der Einbeziehung evidenzbasierter Verfahren (HPV-Diagnostik) und der Einführung eines organisierten Screenings, wie es in den Europäischen Leitlinien von 2007 vorgesehen ist und unterstützen das damit verfolgte Ziel, die Teilnahmerate an der Krebsfrüherkennungsuntersuchung zu verbessern und die Rate sowohl an Neuerkrankungen als auch an Sterbefällen am Zervixkarzinom zu senken.

Ebenso halten wir die ausdrückliche Beibehaltung des Anspruchs auf eine jährliche klinische Untersuchung für wichtig, da sich gezeigt hat, dass viele Frauen diese Konsultation auch für die Beratung zu weiteren Anliegen (Empfängnisregelung, Klimakterium, Angebote der Prävention) nutzen und die Chance besteht, auch psychosoziale Belastungsfaktoren zu erfassen.

Kritisch sehen wir, dass grundlegende Fragen offen bleiben aufgrund fehlender Daten zur subjektiven Belastung und gesundheitsbezogenen Lebensqualität durch die Umstellung des Screeningsystems und dass damit auch nicht gewährleistet ist, das selbstgesteckte Ziel zu erreichen.

Alle drei Beschlussfassungen haben als Ziel benannt, neben der Senkung der Neuerkrankungen an invasiven Zervixkarzinomen und der Zervixkarzinomsterblichkeit, sowie der Entdeckung von Zervixkarzinomen in einem möglichst frühen Stadium, „**gleichzeitig eine Minimierung der Belastungen, die mit einem Früherkennungsprogramm verbunden sein können, zu gewährleisten“** (z.B. unnötige Sorge durch falsch-positive Befunde, Gefahr der Überdiagnose und Übertherapie, Gefahr der Scheinsicherheit bzw. Gefährdung durch falsch-negative Befunde, Ungewissheit während der Wartezeiten auf Befundergebnisse sowie Risiken und Nebenwirkungen der Untersuchungen selbst.)

Ebenso haben alle drei Gremien in ihren Beschlussfassungen wie folgt darauf hingewiesen:

„Keine der Studien lieferte auswertbare Daten zu den patientenrelevanten 4 Endpunkten Gesamtüberleben, krankheitsspezifische Mortalität, unerwünschte Folgen der Screeningstrategie und Veränderung der gesundheitsbezogenen Lebensqualität“

Damit ist die Erfüllung des Zieles „Minimierung der Belastungen“ mit dem jetzt beschlossenen Vorgehen nicht gewährleistet, da zu deren Einschätzung keinerlei objektive Daten vorliegen. Über diese soll jedoch neutral und umfassend aufgeklärt werden, sie sind wichtiger Inhalt der ärztlichen Beratung und damit Voraussetzung für die Entscheidung der Frau über die Inanspruchnahme und über ihre Wahl des geplanten Screeningverfahrens - mit nachhaltiger Auswirkung auf ihre Gesundheit und die gesundheitsbezogene Lebensqualität.

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Aus unserer Sicht wäre die Durchführung von Pilotprojekten vor einer flächendeckenden Umstellung des Screeningverfahrens notwendig gewesen, um diese Belastungen zu evaluieren, wie bereits von anderer Seite angemahnt wurde. (1)

Angesichts des jetzigen Standes der Beschlussfassungen, der solches Vorgehen nicht vorsieht, sehen wir für sowohl für die Beratung als auch für die Evaluation nur noch folgende Änderungsmöglichkeiten – diese jedoch als sehr dringlich an:

1. Stärkung des Stellenwertes einer individuellen ärztlichen Beratung sowohl vor der Entscheidung zum Monitoring als auch bei allen auffälligen Befunden.

2. Begleitende Evaluation zur Erfassung der Belastungen und der gesundheitsbezogenen Lebensqualität unter Einbeziehung der Patientinnen

Begründung:

1.Hinsichtlich des hohen Stellenwertes der in allen Beschlussfassungen geforderten umfassenden Aufklärung der Frau als Grundlage für ihre Entscheidung über die Screening-strategie (HPV- Test oder jährliche Zytologie) bleiben zu viele wichtige Fragen offen, die zu erheblichen Unsicherheiten führen können und die geforderte Neutralität der Beratungs-inhalte nicht gewährleisten. Unsicherheiten betreffen dabei nicht nur die zu beratenden Frauen, sondern gelten ebenso für die beratenden Ärztinnen und Ärzte; es ist absehbar, dass diese zu Lücken und Fehlinformationen führen können.

Umso wichtiger wird damit die gemeinsame Klärung des individuellen Risikos der Frau für die Entstehung eines Zervixkarzinoms aufgrund ihrer gesundheitlichen, partnerschaftlichen und psychosozialen Lebenssituation durch Patientin und Arzt/ Ärztin in einem patientinnenzentrierten Beratungsprozess, der bedarfsweise auch mehrere Gespräche umfassen kann.

Diese Beratung muss sowohl vom zeitlichen als auch honorarmäßigen Aufwand her angemessen gewährleistet sein.

Ziel der Aufklärung soll die informierte Entscheidung der Patientin sein zur Wahl eines Screeningverfahrens (Zytologie allein oder HPV-Test), welches für 5 Jahre dann alternativlos festgelegt wird. Es ist bekannt und durch Untersuchungen belegt, dass die partizipative Entscheidungsfindung als gemeinsame Entscheidung mit dem Arzt/ der Ärztin von den meisten PatientInnen ausdrücklich gewünscht und wahrgenommen wird. (2,3).

Angesichts differierender Angaben für falsch negative HPV-Befunde (4) – besonders für Adenocarcinome- ist eine sichere Grundlage für die Aufklärung über Vor- und Nachteile beider Verfahren und deren mögliche Auswirkungen derzeit aus unserer Sicht nicht ausreichend gegeben und eine informierte Entscheidung der Patientin daher fraglich. Die Gefahr ist damit groß, dass die ärztliche Favorisierung eines Verfahrens – bewusst oder unbewusst- vom Arzt/ Ärztin vermittelt und von der Patientin übernommen wird bzw. ihre Entscheidung unverhältnismäßig beeinflusst.

Ebenso besteht eine nicht geringe Wahrscheinlichkeit dafür, dass sich das geplante Monitoring in seiner Durchführung und Aussage, welche Screeningstrategie hier in Deutschland eine tatsächliche Verbesserung des jetzigen Systems darstellt, als nicht effektiv erweist: bisher haben Frauen den HPV-Test als Zusatzdiagnostik im Zusammenhang mit auffälligen zytologischen Befunden und deren Abklärung vermittelt bekommen oder als fakultative Empfehlung (4) zur erhöhten Sicherheit als zusätzliche Selbstzahler-Leistung (IGEL). Ob und wie die jetzt geplant alternativlose Entscheidung für eine der beiden Screeningverfahren ohne zwischenzeitlich möglichen Wechsel über 5 Jahre von den Frauen akzeptiert und umgesetzt wird, ist weitgehend offen.

Es ist sehr wahrscheinlich, dass Frauen weiterhin zusätzlich zum gewählten Screeningverfahren das jeweils andere Verfahren als individuelle Gesundheitsleistung in Anspruch nehmen und damit das Monitoring in seiner Aussage fragwürdig wird.

2.Der positive Nachweis eines HPV-Befundes als eine sexuell übertragene und übertragbare Infektion bedeutet direkter und stärker als die Mitteilung eines auffälligen zytopathologischen Befundes einen Eingriff in das psychosexuelle Erleben der Frau und in die Paarbeziehung mit möglichen negativen Auswirkungen (6). Diese Befundvermittlung bedarf daher einer ausführlichen, einfühlsamen, patientinnenzentrierten Kommunikation, um Ängste und Irritationen sowie mögliche Partnerschaftskonflikte zu verhindern.

Es ist vorstellbar, dass hinsichtlich der bisher in Studien ermittelten und prognostizierten höheren Nachweisrate an HPV-Infektionen gegenüber auffälligen zytomorphologischen Befunden (7) die Befundmitteilungen zumindest in der ersten Screeningrunde zu häufigeren Irritationen führen – und damit Belastungen nicht vermindert sondern möglicherweise verstärkt werden

Die individuelle ärztliche Aufklärung auf der Basis einer vertrauensvollen Arzt-Patientinnen-Beziehung ist gerade bei abklärungsbedürftigen Befunden daher unbedingt notwendig und darf nicht schriftlichen Befundmitteilungen überlassen werden.

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Gemeinsamer Bundesausschuss

Stellungnahme zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

Deutsche Gesellschaft für Psychosomatische Frauenheilkunde und Geburtshilfe e.V. Vorstand	
28.05.2016	
Stellungnahme / Änderungsvorschlag	**Begründung**
1.Stärkung des Stellenwertes einer individuellen ärztlichen Beratung sowohl vor der Entscheidung zum Monitoring als auch bei auffälligen Befunden	s. Anlage
2. Begleitende Evaluation zur Erfassung der Belastungen und der gesundheitsbezogenen Lebensqualität unter Einbeziehung der Patientinnen	s.Anlage

Gemeinsamer Bundesausschuss

Stellungnahme zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

Beschlussentwurf GKV

Deutsche Gesellschaft für Zytologie	
23. Mai 2016	
Stellungnahme / Änderungsvorschlag	**Begründung**
Beschlussentwurf ***§ 28 (2) e*** ***statt****:* *Die Zytologiebefunde Pap I und Pap IIa sind unauffällige Befunde und werden nur bei klinischen Auffälligkeiten oder ausdrücklichen Wunsch der Versicherten mitgeteilt.* ***richtig****:* *Der zytologische Befund einer Gruppe I ist ein unauffälliger Befund und erübrigt eine Befundmitteilung.*	Die Bezeichnung der zytologischen Befunde als „PAP“ entstammt der Nomenklatur von George Papanicolaou und ist in Deutschland seit den 1970er Jahren obsolet. Wie schon in der Vorgängerversion von 1990 werden die zytologischen Befunde nach der Münchner Nomenklatur III als Befundgruppen („**Gruppe** I-V“) klassifiziert [1]. Ein Befund der Gruppe II-a ist morphologisch tatsächlich unauffällig, wird jedoch vom Zytologen vergeben, weil die untersuchte Frau aufgrund pathologischer Vorbefunde einem erhöhten Risiko unterliegt. Deshalb sind mit diesem Befund je nach Vorbefund Empfehlungen für weitere Maßnahmen verknüpft. In diesem Sinne ist die Gruppe II-a im Rahmen des Abklärungsprozedere (nach auffälliger Zytologie, Histologie oder Kolposkopie) einzuordnen und nicht als „unauffällig“.
Beschlussentwurf ***§ 28 (3) d und § 29 (2) a*** *Die Zytologie-Triage ist nicht erforderlich, wenn ein HPV-Test verwendet wird, der Informationen zu den Genotypen HPV 16 und HPV 18 liefert und mindestens einer dieser Genotypen positiv ist.* ***ersatzlos streichen***	Diese Vorgabe entstammt wie andere Abklärungsstrategien der von uns abgelehnten Konsultationsfassung der S3-Leitlinie und war dort sogar nur als „Empfehlung“ (nicht als „starke Empfehlung“) mit einem sehr niedrigen Evidenzgrad (Grade +) ausgewiesen. In den europäischen Leitlinien findet sich dazu keine Aussage. HPV 16 gehört zu den häufigsten Genotypen, die bei einem HPV-Test nachgewiesen werden und sind bei erstmaligem Nachweis überwiegend Ausdruck einer passageren Infektion. Daher sollte wie beim Nachweis anderer HPV Genotypen mit kanzerogenem Potential eine zytologische Untersuchung erfolgen. Auch bei einer HPV-Infektion mit den Genotypen 16 und 18 können sowohl kolposkopische Normalbefunde vorliegen (z.B. im Falle einer Virusinfektion ohne Läsion) als auch kolposkopische minor changes (Metaplasie oder CIN1) oder major changes (CIN2 oder CIN3), des Weiteren verhindern bestimmte klinische Konstellationen einen aussagekräftigen kolposkopischen Befund. Da die Kolposkopie z. B. den risikolosen Befund einer Metaplasie nicht von dem einer CIN 1 zu unterscheiden vermag und bei diesen minor changes auch Biopsien eine erhebliche Unsicherheit aufweisen [2], sollte bei einer kolposkopischen Untersuchung ein zytologischer Befund vorliegen.
Beschlussentwurf	Diese für den Gesetzestext vorgesehenen Vorgaben für die

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§ 29 *1. Abklärungsalgorithmus …* *a. Bei den Primärscreeningbefunden Pap III-p, III-x, III-e, III-g soll bereits innerhalb von 3 Monaten ein HPV-Test durchgeführt werden, bei II-p, II-g, II-e, IIID1 erst in 6 Monaten. Bei einem positiven HPVTest soll innerhalb von 3 Monaten eine Abklärungskolposkopie erfolgen. Bei einem negativen HPV-Test soll nach 12 Monaten eine klinische Untersuchung und Ko-Testung (Zytologie und HPV-Test) erfolgen. Ist mindestens einer dieser Tests positiv, soll innerhalb 3 Monaten eine Abklärungskolposkopie erfolgen. Bei Frauen unter 25 Jahren soll nur in begründeten Ausnahmefällen eine Abklärungskolposkopie durchgeführt werden. Stattdessen soll die klinische Untersuchung und Ko-Testung (Zytologie und HPV-Test) im Abstand von mindestens 12 Monaten wiederholt werden.* *b. Bei den Primärscreeningbefunden Pap III-D2 soll innerhalb eines Monats eine Abklärungskolposkopie erfolgen.*	Abklärung auffälliger zytologischer Befunde sind offenbar ohne Sachkenntnis erstellt, fachlich unhaltbar und gefährden deshalb die Patientinnen, wie die folgenden Beispiele zeigen. - Hinter den Gruppen III-p und III-g kann sich sowohl eine CIN2/3 bzw. ein AIS verbergen als auch ein invasives Plattenepithel- oder Adenokarzinom: Dies ist Inhalt des Wortgutachtens, das der Zytologe der Befundgruppe beifügt und wovon sinnvollerweise das weitere Prozedere abhängt [3]. Es wäre für die Patientin fatal und für den Frauenarzt justiziabel, z.B. bei Gruppe III-p mit Karzinomverdacht womöglich erst in 3 Monaten einen HPV-Test durchzuführen anstatt einer sofortigen Kolposkopie. Bei Gruppe III-e ist es notwendig, ein Endometriumkarzinom auszuschließen bzw. zu diagnostizieren, bei Gruppe III-x ein Malignom des Uterus oder anderen Ursprungs – hier handelt es sich prinzipiell um nicht HPV-assoziierte Erkrankungen, sodass der HPV-Test keinen sinnvollen Beitrag für die Abklärung liefert und gegebenenfalls sogar zu einer Diagnoseverschleppung führen kann. Nach den 2015 publizierten Empfehlungen der Arbeitsgemeinschaft Zervixpathologie und Kolposkopie [2] ist eine Kolposkopie nach einer erstmalig vergebenen Gruppe III nur verzichtbar, wenn nach dem Wortgutachten des Zytologen kein Karzinomverdacht besteht. - Ein HPV-Test bei einer Gruppe IIID1 ist wenig effektiv, da er in mehr als 80% positiv ist [4]. Die adäquate Abklärung einer Gruppe IIID1 ist eine zytologische Untersuchung in 6 Monaten und bei Persistenz dieses Befundes über mehr als 12 Monate eine Kolposkopie. Die Kolposkopie dient hier nicht der Bestätigung der Diagnose einer CIN1, sondern dem Ausschluss einer höhergradigen CIN bzw. eines Karzinoms. - Eine Kolposkopie sollte auch bei Frauen unter 25 Jahren z.B. bei mehr als 12 Monate persistierender Gruppe IIID1, mehr als 6 Monate persistierender Gruppe IIID2 oder bei Gruppe III-p oder III-g erfolgen, da sich in diesen Fällen nicht selten eine CIN3 findet. - Eine unmittelbare Kolposkopie bei einer erstmalig aufgetretenen Gruppe IIID2 entspricht einer Überdiagnostik. Nach den Empfehlungen der Arbeitsgemeinschaft Zervixpathologie und Kolposkopie [2] wird bei erstmaliger Gruppe IIID2 ohne zusätzliche Risiken eine Kolposkopie innerhalb von 3-6 Monaten

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	favorisiert. Zusammenfassend sind – unabhängig von den im Beschlussentwurf zum Abklärungsprozedere gemachten wissenschaftlich unhaltbaren und laienhaften Vorgaben - detaillierte Vorschriften in einem Gesetzestext grundsätzlich abzulehnen. Komplexe medizinische Sachverhalte mit sich verändernden diagnostischen und therapeutischen Optionen müssen außerdem der individuellen Situation der Patientin angepasst werden, um Schaden von ihr abzuwenden.
§ 29 2. c. *„PAP IIIc“?*	Diese Gruppe ist nicht Bestandteil der Münchner Nomenklatur III.
Tragende Gründe ***2.2. Nutzenbewertung des HPV-Tests im Primärscreening*** *…, so dass inzwischen neben dem Pap-Test auch ein HPV-Tests zur Früherkennung des Zervixkarzinoms verwendet werden kann.*	Die Aussage, dass „auch ein HPV-Test zur Früherkennung des Zervixkarzinoms verwendet werden kann“, ist falsch: mit einem positiven HPV-Test weist man nur eine HPV-Infektion im Range eines Risikofaktors nach, nicht aber ein Zervixkarzinom oder seine Vorstufen. Bei einem positiven HPV-Test liegt nur zu 3-4% eine therapiepflichtige Krebsvorstufe und extrem selten ein Zervixkarzinom vor. Im Gegensatz zu diesem extrem schlechten positiven Prädiktionswert wird der vergleichsweise hohe negative prädiktive Wert gern hervorgehoben, der aber mit ca. 90% für einen Screening-Test mit 5jährigem Intervall ebenfalls inakzeptabel ist (s.u.).
Tragende Gründe ***2.3.3. Screeningstrategien S. 5/6*** *…Es wird ein HPV-basiertes Primärscreening mit mindestens 5 Jahresintervall und unmittelbarer Zytologie-Triage ab einem Alter von 35 Jahren in einem organisierten Programm empfohlen. Das HPV-basierte Screening sollte nicht vor dem Alter von 30 Jahren begonnen werden. Für das Alter 30 – 34 Jahre gibt es keine eindeutige Evidenz für oder gegen ein HPV-basierte Screening.* *…Das HPV-basierte Screening wird Frauen bereits ab dem Alter von 30*	Ein HPV-Test in fünfjährigem Intervall ist als Maßnahme zur Vorsorge nicht geeignet. Der alleinige HPV-Test ist von einer beachtlichen Falsch-Negativ Rate in der Detektion hochgradiger Läsionen und invasiver Karzinome behaftet [5-11]. Insbesondere auch frühinvasive Karzinome weisen eine stark reduzierte Viruslast in der Läsion auf und entgehen damit den HPV-Screening-Verfahren [12]. Folglich ist bei dem vorgeschlagenen 5-Jahres-Modell mit einer Häufung von Intervallkarzinomen zu rechnen [13]. HPV-unabhängige Malignome, die im zytologischen Screening gefunden werden können, werden im primären HPV-Screening als Screeningversager in Kauf genommen. Dies steht ethisch im Widerspruch zum etablierten Vorsorgesystem, in dem keine Patientengruppe definiert ist, die von vornherein von einem Screeningerfolg ausgeschlossen wird. Die Akzeptanz in der weiblichen Bevölkerung ist voraussichtlich auch in Deutschland gering mit folglich starker Zunahme eines sogenannten grauen Screenings [14]. In Finnland, das das angesprochene 5-Jahres-Modell mit Register und Einladung der Screening-Teilnehmerinnen seit Jahren praktiziert, wurden 2000-2008 lediglich etwa 11% der invasiven Zervixkarzinome innerhalb des organisierten Screenings entdeckt [15-17]. Ein

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Jahren angeboten, da die Inzidenz des invasiven Karzinoms bereits in diesem Alter einen deutlichen Anstieg zeigt und am in situ Karzinom erkranken Frauen im Mittel bereits mit 34 Jahren (RKI: Krebs in Deutschland 2015).	„graues“ Screening in Deutschland im Rahmen der Individuellen Gesundheitsleistungen („IGeL“) ginge zu Lasten der nicht teilnehmenden und häufig sozial unterprivilegierten Frauen mit der höchsten Inzidenz an Zervixkarzinomen. Ein primäres HPV-Screening führt zu einer unverhältnismäßig hohen Zahl von Frauen mit einem positiven Testergebnis ohne entsprechende Erkrankung, da die nachgewiesene Virus-DNA nur die Infektion, nicht aber eine Läsion dokumentiert. Die Screening-Teilnehmerinnen würden somit der Gefahr einer Überdiagnostik und Übertherapie ausgesetzt, unnötige Ängste der positiv getesteten Frauen bedeuten eine Reduktion ihrer Lebensqualität [18-20]. Die Empfehlung aus den 2015 von der Europäischen Kommission veröffentlichten Supplements zu den Europäischen Leitlinien, das primäre HPV-Screening mit 35 Jahren zu beginnen [21], wird mit der Begründung ignoriert, dass die Inzidenz des invasiven Karzinoms über 30 bereits deutlich ansteigt und an einer Präkanzerose im Range eines Carcinoma in situ (CIN3) Frauen im Mittel bereits mit 34 Jahren erkranken. Aus den zugänglichen Daten des Robert-Koch-Instituts geht allerdings nicht hervor, ob nicht die Zunahme der Karzinome ab 30 vor allem durch eine Zunahme frühinvasiver Karzinome bedingt ist, wie das in Mecklenburg-Vorpommern der Fall ist [22]. Unabhängig davon, dass das primäre HPV-Screening aus den oben angeführten Gründen ohnehin abzulehnen ist, bedeutet ein Beginn mit bereits 30 Jahren eine Gefährdung der Teilnehmerinnen vor allem wegen der extrem hohen Anzahl falsch positiver Befunde und damit verbundener Überdiagnostik und Übertherapie gerade dieser Frauen im bevorzugten Gebäralter. Es ist unverständlich, warum das 30. Lebensjahr bei der vorliegenden Datenlage und sogar in Widerspruch zu den ansonsten stets herangezogenen Europäischen Leitlinien als Eintrittsalter für das primäre HPV-Screening empfohlen wird. Aus der Erkenntnis, dass Frauen < 30 Jahren häufiger HPV-positiv sind als Frauen > 30 Jahren, wird die Festlegung für ein zytologisches Screening für Frauen < 30 Jahren und ein HPV-Screening > 30 Jahren getroffen. Der Abfall der HPV-Prävalenz erfolgt in Abhängigkeit vom Lebensalter in kleinen Schritten [23, 24]. Die HPV-Prävalenz von 31-jährigen Frauen unterscheidet sich nur marginal von denen 29-jähriger. Bei 35-jährigen Frauen liegt sie lediglich wenige Prozentpunkte unter der von 30-jährigen. Erst nach dem 40. Lebensjahr kommt es zu einem deutlicheren Abfall der HPV-Prävalenz. Die Grenzwertfestlegung bei 30 Jahren für Screeningverfahren und -intervall erfolgt somit willkürlich. Eine sinnvolle Alternative zum jährlichen zytologischen Screening auch nach dem 30. Lebensjahr wäre hingegen das

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	sogenannte Co-Testing ab dem 35. Lebensjahr (zytologische Untersuchung in Kombination mit einem adäquaten HPV-Test) in einem dreijährigen Intervall: die Kompensation der Schwäche der einen Methode durch die Stärke des anderen Verfahrens gewährleistet die Sicherheit für die teilnehmenden Frauen (die geringere Sensitivität der Zytologie und ihre hohe positive Prädiktion im Zusammenspiel mit der hohen negativen Prädiktion und schlechten Spezifität des HPV-Testes). Der Erfolg dieser Vorgehensweise ist in der aktuellen Literatur belegt [8-10, 20, 25, 26]. Insbesondere bei einer Intervallverlängerung von mehr als drei Jahren besteht die Gefahr einer Reduktion der Teilnahmerate am organisierten Screening [27]. Dies muss unbedingt vermieden werden, da unter den Zervixkarzinom-Patientinnen die Nicht-Teilnehmerinnen die meisten und die fortgeschrittenen Karzinome aufweisen [22].
2.3.3. Screeningstrategien S. 6 *Wenn für das TriageVerfahren die konventionelle Zytologie verwendet wird, gibt es zwei Möglichkeiten für die Organisation des Triage-Verfahrens:* *a) Es wird bei allen Frauen, die das HPV-basierte Screening wählen, mit dem Abstrich für den HPV-Test noch ein zusätzlicher Abstrich für die Zytologie abgenommen. Der Abstrich für die konventionelle Zytologie muss auf einem Objektträger fixiert und beim Gynäkologen oder im Labor aufbewahrt werden, bis das Ergebnis des HPV-Tests vorliegt. Ca. 10% der HPV-Tests sind positiv. Das bedeutet, dass ca. 90% der angefertigten Objektträger verworfen werden.* *b) Es wird bei allen Frauen, die das HPV-basierte Screening wählen, nur ein Abstrich für den HPV-Test abgenommen. Wenn der HPV-Test positiv ist, muss die Frau erneut einbestellt*	a) Diese Vorgehensweise ist als indiskutabel abzulehnen. Sie würde bedeuten, dass Untersuchungsmaterial vorliegt, aber keine Untersuchung vorgenommen wird – rechtlich ist dies wahrscheinlich nicht zulässig, insbesondere wenn bei Auftreten von Intervallkarzinomen nachträglich festgestellt wird, dass zum Zeitpunkt der Abnahme für den HPV-Test bereits zytologisch ein Hochrisikobefund hätte nachgewiesen werden können. In der gynäkologischen Praxis könnten diese Objektträger nicht aufbewahrt werden, weil ohne Eindeckung die Gefahr des Materialverlustes besteht. Ein Eindecken des Objektträgers setzt aber die Färbung voraus, sodass die Archivierung nur im zytologischen Labor nach Färbung und Eindeckung erfolgen könnte. Natürlich muss dann auch eine ordnungsgemäße Registrierung incl. Erfassung der Patientendaten vorgenommen werden. Dies müsste in der Gebührenordnung entsprechend als Leistung aufgeführt und bezahlt werden, b) Als einziges Gegenargument gegen eine Einbestellung der Frauen wird genannt: „*Bei diesem Vorgehen besteht das Risiko, dass ein positiver HPV-Test nicht oder verzögert abgeklärt wird.*“ Dieses „Risiko“ besteht bei jedem auffälligen Screening-Befund und ist somit irrelevant.

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und ein Abstrich für die konventionelle Zytologie abgenommen werden. Bei diesem Vorgehen besteht das Risiko, dass ein positiver HPV-Test nicht oder verzögert abgeklärt wird.	
2.3.4. Abklärungsdiagnostik S. 7 *Das zytologiebasierte Screening ist unauffällig bei Pap I und Pap IIa gemäß der Münchner Nomenklatur III. … In diesen Fällen wird das Primärscreening in den vorgegeben Zeitabständen durchgeführt.*	***Begründung s.o. Beschlussentwurf § 28 (2) e*** einfach nur „II-a“ streichen
2.3.4. Abklärungsdiagnostik S. 7/8 *Für das Management auffälliger Screeningbefunde werden für die verschiedenen Screeningstrategien Algorithmen für die Abklärungsdiagnostik vorgegeben. Die Abklärungsdiagnostik orientiert sich an den Empfehlungen der aktuellen deutschen S3 Leitlinien zur Prävention des Zervixkarzinoms (Konsultationsfassung vom 01.03.2016).* ***S.7 und 8*** *(Schema)* ***S. 8*** *Bereits bei Minor Changes ist eine Abklärung durch eine Biopsie erforderlich.*	Gemeinsam mit den anderen an der Versorgung der Frauen im Rahmen des Zervixkarzinom-Früherkennungsprogramms beteiligten Ärzte (Berufsverband der Frauenärzte, Arbeitsgemeinschaft Zervixpathologie und Kolposkopie der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe, Arbeitsgemeinschaft Zytologisch Tätiger Ärzte in Deutschland, Bundesverband deutscher Pathologen und Berufsverband zytologisch tätiger Akademiker in Deutschland) hat die Deutsche Gesellschaft für Zytologie die o.g. Konsultationsfassung der S3-Leitlinie am 10.04.2016 abgelehnt. Dafür waren vor allem fachliche Defizite des Leitlinien-Entwurfs maßgeblich, die sich auch in den vorgeschlagenen Abklärungsalgorithmen niederschlagen. Die Begründung dafür ist in unserem Ablehnungsschreiben enthalten (das der G-BA am 10.04. 2016 erhalten hat) und soll hier nicht im Einzelnen wiedergegeben werden. Bereits weiter oben haben wir aufgeführt, aus welchen Gründen die für den Richtlinientext vorgesehenen Vorgaben für die Abklärung strikt abzulehnen sind. Als weiteres Beispiel für inakzeptable pauschale Vorgaben widerspricht diese Forderung den gültigen Empfehlungen zur Kolposkopie. Es gibt keine Indikation für eine Biopsie bei „minor changes“, da derartige Befunde in der Regel physiologische Veränderungen sind oder maximal einer CIN1 entsprechen. Ausnahmen sind diskrepante Befunde (z.B. zytologisch Gruppe IV, V, Gruppe III mit Wortgutachten „Karzinom denkbar“ in Kombination mit kolposkopischen „minor changes“). Hier sind Target-Biopsien, ggf. Random-Biopsien, ggf. eine Zervix-Kürettage indiziert [2]**.**

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	Grundsätzlich bei „minor changes“ durchgeführte Biopsien bedeuten Überdiagnostik: nicht indizierte invasive Eingriffe, die die Integrität eines Organs verletzen. Sie würden außerdem zu einer nicht vertretbaren Zahl histologischer Abklärungen führen.
2.4. Fazit *… Durch die Anwendung des HPV-Tests im Primärscreening kann die Inzidenz von invasiven Zervixkarzinomen weiter gesenkt werden.*	Diese Behauptung ist nicht belegt. Sie entstammt nicht dem IQWiG-Bericht. Weder in den dabei ausgewerteten Studien noch in irgendeiner anderen Publikation findet sich dafür Evidenz, insbesondere nicht für industrialisierte Länder.

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Gemeinsamer Bundesausschuss

Stellungnahme zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

Beschlussentwurf KBV

Deutsche Gesellschaft für Zytologie	
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Stellungnahme / Änderungsvorschlag	**Begründung**
Beschlussentwurf ***§ 24***	Im Vergleich zu den entsprechenden Passagen in den Entwürfen von GKV und Patientenvertretung ist zu unterstützen, dass im KBV-Entwurf die frühinvasiven Zervixkarzinome (ca. 25% aller Karzinome) ihrer exzellenten Prognose wegen wie die Krebsvorstufen als Zielläsion der Früherkennung benannt werden.
Tragende Gründe ***2.3.3 Screeningstrategien*** *Es wird ein HPV-basiertes Primärscreening mit mindestens 5 Jahresintervall und unmittelbarer Zytologie-Triage ab einem Alter von 35 Jahren in einem organisierten Programm empfohlen. Das HPV-basierte Screening sollte nicht vor dem Alter von 30 Jahren begonnen werden. Für das Alter 30 – 34 Jahre gibt es keine eindeutige Evidenz für oder gegen ein HPV-basierte Screening.* *…Das HPV-basierte Screening wird Frauen bereits ab dem Alter von 30 Jahren angeboten, da die Inzidenz des invasiven Karzinoms bereits in diesem Alter einen deutlichen Anstieg zeigt und am in situ Karzinom Frauen im Mittel bereits mit 34 Jahren erkranken …*	Ein HPV-Test in fünfjährigem Intervall erscheint als Maßnahme zur Vorsorge nicht geeignet. Der alleinige HPV-Test ist von einer beachtlichen Falsch-Negativ-Rate in der Detektion hochgradiger Läsionen und invasiver Karzinome behaftet [1-7]. Insbesondere auch frühinvasive Karzinome weisen eine stark reduzierte Viruslast in der Läsion auf und entgehen damit den HPV-Screening-Verfahren [8]. Folglich ist bei dem vorgeschlagenen 5-Jahres-Modell mit einer Häufung von Intervallkarzinomen zu rechnen [9]. HPV-unabhängige Malignome, die im zytologischen Screening gefunden werden können, werden im primären HPV-Screening als Screeningversager in Kauf genommen. Dies steht ethisch im Widerspruch zum etablierten Vorsorgesystem, in dem keine Patientengruppe definiert ist, die von vornherein von einem Screeningerfolg ausgeschlossen wird. Die Akzeptanz in der weiblichen Bevölkerung ist voraussichtlich auch in Deutschland gering mit folglich starker Zunahme eines sogenannten grauen Screenings [10]. In Finnland, das das angesprochene 5-Jahres-Modell mit Register und Einladung der Screening-Teilnehmerinnen seit Jahren praktiziert, wurden 2000-2008 lediglich etwa 11% der invasiven Zervixkarzinome innerhalb des organisierten Screenings entdeckt [11-13]. Ein „graues“ Screening in Deutschland im Rahmen der Individuellen Gesundheitsleistungen („IGeL“) ginge zu Lasten der nicht teilnehmenden und häufig sozial unterprivilegierten Frauen mit der höchsten Inzidenz an Zervixkarzinomen. Ein primäres HPV-Screening führt zu einer unverhältnismäßig hohen Zahl von Frauen mit einem positiven Testergebnis ohne entsprechende Erkrankung, da die nachgewiesene Virus-DNA nur die Infektion, nicht aber eine Läsion dokumentiert. Die Screening-Teilnehmerinnen würden somit der Gefahr einer Überdiagnostik und Übertherapie ausgesetzt, unnötige Ängste der positiv getesteten Frauen bedeuten eine Reduktion ihrer Lebensqualität [14-16].

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	Die Empfehlung aus den 2015 von der Europäischen Kommission veröffentlichten Supplements zu den Europäischen Leitlinien, das primäre HPV-Screening mit 35 Jahren zu beginnen [17], wird mit der Begründung ignoriert, dass die Inzidenz des invasiven Karzinoms über 30 bereits deutlich ansteigt und an einer Präkanzerose im Range eines Carcinoma in situ (CIN3) Frauen im Mittel bereits mit 34 Jahren erkranken. Aus den zugänglichen Daten des Robert-Koch-Instituts geht allerdings nicht hervor, ob nicht die Zunahme der Karzinome ab 30 vor allem durch eine Zunahme frühinvasiver Karzinome bedingt ist, wie das in Mecklenburg-Vorpommern der Fall ist [18]. Unabhängig davon, dass das primäre HPV-Screening aus den oben angeführten Gründen ohnehin abzulehnen ist, bedeutet ein Beginn mit bereits 30 Jahren eine Gefährdung der Teilnehmerinnen vor allem wegen der extrem hohen Anzahl falsch positiver Befunde und damit verbundener Überdiagnostik und Übertherapie gerade dieser Frauen im bevorzugten Gebäralter. Es ist unverständlich, warum das 30. Lebensjahr bei der vorliegenden Datenlage und sogar in Widerspruch zu den ansonsten stets herangezogenen Europäischen Leitlinien als Eintrittsalter für das primäre HPV-Screening empfohlen wird. Aus der Erkenntnis, dass Frauen < 30 Jahren häufiger HPV-positiv sind als Frauen > 30 Jahren, wird die Festlegung für ein zytologisches Screening für Frauen < 30 Jahren und ein HPV-Screening > 30 Jahren getroffen. Der Abfall der HPV-Prävalenz erfolgt in Abhängigkeit vom Lebensalter in kleinen Schritten [19, 20]. Die HPV-Prävalenz von 31-jährigen Frauen unterscheidet sich nur marginal von denen 29-jähriger. Bei 35-jährigen Frauen liegt sie lediglich wenige Prozentpunkte unter der von 30-jährigen. Erst nach dem 40. Lebensjahr kommt es zu einem deutlicheren Abfall der HPV-Prävalenz. Die Grenzwertfestlegung bei 30 Jahren für Screeningverfahren und -intervall erfolgt somit willkürlich. Eine sinnvolle Alternative zum jährlichen zytologischen Screening auch nach dem 30. Lebensjahr wäre hingegen das sogenannte Co-Testing ab dem 35. Lebensjahr (zytologische Untersuchung in Kombination mit einem adäquaten HPV-Test) in einem dreijährigen Intervall: die Kompensation der Schwäche der einen Methode durch die Stärke des anderen Verfahrens gewährleistet die Sicherheit für die teilnehmenden Frauen (die geringere Sensitivität der Zytologie und ihre hohe positive Prädiktion im Zusammenspiel mit der hohen negativen Prädiktion und schlechten Spezifität des HPV-Testes). Der Erfolg dieser Vorgehensweise ist in der aktuellen Literatur belegt [4-6, 16, 21, 22]. Insbesondere bei einer Intervallverlängerung von mehr als drei Jahren besteht die Gefahr einer Reduktion der Teilnahmerate am organisierten Screening [23]. Dies muss

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	unbedingt vermieden werden, da unter den Zervixkarzinom-Patientinnen die Nicht-Teilnehmerinnen die meisten und die fortgeschrittenen Karzinome aufweisen [18].
2.3.4 Abklärungsdiagnostik	Wir begrüßen ausdrücklich, dass in diesem Entwurf für das Management auffälliger Screening-Befunde keine detaillierten Algorithmen vorgegeben werden. Bei der Vielfalt von Befundkonstellationen und unterschiedlichsten Gegebenheiten für die einzelne Screening-Teilnehmerin ist ein allgemeingültiger Algorithmus nicht festzuschreiben, im Übrigen fehlt dafür die Evidenz. Bei Vorliegen einer akzeptierten S3-Leitlinie zur Prävention des Zervixkarzinoms könnten deren Empfehlungen angewendet werden. Dies ist in absehbarer Zeit leider nicht der Fall, da die Konsultationsfassung vom 29.03.2016 von sämtlichen potentiellen Anwendern als fehlerbehaftet und nicht umsetzbar eingestuft wurde. Deshalb ist nach wie vor eine Abklärung entsprechend der Empfehlungen der Münchner Nomenklatur III (Addendum, publiziert im Januar 2015 in „Frauenarzt“ [24]) und der Empfehlungen der Arbeitsgemeinschaft Zervixpathologie und Kolposkopie (publiziert im September 2015 in gyn [25]) vorzunehmen. Die notwendigen Maßnahmen werden im Konsens mit der Patientin an ihre individuelle Situation angepasst.
Anlage I ***HPV-Impfstatus*** ***Zytologische Untersuchung*** *1. Abstrich-Qualität* *Material nicht verwertbar* *Endozervikale Zellen vorhanden / nicht vorhanden* *2. Proliferationsgrad* *3. Flora* *4. Befundgruppe* *5. Bemerkung ggf. Freitext* *6. Empfohlene Maßnahme* *Zytologische Kontroll-Untersuchung (ggf. nach Entzündungsbehand-lung/Östrogenbehandlung bzw. nach Intervall) HPV-Test* *Kolposkopie ggf. inkl. Histologie* *Sonstiges*	Hier sollte der Impfstoff erfasst werden (bisher kamen 2fach- und 4fach-Impfstoffe zum Einsatz, jetzt auch ein nonavalenter Impfstoff). 2. und 3. müssen zwar vom Zytologen im Befund dokumentiert werden, sind jedoch im Rahmen der elektronischen Dokumentation zur Datenerfassung entbehrlich. 5. und 6. sollte unbedingt nur als Freitext erfasst werden

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Stellungnahme zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

Beschlussentwurf Patientenvertretung

Deutsche Gesellschaft für Zytologie	
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Stellungnahme / Änderungsvorschlag	**Begründung**
Beschlussentwurf ***§ 28 (2) e*** ***statt****:* *Die Zytologiebefunde Pap I und Pap IIa sind unauffällige Befunde und werden nur bei klinischen Auffälligkeiten oder ausdrücklichen Wunsch der Versicherten mitgeteilt.* ***richtig****:* *Der zytologische Befund einer Gruppe I ist ein unauffälliger Befund und erübrigt eine Befundmitteilung.*	Die Bezeichnung der zytologischen Befunde als „PAP“ entstammt der Nomenklatur von George Papanicolaou und ist in Deutschland seit den 1970er Jahren obsolet. Wie schon in der Vorgängerversion von 1990 werden die zytologischen Befunde nach der Münchner Nomenklatur III als Befundgruppen („**Gruppe** I-V“) klassifiziert [1]. Ein Befund der Gruppe II-a ist morphologisch tatsächlich unauffällig, wird jedoch vom Zytologen vergeben, weil die untersuchte Frau aufgrund pathologischer Vorbefunde einem erhöhten Risiko unterliegt. Deshalb sind mit diesem Befund je nach Vorbefund Empfehlungen für weitere Maßnahmen verknüpft. In diesem Sinne ist die Gruppe II-a im Rahmen des Abklärungsprozedere (nach auffälliger Zytologie, Histologie oder Kolposkopie) einzuordnen und nicht als „unauffällig“.
Beschlussentwurf ***§ 28 (3) d und § 29 (2) a*** *Die Zytologie-Triage ist nicht erforderlich, wenn ein HPV-Test verwendet wird, der Informationen zu den Genotypen HPV 16 und HPV 18 liefert und mindestens einer dieser Genotypen positiv ist.* ***ersatzlos streichen***	Diese Vorgabe entstammt wie andere Abklärungsstrategien der von uns abgelehnten Konsultationsfassung der S3-Leitlinie und war dort sogar nur als „Empfehlung“ (nicht als „starke Empfehlung“) mit einem sehr niedrigen Evidenzgrad (Grade +) ausgewiesen. In den europäischen Leitlinien findet sich dazu keine Aussage. HPV 16 gehört zu den häufigsten Genotypen, die bei einem HPV-Test nachgewiesen werden und sind bei erstmaligem Nachweis überwiegend Ausdruck einer passageren Infektion. Daher sollte wie beim Nachweis anderer HPV Genotypen mit kanzerogenem Potential eine zytologische Untersuchung erfolgen. Auch bei einer HPV-Infektion mit den Genotypen 16 und 18 können sowohl kolposkopische Normalbefunde vorliegen (z.B. im Falle einer Virusinfektion ohne Läsion) als auch kolposkopische minor changes (Metaplasie oder CIN1) oder major changes (CIN2 oder CIN3), des Weiteren verhindern bestimmte klinische Konstellationen einen aussagekräftigen kolposkopischen Befund. Da die Kolposkopie z. B. den risikolosen Befund einer Metaplasie nicht von dem einer CIN 1 zu unterscheiden vermag und bei diesen minor changes auch Biopsien eine erhebliche Unsicherheit aufweisen [2], sollte bei einer kolposkopischen Untersuchung ein zytologischer Befund vorliegen.

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Beschlussentwurf ***§ 29*** *1. Abklärungsalgorithmus …* *a. Bei den Primärscreeningbefunden Pap III-p, III-x, III-e, III-g soll bereits innerhalb von 3 Monaten ein HPV-Test durchgeführt werden, bei II-p, II-g, II-e, IIID1 erst in 6 Monaten. Bei einem positiven HPVTest soll innerhalb von 3 Monaten eine Abklärungskolposkopie erfolgen. Bei einem negativen HPV-Test soll nach 12 Monaten eine klinische Untersuchung und Ko-Testung (Zytologie und HPV-Test) erfolgen. Ist mindestens einer dieser Tests positiv, soll innerhalb 3 Monaten eine Abklärungskolposkopie erfolgen. Bei Frauen unter 25 Jahren soll nur in begründeten Ausnahmefällen eine Abklärungskolposkopie durchgeführt werden. Stattdessen soll die klinische Untersuchung und Ko-Testung (Zytologie und HPV-Test) im Abstand von mindestens 12 Monaten wiederholt werden.* *b. Bei den Primärscreeningbefunden Pap III-D2 soll innerhalb eines Monats eine Abklärungskolposkopie erfolgen.*	Diese für den Gesetzestext vorgesehenen Vorgaben für die Abklärung auffälliger zytologischer Befunde sind offenbar ohne Sachkenntnis erstellt, fachlich unhaltbar und gefährden deshalb die Patientinnen, wie die folgenden Beispiele zeigen. - Hinter den Gruppen III-p und III-g kann sich sowohl eine CIN2/3 bzw. ein AIS verbergen als auch ein invasives Plattenepithel- oder Adenokarzinom: Dies ist Inhalt des Wortgutachtens, das der Zytologe der Befundgruppe beifügt und wovon sinnvollerweise das weitere Prozedere abhängt [3]. Es wäre für die Patientin fatal und für den Frauenarzt justiziabel, z.B. bei Gruppe III-p mit Karzinomverdacht womöglich erst in 3 Monaten einen HPV-Test durchzuführen anstatt einer sofortigen Kolposkopie. Bei Gruppe III-e ist es notwendig, ein Endometriumkarzinom auszuschließen bzw. zu diagnostizieren, bei Gruppe III-x ein Malignom des Uterus oder anderen Ursprungs – hier handelt es sich prinzipiell um nicht HPV-assoziierte Erkrankungen, sodass der HPV-Test keinen sinnvollen Beitrag für die Abklärung liefert und gegebenfalls sogar zu einer Diagnoseverschleppung führen kann. Nach den 2015 publizierten Empfehlungen der Arbeitsgemeinschaft Zervixpathologie und Kolposkopie [2] ist eine Kolposkopie nach einer erstmalig vergebenen Gruppe III nur verzichtbar, wenn nach dem Wortgutachten des Zytologen kein Karzinomverdacht besteht. - Ein HPV-Test bei einer Gruppe IIID1 ist wenig effektiv, da er in mehr als 80% positiv ist [4]. Die adäquate Abklärung einer Gruppe IIID1 ist eine zytologische Untersuchung in 6 Monaten und bei Persistenz dieses Befundes über mehr als 12 Monate eine Kolposkopie. Die Kolposkopie dient hier nicht der Bestätigung der Diagnose einer CIN1, sondern dem Ausschluss einer höhergradigen CIN bzw. eines Karzinoms. - Eine Kolposkopie sollte auch bei Frauen unter 25 Jahren z.B. bei mehr als 12 Monate persistierender Gruppe IIID1, mehr als 6 Monate persistierender Gruppe IIID2 oder bei Gruppe III-p oder III-g erfolgen, da sich in diesen Fällen nicht selten eine CIN3 findet. - Eine unmittelbare Kolposkopie bei einer erstmalig aufgetretenen Gruppe IIID2 entspricht einer Überdiagnostik. Nach den 2015 publizierten Empfehlungen der Arbeitsgemeinschaft Zervixpathologie und Kolposkopie [2] wird bei erstmaliger Gruppe IIID2

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	ohne zusätzliche Risiken eine Kolposkopie innerhalb von 3-6 Monaten favorisiert. Zusammenfassend sind – unabhängig von den im Beschlussentwurf zum Abklärungsprozedere gemachten wissenschaftlich unhaltbaren und laienhaften Vorgaben - detaillierte Vorschriften in einem Gesetzestext grundsätzlich abzulehnen. Komplexe medizinische Sachverhalte mit sich verändernden diagnostischen und therapeutischen Optionen müssen außerdem der individuellen Situation der Patientin angepasst werden, um Schaden von ihr abzuwenden.
§ 29 2. c. *„PAP IIIc“?*	Diese Gruppe ist nicht Bestandteil der Münchner Nomenklatur III.
Tragende Gründe ***2.2. Nutzenbewertung des HPV-Tests im Primärscreening*** *…, so dass inzwischen neben dem Pap-Test auch ein HPV-Tests zur Früherkennung des Zervixkarzinoms verwendet werden kann.*	Die Aussage, dass „auch ein HPV-Test zur Früherkennung des Zervixkarzinoms verwendet werden kann“, ist falsch: mit einem positiven HPV-Test weist man nur eine HPV-Infektion im Range eines Risikofaktors nach, nicht aber ein Zervixkarzinom oder seine Vorstufen. Bei einem positiven HPV-Test liegt nur zu 3-4% eine therapiepflichtige Krebsvorstufe und extrem selten ein Zervixkarzinom vor. Im Gegensatz zu diesem extrem schlechten positiven Prädiktionswert wird der vergleichsweise hohe negative prädiktive Wert gern hervorgehoben, der aber mit ca. 90% für einen Screening-Test mit 5jährigem Intervall ebenfalls inakzeptabel ist (s.u.).
Tragende Gründe ***2.3.1. Ziele und Grundlagen des Zervixkarzinom-Screenings*** *… Gleichzeitig ist eine Minimierung der Belastungen, die mit einem Früherkennungsprogramm verbunden sein können, zu gewährleisten (z.B. unnötige Sorge durch falsch-positive Befunde, Gefahr der Überdiagnose und Übertherapie, Gefahr der Scheinsicherheit bzw. Gefährdung durch falsch-negative Befunde…)*	Als ein Ziel des Zervixkarzinom-Screenings wird hier die Minimierung falsch positiver Screening-Ergebnisse angestrebt. In Widerspruch dazu steht die Befürwortung eines primären HPV-Screening, das mit einer ca. 95%igen Falsch-positiv-Rate vergesellschaftet ist. Als weiteres Ziel wird die Minimierung falsch negativer Screening-Befunde genannt. Auch diese Zielstellung wird durch die Propagierung eines primären alleinigen HPV-Screening mit fünfjährigen Intervallen konterkariert, weil falsch negative HPV-Tests kombiniert mit großem Intervall die Screening-Teilnehmerinnen gefährden (s.u.).
Tragende Gründe ***2.3.3. Screeningstrategien*** ***S. 8***	Ein HPV-Test in fünfjährigem Intervall erscheint als Maßnahme zur Vorsorge nicht geeignet. Der alleinige HPV-Test ist von einer beachtlichen Falsch-

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…Es wird ein HPV-basiertes Primärscreening mit mindestens 5 Jahresintervall und unmittelbarer Zytologie-Triage ab einem Alter von 35 Jahren in einem organisierten Programm empfohlen. Das HPV-basierte Screening sollte nicht vor dem Alter von 30 Jahren begonnen werden. Für das Alter 30 – 34 Jahre gibt es keine eindeutige Evidenz für oder gegen ein HPV-basierte Screening. *…Das HPV-basierte Screening wird Frauen bereits ab dem Alter von 30 Jahren angeboten, da die Inzidenz des invasiven Karzinoms bereits in diesem Alter einen deutlichen Anstieg zeigt und am in situ Karzinom erkranken Frauen im Mittel bereits mit 34 Jahren (RKI: Krebs in Deutschland 2015).*	Negativ Rate in der Detektion hochgradiger Läsionen und invasiver Karzinome behaftet [5-11]. Insbesondere auch frühinvasive Karzinome weisen eine stark reduzierte Viruslast in der Läsion auf und entgehen damit den HPV-Screening-Verfahren [12]. Folglich ist bei dem vorgeschlagenen 5-Jahres-Modell mit einer Häufung von Intervallkarzinomen zu rechnen [13]. HPV-unabhängige Malignome, die im zytologischen Screening gefunden werden können, werden im primären HPV-Screening als Screeningversager in Kauf genommen. Dies steht ethisch im Widerspruch zum etablierten Vorsorgesystem, in dem keine Patientengruppe definiert ist, die von vornherein von einem Screeningerfolg ausgeschlossen wird. Die Akzeptanz in der weiblichen Bevölkerung ist voraussichtlich auch in Deutschland gering mit folglich starker Zunahme eines sogenannten grauen Screenings [14]. In Finnland, das das angesprochene 5-Jahres-Modell mit Register und Einladung der Screening-Teilnehmerinnen seit Jahren praktiziert, wurden 2000-2008 lediglich etwa 11% der invasiven Zervixkarzinome innerhalb des organisierten Screenings entdeckt [15-27]. Ein „graues“ Screening in Deutschland im Rahmen der Individuellen Gesundheitsleistungen („IGeL“) ginge zu Lasten der nicht teilnehmenden und häufig sozial unterprivilegierten Frauen mit der höchsten Inzidenz an Zervixkarzinomen. Ein primäres HPV-Screening führt zu einer unverhältnismäßig hohen Zahl von Frauen mit einem positiven Testergebnis ohne entsprechende Erkrankung, da die nachgewiesene Virus-DNA nur die Infektion, nicht aber eine Läsion dokumentiert. Die Screening-Teilnehmerinnen würden somit der Gefahr einer Überdiagnostik und Übertherapie ausgesetzt, unnötige Ängste der positiv getesteten Frauen bedeuten eine Reduktion ihrer Lebensqualität [18-20]. Die Empfehlung aus den 2015 von der Europäischen Kommission veröffentlichten Supplements zu den Europäischen Leitlinien, das primäre HPV-Screening mit 35 Jahren zu beginnen [21], wird mit der Begründung ignoriert, dass die Inzidenz des invasiven Karzinoms über 30 bereits deutlich ansteigt und an einer Präkanzerose im Range eines Carcinoma in situ (CIN3) Frauen im Mittel bereits mit 34 Jahren erkranken. Aus den zugänglichen Daten des Robert-Koch-Instituts geht allerdings nicht hervor, ob nicht die Zunahme der Karzinome ab 30 vor allem durch eine Zunahme frühinvasiver Karzinome bedingt ist, wie das in Mecklenburg-Vorpommern der Fall ist [22]. Unabhängig davon, dass das primäre HPV-Screening aus den oben angeführten Gründen ohnehin abzulehnen ist, bedeutet ein Beginn mit bereits 30 Jahren eine Gefährdung der Teilnehmerinnen vor allem wegen der extrem hohen Anzahl falsch positiver Befunde und damit verbundener Überdiagnostik

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	und Übertherapie gerade dieser Frauen im bevorzugten Gebäralter. Es ist unverständlich, warum das 30. Lebensjahr bei der vorliegenden Datenlage und sogar in Widerspruch zu den ansonsten stets herangezogenen Europäischen Leitlinien als Eintrittsalter für das primäre HPV-Screening empfohlen wird. Aus der Erkenntnis, dass Frauen < 30 Jahren häufiger HPV-positiv sind als Frauen > 30 Jahren, wird die Festlegung für ein zytologisches Screening für Frauen < 30 Jahren und ein HPV-Screening > 30 Jahren getroffen. Der Abfall der HPV-Prävalenz erfolgt in Abhängigkeit vom Lebensalter in kleinen Schritten [23, 24]. Die HPV-Prävalenz von 31-jährigen Frauen unterscheidet sich nur marginal von denen 29-jähriger. Bei 35-jährigen Frauen liegt sie lediglich wenige Prozentpunkte unter der von 30-jährigen. Erst nach dem 40. Lebensjahr kommt es zu einem deutlicheren Abfall der HPV-Prävalenz. Die Grenzwertfestlegung bei 30 Jahren für Screeningverfahren und -intervall erfolgt somit willkürlich. Eine sinnvolle Alternative zum jährlichen zytologischen Screening auch nach dem 30. Lebensjahr wäre hingegen das sogenannte Co-Testing ab dem 35. Lebensjahr (zytologische Untersuchung in Kombination mit einem adäquaten HPV-Test) in einem dreijährigen Intervall: die Kompensation der Schwäche der einen Methode durch die Stärke des anderen Verfahrens gewährleistet die Sicherheit für die teilnehmenden Frauen (die geringere Sensitivität der Zytologie und ihre hohe positive Prädiktion im Zusammenspiel mit der hohen negativen Prädiktion und schlechten Spezifität des HPV-Testes). Der Erfolg dieser Vorgehensweise ist in der aktuellen Literatur belegt [8-10, 20, 25, 26]. Insbesondere bei einer Intervallverlängerung von mehr als drei Jahren besteht die Gefahr einer Reduktion der Teilnahmerate am organisierten Screening [27]. Dies muss unbedingt vermieden werden, da unter den Zervixkarzinom-Patientinnen die Nicht-Teilnehmerinnen die meisten und die fortgeschrittenen Karzinome aufweisen [22].
2.3.4. Abklärungsdiagnostik S. 10 *Das zytologiebasierte Screening ist unauffällig bei Pap I und Pap IIa gemäß der Münchner Nomenklatur III. … In diesen Fällen wird das Primärscreening in den vorgegeben Zeitabständen durchgeführt.*	***Begründung s.o. Beschlussentwurf § 28 (2) e*** einfach nur „II-a“ streichen
2.3.4. Abklärungsdiagnostik	Gemeinsam mit den anderen an der Versorgung der Frauen im Rahmen des Zervixkarzinom-Früherkennungsprogramms

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Für das Management auffälliger Screeningbefunde werden für die verschiedenen Screeningstrategien Algorithmen für die Abklärungsdiagnostik vorgegeben. Die Abklärungsdiagnostik orientiert sich an den Empfehlungen der aktuellen deutschen S3 Leitlinien zur Prävention des Zervixkarzinoms (Konsultationsfassung vom 01.03.2016). ***S.10/11** (Schema)* ***S. 11*** *Bereits bei Minor Changes ist eine Abklärung durch eine Biopsie erforderlich.*	beteiligten Ärzte (Berufsverband der Frauenärzte, Arbeitsgemeinschaft Zervixpathologie und Kolposkopie der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe, Arbeitsgemeinschaft Zytologisch Tätiger Ärzte in Deutschland, Bundesverband deutscher Pathologen und Berufsverband zytologisch tätiger Akademiker in Deutschland) hat die Deutsche Gesellschaft für Zytologie die o.g. Konsultationsfassung der S3-Leitlinie am 10.04.2016 abgelehnt. Dafür waren vor allem fachliche Defizite des Leitlinien-Entwurfs maßgeblich, die sich auch in den vorgeschlagenen Abklärungsalgorithmen niederschlagen. Die Begründung dafür ist in unserem Ablehnungsschreiben enthalten (das der G-BA am 10.04.2016 erhalten hat) und soll hier nicht im Einzelnen wiedergegeben werden. Bereits weiter oben haben wir aufgeführt, aus welchen Gründen die für den Richtlinientext vorgesehenen Vorgaben für die Abklärung strikt abzulehnen sind. Als weiteres Beispiel für inakzeptable pauschale Vorgaben widerspricht diese Forderung den gültigen Empfehlungen zur Kolposkopie. Es gibt keine Indikation für eine Biopsie bei „minor changes“, da derartige Befunde in der Regel physiologische Veränderungen sind oder maximal einer CIN1 entsprechen. Ausnahmen sind diskrepante Befunde (z.B. zytologisch Gruppe IV, V, Gruppe III mit Wortgutachten „Karzinom denkbar“ in Kombination mit kolposkopischen „minor changes“). Hier sind Target-Biopsien, ggf. Random-Biopsien, ggf. eine Zervix-Kürettage indiziert [2]**.** Grundsätzlich bei „minor changes“ durchgeführte Biopsien bedeuten Überdiagnostik: nicht indizierte invasive Eingriffe, die die Integrität eines Organs verletzen. Sie würden außerdem zu einer nicht vertretbaren Zahl histologischer Abklärungen führen.
6. Fazit und Ausblick *… Durch die Anwendung des HPV-Tests im Primärscreening kann die Inzidenz von invasiven Zervixkarzinomen weiter gesenkt werden.*	Diese Behauptung ist nicht belegt. Sie entstammt nicht dem IQWiG-Bericht. Weder in den dabei ausgewerteten Studien noch in irgendeiner anderen Publikation findet sich dafür Evidenz, insbesondere nicht für industrialisierte Länder.

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Gemeinsamer Bundesausschuss

Stellungnahme zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

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26. Mai 2016	
Stellungnahme / Änderungsvorschlag	**Begründung**
(1) Verwendung einer Nukleinsäure-Konservierungslösung als Transportmedium	In § 28 (3) b, sowie § 30 (3) b BE GVK-SV (analog § 28 (3) PatV) wird vorgeschlagen, die Proben für einen HPV-Direktnachweis mit einem Transportmedium zu versetzen das für die Dünnschicht-Zytologie optimiert wurde. Aus unserer Sicht würde dadurch die Leistungsfähigkeit dieser Tests negativ beeinflusst. Außerdem ist die Aufreinigung der viralen DNA aus der zytologischen Abstrichprobe aus Dünnschicht-zytologischen Transportmedien unnötig aufwändig und fehleranfällig. Weiterhin weisen kommerziell konfektionierte Dünnschicht-Zytologische Transportmedien in der Regel ein zu großes Volumen auf, was zu einer unnötigen Verdünnung und damit zu einer schlechteren Diagnostik führt. Formalin-haltige zytologische Transportmedien zerstören die DNA, was zusätzlich die Sensitivität DNA-basierter HPV-Nachweise verringert. Dünnschichtzytologie ist in Deutschland aus gutem Grund nicht Bestandteil des gesetzlichen Früherkennungsprogramms (Vergleiche Stellungnahme 4). Wir schlagen daher vor, die Verwendung einer Nukleinsäure-Konservierungslösung für den Probentransport vorzuschreiben (vergleiche Stellungnahme 5).
(2) Einsatz von HPV-Typisierungs-Tests	In § 29 BE GVK-SV wird für die Abklärungsdiagnostik der Einsatz nicht weiter spezifizierter HPV-Direktnachweise gefordert. Bei der Abklärung auffälliger Befunde des Primärscreening sollten ausschließlich Reagenzien zum Einsatz kommen, die HPV nicht nur nachweisen, sondern auch typisieren. Mit den verschiedenen HPV-Subtypen sind unterschiedliche Risiken verbunden, an Gebärmutterhalskrebs zu erkranken, daher ist es wichtig, die verschiedenen Subtypen zu unterscheiden. Weiterhin erhöhen multiple HPV-Infektionen das Risiko einer Patientin, an Gebärmutterhalskrebs zu erkranken, Mehrfach-Infektionen können ausschließlich durch typisierende HPV-Direktnachweiseerkannt werden. Außerdem ermöglicht es die HPV-Typisierung, persistierende von Neuinfektionen zu unterscheiden. Die in den TrGr der drei Entwürfe dargestellten Strategien zum Management von Screening-Befunden untermauern die Bedeutung der Typisierung.
(3) Abklärungsdiagnostik	In § 29 BE GVK-SV wird für die Abklärungsdiagnostik der

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mittels HPV-Direktnachweisen die nicht auf dem Nachweis der Gene L1, E1 oder E2 Gens beruhen	Einsatz nicht weiter spezifizierter HPV-Direktnachweise gefordert. Eine Voraussetzung für die vollständige maligne Transformation einer Wirtszelle ist die Integration der HPV-DNA ins Wirtsgenom. Während dieses Vorgangs werden Genabschnitte der Virus-DNA zerstört, häufig ist das E2-, E1- oder L1-Gen betroffen. HPV-Direktnachweise, die auf dem Nachweis dieser Gene beruhen, können zu falsch-negativen Ergebnissen führen. Daher sollten ausschließlich HPV-Direktnachweise verwendet werden, die nicht auf dem Nachweis der Gene E1, E2 oder L1, sondern z.B. auf dem Nachweis der Gene E6 oder E7 beruhen, deren Transkriptionsprodukte das eigentliche onkogene Potential aufweisen.
(4) Zusätzlich zu den 2005 von der IARC als krebserregend eingestuften HPV sollte auf weitere high-risk-HPV (hrHPV) und intermediate-risk-HPV (irHPV)-Subtypen getestet werden	In § 29 BE GVK-SV (analog § 30 PatV) wird gefordert, dass die zu verwendenden HPV-Direktnachweise die Subtypen 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 und 68 identifizieren können. Damit wird man aber dem aktuellen Stand der Technik und Wissenschaft bei weitem nicht gerecht, nach dem auch weitere hrHPV und irHPV-Subtypen ein hohes onkogenes Potential besitzen. Aus diesem Grunde sollten nur HPV-Direktnachweise zur Anwendung kommen, die neben den oben beschriebenen Subtypen auch die Subtypen 26, 53, 66, 73 und 82 erfassen, deren pathogenetisches Potential in den letzten 10 Jahren bewiesen wurde.
(5) Kein Einsatz von Dünnschichtzytologie	§ 28 (3) d BE GVK-SV: Es gibt keine Hinweise darauf, dass die Dünnschichtzytologie einem fachgerecht durchgeführten PAP-Test überlegen ist. Mit der Dünnschichtzytologie würden hohe Zusatzkosten für das Gesundheitssystem generiert, ohne einen diagnostischen Mehrwert zu erzielen. Die Berücksichtigung der Dünnschichtzytologie in der Gebärmutterhalskrebsvorsorge ist daher abzulehnen. Die organisatorischen Vorteile der gleichzeitigen Abnahme einer Probe für HPV-Direktnachweise und etwaige zytologische Untersuchungen lassen sich ebenso durch die in 2.3.3 TrGr des GVK-SV genannten alternativen Möglichkeiten wirtschaftlicher und, aus Sicht der HPV-Testung, sachgerechter realisieren.
(6) Sensitivität und Spezifität von HPV-Direktnachweisen sollten in Bezug auf unabhängige HPV-Nachweise beurteilt werden	In § 30 (3) b BE GVK-SV werden Qualitätskriterien von HPV-Direktnachweisen definiert, die sich auf „etablierte und validierte“ HPV-Direktnachweise beziehen. Dieses Vorgehen ist aus unserer Sich wissenschaftlich problematisch. Es ist nicht ersichtlich, auf welche HPV-Nachweise mit dieser Formulierung Bezug genommen wird. Bei der Beschreibung der Sensitivität und Spezifität sollte auf nicht kommerzielle Standardsysteme, wie z.B. den GP5+/6+-Assay, Bezug genommen werden. Aus unserer Sicht ist es nicht sinnvoll, HPV-Direktnachweise auszuschließen, die in zytologisch-negativen Proben mehr HPV

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	Infektionen aufzeigen als derzeit etablierte HPV-Testsysteme. Ein ausschließlicher Verweis auf ältere Methoden verhindert neue Erkenntnisse durch verbesserte Testsysteme und widerspricht zusätzlich der Forderung an die Testsysteme, möglichst sensitiv zu sein.
(7) Strukturqualität von HPV-Direktnachweisen sollte an unabhängigen Tests gemessen werden	In § 31 (4) BE KBV wird gefordert, für ein Screening nur solche HPV-Direktnachweise zuzulassen, die bestimmte Leistungsdaten im Vergleich zu dem kommerziellen System HC2 von Qiagen aufweisen. Aus unserer Sicht sollte man sich bei der Qualitätsbewertung auf unabhängige Verfahren beziehen, z.B. den GP5+/6+-Assay (vergleiche auch Stellungnahme 2, 3, 4, 6)
(8) Umfassende Information und Aufklärung der Patienten, aber auch der Gynäkologen	2.3.2.3 TrGr PatV (analog § 27 BE KBV / GVK-SV) Aufgrund unserer bisherigen Erfahrungen bedürfen viele Gynäkologen in Bezug auf HPV-Infektionen und HPV-Direktnachweise noch der Unterrichtung, nicht nur die Patienten. Daher ist es aus unserer Sicht wichtig, nicht nur die Patientinnen umfassend und objektiv über die zur Auswahl stehenden Methoden zu informieren, sondern auch die Gynäkologen.
(9) Einladung zum Zervixkarzinom-Screening sollte umfassend und verständlich sein	Wir unterstützen ausdrücklich die in den TrGr der PatV unter 2.3.2.1 geforderte umfassende Information der Patienten, um eine individuelle Entscheidung unter Abwägung der Vor- und Nachteile, auch über das 61. Lebensjahr hinaus, zu ermöglichen.
(10) Ausweitung des Screenings über das 61. Lebensjahr hinaus	Da es im höheren Alter einen erneuten deutlichen Anstieg des Zervixkarzinoms gibt, sollte das individuelle Zervixkarzinom-Screening nicht vor dem 70. Lebensjahr beendet werden. Das Screening kann im Alter von 70 Jahren beendet werden, wenn mindestens ein aktueller HPV-negativer Befund vorliegt der nicht auf E1, E2 oder L1 beruht (vergleiche Stellungnahme 3).
(11) Selbstabnahme um Non-Respondern einen weiteren Zugang zum Zervixkarzinomscreening zu ermöglichen	Neben den konsensfähigen Einladungsintervallen zum Zervixkarzinom-Screening sollte Non-Respondern die Möglichkeit zur Selbstabnahme einer Probe für HPV-Direktnachweise geboten werden, da die Hauptrisikogruppe für ein invasives Zervixkarzinom in den Ländern mit etabliertem Früherkennungssystem diejenigen Frauen sind, die selten oder gar nicht an den Vorsorgeuntersuchungen teilnehmen.

Gemeinsamer Bundesausschuss

Stellungnahme zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

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30.05.2016	
Stellungnahme / Änderungsvorschlag	**Begründung**
<u>Beschlussentwurf der KBV:</u> Die Nennung eines bestimmten validieren HPV-Tests als Referenztest im Beschlusstext („Digene Hybrid Capture 2“, Qiagen) halten wir für nicht adäquat. Die Bezeichnung „etablierter und validierter HPV-Test“ ist hier der verwendeten Formulierung vorzuziehen. Wenn mögliche Referenztests genannt werden sollen, dann sollte aktuell sowohl der HC2 als auch der GP5+/6+ genannt werden.	Die Nennung eines bestimmten HPV-Tests macht keinen Sinn denn diese Formulierung ist nicht zukunftssicher. Die Kriterien wann ein Test als validiert gilt sind in den „Tragenden Gründen“ beschrieben. Der „Digene Hybrid Capture 2“ (Qiagen) ist unserer Meinung nach nicht der einzige validierte Test (siehe unten) und weitere etablierte und validierte Tests könnten im Laufe der Zeit hinzukommen. Die Formulierung hinsichtlich der Kriterien, wann ein Test als etabliert und validiert gilt in den „Tragenden Gründen“ (TG) ist exakt dieselbe wie in den TGs der anderen beiden Entwürfe: *„Ein etablierter und validierter HPV-Test hat in mindestens einer großen randomisiert kontrollierten Längsschnittstudie im Vergleich zur Zytologie bessere Ergebnisse gezeigt und in der zweiten Screeningrunde konnte in dem HPV-Arm die Inzidenz von CIN 3+ gesenkt werden.“* Und doch kommt die KBV hier zum Schluss, dass dies nur für HC2 gilt, während GKV-SV und Patientenvertretung den GP5+/6+ ebenfalls als validiert anerkennt. Hier sollte sowohl der HC2 als auch der GP5+/6+ genannt werden, denn: • die „Meijer-Guideline" selbst nennt den GP5+/6+ validiert • die Meta-Analyse von Arbyn et al. (*Which high-risk HPV assays fulfil criteria for use in primary cervical cancer screening?* Clin Microbiol Infect. 2015 Sep;21(9):817-26.) nutzt beide Assays als Referenztests hinsichtlich der Testbewertung anhand der Meijer-Kriterien • auch das VALGENT Protokoll nutzt den GP5+/6+ als Referenzmethode (Arbyn et al., *VALGENT: A protocol for clinical validation of human papillomavirus assays.* J Clin Virol. 2015 Oct 8. pii: S1386-6532(15)00683-6)

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Stellungnahme zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

Hologic Deutschland GmbH	
30.05.2016	
Stellungnahme / Änderungsvorschlag	**Begründung**
<u>Dünnschichtzytologie</u> Klinisch-validierte Dünnschichtzytologie-Verfahren können sowohl für Frauen ab 20 Jahren als auch für Frauen ab 30 Jahren im Zytologie-basierten Zervixkarzinom-Screening alternativ zur konventionellen Zytologie eingesetzt werden. Im HPV-basierten Primärscreening für Frauen ab 30 Jahren ist ein Proben-Transportmedium zu verwenden, mit dem gemäß den Herstellerangaben zusätzlich eine Dünnschichtzytologie durchgeführt werden kann.	In der im Februar 2016 veröffentlichten **Konsultationsfassung S3-Leitlinie Prävention des Zervixkarzinoms** äußert sich die Expertenkommission wie folgt: **6.4 Evidenzbasiertes Statement** Es gibt keinen Beleg dafür, dass sich die Dünnschicht-Zytologie (FDA-zugelassene Tests) und der zytologische Standard-Abstrich hinsichtlich der Testgenauigkeit für CIN 2+ unterscheiden. **6.5 Konsensbasierte Empfehlung** Die Dünnschicht-Zytologie (FDA zugelassene Tests) kann im Screening eingesetzt werden. Aus dem Probenmaterial für die Dünnschicht-Zytologie können Zusatztests ohne Wiedereinbestellung der Frau durchgeführt werden. **6.2.3. Zusammenfassung** […] „Überlegungen, die Dünnschichtzytologie im Primärscreening einzusetzen, beruhen auf zusätzlichen Vorteilen wie eine verbesserte Probenqualität, kürzere Mikroskopiedauer und die Möglichkeit, Zusatztests durchzuführen.“ […] --- Die Europäischen Leitlinien 2015 empfehlen für das HPV-basierte Screening, dass der Abstrich für die Zytologie-Triage bereits bei der Screeninguntersuchung abgenommen wird. So ist bei einem positiven HPV-Test keine erneute Einbestellung der Patientin erforderlich. • **European Guidelines for Quality Assurance in Cervical Cancer Screening,** 2nd Edition – Supplements, European Union 2015 Für das HPV-basierte Screening soll daher ein Probentransportmedium verwendet werden, mit dem bei einem positiven HPV-Test gemäß den Herstellerangaben eine Dünnschichtzytologie angefertigt werden kann. Als Triage-Verfahren bietet die Dünnschichtzytologie organisatorische Vorteile, mit denen Kosten für unnötige Abstriche oder Arztbesuche eingespart werden können. Ebenso bietet der Einsatz der Dünnschichtzytologie im Zytologie-basierten Screening dieselben Vorteile bei der HPV-Triage. --- Mehrere Meta-Analysen haben der Dünnschichtzytologie eine im Vergleich zur konventionellen Zytologie mindestens

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	gleichwertige Sensitivität und Spezifität für die Detektion niedrig- und höhergradiger Läsionen bescheinigt: • Bernstein et al., **Liquid-based cervical cytologic smear study and conventional Papanicolaou smears: A metaanalysis of prospective studies comparing cytologic diagnosis and sample adequacy.** Am J Obstet Gynecol 2001 • Abulafia et al., **Performance of ThinPrep liquid-based cervical cytology in comparison with conventionally prepared Papanicolaou smears: A quantitative survey.** Gynecol Oncol 2003 • Davey et al., **Effect of study design and quality on unsatisfactory rates, cytology classifications, and accuracy in liquid-based versus conventional cervical cytology: A systematic review.** Lancet 2006 • Arbyn et al., **Liquid Compared With Conventional Cervical Cytology. A Systematic Review and Meta-analysis.** Obstet Gynecol 2008 Für das Dünnschichtzytologie-Verfahren ThinPrep Pap Test im Speziellen liegen hierzu über 200 peer-reviewed Publikationen vor, u.a. auch Daten aus Deutschland. In der randomisierten Rhein-Saar Studie war die Sensitivität der Dünnschichtzytologie im Vergleich zur konventionellen Zytologie unter Routinebedingungen statistisch signifikant höher (relative Sensitivität 2,74 (95% Konfidenzintervall 1,66-4,53): • Klug et al., **A randomized trial comparing conventional cytology to liquid-based cytology and computer assistance.** Int J Cancer, 2013 --- Der generelle Einsatz dünnschichtzytologischer Verfahren bietet dem Gynäkologen den Vorteil mit einer einzigen Methode (Entnahmeinstrument + Probentransportmedium) für alle Frauen im Zervixkarzinom-Screening eine einheitlich standardisierte Abstrichtechnik mit gleicher Präparategüte zu gewährleisten. Damit können alle vorgesehenen Screening-Algorithmen gleichwertig abgedeckt und statistisch ausgewertet werden: • Zytologie-basiertes Screening für Frauen ab 20 Jahren (inkl. HPV-Triage) • HPV-basiertes Primärscreening für Frauen ab 30 Jahren (inkl. Zytologie-Triage) • Co-Testung für Frauen ab 30 Jahren (Zytologie + HPV) Durch eine breite Anwendung der Dünnschichtzytologie sowohl im zytologischen Primärscreening als auch im HPV-basierten Screening (Triage) wird die Befundung auffälliger Präparate und die Diagnosequalität vereinheitlicht. Das ThinPrep-Verfahren erlaubt zusätzlich eine vollautomatisierte und standardisierte Aufarbeitung dünnschichtzytologischer Abstriche (Qualitätssicherung).

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	Der ThinPrep Pap Test ist ein CE-IVD markiertes dünnschichtzytologisches Verfahren, das von der FDA u.a. mit den nachfolgenden Prädikaten zugelassen wurde: • Ersatz für den konventionellen Abstrich • Probenqualität signifikant verbessert im Vergleich zum konventionellen Präparat • Signifikant effektiver in der Detektion von niedrig- und höhergradigen Läsionen im Vergleich zum konventionellen Pap-Abstrich
Es dürfen nur Dünnschichtzytologie-Verfahren verwendet werden, deren Probentransportmedium • gemäß den Herstellerangaben für den verwendeten HPV-Test und • nach der Aliquot-Entnahme für den HPV-Test gemäß den Herstellerangaben noch zur zytologischen Untersuchung geeignet ist.	Es muss gewährleistet sein, dass das im Screening verwendete Probentransportmedium während der gesamten Prozesskette (HPV-Testung und Zytologie) unabhängig vom Screening-Algorithmus ausschließlich den Herstellerangaben entsprechend eingesetzt werden darf. Das bedeutet unter anderem, dass das im Screening verwendete Probentransportmedium die notwendige Aliquot-Entnahme zur HPV-Testung gewährleisten muss, ohne Qualitätsverlust für eine nachfolgende zytologische Untersuchung (Triage) aus dem verbleibenden Flüssigkeitsvolumen. --- Die ThinPrep “PreservCyt Lösung” ist ein CE-IVD markiertes Probentransportmedium, dass auch von der FDA zur molekularen Testung mit nachfolgend aufgeführten HPV Tests zugelassen wurde: • Hologic APTIMA HPV Assay • Hologic APTIMA HPV 16, 18/45 Genotype Assay • Hologic Cervista HPV HR • Hologic Cervista HPV 16/18 • Qiagen Hybrid Capture 2 • Roche cobas HPV Test In allen wichtigen klinischen Studien zur Validierung und Zulassung von verschiedenen HPV Testverfahren wurde die ThinPrep “PreservCyt Lösung” als universelles Probentransportmedium und der ThinPrep Pap Test als zytologisches Vergleichsverfahren verwendet: • **ALTS (hc2)** – Solomon et al., J Natl Cancer Inst, 2000 • **ARTISTIC (hc2)** – Kitchener et al., Health Technol Assess, 2009 • **NTCC (hc2)** – Ronco et al., J Natl Cancer Inst., 2006 • **FOCAL (hc2)** – Ogilvie et al., BMC Cancer, 2010 • **Cervista HPV** – Einstein et al., Gynecol Oncol, 2010 • **ATHENA (cobas HPV)** – Stoler et al., Am J Clin Pathol, 2011 • **CLEAR (Aptima HPV)** – Reid et al., Am J Clin Pathol, 2015
<u>Co-Testung</u>	Verschiedene Publikationen zeigen, dass der alleinige Einsatz der HPV-Testung im Primärscreening auch Nachteile mit sich

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Im vorgesehenen Optionsmodell sollen Frauen ab dem Alter von 30 Jahren zwischen folgenden Leistungen wählen:

- Jährliches Zytologie-basiertes Zervixkarzinomscreening
- HPV-basiertes Screening im Abstand von 3 Kalenderjahren.

  Der Einstieg in das primäre HPV-Screening erfolgt mit 2 Co-Testung-Runden (zytologische Untersuchung und HPV-Test) im Abstand von 3 Kalenderjahren.
- Co-Test-basiertes Screening (zytologische Untersuchung und HPV-Test) im Abstand von 3 Kalenderjahren

Es ist jeweils ein Probentransportmedium zu verwenden mit dem gemäß den Herstellerangaben sowohl eine Dünnschichtzytologie als auch ein HPV-Test durchgeführt werden kann.

Bei unbekannten oder nicht vorhandenen Vorbefunden erfolgt ab dem Alter von 30 Jahren der Einstieg in das Screening mittels einer Co-Testung.

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bringt. Dabei ist im Besonderen eine hohe falsch-negativ Rate beim Nachweis hochgradiger Läsionen und des invasiven Zervixkarzinoms problematisch. Diesem Umstand kann durch den Einsatz der Co-Testung Rechnung getragen werden.

- Blatt et al., **Comparison of cervical cancer Screening results among 256,684 women in multiple clinical practices.** Cancer Cytopathol 2015
- Katki et al., **Cervical cancer risk for 330,000 women undergoing concurrent HPV testing and cervical cytology in routine clinical practice at a large managed care organization.** Lancet Oncol 2011
- Tao et al., **History of high-risk HPV and Pap test results in a large cohort of patients with invasive cervical carcinoma: experience from the largest women's hospital in China.** Cancer Cytopathol 2015
- Saslow et al., **American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer.** Am J Clin Pathol. 2012
- Austin, Zhao, **Is 58% sensitivity for detection of cervical intraepithelial neoplasia 3 and invasive cancer optimal for cervical screening?** CytoJournal 2014

In der aktuellen Publikation **Primary HPV testing: A proposal for co-testing in initial rounds of screening to optimise sensitivity of cervical cancer screening** (Cytopathology 2016) empfiehlt A. Herbert vom St Thomas' Hospital in London, UK:

- "No screening test is perfect but HPV primary screening has a false-negative rate that might compromise a successful screening programme if introduced without the back up of cytology, particularly in the early rounds of screening when the prevalence of the disease is exceptionally high. Cytology and HPV co-testing for the first two screening tests would be suitable for a low prevalence vaccinated population as well as for women in that population who had not been vaccinated. It would provide an optimal sensitivity of screening, allow information to be gathered about the sensitivity and specificity of new HPV tests and would not compromise the accuracy of cytological screening although reducing the volume of negative tests by about 60%. This proposal should be debated openly before an irrevocable decision is made to introduce primary HPV screening on its own."

In der im Februar 2016 veröffentlichten **Konsultationsfassung S3-Leitlinie Prävention des Zervixkarzinoms** äußert sich die Expertenkommission wie folgt:

7.4 Statement

Organisierte Screening-Programme mit Intervallen von 3 oder 5 Jahren, die auf HPV-Testung allein oder HPV-Kotestung mit Zytologie basiert sind, führen bei Frauen, die älter als 30 Jahre sind, nach drei oder fünf Jahren in der zweiten Screeningrunde zu einer signifikant deutlicheren Senkung der Neuerkrankungen

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	an CIN 3+ (82/100.000) als Programme, die auf einem alleinigen organisierten zytologischen Screening mit Intervallen von 3 oder 5 Jahren basieren (159/100.000; RR 0,59). **Stellungnahme der Deutschen Gesellschaft für Zytologie (DGZ) zum Beschluss des Gemeinsamen Bundesausschusses über eine Beauftragung des Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen: Erstellung von Einladungsschreiben und Versicherteninformationen zum Zervixkarzinomscreening vom 19. März 2015** […] 3. Eine sinnvolle Alternative zum jährlichen zytologischen Screening auch nach dem 30. Lebensjahr wäre hingegen das sogenannte Co-Testing ab dem 35. Lebensjahr (zytologische Untersuchung in Kombination mit einem adäquaten HPV-Test) in einem dreijährigen Intervall: die Kompensation der Schwäche der einen Methode durch die Stärke des anderen Verfahrens gewährleistet die Sicherheit für die teilnehmenden Frauen (die geringere Sensitivität der Zytologie und ihre hohe positive Prädiktion im Zusammenspiel mit der hohen negativen Prädiktion und schlechten Spezifität des HPV-Testes) […]
HPV-Testung Für das Primärscreening und die Abklärungsdiagnostik dürfen nur Hochrisiko-HPV- Tests verwendet werden, die folgende Kriterien erfüllen: • Detektion der Hochrisiko-HPV-Typen 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 und 68, • Mindestens 90% der Sensitivität eines etablierten und validierten HPV-Tests für CIN2+ und mindestens 98% Spezifität eines etablierten und validierten HPV-Tests für CIN2+. Der Anteil positiver Testergebnisse in zytologisch negativen Frauen einer Screeningpopulation soll nicht größer als der von validierten und etablierten HPV-Tests sein. Die Inter- und Intra-Labor-Reproduzierbarkeit muss mindestens 87% betragen. • Es sollen nur Testverfahren verwendet werden, die eine FDA-Zulassung besitzen	Analog der Konsultationsfassung *S3-Leitlinie Prävention des Zervixkarzinoms* sollen sowohl DNA als auch RNA HPV-Tests im Screening und in der Triage eingesetzt werden, welche die Meijer-Kriterien erfüllen und die 13 HR-HPV-Typen detektieren. Darüber hinaus wird als zusätzliches klinisches Validierungskriterium eine FDA-Zulassung gefordert, da die CE-IVD-Richtlinie keine unabhängige klinische Zulassung für HPV-Tests verlangt und es bei dem HPV-Nachweis, wie bei keinem anderen molekulardiagnostischen Screeningverfahren, mehr auf die klinische Sensitivität und Spezifität ankommt, als auf den die analytische Leistungsfähigkeit für den HPV-Nachweis selbst. Derartige klinische Leistungsaspekte werden für die CE-IVD Zulassung nicht berücksichtigt, spielen aber in diesem Kontext eine übergeordnete Rolle In der im Februar 2016 veröffentlichten **Konsultationsfassung S3-Leitlinie Prävention des Zervixkarzinoms** äußert sich die Expertenkommission wie folgt: **7.1 Konsensbasierte Empfehlung** Es sollen nur HPV Testverfahren angewendet werden, die alle folgenden Kriterien erfüllen (nach Meijer et al. und Stoler et al.): 1. Detektion der Hochrisiko-HPV-Typen 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 und 68 2. Mindestens 90% der Sensitivität eines etablierten und validierten HPV-Tests* für CIN2+ 3. Mindestens 98% Spezifität eines etablierten und validierten HPV-Tests* für CIN2+. Der Anteil positiver Testergebnisse in zytologisch negativen Frauen einer Screeningpopulation soll nicht größer sein als der von validierten und etablierten HPV-Tests*.

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	4. Es sollten Testverfahren verwendet werden, die eine FDA-Zulassung besitzen. **Tabelle 7.1 Liste von HPV-Testverfahren, die die oben genannten Kriterien erfüllen (Stand Dezember 2015):** • Digene Hybrid Capture 2 High-Risk HPV DNA Test (QIAGEN Gaithersburg, Inc.) • cobas HPV Test (Roche Diagnostics) • Cervista™ HPV HR and Genfind™ DNA Extraction Kit (Hologic) • APTIMA HPV Assay (Hologic)

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Stellungnahme zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

KARL STORZ GmbH & Co. KG	
13.05.2016	
Stellungnahme / Änderungsvorschlag	**Begründung**
§29 Abklärungsdiagnostik **Punkt 3.a** der Beschlussvorschläge des GKV-SV sowie der Patientenvertretung: Der Begriff „**Kolposkop“ sollte ersetzt werden durch „Kolposkop oder Bildschirmgestützten optischen System mit Vergrößerung**“	Bei einem Kolposkop handelt es sich um ein „Operationsmikroskop“, das durch einen binokularen Einblick und einer bestimmten Vergrößerung im Okular definiert ist. Im Beschlussvorschlag wird nur das Kolposkop genannt, um eine kolposkopische Untersuchung durchzuführen. **Dadurch werden neuere Verfahren, so z.B. die Bildschirmgestützten, optischen Systeme und somit auch bestimmte Produkte bzw. deren Hersteller vom Einsatz im Screening ausgeschlossen**. Zudem ermöglichen diese neuen Verfahren auch den Einsatz digitaler Filter mit denen Kontrast und Farbe verändert werden können, was zu einer verbesserten Diagnostik führen kann. Der Formulierungsvorschlag „Kolposkop oder Bildschirmgestützte optische Systeme mit Vergrößerung“ umfasst sowohl die üblichen Kolposkope als auch das neuere und komfortablere Verfahren der bildschirmgestützten Vergrößerung z.B. durch VITOM. Die Vergleichbarkeit bildschirmgestützter Vergrößerung mittels VITOM mit der Kolposkopie wurde bereits in Studien belegt: • Vercellino GF, Erdemoglu E, Chiantera V, et al. Validity of the colposcopic criteria inner border sign, ridge sign, and rag sign for detection of high-grade cervical intraepithelial neoplasia. Obstet Gynecol 2013;121:624-31. • Vercellino GF, Erdemoglu E, Chiantera V, et al. Clinical relevance of objectifying colposcopy. Arch Gynecol Obstet 2015;291:907-15. • Schneider A, Rakozy C, Stolte C, et al. Correlation between VITOM videocolposcopy and histopathology for pathognomonic grading criteria. Arch Gynecol Ostet 2015;292:1361-6. • Vervelino GF, Chiantera V, Gassmann J, et al. Prospective Comparison of Loop Excision under Colposcopic Guidance versus VITOM Guidance. Geburtshilfe Frauenheilkd 2012;72:945-8. • Vercellino GF, Erdemoglu E, Chiantera V, et al. A multicentric randomized study comparing two techniques of magnification assisted loop excision of high-grade cervical intraepithelial neoplasia: video exoscopy and colposcopy. Arch Gynecol Obstet 2014;289:1301-7. • Schneider A, Wagner, Rakozy C, et al. Cervical strip biopsy for high grade CIN: a valid alternative to conventional punch

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13.05.2016	
	technique. Geburtsh Frauenheilk im Druck. • Vercellino GF et al: Evaluation of the VITOM in digital high-definition video exocolposcopy. J Low Genit Tract Dis 2011; 15(4)292-5.
§29 Abklärungsdiagnostik **Punkt 4. Aufzählungspunkt 6** der Beschlussvorschläge des GKV-SV sowie der Patientenvertretung: Der Begriff **„Kolposkop“ sollte ersetzt werden durch „Kolposkop oder Bildschirmgestütztes optisches System mit Vergrößerung“**	Siehe oben

Gemeinsamer Bundesausschuss

Stellungnahme zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

Medac Gesellschaft für klinische Spezialpräparate mbH	
31.05.2016	
Stellungnahme / Änderungsvorschlag	**Begründung**
Keine Angaben über die Detektion von HPV-Hochrisikotypen bzw. Genotypisierung	*Zum Entwurf des § 30 der Patientenvertretung und GKV Spitzenverband:* Damit andere Testmethoden als solche, die auf der DNA - Analyse basieren, wie bspw. RNA-basierte oder molekularpathologische (PCR-) Tests, im neuen Screening angewendet werden können, darf im Richtlinientext nicht auf die Detektion von DNA der Hochrisikotypen abgestellt werden (siehe Abs. 3a). Daher muss im Sinne der Methodenvielfalt auf derartige Formulierungen verzichtet werden, da sie ungewollt zu Einschränkungen führen. Die Formulierung „Detektion der Hochrisiko HPV Typen 16,…“ ist für das Anforderungsverständnis ausreichend und entspricht den Kriterien, die als Basis angelegt worden sind.
Verzicht auf Nennung einzelner Tests eines Herstellers, auch nicht als Referenztest	*Zum Entwurf des § 30 Abs. 4 der KBV*: Die Nennung eines bestimmten Tests als Referenz in einer Richtlinie wird abgelehnt, da sie nicht praktikabel ist und den aktuellen medizinischen Stand der Technik nicht ausreichend abbilden kann.

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Gemeinsamer Bundesausschuss

Unterausschuss “Methodenbewertung”

Postfach 12 06 06

D-10596 Berlin

Hilden, 30. Mai 2016

Stellungnahme zur Änderung der Krebsfrüherkennungs-Richtlinie (KFE-RL) “Zervixkarzinom-Screening”

Sehr geehrte Damen und Herren,

in der Anlage übersenden wir Ihnen die Stellungnahme der QIAGEN GmbH zu den vorgelegten Beschlussentwürfen zur Änderung der KFE-RL „Zervixkarzinom-Screening“.

Für Rückfragen stehen wir Ihnen gern zur Verfügung.

Mit freundlichen Grüßen

i.A. H. Götte

Dr. Hartmut Götte
Director, Head of Local Marketing EMEA
Tel. +49-2103-2911613
Email: hartmut.goette@qiagen.com

Anlage (Versand per email):
Stellungnahme QIAGEN GmbH zur Änderung der KFE-RL

Gemeinsamer Bundesausschuss

Stellungnahme zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

QIAGEN GmbH, QIAGEN Straße 1, 40724 Hilden	
30.05.2016	
Stellungnahme / Änderungsvorschlag	**Begründung**
[BE aller Parteien] § 25: Ab dem Alter von 30 Jahren können Frauen das HPV-basierte Zervixkarzinom-screening im Abstand von (3 -) 5 Kalenderjahren in Anspruch nehmen.	Die Überlegenheit des HPV-basierten Screenings ist in vielen Studien und Pilotprojekten ausreichend nachgewiesen worden. Daher sollte das Optionsmodell für die Altersklasse ab 30 Jahren, auch im Sinne einer zielgerichteten Verbesserung der Zervixkarzinom-Vorsorge, fallengelassen werden. In den Europäischen Leitlinien, Suppl. 2 sowie in der S3-Leitlinie „Prävention des CxCA“ in ihrer Konsultationsfassung wird die Überlegenheit eines organisierten Screening-Programms, das auf HPV-Testung (oder HPV-Cotestung) basiert, begründet und befürwortet, wobei ein Zeitraum von 3 bis zu 5 Jahren empfohlen wird. Dies sollte folgerichtig in dem neuen Screening-Programm umgesetzt werden.
[GKV-SV-BE] § 28.3 (d): Bei einem positiven HPV-Test wird aus dem gleichen Untersuchungsmaterial eine Dünnschichtzytologie als Triage-Verfahren durchgeführt. Die weitere Abklärung eines positiven HPV-Tests erfolgt gemäß § 29. ~~*Die Zytologie-Triage ist nicht erforderlich, wenn ein HPV-Test verwendet wird, der Informationen zu den Genotypen HPV 16 und HPV 18 liefert und mindestens einer dieser Genotypen positiv ist.*~~ § 29.2 (a): Bei einem positiven HPV-Test im Primärscreening soll aus dem gleichen Untersuchungsmaterial eine Zytologie-Triage durchgeführt werden. ~~*Die Zytologie-Triage ist nicht erforderlich, wenn ein HPV-Test verwendet wird, der Informationen zu den*~~	Die Aufgabe einer zielgerichteten Triage-Strategie ist vor allem auch die Vermeidung des Anstiegs der Anzahl der Abklärungs-kolposkopien und ggf. der folgenden invasiven Maßnahmen im Screening-Programm, d.h., die Vermeidung von Übertherapie und potentiellem Schaden für die betroffenen Frauen. Die direkte Kolposkopie-Abklärung von HPV16/18-positiven HPV-Testbefunden ist abzulehnen, da dies nach bisherigen Ergebnissen und Erkenntnissen ein hohes Risiko für eine Überdiagnose und Übertherapie im Screening-Follow-up birgt. Analysen zur besten Triage-Strategie aus einer großen Screeningstudie in Holland zeigten, dass ein HPV-Primärscreening mit Zytologie-Triage aller HPV-positiven Frauen und erneuter Zytologie nach 6 (-12) Monaten einen hohen negativen prädiktiven Wert (NPV) von 98,5% für CIN3+, den höchsten positiven prädiktiven Wert (PPV) von 34,0% und die geringste Rate an Abklärungskolposkien (44,8% der HPV-positiven Frauen) ausweist. Demgegenüber führt die Einbeziehung von HPV16/18-Testung in die Triage-Strategie bei einer nicht signifikanten Steigerung des NPV zu einer Verringerung des PPV (25,6%) und zu einem signifikanten Anstieg der Abklärungskolposkopien auf 62,1% der HPV-positiven Frauen. Vergleichbare Ergebnisse finden sich bei Analyse aus anderen Studien (Rijkaardt et al. (2012) Int. J. Cancer 130, 602; Dijkstra (2014) Cancer Epidemiol Biomarkers Prev 23, 55 u.a.). Daher wird auch in den Europäischen Leitlinien, Suppl.2, 2015,

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30.05.2016	
~~*Genotypen HPV 16 und HPV 18 liefert und mindestens einer(...)*~~ **[PatV-SV-BE]** § 28.3 (d): Bei einem positiven HPV-Test wird aus dem gleichen Untersuchungsmaterial eine Dünnschichtzytologie als Triage-Verfahren durchgeführt. Die weitere Abklärung eines positiven HPV-Tests erfolgt gemäß § 29. ~~*Die Zytologie-Triage ist nicht erforderlich, wenn ein HPV-Test verwendet wird, der Informationen zu den Genotypen HPV 16 und HPV 18 liefert und mindestens einer dieser Genotypen positiv ist.*~~ § 29.2 (a): Bei einem positiven HPV-Test im Primärscreening soll aus dem gleichen Untersuchungsmaterial eine Zytologie-Triage durchgeführt werden. ~~*Die Zytologie-Triage ist nicht erforderlich, wenn ein HPV-Test verwendet wird, der Informationen zu den Genotypen HPV 16 und HPV 18 liefert und mindestens einer(...)*~~	S. 6) ausdrücklich die unmittelbare Zytologie-Triage **für alle positiven HPV-Testbefunde** empfohlen. Für andere Triage-Methoden wie HPV16/18-Positivität besteht nach Erkenntnissen der Autoren der Europäischen Leitlinien (Suppl. 2, 2015, S. 47) bisher keine ausreichende Evidenz für den Einsatz in organisierten Programmen. Dies spiegelt sich auch im Entwurf der deutschen S3-Leitlinie „Prävention des CxCA“ wieder, die bezüglich des Einsatzes alternativer Triage-Marker den niedrigsten (unzuverlässigsten) Evidenzgrad ausweist.
[KBV-BE] § 31.4: ~~Es dürfen nur solche HPV-Tests verwendet werden, bei denen in validen Studien nachgewiesen wurde, dass sie bezüglich der diagnostischen Güte auf Ebene von CIN II+ Befunden über eine mindestens gleichwertige Sensitivität und Spezifität verfügen wie der~~	Für nicht-DNA-basierte Methoden und Marker fehlen bisher Longitudinal-Daten (mind. 5-Jahres-Daten), so dass ein Einsatz im Primärscreening bisher nicht empfohlen werden kann (s. Euopäische Leitlinien, Suppl.2, 2015; S3-Leitlinie „Prävention des CxCA“ Konsultationsfassung, 2016). Die Validierung von HPV-DNA-Tests umfasst insbesondere auch die Reproduzierbarkeit der HPV-Testergebnisse („intra-/interlaboratory“), dies sollte hier ergänzt werden (s. Europäische Leitlinien, Suppl. 2, 2015; International Guidelines, Meijer 2009).

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~~„Digene Hybrid Capture 2“ High-Risk HPV DNA Test (Qiagen; relative Sensitivität ≥ 0.90 und relative Spezifität ≥ 0.98).~~ Für das Primärscreening und die Abklärungsdiagnostik dürfen nur Hochrisiko-HPV- Tests verwendet werden, die folgende Kriterien erfüllen: (a) Detektion der DNA der Hochrisiko-HPV-Typen 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 und 68. (b) Validierter HPV-Test oder mindestens 90% der Sensitivität eines etablierten und validierten HPV-Tests für CIN2+ und mindestens 98% Spezifität eines etablierten und validierten HPV-Tests für CIN2+. Der Anteil positiver Testergebnisse in zytologisch negativen Frauen einer Screeningpopulation soll nicht größer als der von validierten und etablierten HPV-Tests sein. Die Inter- und Intra-Labor-Reproduzierbarkeit muss mindestens 87% betragen. Die Erfüllung dieser Anforderungen muss in mindestens einer aussagekräftigen Validierungsstudie nachgewiesen sein. Die HPV-Tests sollen genau nach Herstellerangaben durchgeführt werden. Im Primärscreening ist für den HPV-Test ein Probentransportmedium für Dünnschicht-Zytologie zu verwenden, das vom Hersteller als kompatibel aufgeführt wird.	
[GKV-SV-TrGr] Kap. 2.3.5.2 (2. Absatz): (…) Der GP5+/6+-PCR ***EIA-***	In den Tragenden Gründen (wie auch in den Beschlussentwürfen) wird ausdrücklich die Verwendung validierter HPV-

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Test und der HC2-***Test*** gelten als validierte Tests. Diese können ~~jedoch nur~~ als Referenzverfahren für die Validierung von DNA-HPV-Tests verwendet werden. Die anderen HPV-Tests müssen in einer Studie mit Screeningpopulation und einem validierten HPV-Test als Referenzverfahren (…) **[KBV-TrGr]** Kap. 2.3.5.2 (2. Absatz): (…) Der ***GP5+/6+-PCR EIA-Test und der HC2-Test gelten als validierte Tests***. ~~„Digene Hybrid Capture 2 High-Risk HPV DNA Test (Qiagen) gilt als validierter Test. Dieser kann jedoch nur~~ ***Diese können*** als Referenzverfahren für die Validierung von DNA-HPV-Tests verwendet werden. Die anderen HPV-Tests müssen in einer Studie mit Screeningpopulation und einem validierten HPV-Test als Referenzverfahren (…) **[PatV-TrGr]** Kap. 2.3.5.2 (2. Absatz): (…) Der GP5+/6+-PCR ***EIA-Test*** und der HC2-***Test*** gelten als validierte Tests. Diese können ~~jedoch nur~~ als Referenzverfahren für die Validierung von DNA-HPV-Tests verwendet werden. Die anderen HPV-Tests müssen in einer Studie mit Screeningpopulation und einem validierten HPV-Test als Referenzverfahren (…)	DNA-Tests gefordert, validiert gemäß der Anforderung der International Guidelines (Meijer 2009). Der HC2 HPV-Test ist der am umfangreichsten in unabhängigen Screeningstudien validierte HPV-Test und ist damit gleichzeitig der Referenztest für alle andere eventuell zu verwendenden HPV-Tests. Zudem ist der HC2 HPV-Test der in Deutschland und auch weltweit am weitesten verbreitete und etablierte HPV-Test in Screening und Triage-Testung. Die in den Tragenden Gründen gewählte Formulierung ist missverständlich und kann den Eindruck erwecken, dass der validierte und als Referenz dienende HC2 HPV-Test ausschließlich zur Validierung von anderen Tests verwendet werden kann und nicht im vorliegenden Screening-Programm. Daher ist eine Anpassung der Formulierung analog zu den Europäischen Leitlinien, Suppl. 2, 2015, S. 40) geboten: “(…)The reported validation criteria are based on the performance of the above two HPV test methods, HC2 and GP5+/6+ PCR; they can be used to assess the suitability of new candidate HPV DNA tests (…)”.

QIAGEN GmbH

Hilden, 30.05.2016

Gemeinsamer Bundesausschuss

Stellungnahme zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

Roche Diagnostics Deutschland GmbH		
13. Mai 2016		
Stellungnahme / Änderungsvorschlag	**Begründung**	
§24 Ziele und Grundlagen des Zervixkarzinom-Screenings: **Rechtliche Grundlage ist zeitlich zu berücksichtigen. Vorgaben der Europäischen Leitlinie sind dabei maßgeblich.**	"Das Krebsfrüherkennungs- und -registergesetz (KFRG) wurde am 09. April 2013 vom Deutschen Bundestag verabschiedet. Das Gesetz ist mittlerweile im SGB V verankert. Auf Basis des KFRG soll das derzeitige Zervixkarzinom-Screening in Deutschland an die Vorgaben der Europäischen Leitlinie angepasst werden" (Bundesgesundheitsblatt 2014 57:294–301, Februar 2014). "Der Gemeinsame Bundesausschuss regelt bis zum 30. April 2016 in Richtlinien nach §92 das Nähere über die Durchführung der organisierten Krebsfrüherkennungsprorgramme für Früherkennungsuntersuchungen, für die bereits Europäische Leitlinien zur Qualitätssicherung nach Absatz 1, Satz 1 vorliegen" (Seite 618, Absatz (2), Gesetz zur Weiterentwicklung der Krebsfrüherkennung und zur Qualitätssicherung durch klinische Krebsregister (KFRG) vom 3. April 2013). Diese zeitliche Frist ist überschritten worden.	
§24 Ziele und Grundlagen des Zervixkarzinom-Screenings: **Europäische Leitlinie ist zu berücksichtigen.**	Kernpunkte der Europäischen Leitlinie: Klare Aussage in Richtung Präferenz des HPV-Primärscreenings (S.3 Tabelle 1; Punkt 1.1). Die Leitlinie empfiehlt den nationalen Gesundheitssystemen, sich für **eine** Screening-Strategie für eine vorgegebene Altersgruppe zu entscheiden und lehnt das Ko-Screening ab (S.3 Tabelle 1; Punkt 1.2). Das Optionsmodell folgt nicht dieser Empfehlung. Desweiteren sollen qualitätsgeprüfte Labore ermächtigt werden, die HPV-Testung durchzuführen (S.4 Tabelle 2; Punkt 1.35).	
§25 Anspruchsvoraussetzungen: **Frauen ab 30 Jahren nehmen am HPV-Primärscreening teil.**	Das vorgeschlagene Optionsmodell ist aus folgendenden Gründen kritisch zu betrachten: 1.) Die Europäische, die deutsche S3-Leitlinie (aktuell in Konsultationsfassung) und die Leitlinien anderer Länder präferieren evidenzbasiert das HPV-Primärscreening (S3-Leitlinie S.77 und 78; Tabelle 8.1). 2.) Die Europäische Leitlinie empfiehlt die Verwendung nur **eines** Primär-Screeningtests in einer vorgegebenen Altersgruppe (S.3 Tabelle 1; Punkt 1.2).	

	3.) Zusätzlich sieht die Europäische Leitlinie keinen Vorteil in einer Ko-Testung (S.3 Tabelle 1; Punkt 1.2). 4.) Die S3-Leitlinie (aktuell in Konsultationsfassung) empfiehlt ein Screening-Intervall beim HPV-Primärscreening von mindestens 3 Jahren (S. 80 Punkt 8.8), beim Zytologie-Primärscreening von Frauen in der Altersgruppe 25 bis 29 Jahre alle 2 Jahre (S.79 Punkt 8.7). 5.) Der Erfolg des Optionsmodells wird aufgrund der kritischen Haltung verschiedener Berufs- und Fachverbände gegenüber einer HPV-Testung als gefährdet angesehen. 6.) Die geplante *"real world"* Daten-Evaluation nach dem Zeitraum von mindestens 6 Jahren zum Vergleich der beiden Screening-Strategien ist kritisch zu sehen, da es sich um keine kontrollierte Studie handelt. Eine Schlussfolgerung zur Entscheidungsfindung zukünftiger Screening-Strategien würde somit nicht den Anforderungen evidenzbasierter klinischer Studien standhalten. 7.) Das deutsche *"real world"* Wolfsburger Modell, welches den Anforderungen evidenzbasierter Studien standhält, die Europäische Leitlinie, die S3-Leitlinie (aktuell in Konsultationsfassung) und der Report des IQWiG favorisieren ein HPV-Primärscreening. Jede Forderung nach weiteren Daten ist nicht im Sinne der Patientinnen. 8.) Die bereits vom G-BA als Eckpunkte-Papier veröffentlichte Perspektive zum HPV-Primärscreening ist in den aktuellen drei Versionen des GKV-SV, der KBV und der Patientenvertretung nicht enthalten: "Perspektivisch wird ein organisiertes Früherkennungsprogramm mit einer HPV-Untersuchung alle 5 Jahre bei Wegfall der zytologischen Screeninguntersuchungen ermöglicht (G-BA Eckpunkte für ein organisiertes Früherkennungsprogramm für Gebärmutterhalskrebs, 19. März 2015)."	
§28 Untersuchungen im Primär-Screening (GKV-SV und Patientenvertretung): **Beim HPV-Primärscreening ist ein flüssigkeitsbasiertes Transportmedium zu verwenden.**	Es ist ein Transportmedium zu verwenden, mit dem die HPV-Testung erfolgen und bei positivem Befund die Abklärung aus dem selben Medium durchgeführt werden kann. Dadurch ist ein erneutes Einbestellen der Patientin bei positivem HPV-Befund nicht mehr nötig, so dass die Compliance-Rate einer Abklärung erhöht wird. Zudem erhält die Patientin das Ergebnis der HPV-Testung und im positiven Fall die weitere Abklärung als ein konsolidiertes Ergebnis, was unnötige Verunsicherung eliminiert.	

§29 Abklärungsdiagnostik: **Bei der Triage ist die S3-Leitlinie (aktuell in Konsultationsfassung) zu berücksichtigen.**	Der IQWiG Report empfiehlt **ein** HPV-Primärscreening, macht jedoch keine Empfehlung zum Abklärungsmechanismus, da in den untersuchten Studien unterschiedliche Mechanismen verwendet wurden. Die S3-Leitlinie (aktuell in Konsultationsfassung) hingegen macht klare evidenzbasierte Empfehlungen, die es nun bei der Erstellung der Richtlinie zu berücksichtigen gilt (Algorithmen auf Seite 102, Punkt 10.8.1 und Seite 103, Punkt 10.8.2).	
§30 Abklärung und Kontrolle (KBV) bzw. §29 (GKV-SV und Patientenvertretung): **Abklärungsdiagnostik bei auffälliger Zytologie gemäß S3-Leitlinie (aktuell in Konsultationsfassung) für Screening von Frauen in der Altersgruppe 20 bis 29 Jahre.**	Die S3-Leitlinie (aktuell in Konsultationsfassung) empfiehlt für die Altersgruppe von 25 bis 30 Jahren den Algorithmus auf Seite 102, Punkt 10.8.1 und für die Altersgruppe ab 30 Jahren den Algorithmus auf Seite 103, Punkt 10.8.2 zur Abklärung zytologisch auffälliger Befunde. Die Algorithmen schreiben je nach Pap-Befund die HPV-Testung beziehungsweise die p16/Ki-67 Biomarker-Zytologie vor.	
§30 Vorgaben zur Strukturqualität (entsprechend §31 KBV Vorschlag): **Wir unterstützen den Vorschlag von GKV-SV und Patientenvertretung.**	Nur DNA-basierte HPV-Tests garantieren die notwendige Langzeitsicherheit für ein HPV-basiertes Screening (Europäische Leitlinie, S.40).	
§30 Vorgaben zur Strukturqualität (entsprechend §31 KBV Vorschlag): **Kriterien für eine aussagekräftige Validierungsstudie für das HPV-Primärscreening sind zu definieren.**	Die S3-Leitlinie beschreibt grundlegende Anforderungen an einen HPV-Test (Kapitel 7.1, ab Seite 58) und benennt nur **einen** Test, der diese Kriterien für ein HPV-Primärscreening erfüllt.	
§30 Vorgaben zur Strukturqualität (GKV-SV): **Kriterien zur internen und externen Qualitätssicherung der BÄK (RiLiBÄK für Labormedizinische Untersuchungen) sind zu bestimmen.**	Wir unterstreichen die Forderung des GKV-SV zur Teilnahme und Erfüllung interner und externer Qualitätssicherungsmaßnahmen der BÄK im Bereich labormedizinischer Untersuchnungen (RiLiBÄK). Dies kommt auch der Forderung der Europäischen Leitlinie nach qualitätsgeprüften Laboren nach (S.4 Tabelle; Punkt 1.35).	
§30 Vorgaben zur Strukturqualität: **Selbstentnahme ist zu ermöglichen.**	Zur Erhöhung der Teilnahmerate beim HPV Primärscreening empfehlen wir gemäß S3-Leitlinie (aktuell in Konsultationsfassung) die Möglichkeit zur Selbstentnahme für Frauen, die wiederholt nicht auf die Einladungen ihrer Krankenkasse reagieren (Kapitel 13.3 ab S.127 Empfehlungsgrad B mit Grade +++).	

Gemeinsamer Bundesausschuss

Stellungnahme zur Änderung der Richtlinie über die Früherkennung von Krebserkrankungen: Zervixkarzinom-Screening

VDGH e.V. – Verband der Diagnostica Industrie, Neustädtische Kirchstr. 8, 10117 Berlin	
30.05.2016	
Stellungnahme / Änderungsvorschlag	**Begründung**
Zu § 25 Anspruchsvoraussetzungen **Änderungsvorschlag: Direkter Einstig in ein HPV Screening für Frauen ab 30 Jahre mit einem Screening Intervall von 3 – 5 Jahren**	Aus den Formulierungen in allen Teilbeschlüssen ist nicht ersichtlich, ob das in § 25 vorgeschlagene Optionsmodell auf die in dem Eckpunktepapier vom 19.03.2015 beschriebene sechs-jährige Übergangsfrist beschränkt sein soll oder dauerhaft Eingang in die ärztliche Versorgung findet. Der VDGH plädiert dafür, das Optionsmodell, für die Altersklasse ab 30 Jahren, fallen zu lassen. Die Überlegenheit des HPV Screenings ist mit Studien ausreichend nachgewiesen worden. Die in Konsultationsfassung vorliegende S3 Leitlinie Prävention des Zervixkarzinoms hat die Überlegenheit eines organisierten Screeningprogrammes, das auf HPV Testung oder HPV Kotestung basiert, bejaht und sogar einen Zeitraum von 3 oder 5 Jahren befürwortet (Konsultationsfassung S3 Leitlinie Prävention des Zervixkarzinoms, Seite 69). Auch haben sich alle stimmberechtigten Bänke des G-BA und die Patientenvertretung in der öffentlichen Sitzung am 20.03.2016 dahingehend einstimmig geäußert, dass man ein alleiniges HPV Screening anstrebe. Aufgrund des Nachweises der Überlegenheit des HPV Screenings (s.o.) sollte auf das Optionsmodell verzichtet werden und der direkte Einstieg in ein reines HPV Programm erfolgen.
Ko-Testung bei unbekanntem/unklarem Vorbefund	Bei Beibehaltung Optionsmodell: Ko-Testung ist bei unklarem/unbekanntem Vorbefund zwingend erforderlich. Daher ist der Entwurf des GKV Spitzenverbandes abzulehnen, da dieser bei unklaren/unbekannten Vorbefunden keine Ko-Testung vorsieht.

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Zu § 30 Vorgaben zur Strukturqualität **Differenzierung der Tests, die im Primärscreening eingesetzt werden und solcher, die in der Abklärungsdiagnostik Anwendung finden**	Es wird in § 30 aller Entwürfe keine wirkliche Differenzierung in den Anforderungen an Tests im Primärscreening und in der Abklärungsdiagnostik vorgenommen. Die genannten Kriterien, die sich auf die Auswertungen nach Meijer et al richten, sind ausschließlich für das Primärscreening für Frauen ab 30 Jahren entwickelt worden. Insbesondere bei der Abklärungsdiagnostik ist die Bedeutung der Spezifität der Tests jedoch sehr viel wichtiger als im Screening, da hier bereits Verdachtsmomente einer Erkrankung vorliegen. Es ist ein Unterschied, ob Sensitivität und Spezifität eines Tests auf eine symptomlose Screeningpopulation eingestellt sind oder auf eine Patientenkohorte, bei der der Verdacht einer Erkrankung bereits vorliegt.
Keine Formulierung der Detektion der DNA von HPV-Hochrisikotypen	*Zum Entwurf des § 30 der Patientenvertretung und GKV Spitzenverband:* Damit andere Testmethoden als solche, die auf der DNA - Analyse basieren, wie bspw. RNA-basierte oder molekularpathologische (PCR-) Tests, im neuen Screening angewendet werden können, darf im Richtlinientext nicht auf die Detektion von DNA der Hochrisikotypen abgestellt werden (siehe Abs. 3a). Daher muss im Sinne der Methodenvielfalt auf derartige Formulierungen verzichtet werden, da sie ungewollt zu Einschränkungen führen. Die Formulierung „Detektion der Hochrisiko HPV Typen 16,…“ ist für das Anforderungsverständnis ausreichend und entspricht den Kriterien, die als Basis angelegt worden sind.
Verzicht auf Nennung einzelner Tests eines Herstellers, auch nicht als Referenztest	*Zum Entwurf des § 30 Abs. 4 der KBV*: Die Nennung eines bestimmten Tests als Referenz in einer Richtlinie wird abgelehnt, da sie nicht praktikabel ist und den aktuellen medizinischen Stand der Technik nicht ausreichend abbilden kann.
Verzicht auf zusätzliche Validierungsstudien	Angesichts der dezidierten Vorgaben zur Testgüte, sind zusätzliche Vorgaben im Sinne von zusätzlichen Validierungsstudien nicht nachvollziehbar. Daher ist auf diese zu verzichten.

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Aufnahme in den finalen Richtlinientext, dass beim HPV Primärscreening ein Probentransportmedium zu verwenden ist, was vom Hersteller empfohlen wurde und daher als kompatibel gilt.	Um die Probenqualität zu gewährleisten ist beim HPV Screening ein Probentransportmedium für die Dünnschichtzytologie zu verwenden, was vom Hersteller empfohlen wird. Diese Angabe fehlt im Entwurf der KBV, ist für die Ergebnisqualität der Probe aber entscheidend.

VDGH e.V.

Berlin, 30.05.2016