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ICO Monograph Series on HPV and Cervical Cancer: General Overview

Overview of Human Papillomavirus-Based and Other Novel Options for Cervical Cancer Screening in Developed and Developing Countries

Jack Cuzick[a,*], Marc Arbyn[b], Rengaswamy Sankaranarayanan[c], Vivien Tsu[d], Guglielmo Ronco[e], Marie-Helene Mayrand[f], Joakim Dillner[g], Chris J.L.M. Meijer[h]

[a] *Cancer Research UK Centre for Epidemiology, Mathematics and Statistics, Wolfson Institute of Preventive Medicine, London, United Kingdom*
[b] *Unit of Cancer Epidemiology, Scientific Institute of Public Health, Brussels, Belgium*
[c] *Screening Group, International Agency for Research on Cancer, Lyon, France*
[d] *PATH, Seattle, WA, USA*
[e] *Unit of Cancer Epidemiology, Centre for Cancer Prevention Piemonte, Torino, Italy*
[f] *Departments of Obstetrics and Gynecology, and Social and Preventive Medicine, University of Montreal CHUM, Montreal, Canada*
[g] *Department of Medical Microbiology, Lund University, Malmö, Sweden*
[h] *Department of Pathology, Vrije Universiteit University Medical Centre, Amsterdam, The Netherlands*

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ABSTRACT

Screening for cervical cancer precursors by cytology has been very successful in countries where adequate resources exist to ensure high quality and good coverage of the population at risk. Mortality reductions in excess of 50% have been achieved in many developed countries; however the procedure is generally inefficient and unworkable in many parts of the world where the appropriate infrastructure is not achievable.

A summary and update of recently published meta-analyses and systematic reviews on four possible clinical applications of human papillomavirus (HPV) DNA testing is provided in this article: (1) triage of women with equivocal or low-grade cytological abnormalities; (2) follow-up of women with abnormal screening results who are negative at colposcopy/biopsy; (3) prediction of the therapeutic outcome after treatment of cervical intraepithelial neoplasia (CIN), and most importantly (4) primary screening HPV DNA test, solely or in combination with Pap smear to detect cervical cancer precursors. There are clear benefits for the use of HPV DNA testing in the triage of equivocal smears, low-grade smears in older women and in the post-treatment surveillance of women after treatment for CIN. However, there are still issues regarding how best to use HPV DNA testing in primary screening. Primary screening with Hybrid Capture® 2 (HC2) generally detects more than 90% of all CIN2, CIN3 or cancer cases, and is 25% (95% CI): 15–36%) relatively more sensitive than cytology at a cut-off of abnormal squamous cells of undetermined significance (ASC-US) (or low-grade squamous intraepithelial lesions (LSIL) if ASC-US unavailable), but is 6% (95% CI: 4–7%) relatively less specific. Several approaches are currently under evaluation to deal with the lower specificity of HPV DNA testing as associated with transient infection. These include HPV typing for HPV-16 and -18/45, markers of proliferative lesions such as p16 and mRNA coding for the viral E6 and/or E7 proteins, with a potential clinical use recommending more aggressive management in those who are positive.

In countries where cytology is of good quality, the most attractive option for primary screening is to use HPV DNA testing as the sole screening modality with cytology reserved for triage of HPV-positive women. Established cytology-based programmes should also be gradually moving towards a greater use of HPV DNA testing to improve their efficacy and safely lengthen the screening interval. The greater sensitivity of HPV DNA testing compared to cytology argues strongly for using HPV DNA testing as the primary screening test in newly implemented programmes, except where resources are extremely limited and only programmes based on visual inspection are affordable. In such countries, use of a simple HPV DNA test followed by immediate 'screen and treat' algorithms based on visual inspection in those who are HPV-positive are needed to minimise the number of visits and make best use of limited resources. A review of studies for visual inspection methods is presented.

The fact that HPV is a sexually transmitted infection may lead to anxiety and concerns about sexual relationships. These psychosocial aspects and the need for more information and educational programmes about HPV are also discussed in this article.

* Corresponding author. Tel.: +44 207 014 0227; fax: +44 207 014 0269.
E-mail address: jack.cuzick@cancer.org.uk (J. Cuzick).

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1. Introduction

Cervical cancer arises in the transformation zone of the uterine cervix. This is the area which undergoes physiological metaplasia from glandular to squamous epithelium at the onset of adolescence. Human papillomavirus (HPV) infection is very common in young women after the onset of sexual activity and, when it persists, the viral oncoproteins produce perturbation of the cell-cycle controls resulting in cervical intraepithelial neoplasia (CIN). At their mildest (CIN1), these lesions are generally no more than manifestations of HPV infection, but at their most severe (CIN3) the risk of progression to cancer is higher if not detected and treated. Fortunately, the transition to cancer usually takes years or decades, thus allowing the opportunity for detection by exfoliative cytology. The peak incidence of HPV infection occurs at about age 20, the peak incidence/detection of CIN3 occurs at about age 30, and the peak incidence of cancer occurs in the 40 s. It is estimated that without secondary prevention, cervical cancer would occur in around 3–5% of women who acquire a high-risk HPV infection, although for every cancer that occurs a far larger number of CIN lesions develop, of which the majority will spontaneously regress. Most of the pre-malignant and malignant lesions are of the squamous type, but around 15% are of the glandular type. HPV types -16 and 18 are the dominant oncotypes in squamous lesions but type -18 is relatively more important in glandular lesions.

The recognition of the strong causal relationship between persistent infection of the genital tract with high-risk HPV types and occurrence of cervical cancer has resulted in the development of a number of HPV DNA or RNA detection systems for screening [1]. Detection of high-risk HPV DNA is considered to be potentially useful in four clinical applications: (1) as a primary screening test, solely or in combination with a Pap smear to detect cervical cancer precursors; (2) as a triage test to select which women who have minor cytological lesions in their Pap smears are in need of referral for colposcopic diagnosis and treatment; (3) in the continuing management of women referred for colposcopy for whom no lesion could be visualised; and (4) as a follow-up test for women treated for high-grade intraepithelial lesion with local ablative or excisional therapy to more rapidly and accurately identify women who have or have not been cured by their treatment.

In this article we summarise and update recent meta-analyses and systematic reviews on the performance of HPV DNA testing in each of these clinical applications. We then consider the best way to use HPV DNA testing and review newer approaches and technologies which may provide further improvement to screening algorithms. Finally, we briefly review some psychosocial aspects of the impact of introducing HPV DNA testing in screening programmes.

2. Cytological Screening

Since the development of cytology-based cervical cancer screening using the Pap smear in the mid-20th century, Pap smears and new cytology-based technologies such as liquid-based cytology have been implemented for secondary prevention of cervical cancer. Although some have argued that there is no direct evidence of the impact of cytology screening on cervical cancer, such as evidence from a randomised clinical trial, there are overwhelming and convincing epidemiologic data to infer the impact of successfully implemented cytology screening on reducing cervical cancer rates. Strong evidence for this comes from ecological correlations of incidence/mortality trends of cervical cancer with screening activities in populations as recently reviewed [1]. This has been most clearly demonstrated in Nordic countries and in the United Kingdom [2–4]. Case-control studies of women who developed cancer also provide convincing additional evidence [5,6]. In the United States of America, rates have also fallen by 75% or more since the 1960s, although rates remain high in regions typified by low resources as well as poor access and presence of social/cultural barriers to screening. In Central and South America, coverage may be high in places, but the quality of the cytology programmes and access to treatment are typically poor, and rates of cervical cancer remain some of the highest documented in the world. A notable exception is Chile, where high quality cytology-based screening has had a substantial impact on cancer incidence and mortality [7].

Cytology is a subjective test and in programmes without quality control/quality assurance it is virtually impossible to achieve and maintain the clinical performance of cytology. Cytology is labour intensive and to date has been refractory to high-throughput automated screening. Despite the low cost of consumables and because of the three reasons cited above, high-quality cytology is expensive in absolute terms and may not necessarily be the most cost-effective option for screening [8].

Liquid-based cytology has logistical and operational advantages (interpretation at higher speed, lower rate of unsatisfactory smears and possibility of ancillary molecular testing using remnant fluid), but is more expensive and is neither more sensitive nor more specific than conventional cytology with respect to detection of histologically confirmed high-grade CIN [9].

We must continue to recognise both the strengths and limitations of cytology for cervical cancer screening. In populations vaccinated against HPV-16/18 we should anticipate that the positive predictive value (PPV) of cervical screening will be reduced because there will be fewer high-grade lesions among women with cytological abnormalities. It is therefore rational to develop multiple, viable modalities for cervical cancer prevention, including methods that achieve similar or better screening performance than cytology alone but also meet the demands of underserved populations, such as low cost, the need for fewer than three visits (cytology, diagnostic colposcopy and treatment) in each intervention (screening) cycle and/or fewer interventions in a lifetime due to a greater negative reassurance of a single intervention. It is naive to think that one modality, whether it be cytology-based screening, visual inspection with acetic acid (VIA), HPV DNA testing or HPV vaccination will meet the demands of all populations throughout the world. Importantly, each screening method must be validated for its technical performance and must be cost-effective within the capacity of the region in which it is to be adopted. In other words, the cost-utility of one method *versus* another must be evaluated within the limits of acceptable expenditures and available resources in different settings.

3. Updated meta-analyses and new results for HPV DNA testing

Here we briefly update the results of previous meta-analyses [10–12] and identify new areas where data on important questions are beginning to appear. Details of the methodology used have been described previously [11].

3.1. Triage of atypical squamous cells of undetermined significance

3.1.1. Absolute accuracy of HPV DNA testing

We retrieved 22 studies, where the accuracy of Hybrid Capture® 2 (HC2) (Qiagen Gaithersburg, Inc. MD, USA (previously Digene Corp.)) for triage of women with findings of abnormal squamous cells of undetermined significance (ASC-US) could be assessed [Table 1: a1–a22]. On average, in 8.7% (95% confidence interval

Table 1
References of studies included in the meta-analyses

Code[a]	1st author, journal year; volume:pages
a,b: Triage of women with ASC-US (a) or LSIL (b) using HC2	
a1	Manos M et al., JAMA 1999; 281:1605–10
a2,b1	Bergeron C et al., Obstet Gynecol 2000;95:821–7
a3,b2	Lytwyn A et al., J Can Med Ass 2000;163:701–7
a4	Shlay JC et al., Obstet Gynecol 2000; 96:410–6
a5	Morin C et al., J Reprod Med 2001;46:799–805
a6,b3	Bell JS et al., BMJ 2001; 322:894–5
a7	Solomon D et al., J Natl Cancer Inst 2001;93:293–9
a8,b4	Zielinski D et al., J Pathol 2001;195:300–6
a9,b5	Kulasingam SL et al., JAMA 2002;288:1749–57
a10,b6	Pretorius RG et al., J Reprod Med 2002;47:290–6
b7	Sherman ME et al., J Natl Cancer Inst 2002;94:102–7
a11	Cuzick J et al., Lancet 2003;362:1871–6
a12,b8	Gershengorn HB et al., BMC Infect Dis 2003;3:1
a13	Lonky NM et al., Obstet Gynecol 2003;101:481–9
a14	Wensveen C et al., Acta Obstet Gynecol Scand 2003;82:883–9
a15,b9	Andersson S et al., Acta Obstet Gynecol Scand 2005;84:996–1000
a16,b10	Carozzi FM et al., Cancer 2005;105:2–7
a17	Dalla Palma P et al., Cytopathology 2005;15:22–6
a18	Giovannelli L et al., J Clin Virol 2005;33:281–6
a19	Bergeron C et al., Gynecol Obstet Fertil 2006;34:312–6
a20	Kiatpongsan S et al., Int J Gynecol Cancer 2006;16:262–5
a21,b11	Ronco G et al., Eur J Cancer 2007:43:476–80
a22	Kelly D et al., Cancer 2006;108:494–500
c: Post-treatment surveillance (follow-up after treatment of CIN)	
c1	Elfgren K et al., Am J Obstet Gynecol 1996;174:937–42
c2	Chua KL et al., Gynecol Oncol 1997;66:108–13
c3	Distefano AL et al., Infect Dis Obstet Gynecol 1998;6:214–9
c4	Bollen LJ et al., Gynecol Oncol 1999;72:199–201
c5	Nagai Y et al., Gynecol Oncol 2000;79:294–9
c6	Jain S et al., Gynecol Oncol 2001;82:177–80
c7	Lin CT et al., Am J Obstet Gynecol 2001;184:940–5
c8	Nobbenhuis MA et al., Br J Cancer 2001;84:796–801
c9	Paraskevaidis E et al., Obstet Gynecol 2001;98:833–6
c10	Bekkers RL et al., Int J Cancer 2002;102:148–51
c11	Bar-Am A et al., Gynecol Oncol 2003;91:149–53
c12	Houfflin Debarge V et al., Gynecol Oncol 2003;90:587–92
c13	Zielinski GD et al., Gynecol Oncol 2003;91:67–73
c14	Cecchini S et al., Tumori 2004;90:225–8
c15	Sarian LO et al., Gynecol Oncol 2004;94:181–6
c16	Hernadi Z et al.,Eur J Obstet Gynecol Reprod Biol 2005;118: 229–34
d: Primary screening	
d1[b]	Cuzick J et al., Lancet 1995;345:1533–6
d2[b]	Cuzick J et al., Br J Cancer 1999;81:554–8
d3	Kuhn L et al., J Natl Cancer Inst 2000;92:818–25
d4	Ratnam S et al., Cancer Epidemiol Biomarkers Prev 2000;9:945–51
d5	Schiffman M et al., JAMA 2000;283:87–93
d6[b]	Schneider A et al., Int J Cancer 2000;89:529–34
d7	Belinson J et al., Gynecol Oncol 2001;83:439–44
d8	Blumenthal PD et al., Int J Gynaecol Obstet 2001;72:47–53
d9	Clavel C et al., Br J Cancer 2001;84:1616–23
d10[b]	Oh YL et al., Cytopathology 2001;12:75–83
d11[b]	Paraskevaidis E et al., Gynecol Oncol 2001;82: 355–9
d12[b]	Kulasingam SL et al., JAMA 2002;288:1749–57
d13	Syrjanen S et al., J Low Tract Dis 2002;6:97–110
d14	Belinson J et al., Int J Gynecol Cancer 2003;13:819–26
d15	Coste J et al., BMJ 2003; 326:733
d16	Cuzick J et al., Lancet 2003;362:1871–6
d17	Petry KU et al., Br J Cancer 2003;88:1570–7
d18	Salmeron J et al., Cancer Causes Control 2003;14:505–12
d19–21	Sankaranarayanan R et al., Int J Cancer 2004; 112:341–7
d19–21	Sankaranarayanan R et al., J Med Screen 2004;11:77–84
d22[b]	Agorastos T et al., Gynecol Oncol 2005;96:714–20
d23	Bigras G et al., Br J Cancer 2005;93:575–81
d24[c]	Kotaniemi-Talonen L et al., Br J Cancer 2005;93:862–7
d25[c]	Sankaranarayanan R et al., Int J Cancer 2005;116:617–23
d26	Sarian LO et al., J Med Screen 2005;12:142–9
d27[c]	Ronco G et al., J Natl Cancer Inst 2006;98:765–74
d27[c]	Ronco G et al., Lancet Oncol 2006;7:547–55
d28	Almonte M et al., Int J Cancer 2007;121:796–802
d29[b,c]	Bulkmans NW et al., Lancet 2007;370:1764–72
d30[c]	Naucler P et al., N Engl J Med 2007,357:1589–97
d31[b,c]	Mayrand MH et al., N Engl J Med 2007,357:1579–88

[a] The first character refers to the clinical application: a (triage of ASC-US).
[b] Primary screening with polymerase chain reaction (PCR).
[c] Randomised controlled trials comparing cytology with HPV or combined cytology and HPV primary screening.
ASC-US: abnormal squamous cells of undetermined significance; HC2: Hybrid Capture® 2 (Qiagen Gaithersburg, Inc. MD, USA (previously Digene Corp.); LSIL: low-grade squamous intraepithelial lesion.

(CI): 6.9–10.5%) and 3.9% (95% CI: 2.4–5.5%) of cases, underlying CIN2+ or CIN3+ was found (Table 2). The variation of the accuracy of HC2 triage in detecting these high-grade CIN lesions is displayed in the forest plots in Fig. 1 [Table 1: a8–a21,b1–b11]. Overall, HC2 had a sensitivity of 93.1% (95% CI: 91.1–95.1%) and 95.5% (95% CI: 92.7–98.2%) for detecting respectively CIN2+ or CIN3+. The pooled specificity was 62.3% (95% CI: 57.6–67.1%) when the outcome was CIN2+ and 60.5% (52.9–68.2%) for CIN3+. Inter-study heterogeneity was not statistically significant for sensitivity but very significant for specificity. Between 23% and 57% of women tested positive (pooled rate of 43.0; 95% CI: 37.8–48.2%).

3.1.2. *Relative accuracy of HPV DNA testing compared to Pap testing*

In seven studies, where also a repeat Pap smear was taken, the sensitivity of HC2 was on average 14% higher than repeat cytology, considering ASC-US or worse as a positive result, for detection of CIN2+ (ratio: 1.14; 95% CI: 1.08–1.20). HC2 and cytology triage showed a similar specificity (ratio: 0.99; 95% CI: 0.88–1.10).

3.2. *Triage of low-grade squamous intraepithelial lesions*

Little new data have appeared since the previous report and only the main findings are summarised below [10]. The value of HPV DNA testing in this context depends on which actions would have been taken if it were not used. If all women would have been referred to colposcopy then it can help to lower referral rates, whereas if standard management is to retest six months later then immediate referral of HPV-positive women will increase referral rates.

3.2.1. *Absolute accuracy of HPV DNA testing*

The sensitivity of HC2 triage of women with an index smear showing low-grade squamous intraepithelial lesions (LSIL) was very high: 97.2% (95% CI: 95.6–98.8%), pooled from 11 studies for the outcome of CIN2+ [Table 1: b1–b11] and 97.1% (95% CI: 94.0–100%), pooled from six studies for CIN3+ [Table 1: b4–b7,b9,b11]. However its specificity was very low: 30.6% (95% CI: 22.7–38.6%) for CIN2+ and 26.1% (95% CI: 15.1–37.1%) for CIN3+ (Table 2). Histologically confirmed CIN2+ and CIN3+ were present in respectively 17.6% (95% CI: 11.8–23.3%) and 7.4% (95% CI: 2.9–12.0%). The very large majority of women with LSIL had a positive HC2 result: pooled estimate of 74.4% (95% CI: 67.0–81.9%; range: 58–85%). However, a recent paper found that for women aged 35 or more, the HPV positivity rate was much lower than for younger women and that the potential value of HPV DNA testing as an adjunct to cytology in this group was substantially better than for younger women [13]. Similar observations were made in the HPV in Addition to Routine Testing (HART) study [14]. However, another study found a high rate of HPV positivity in

Table 2
Summary of meta-analyses on the test performance of HPV DNA testing using HC2 or PCR in three possible clinical applications

Application	Test	Test cut-off	Outcome	Studies	Sensitivity			Specificity			Test positivity rate	Prevalence of outcome at final diagnosis
					Pooled estimate (95% CI)	p	Range (%)	Pooled estimate (95% CI)	p	Range (%)	Pooled estimate (95% CI)	Pooled estimate (95% CI)
Triage ASC-US	HC2	1 pg/mL	CIN2+	22	93.1 (91.1–95.1)	0.39	60–100	62.3 (57.6–67.1)	<0.001	37–80	43.0 (37.8–48.2)	8.7 (6.9–10.5)
			CIN3+	9	95.5 (92.7–98.2)	0.94	75–100	60.5 (52.9–68.2)	<00.01	49–70	–	3.9 (2.4–5.5)
Triage LSIL	HC2	1 pg/mL	CIN2+	11	97.2 (95.6–98.8)	0.86	89–100	30.6 (22.7–38.6)	<0.001	19–48	74.4 (67.0–81.9)	17.6 (11.8–23.3)
			CIN3+	6	97.1 (94.0–100)	0.99	97–100	26.1 (15.1–37.1)	<0.001	17–46	–	7.4 (2.9–12.0)
Prediction treatment failure	HC2/PCR	Diverse	Recurrent CIN[a]	16	94.4 (90.9–97.9)	0.41	67–100	75.0 (68.7–81.4)	<0.001	44–100	32.4 (23.6–41.2)[a]	10.2 (6.7–13.8)
	HC2	1 pg/mL	CIN2+	19	89.7 (86.4–93.0)	<0.001	50–100	88.2 (86.2–90.1)	<0.001	61–95	13.4 (11.2–15.7)	2.1 (1.7–2.5)
			CIN2+	8[b]	98.1 (96.8–99.4)	<0.40	84–100	91.7 (90.3–93.1)	<0.001	85–95	9.3 (7.7–10.8)	0.9 (0.7–1.2)
			CIN3+	10/9	90.3 (85.3–95.4)	<0.001	62–98	90.6 (88.7–92.6)	<0.001	84–95	–	1.0 (0.7–1.3)
Primary screening	PCR	+signal	CIN2+	7	84.2 (77.0–91.5)	<0.001	64–95	95.1 (93.4–96.8)	<0.001	79–99	6.8 (4.8–8.7)	2.2 (1.4–3.0)
	HC2 and cytology	1 pg/mL or ASC-US+	CIN2+	8[c]	99.4 (97.9–100)	0.98	98–100	88.2 (85.8–90.5)	<0.001	69–94	13.3 (10.7–15.9)	1.0 (0.7–1.3)

[a] If multiple visits per patient were documented, values from the visit near 6 months after treatment were chosen for pooling.
[b] Restricted to studies conducted in North America or Europe.
[c] After exclusion of the studies conducted in India [Table 1: d19–d21] and Zimbabwe [Table 1: d8].
The three possible clinical applications described above include triage of minor cytological abnormalities (ASC-US or LSIL), prediction of residual or recurrent CIN after treatment and primary cervical cancer screening. Sensitivity and specificity (pooled estimate, p value for inter-study heterogeneity and range (minimum and maximum observed value) to detect histologically confirmed CIN2+ or CIN3+, pooled test positivity rate, and prevalence of CIN. ASC-US: atypical squamous cells of undetermined significance; CI: confidence interval; CIN: cervical intraepithelial neoplasia; HC2: Hybrid Capture 2® (Qiagen Gaithersburg, Inc. MD, USA (previously Digene Corp.); LSIL: low-grade squamous intraepithelial lesions; PCR: polymerase chain reaction.

women older than 35 with only a small decreasing gradient with age, suggesting that specificity may not be improved very much in this group by using HPV DNA testing before referring to colposcopy [15]. Further work is needed to synthesise all the data on HPV triage of LSIL according to age.

3.3. Subsequent management after negative findings on colposcopy/biopsy

Historically, colposcopically directed biopsies have been the clinical reference standard for diagnosing and grading pre-cancer into CIN1, 2, or 3. However, the choice of biopsy site and the histopathological diagnosis of resultant biopsies tend to be variable and subjective. Clinicians rely on colposcopy to determine the presence or absence of epithelial lesions, find the area of the cervix with the highest degree of disease, and direct the biopsy for histological diagnosis.

Although the sensitivity of screening has improved considerably in the past decade, colposcopy has not advanced given the weak correlations between visual changes and disease severity and lack of reproducibility among assessors. Even highly experienced assessors have false negative colposcopy rates as high as 20–40% in patients with a histological diagnosis of pre-cancer [16].

Another use of HPV DNA testing related to triage is in women who are referred for colposcopy because of abnormal smears, but who do not have any visible lesion on colposcopy or for whom a biopsy yields negative histology. For these women, a negative HPV test at or near the time of colposcopy provides additional reassurance that there is unlikely to be any undetectable disease, while being HPV-positive (especially for types -16 and 18), and indicates a continuing risk and a need for short-term repeat testing [17]. Especially for type -18, the possibility of an adenocarcinoma or its precursor lesion, adenocarcinoma in situ, should be excluded by careful examination of the endocervical canal.

3.4. Surveillance after treatment of cervical intraepithelial neoplasia

3.4.1. Absolute accuracy

Sixteen studies were identified that matched predefined inclusion criteria [Table 1: c1–c16]. Studies were heterogeneous with respect to design, timing of visits, choice of HPV testing methods and the assessment of disease status at entry and end of follow-up. The results are briefly summarised in Table 2. Treatment failure, expressed in terms of residual or recurrent CIN, occurred on average in 10.2% (95% CI: 6.7–13.8) of treated cases. The sensitivity of HPV DNA detection in predicting treatment failure ranged from 67% to 100% and was on average 94.4% (95% CI: 90.9–97.9%). The specificity of HPV DNA testing for predicting treatment success was statistically very heterogeneous among studies and varied between 44% and 100%. Therefore, the pooled specificity of 75.0% (95% CI: 68.7–81.4%) cannot be considered as a good summary of all studies.

3.4.2. Relative accuracy

Overall, HPV DNA detection after treatment predicted residual or recurrent CIN with significantly higher sensitivity (ratio: 1.16; 95% CI: 1.02–1.33) and not significantly lower specificity (ratio: 0.96; 95% CI: 0.91–1.01) than follow-up cytology [10]. In studies where lesions were treated by excision, HPV DNA testing predicted treatment outcome with higher sensitivity and similar specificity to histological assessment of the section margins, (relative sensitivity: 1.31; 95% CI: 1.11–1.55; and relative specificity: 1.05; 95% CI: 0.96–1.15).

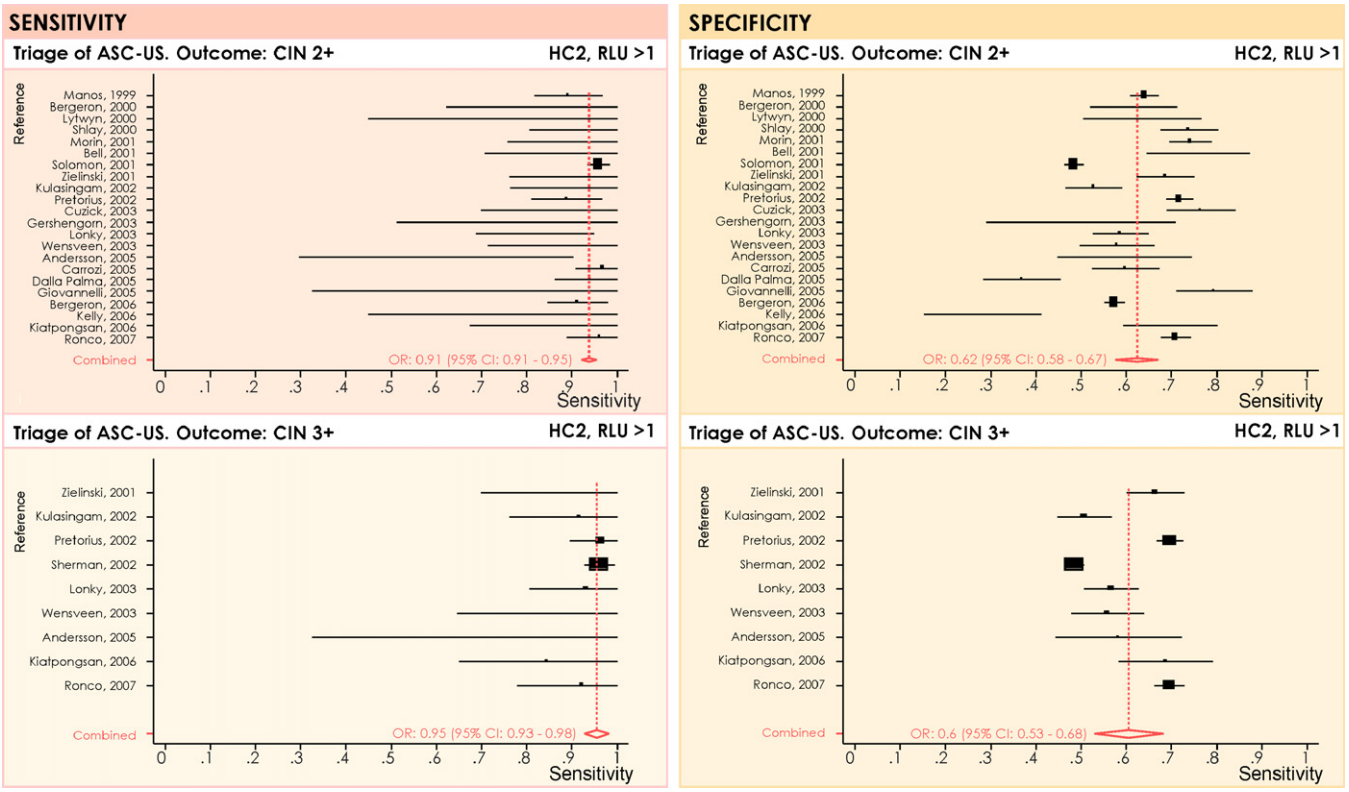

Fig. 1. Meta-analyses of the sensitivity (left) and specificity (right) of triage of women with cytological findings of ASC-US using the Hybrid Capture® 2 assay (RLU > 1) for identifying underlying CIN2 or worse (upper) or CIN3 or worse (lower). ASC-US: abnormal squamous cells of undetermined significance; CI: confidence interval; CIN2+: CIN grade 2 or worse; CIN3+: CIN grade 3 or worse; HC2: Hybrid Capture® 2 (Qiagen Gaithersburg, Inc. MD, USA (previously Digene Corp.); OR: odds ratio; RLU: relative light unit. [Table 1: a8–a21,b1–b11].

3.5. *Primary screening*

3.5.1. *Absolute cross-sectional accuracy*

A total of 25 cross-sectional studies - where women were tested concomitantly with a Pap smear and an HPV assay in the framework of primary screening were identified [Table 1: d1–d23,d26,d28,d30]. In addition, three randomised trials with an experimental arm including combined testing with cytology and HPV DNA detection could be added [Table 1: d27,d29,d30]. One series of cross-sectional studies, carried out in three different areas in India but described in one report, were considered as separate studies [Table 1: d19–d21]. In eleven studies, women were referred for confirmation of disease status only when at least one screening test was positive. In nine studies a random sample of screen negatives was referred allowing adjustment for verification bias, whereas in seven other studies, all enrolled subjects were submitted to colposcopy with biopsy if colposcopically suspicious.

Overall, the sensitivity of HC2 for finding underlying high-grade intraepithelial neoplasia was 89.7% (95% CI: 86.4–93.0%)) but varied over a large range between 50% [Table 1: d19] and 100% [Table 1: d9] (see Table 2). The observed sensitivity of HC2 for CIN2+ was extremely low in the three cross-sectional studies conducted in India: respectively 50, 70 and 80% [Table 1: d19–d21], and was also lower than average in other developing countries (77% in Peru [Table 1: d28]), 81% in Zimbabwe [Table 1: d8], 83% in Brazil [Table 1: d26], 88% in South-Africa [Table 1: d3]). However, a study conducted in a jungle area of Peru [Table 1: d28], the sensitivity of HPV DNA testing with HC2 for carcinoma in situ was very high (96%) compared to low rates for conventional cytology (32%), VIA (42%) or liquid-based cytology (81%), and the specificity for CIN2+ was better than for liquid-based cytology [Table 1: d32]. The sensitivity of HC2 for CIN2+ was consistently high in eight studies conducted in Europe and North America: pooled estimate of 98.1% (95% CI: 96.8–99.4%; p for inter-study heterogeneity: 0.4) [Table 1: d4,d9,d15–17,d23,d27,d30]. The pooled specificity of HC2 in excluding high-grade cervical pre-cancer was 88.2% (95% CI: 86.2–90.1%; range: 61–95%). In North America and Europe, the pooled specificity was higher: 91.7% (95% CI: 90.3–93.1%; range: 85–95%).

In nine studies, a polymerase chain reaction (PCR) system was used for detecting HPV DNA sequences [Table 1: d1,d2,d6,d10–d12,d22,d29,d31]. Its pooled sensitivity for CIN2+ (84.2%; 95% CI: 77.0–91.5%) was lower, but its pooled specificity (95.1%; 95% CI: 93.4–96.8%) was higher compared to the HC2 was compared assay. However, these studies used different primers and detection of amplified sequences, and significant heterogeneity was seen. For instance, the sensitivity was 95% in a German study where general primers (GP)5+/GP6+ were used followed by hybridisation with a cocktail of oligonucleotides of 14 high-risk HPV types [Table 1: d6] and only 64% in a British study where the PCR/Sharp assay was used (MY09/MY11 primers, hybridisation with 10 high-risk types) [Table 1: d2]. However, when good quality control procedures are used for currently accepted consensus PCR systems the variability is much less [18]. Guidelines for quality control and test parameters are currently being developed.

The sensitivity and specificity of HPV DNA testing in finding CIN2 or CIN3 or cervical cancer showed substantial and statistically very significant heterogeneity, even when separated by type of HPV test system. The main factor that explained heterogeneity was the geographical continent. Studies conducted in Europe or North America, where HC2 was used, showed better performance. The diagnostic odds ratio (dOR) did not vary significantly by completeness of gold standard verification, indicating that verification bias was limited.

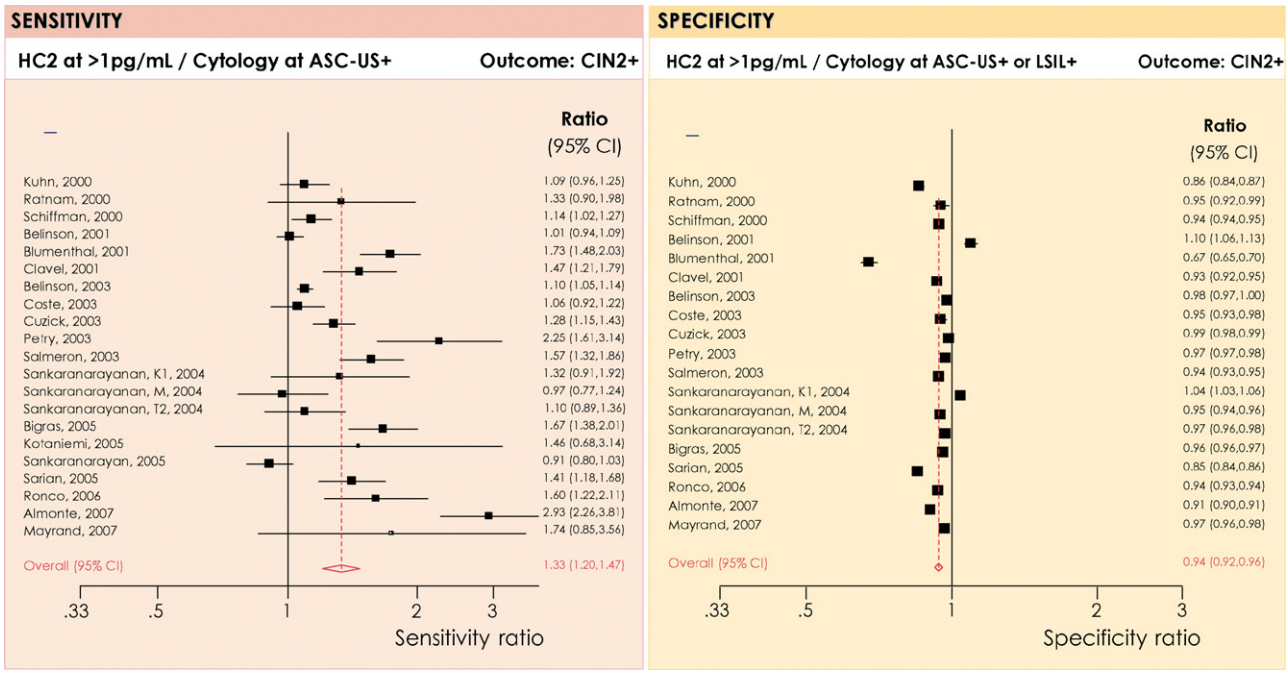

Fig. 2. Relative sensitivity (left) and specificity (right) of HPV testing using the Hybrid Capture® 2 assay compared to cytology in primary screening studies. ASC-US: abnormal squamous cells of undetermined significance; CI: confidence interval; CIN2+: CIN grade 2 or worse; HC2: Hybrid Capture® 2 (Qiagen Gaithersburg, Inc. MD, USA (previously Digene Corp.); LSIL: low-grade squamous intraepithelial lesion.
[Table 1: c8,d3–d5,d7–d9,d14–d21,d23–d28,d31].

3.5.2. *Relative cross-sectional accuracy*

In addition to the cross-sectional studies, the baseline results of six randomised clinical trials comparing HPV *versus* cytology screening were included in the meta-analysis of the relative sensitivity (see Table 3) [Table 1: d24,d25,d27,d29–d31]. In Fig. 2 [Table 1: c8,d3–d5,d7–d9,d14–d21,d23–d28,d31], the sensitivity of HC2 was compared with that of cytology at ASC-US+ (or LSIL+ when ASC-US+ was not available) from 21 studies including four randomised trials, where the outcome was CIN2+. Overall, the sensitivity of HC2 was 33% (95% CI: 20–47%) higher than equivocal- or low- grade cytology. Results from two trials conducted in India show that the detection rate of CIN2+ was lower in the HPV screened arm compared to cytology [Table 1:d20–21]. In all other studies, the sensitivity of HC2 was higher, varying from +1% to +193%. The pooled specificity of HC2 was overall 6% lower than cytology (ratio: 0.94; 95% CI: 0.92–0.98%; range: 0.67–1.10) (see Fig. 2 and Table 2). PCR was also more sensitive than cytology for detecting CIN2+ (ratio: 1.27; 95% CI: 1.06–1.53) (see Table 3).

The highest values of relative sensitivity were observed in Germany (1.63 [Table 1: d6], 2.15 [Table 1: d17]) and Peru (2.93 [Table 1: d28]), which was due to the particularly poor sensitivity of cytology in these studies.

The combination of cytology with HC2 was respectively higher than cytology alone (at cutoff ASC-US+) for the detection of respec-

Table 3
Relative accuracy in primary screening of HPV testing *versus* cytological screening or of combined screening *versus* testing with one test in order to find underlying CIN2 or CIN3 or worse

Comparison (test 1/test 2)	Outcome	Relative sensitivity			Relative specificity		
		pooled estimate (95%CI)	Range	Number of studies	Pooled estimate (95%CI)	Range	Number of studies[a]
HC2/Cyto. (ASC-US+)	CIN2+	1.29 (1.17–1.43)	0.87–2.93	19	0.96 (0.95–0.97)	0.86–1.10	16
HC2/Cyto. (LSIL+)		1.42 (1.27–1.59)	1.09–2.35	14	0.90 (0.89–0.92)	0.67–1.03	13
HC2/Cyto. (ASC-US/LSIL+)		1.33 (1.20–1.47)	0.91–2.93	21	0.94 (0.92–0.98)	0.67–1.10	19
PCR/Cyto. (ASC-US+)		1.27 (1.06–1.53)	0.75–3.57	8	0.98 (0.94–1.02)	0.86–1.08	6
PCR/Cyto. (LSIL+)		1.61 (0.84–3.09)	0.82–5.10	3	0.92 (0.89–0.95)	0.81–1.00	3
HC2/Cyto. (ASC-US+)	CIN3+	1.32 (1.06–1.64)	0.97–2.63	10	0.98 (0.97–1.00)	0.90–1.10	7
HC2/Cyto. (LSIL+)		1.31 (1.13–1.53)	0.97–2.32	9	0.94 (0.93–0.96)	0.85–1.03	7
Cyto. (ASC+) & HC2/Cyto (ASC-US+)	CIN2+	1.46 (1.34–1.59)	1.06–2.30	11	0.94 (0.93–0.94)	0.89–0.96	10
Cyto. (ASC+) & HC2/Cyto (ASC-US+)	CIN3+	1.35 (1.21–1.52)	1.02–2.18	7	0.93 (0.93–0.94)	0.89–0.95	5
Cyto. (ASC-US+) & HC2/HC2+	CIN2+	1.06 (1.05–1.06)	1.02–1.37	11	0.95 (0.94–0.96)	0.81–0.99	10
Cyto. (ASC-US+) & HC2/HC2+	CIN3+	1.04 (1.03–1.05)	1.02–1.17	7	0.93 (0.91–0.95)	0.81–0.99	5

[a] Meta-analyses of the relative specificity do not include randomised clinical trials, neither cross-sectional studies, where the absolute specificity of the two considered tests was not reported. ASC-US: atypical squamous cells of undetermined significance; CI: confidence interval; CIN: cervical intraepithelial neoplasia; CIN2+: CIN grade 2 or worse; CIN3+: CIN grade 3 or worse; Cyto: cytology; HC2: Hybrid Capture® 2 (Qiagen Gaithersburg, Inc. MD, USA (previously Digene Corp.); LSIL: low-grade squamous intraepithelial lesions; PCR: polymerase chain reaction.

tively CIN2+ or CIN 3+ (46%; 95% CI: 0.34–0.59); and 35%; 95% CI: 21–52%), whereas the specificity was 7% lower (95% CI: 6–7%). Adding a Pap smear to the HC2 test and considering ASC-US or worse as a positive cytological result increased the sensitivity of HC2 for CIN2+ or CIN3+ by 6% and 4%, respectively, but resulted in a loss in specificity of 5% (95% CI: 4–6%) and 7% (95% CI: 5–9%).

In general, adding cytology to HPV DNA testing adds little to overall sensitivity, but does reduce specificity. It would appear that the most useful role for cytology is to triage women whose primary HPV DNA screening test is positive to avoid referral and over-treatment of women with minimal or no detectable cytologic abnormality and who are likely to have transient infections.

3.6. Duration of disease-free interval

Several studies have shown that HPV negativity alone or in combination with negative cytology signifies a longer disease-free interval against CIN2+ than being negative for cytology alone. Early studies measured HPV retrospectively and did not use it for management. Sherman ME et al. followed 20,810 women for 10 years and found that in cytologically negative women lesions were diagnosed much more rapidly in those who were HPV-positive compared to women who were HPV-negative [19]. In two Danish cohorts of women aged 22–32 years and 40–50 years HPV DNA was measured retrospectively and again not used for triage. The authors concluded that HPV DNA testing at five-yearly intervals offers protection similar to cytology testing at three-yearly intervals [20]. Clavel C et al. reported that 5 of 4,401 women with negative cytology and HPV DNA tests and followed-up for a median of 34 months developed high-grade lesions, compared to 29 of 501 women who were initially cytology-negative but HPV-positive and concluded that a screening interval of three to five years was safe in double negative women [21]. Similar conclusions were obtained by Bulkmans NW et al. in a cohort of 2,810 cytology-negative women followed for five years, where 4 of 62 HPV-positive women developed CIN3+ compared to 1 of 2,175 HPV-negative women [4]. Schlecht NF et al. reported on the development of cytologic abnormalities in 2,404 women in a Brazilian cohort, and found that cytologic lesions persisted longer and progressed more rapidly in HPV-positive women [22]. Long-term follow-up of the Hammersmith cohort and two large recent randomised trials in Sweden and The Netherlands have all shown that the higher detection rate for CIN2+, when HPV DNA testing was used as part of the initial screening process, led to lower rates of CIN3+ at the subsequent screening round and indicates that HPV DNA tests are highly sensitive to detect prevalent cases [23–25]. In the Hammersmith study, the cumulative proportion of CIN2+ within five-years after a negative HPV DNA test, when most women would have had at least one routine repeat smear was about half as high as for women who were originally cytology-negative (0.6% *versus* 1.2%), and only after six or more years do the CIN2+ rates in women originally HPV-negative approach those seen after three years in women who were originally cytology-negative.

In the Swedish study of women aged 32–38, the detection rate for CIN2+ associated with the addition of HPV DNA testing was increased 51% percent at the initial screen, but 42% lower in the follow-up period (mean: 4.1 years). For the Dutch study, the detection rate of CIN3+ was 70% higher initially but 55% lower in the 6.5 year mean follow-up period.

The fact that the higher detection rate for CIN2+ when HPV DNA testing was used as part of the initial screening process led to lower rates of disease at the subsequent screening round [24,25]. It also suggests that there is minimal over-diagnosis for women aged over 30, as the cumulative CIN2+ rates over two rounds were similar in all three studies, and also that the screening interval can be safely extended to at least 6 years with HPV DNA testing. The limited data on follow-up beyond six to seven years does not allow evaluation of longer screening intervals at this time and further work is needed to see if even longer intervals might be safe, particularly for women with two or more negative HPV tests.

4. New ways to use existing technologies

4.1. HPV DNA testing as the sole primary screening test

From the meta-analyses summarised above, it is abundantly clear that HPV DNA testing is substantially more sensitive than cytology at detecting high-grade CIN. However, HPV testing is somewhat less specific than cytology due primarily to the detection of transient infections that have not produced cytologic changes. Basic principles suggest that in such circumstances the more sensitive test should be applied first (i.e., HPV DNA testing) and the more specific test (i.e., cytology) should then be used only for HPV-positive women to determine management. Management of HPV-positive, cytology-negative women presents a new challenge. Results from the HART, Swedish and the Amsterdam (POBASCAM) studies suggest they can safely be managed by repeating the testing with both cytology and HPV after one year and this is being further explored in several ongoing studies [14,24,25]. Women double negative at that time could be returned to routine screening while positives could be referred to colposcopy. This approach of using HPV DNA testing as the sole primary screening modality has several advantages: HPV DNA detection assays provide an automated, objective and very sensitive test. This allows for better quality control and reduces the basis for medico-legal claims; (2) cytology can thus be reserved for the 5–15% of women who are HPV-positive. This facilitates high quality cytology and allows the employment of fewer, more focused cyto-screeners; (3) it also avoids the unnecessary triage of HPV-negative ASC-US/LSIL; and (4) a longer screening interval is likely to be safe which would improve both the cost and convenience of screening.

A possible algorithm is shown in Fig. 3 although this may need modification to satisfy local requirements and reflect refinements to HPV DNA testing such as typing for HPV-16 and 18 and use of mRNA or $p16^{ink4a}$ to minimise the number of women on short-term follow-up [17]. In addition, issues of when to start screening and the appropriate screening interval are still controversial.

Several advantages of HPV DNA testing as the sole primary screening modality have now been clearly demonstrated and large, simple, pragmatic demonstration/implementation projects are at present needed, ideally comparing this approach to cytology alone to assess the impact of primary HPV screening on cancer incidence and mortality. However HPV infections are very common, especially in young women, and usually clear spontaneously, so that over-reaction to the detection of HPV DNA carries a risk of unnecessary colposcopies, psychological distress and the possibility of over-treatment. Thus, it is essential that HPV testing-based screening is introduced within an organised programme with ongoing process and outcome evaluation rather than in an opportunistic setting.

4.2. Self sampling for HPV DNA

When compared to cytology, the requirements for a good sample are less rigorous for HPV DNA testing. Several studies have evaluated the diagnostic accuracy of self-collected vaginal specimens using swabs, tampons, or brushes for HPV. Ogilvie GS et

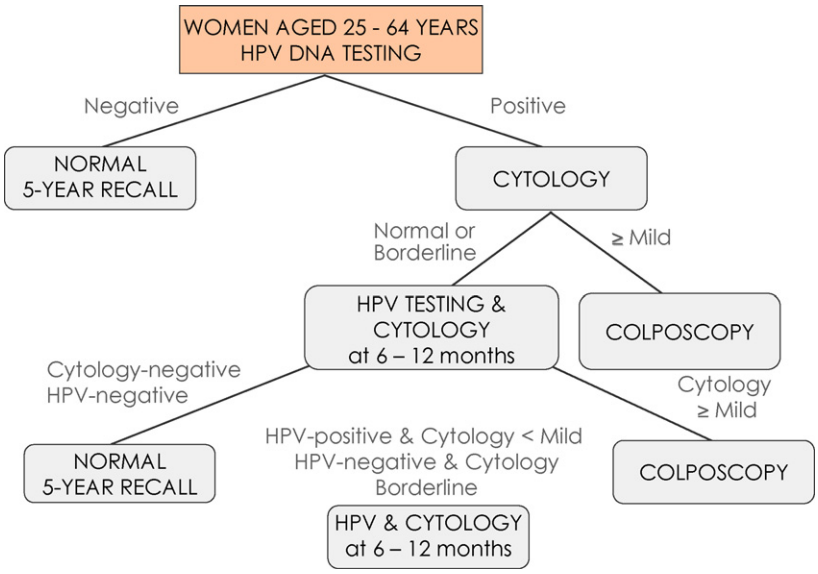

Fig. 3. Proposed new screening algorithm which employs HPV DNA testing as the primary screening test and uses cytology to triage HPV positive women.

al. have produced an overview of studies which compare this to clinician-collected vaginal samples [26]. They found an overall relative sensitivity of 74% and specificity of 84% for the self-taken sample. Although clearly not as good as a clinician taken sample, this sensitivity compares favourably to cytology where sensitivity for CIN2+ is typically less than 70%. Other studies have also shown good sensitivity for self-sampled HPV DNA when histologic CIN2+ is the gold standard.

Furthermore Nobbenhuis MA et al. found that women prefer self-sampling to a clinician taken sample and that the sensitivity for CIN2+ was superior to that achieved by cytology, but not as good as a clinician/nurse taken sample [27]. Similar results have been reported by Brink AA et al. [28] and Szarewski A et al. [29]. These results suggest that self-sampling for HPV DNA could be a valuable screening method for women who refuse to attend clinician-based screening and an important way of improving population coverage of screening [30]. However with currently existing technologies a clinician taken sample is to be preferred when this is possible.

5. Future screening algorithms

5.1. Use of HPV typing information

The results of studies using new technologies suggest that some of these newer tests initially could be used to minimise over-referral for colposcopy and treatment while still maintaining a high sensitivity, especially if HPV DNA testing is used as the primary screening test [17]. Tests that could identify HPV-positive, cytology-negative women at low-risk of high-grade disease would improve the efficiency of the screening process by avoiding short-term follow-up of low-risk women. While results from mRNA and $p16^{ink4a}$ look promising, the use of HPV typing to identify types -16 and 18 separately from other high-risk types has been most fully explored. HPV-16 has been shown in many studies to be more persistent and more often associated with high-grade lesions than other high-risk types and because HPV-18 is more often associated with difficult to detect or visualise lesions in the endocervical canal, persistent HPV-18 findings, even in the absence of other cytologic or colposcopic

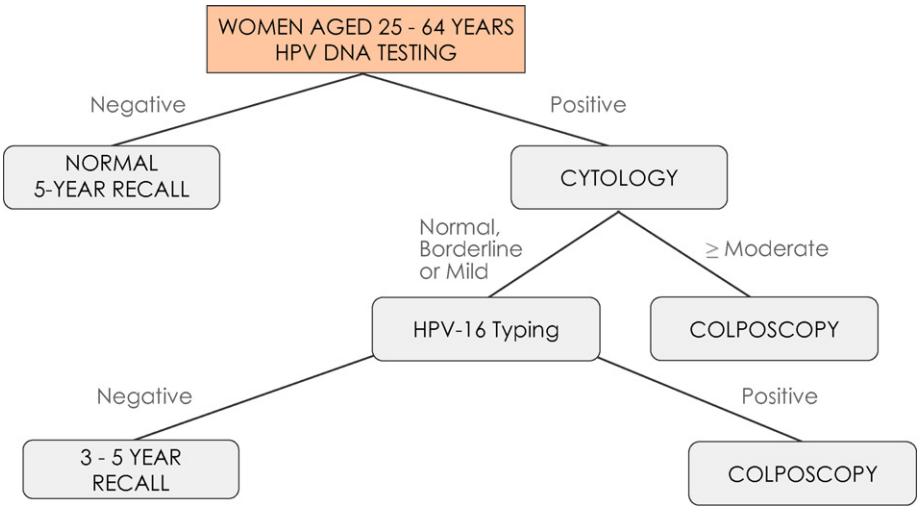

Fig. 4. Proposed potential future screening algorithm. This algorithm employs HPV testing as the primary test and uses cytology to triage HPV positive women to eliminate short follow up group. Triage with p16 and mRNA may also be useful, but this is less well established.

abnormalities, should lead to a thorough examination of the endocervix to exclude hidden lesions. One particular approach using only HPV-16 is suggested in Fig. 4, but algorithms will certainly evolve as more data become available to support the use of other tests.

5.2. Screening in vaccinated cohorts

As successive cohorts of vaccinated young women reach screening age, the reduction in cervical lesions will lead to a decrease in rates of colposcopy referral to about 40%–60% or less of the existing case loads in most Western countries, based on initial findings from the vaccination trials [31]. Such reductions are likely to translate into initial savings to the health care system or to individuals but the vaccine-induced decrease in cervical lesions may lead to a degradation of performance characteristics of cytology (because of a decreased expectation of abnormalities on a day's smear workload) with consequent concerns related to the need for heightened quality assurance. Thus, the PPV of cytology may decline paralleling high vaccine uptake because clinically relevant lesions will become less common. This will lead to a decline in the performance of cytology because of a decrease in the signal (squamous abnormalities) to noise (inflammation and reactive atypias) ratio that characterises the subjective and tedious work of reading and interpreting smears. Simply making cytology screening less frequent may not be a viable strategy to achieve a cost-effective combination of vaccination and screening in light of the aforementioned potential problems that may plague cytology performance in conditions of low lesion prevalence. HPV DNA testing has the screening performance characteristics that would make it an ideal primary cervical cancer screening test in such conditions. Use of HPV typing will also help to indicate if the lesions seen are a result of breakthrough from types -16 and 18 or due to other high-risk HPV types.

6. Screening in low-resource settings – visual inspection methods

The challenges associated with developing and maintaining screening programmes in low-resource countries have stimulated the search for alternative methods of screening that would overcome the many barriers identified with the 'classic' three visit cytology-based approach. The following requirements are essential to screen successfully in low-resource settings: (1) screening, diagnosis and treatment should be provided on-site or in clinics accessible to the majority of at-risk women; (2) availability of reproducible, validated, low-cost, low-technology screening tests that can lead to immediate treatment of abnormalities; (3) wide coverage of at-risk women; (4) appropriate educational programmes directed towards health workers and women to ensure correct implementation and high participation; and (5) built-in mechanism for evaluation of the screening programme.

The first two of these apply particularly to low-resource settings, while the last three are universal requirements for any effective screening programme. A number of different tests have been developed and investigated over the years as alternative screening tests to cytology (Table 4). The two most widely studied alternative approaches to cervical cancer prevention are VIA or visual inspection with Lugol's iodine (VILI) and HPV DNA testing. HPV DNA testing is being considered as an additional test to the conventional Pap screening test or as a stand-alone screening test in older women.

6.1. Visual inspection with acetic acid

VIA, also known as direct visual inspection (DVI), the acetic acid test (AAT) or cervicoscopy, involves examination of the cervix with the naked eye, using a bright light source, one minute after application of 3–5% dilute acetic acid using a cotton swab or a spray. Detection of well-defined aceto-white areas close to the squamocolumnar junction (SCJ) indicates a positive test. Although aceto-whitening can occur in immature squamous metaplasia and in inflamed and regenerating cervical epithelium, aceto-whitening associated with CIN is well demarcated, intensely opaque and localised to the transformation zone. Early microinvasive cancers also turn white after application of acetic acid. Aceto-whitening is thought to be due to a reversible coagulation of intracellular proteins following acetic acid application. The higher concentrations of intracellular proteins in neoplasia lead to the dense aceto-whitening following acetic acid application. One of the main advantages of VIA is that it yields an immediate result, thus making it possible for treatment of abnormal lesions at the same visit - the so-called 'screen-and-treat' approach, without colposcopy or histological sampling [32]. This method is inexpensive and can be carried out using modest equipment and widely available consumables without the need for a laboratory infrastructure. A range of personnel including doctors, nurses, midwives and paramedical health workers can be rapidly trained to perform VIA in short courses of 5–10 days duration [33]. A wide range of teaching materials are now available for VIA training courses, making VIA particularly attractive as a screening test in low-resource settings.

The test characteristics of VIA have been evaluated in several cross-sectional studies in less-developed countries [34]. These studies together have involved more than 150,000 women and have reported promising results that support its use as an alternative to cervical cytology. The sensitivity of VIA to detect high-grade precursor lesions and invasive cervical cancer has varied from 49 to 96% and the specificity from 49 to 98% [34]. However, many of these

Table 4
Performance and characteristics of different screening methods

Screening test	Sensitivity[a]	Specificity[a]	Characteristics
Conventional cytology	Moderate (44–78%)	High (91–96%)	Requires adequate healthcare infrastructure; laboratory based; stringent training and quality control
HPV DNA testing	High (66–100%)	Moderate (61–96%)	Laboratory-based; high throughput; objective, reproducible and robust; currently expensive
Visual inspection methods			Low technology; low cost
VIA	Moderate (67–79%)	Low (49–86%)	Linkage to immediate treatment
VIAM	Moderate (62–73%)	Low (86–87%)	possible; suitable for low-resource
VILI	Moderate to high (78–98%)	Low (73–93%)	settings
Colposcopy	Low (44–77%)	Low (85–90%)	Expensive; inappropriate for low-resource settings

[a] Ranges of sensitivity and specificity adapted from reference [33].
VIA: visual inspection with acetic acid; VIAM: magnified visual inspection with acetic acid; VILI: visual inspection with Lugol's iodine.

studies suffered from verification bias which occurs when only a subset of all screened women, commonly women who are screen positive, is subject to definitive assessment of final disease status using the reference diagnostic investigation (gold standard), which conventionally is colposcopically directed biopsy and thus the true disease status is not known for a large fraction of the individuals in the study. However, colposcopy has a relatively low sensitivity and is currently being challenged as new prevention strategies are emerging [35]. Moreover, due to correlation between visual screening tests and colposcopy-based gold standard, accuracy estimates of the screening tests tend to be inflated [36]. Under such circumstances, the estimates for sensitivity and specificity must be corrected to account for those with unknown final disease status. Pooled estimates of sensitivity vary from 62 to 80% and specificity from 77 to 84% for VIA to detect high-grade CIN, after adjusting for the effects of verification bias [34]. Denny L et al. investigated the influence of concurrent sexually transmitted infections on the test characteristics of VIA in a South African study and found that there were no significant differences in the sensitivity and specificity of VIA relating to the presence or absence of *N. gonorrhea*, *C. trachomatis* or *T. vaginalis*. The specificity of VIA was, however, significantly lower among human immunodeficiency virus (HIV)-positive women [37]. A study that modeled the cost-effectiveness of a variety of cervical cancer screening strategies in India, Kenya, Peru, South Africa and Thailand reported that screening women once in their lifetime, at the age of 35 years, with a one- or two-visit screening strategy involving VIA, would reduce the lifetime risk of cancer by approximately 25–36%, and cost less than 500 international dollars per year of life saved [8]. Relative cancer risk declined by an additional 40% with two screenings at 35 and 40 years of age, resulting in a cost per year of life saved that was less than each country's per capita gross domestic product (GDP), which is a very cost-effective result according to the Commission on Macroeconomics and Health. The study concluded that VIA in one clinical visit (with immediate treatment of positive cases) or two clinical visits (followed by treatment in a subsequent visit) is one of the most cost-effective alternatives to conventional three-visit cytology-based screening programmes in resource-poor settings.

The efficacy of VIA screening in reducing cervical cancer incidence and mortality has been addressed in randomised, controlled trials in India. The impact of screening by a single round of VIA, cytology, or HPV DNA testing on cervical cancer incidence and mortality has been investigated in a cluster randomised controlled trial in the Osmanabad District in India, where 52 clusters with a total of 142,701 women aged 30–59 years were randomised into 4 groups for a single round of screening by trained midwives with either VIA, cytology, HPV DNA testing or to a control group who received health education [38]. Test positivity rates were 14.0% for VIA, 7.0% for cytology, and 10.3% for HPV DNA testing. The detection rate of CIN2–3 lesions was similar in all intervention arms (0.7% for VIA, 1.0% for cytology and 0.9% for HPV DNA testing) ($p = 0.06$). The study populations are currently being followed-up for cervical cancer incidence and mortality and more updated results are expected in 2008.

In a cluster randomised controlled trial in the Dindigul district in India, of the 114 study clusters, 57 were randomised to a single round of VIA by trained nurses and 57 to a control group who received health education [39]. Of the 49,311 eligible women aged 30–59 years in the VIA group, 31,343 (63.6%) were screened and 30,958 women in the control group received education about cervical cancer and routine care. During the seven years following the beginning of screening, there were 167 cervical cancer cases and 83 cervical cancer deaths in the intervention group, compared with 158 cases and 92 deaths in the control group (incidence hazard ratio: 0.75; 95% CI: 0.55–0.95; and mortality hazard ratio: 0.65; 95% CI: 0.47–0.89) [39]. The greatest reduction in incidence and mortality rates were observed for the 30–39 year age group. The authors concluded that good training of providers and sustained quality assurance are vital for VIA screening to succeed in preventing cervical cancer in routine settings. While these results demonstrated the value of VIA in primary screening, ultimately VIA may be best suited to function as a triage/treatment activity following a new HPV test based on FastHPV technology (Qiagen Gaithersburg, Inc. MD, USA (previously Digene Corp.)) as part of a screen and treat algorithm (Section 6.3 and Fig. 5).

6.2. Visual inspection with Lugol's iodine

VILI involves examination of the cervix with the naked eye to identify mustard-yellow areas on the cervix after application of Lugol's iodine. A multi-centre study in India and Africa involving around 49,000 women concurrently evaluated VIA and VILI by independent providers, using a common protocol [40]. The pooled sensitivity and specificity to detect high-grade CIN were 92 and 85% for VILI, respectively as opposed to 77 and 86% for VIA, thus indicating a higher sensitivity than VIA in this study but similar specificity. In a Latin American study involving about 3,000 women, VILI had a significantly lower sensitivity of 53% and a specificity of 78% to detect high-grade CIN [41].

6.3. 'Screen and treat' approach to cervical cancer prevention

Regardless of the screening test used, screening must be linked to treatment to ensure programme effectiveness. This can be done using the traditional approach (screen, diagnose, confirm and treat), intermediate approach (screen, diagnose and treat with

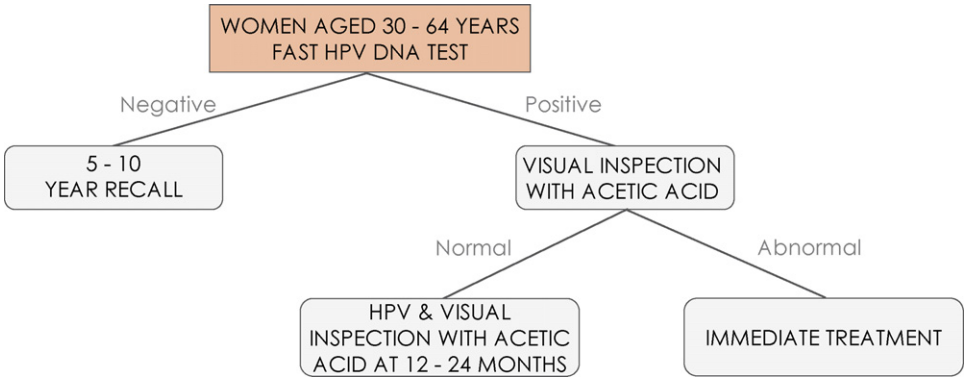

Fig. 5. Proposed HPV DNA-based screening algorithm for developing countries.

post-treatment biopsy confirmation), or the 'screen and treat' approach (treatment is based on the results of screening test alone). With all 'screen and treat' algorithms, any lesion suspicious for cancer is referred. Cryotherapy and loop electrosurgical excision procedure (LEEP) are two safe, effective, relatively simple and inexpensive outpatient methods used for the treatment of pre-cancer. The major practical differences between the two methods are that LEEP involves excision of the tissue and hence provides a tissue specimen that allows for histological verification of the diagnosis, LEEP equipment is considerably more expensive, and LEEP requires more training to use safely. On the other hand, cryotherapy is an ablative method that involves destroying the tissue and thereby leaves no sample for histology, but it can be safely conducted by non-specialist providers including nurses with proper training. The Alliance for Cervical Cancer Prevention (ACCP) has produced a document which provides further material on this subject [42].

In an attempt to overcome the obstacles posed by traditional cytology-based screening programmes, a number of studies have investigated an approach where screening is linked to either immediate treatment in a single-visit strategy or shortly after the screening test is performed. Denny L et al. performed a randomised, controlled trial of 6,555 non-pregnant, unscreened women aged 35–65 years [43]. All women were screened using HPV DNA testing with HC2 and with VIA. Women were randomised thereafter to one of three groups: cryotherapy if the HPV DNA test was positive, cryotherapy if VIA was positive or delayed treatment regardless of the result of the screening test. The prevalence of high-grade CIN (defined histologically) was significantly lower in the two 'screen and treat' groups at 6 and 12 months post-randomisation compared to the delayed evaluation group. The safety and feasibility of the 'screen and treat' approach were also confirmed in a study conducted in Thailand [32]. VILI has not been fully evaluated in a 'screen and treat' context.

Based on these studies an approach based on initial screening by HPV DNA testing followed by 'screen and treat' using VIA in HPV-positive women is an attractive option. Such an algorithm is outlined in Fig. 5. This approach could be further combined with a mother-daughter approach in which daughters are vaccinated and mothers screened at the same visit, with treatment of the HPV-positive mothers scheduled to coincide with the next vaccine injection in the daughters.

7. Psycho-social aspects of HPV DNA testing

Discovery of the viral aetiology of cervical cancer and development of tests to detect HPV DNA in cervical cells have significant implications for strategies to prevent cervical cancer. They also have implications for health education and quality of life. Awareness that a sexually-transmitted infection (STI) is the causal agent in cervical cancer could affect attitudes towards the disease, and care is needed to minimise any reduction in screening coverage that could come from the association with STIs. The high prevalence of HPV infection means that large numbers of women will receive positive HPV results and will therefore need advice and support. Promoting understanding of HPV without creating anxiety will be a challenge for psychosocial researchers.

7.1. Public awareness of HPV

Inclusion of HPV DNA testing in cervical screening programmes means that women will need to understand the role of HPV infection if they are to make informed choices. At present the public is largely unaware of HPV or its role in cervical cancer, although there is recognition of a link between cervical cancer and sexual behaviour. A population-based survey in the United Kingdom in 1999 found that fewer than 30% of people identified 'infection' as a possible cause of cervical cancer, with almost none mentioning HPV [44]. In a group of relatively well-educated women attending a 'well-woman' service that offered cervical screening, only 30% said they had heard of HPV and fewer than half of them were aware of the link with cervical cancer [45]. Similar results have been reported from North America [46]. However, awareness is currently increasing due to marketing campaigns set up by companies manufacturing prophylactic vaccines. In a review, Anhang R et al. conclude that most women in the United States of America have not heard of HPV, and those who have are unaware of its link with cancer [47]). Education of general practitioners is also a key component of any awareness programme, as they have a major influence on the conduct of screening. In the Dutch POBASCAM study, communication with general practitioners was vital in maintaining high compliance rates [48].

7.2. Reactions to being informed about HPV

Qualitative studies with women from a range of backgrounds have explored reactions to receiving information about HPV. The information typically includes the name of the virus, the mode of transmission, the prevalence of transient infection and the associations with cervical abnormalities and cervical cancer. Most women are astonished by the information and many are shocked that they didn't know about it before. All the qualitative studies in the field find that women want more information about HPV [49,50]. Women want their health providers to be well-informed about the disease in order to answer their questions without giving confusing and inconsistent information. Health professionals' knowledge of HPV has not received much attention, but the experience of women with positive test results suggests that many have limited knowledge about HPV. Education of health professionals should be a priority.

Women's reactions to hearing about the test include confusion and anxiety about the association with STIs as well as issues of fidelity and trust in relationships [49,51]. Anhang R et al. identified confusion about the relationship between Pap testing and HPV DNA testing, and uncertainty about the level of risk [49]. Women from some ethnic and religious backgrounds express fears that community leaders could be less supportive of cervical screening if they were aware of the link with sexual transmission [50]. The association between HPV and genital warts can compound women's worry about infection if warts already carry negative connotations. Most women outside of stable relationships express concern about preventing infection in the future, either for themselves or for their partners, and the message that condoms are not fully protective can be confusing because it appears to contradict other 'safe sex' messages.

Interestingly, at least in the context of discussion of self-testing, most women who have taken part in focus groups express the wish to know their HPV status [51]. Fears that women will be reluctant to take part in testing when they know about the HPV connection may not be realised if clear information is made widely available. Information about HPV is currently provided by the European Consortium for Cervical Cancer Education (ECCCE) via its website (http://www.eccce.org) in several languages.

8. Conclusions

From this updated review, we can conclude that for the detection of underlying high-grade CIN, HPV DNA testing is more sensitive than the cytological examination of a Pap smear, in several clinical

applications. The clearest use is for the triage of ASC-US cytology, especially when the initial sample was liquid-based, in which case the cost-effectiveness in avoiding unnecessary colposcopies is undoubted. In women with LSIL cytology, the HPV positivity is much higher, especially in younger women, where HPV DNA testing offers few additional gains. However for women aged 35 and above, HPV DNA testing is more specific with the potential to avoid about 50% of colposcopies with HPV triage of LSIL cytology, and could become an attractive option. Several studies have shown that the likelihood of subsequently finding a high-grade lesion after a negative colposcopy is increased in women who are HPV-positive. No study to date has specifically compared possible management strategies and further research in this area is warranted.

Several studies document the ability of HPV DNA testing to rapidly and accurately identify women with incomplete excision after treatment for CIN2+. The disappearance of HPV indicates that increased surveillance is not necessary. The continued detection of the same type of HPV after a period of 12 to 18 months after treatment signals a high likelihood of residual disease.

The biggest gains are likely to be made in using HPV DNA testing in primary screening. With current DNA based tests this can now only be considered for women above the age of 30 or 35, either alone or as an adjunct to cytology. There is clear evidence for higher sensitivity and a longer disease-free interval after a negative result, offering the prospects for longer screening intervals and later ages for beginning screening. These alternatives now need to be pursued via large, ideally randomised, demonstration/implementation projects within organised screening programmes. Countries newly embarking on screening programmes should use HPV DNA testing as their primary screening test, except where resources are severely limited, in which case VIA based programmes are a viable alternative. For countries with successful cytology based programmes, a gradual transition to HPV DNA testing should take place to improve efficacy and safely lengthen the screening interval. Management of HPV-positive, but cytology negative women remains a challenge, and new technologies using HPV typing, mRNA expression of p16 positivity may help to minimise the number of such women who would be placed on short-term follow-up schedules, but this should not be an impediment to using HPV DNA based testing now for primary screening.

In the developing world, where cytology seems impractical, 'screen and treat' algorithms based on visual inspection techniques offer new opportunities. HPV testing based on FastHPV technology could accurately identify a small subset of women most likely to have a high-grade lesion and may improve the efficiency of the process.

Public understanding about HPV has lagged behind the scientific and technical advances. Because HPV testing has significant social and psychological consequences, there is an urgent need for health education. When women are tested for HPV, they want information and guidance both from their health care providers and through open sources. HPV information is complex, and many women remain confused after having read educational materials. Ensuring that HPV information is accessible to people at all levels of health literacy will be important. This should address many of the psychosocial issues posed by HPV testing and help ensure that women benefit from the scientific advances that will ultimately contribute to world-wide control of cervical cancer.

A new challenge will be to integrate screening with incipient HPV vaccination programmes. Assuming that vaccination leads to a long-term reduction in HPV-16/18 related disease, relatively more cytologic abnormalities will be false positives and more HPV infections will be of lower risk high-risk types. In this context, primary screening with HPV DNA testing instead of cytology may circumvent this problem, although optimal management will require that we know more about the progressive potential of these 'other' high-risk types. In the end, if durable multi-valent vaccines are developed, we will be in the ideal position of eliminating screening completely, but there will be a long period of time where less frequent HPV DNA-based screening will provide cost-effective protection for disease caused by the types not included in the current vaccines.

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