

# CERVICAL CANCER SCREENING

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## 4.4 HPV testing

### 4.4.1 Technical descriptions

#### (a) Introduction

It has long been recognized that there is a strong etiological link between persistent infection with certain HPV types and subsequent development of cervical precancer and cancer. This has led to the idea that the detection of sequences of the HPV genome could become an alternative screening tool that could replace screening by the microscopic examination of cervical cells ([IARC, 2005, 2007, 2012](#); [Bouvard et al., 2009](#); see also Sections 1.2.1 and 1.2.2).

The HPV genome is a circular, double-stranded DNA molecule that codes for two late proteins (L1 and L2), which form the capsid, and several early (E) genes, which code for various proteins that are important for diverse viral functions. The E6 and E7 proteins are essential for the transformation of infected cells towards neoplasia ([IARC, 2007, 2012](#)).

Large RCTs have demonstrated that women with a negative hrHPV DNA test result have lower risks of CIN3 and cervical cancer than women with normal cervical cytology; therefore, many countries are moving towards screening with HPV tests ([Arbyn et al., 2012](#); [Huh et al., 2015](#); [Machalek et al., 2019](#); [Ronco et al., 2014](#); [von Karsa et al., 2015](#)). Currently, a multitude of hrHPV assays are available, but only a few have been clinically validated for use in cervical cancer screening against internationally agreed clinical criteria ([Poljak et al., 2020](#)). This section discusses HPV nucleic acid tests that detect DNA or RNA sequences of alpha HPV types that are considered to be carcinogenic, i.e. the 12 types classified as carcinogenic to humans (Group 1): HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. HPV68, which is probably carcinogenic to humans (Group 2A), and HPV66, which is possibly carcinogenic to humans (Group 2B), are often included in the panel of types targeted

by the hrHPV tests ([Bernard et al., 2010](#); [IARC, 2012](#)), although their etiological fraction in cervical cancer carcinogenesis is very low and their inclusion decreases the clinical specificity of such tests (see Sections 1.2.1 and 1.2.2 and Figs. 1.9 and 1.10).

#### (b) Categories of HPV nucleic acid tests

hrHPV assays can be classified by the following parameters: the nucleic acid targeted (viral genomic DNA [HPV DNA tests] or viral messenger RNA [mRNA] [HPV RNA tests]), the viral genes targeted, the level of genotyping detail, whether signal amplification (e.g. hybrid capture) or target amplification (e.g. polymerase chain reaction [PCR] or next-generation sequencing) is used, the method of identification of amplicons, the output result (qualitative or quantitative), and the inclusion of internal controls that check the validity of the specimen. An inventory of more than 200 HPV tests that were available in 2020 and are classified according to these principles is available in [Poljak et al. \(2020\)](#).

The main applied test systems used to identify HPV nucleic acid sequences are hybridization and PCR. In hybrid capture, RNA probes hybridize with complementary HPV DNA if present in a sample; the DNA/RNA hybrids are subsequently captured by anti-DNA/RNA antibodies coupled to an enzyme that generates a chemical reaction and yields a quantified light signal ([Lorincz, 1997](#)). In PCR systems, one or more adjacent pairs of oligonucleotide primers directed to the 3' and 5' ends of a target sequence will bind to it and initialize amplification of the DNA between the primers by the temperature-sensitive Taq DNA polymerase. The amplified target DNA is called an amplicon. After multiple cycles of amplification, controlled by alternating the temperature, a large number of amplicons are generated. PCRs targeting short amplicons are analytically more sensitive than those targeting a longer amplicon ([Iftner & Villa, 2003](#)). Diverse systems are used to identify the amplicons. In real-time PCR, a

quantified light signal is generated that is correlated with the amount of target DNA ([Josefsson et al., 1999](#)). Real-time PCR can also be applied in multiplex format, in which the presence of and viral load of multiple carcinogenic HPV types can be assessed simultaneously and with control of the amount of input DNA ([Moberg et al., 2004](#)).

The identification of hrHPV DNA indicates the presence of the virus, whereas the presence of hrHPV RNA may serve as an indication of viral activity, and it has therefore been proposed by some researchers to be a more specific marker of cervical neoplasia than DNA ([Haedicke & Iftner, 2016](#)).

HPV tests can target multiple sequences throughout the viral genome or specific parts of a given viral gene. Many tests target the well-conserved part of the *L1* gene, whereas others target *E* genes. Viral integration in the human genome, which often occurs in the *E2* region, results in interruption of HPV DNA and enhanced transcription of the *E6–E7* sequence, which may predispose the cell to neoplastic transformation ([zur Hausen, 2002](#)). However, this molecular pathogenetic pathway has been challenged by HPV genome-wide next-generation sequencing analyses, which indicate that integration into the host DNA can occur almost anywhere throughout the viral genome ([Hu et al., 2015](#); [Dyer et al., 2016](#)). Moreover, no epidemiological evidence is currently available that indicates differences in diagnostic accuracy between tests targeting different genes ([Arbyn et al., 2015](#)).

With regard to the level of detail in HPV genotyping, the following can be distinguished: (i) no genotyping; (ii) limited genotyping, in which the most carcinogenic HPV types, HPV16 or HPV18 with or without HPV45, are distinguished from the other hrHPV types; (iii) extended genotyping, in which more hrHPV types – but not all – are distinguished separately; and (iv) full genotyping assays, which identify all individual hrHPV types of the high-risk group separately.

Some full genotyping tests detect additional individual HPV types that do not belong to the high-risk group. Certain types (HPV types 26, 53, 66, 67, 73, and 82) are possibly carcinogenic to humans (Group 2B). Their inclusion in HPV screening tests would increase the number of false-positive results and increase the burden of follow-up, cost, and harms associated with screening (see also Sections 1.2.1 and 1.2.2). Epidemiological research is under way to investigate whether all 12 HPV types classified as carcinogenic to humans (Group 1) should be routinely detected in primary HPV screening in an optimally efficient screening programme.

### (c) *Clinical applications of HPV testing*

HPV tests can be used for several clinical purposes: (1) as a primary cervical cancer screening test, alone or in combination with cytology (co-testing); (2) as a triage test for women with minor abnormal cervical cytology in the context of cytology-based screening; (3) for the triage of women with a positive primary hrHPV screening test result by genotyping, or as delayed triage when the reflex triage test result is negative; and (4) to monitor the success or failure of treatment of a precancerous lesion. Triage of hrHPV-positive women (application 3), distinguishes between (i) reflex triage with genotyping, in which the detection of the most carcinogenic types (HPV16 or HPV18) triggers referral to colposcopy, leaving women who are positive only for other hrHPV types to be triaged further, and (ii) delayed triage of hrHPV-positive women who had a negative reflex HPV triage test result. Reflex triage is the immediate testing with markers using the same specimen used for primary screening. New triage strategies propose to fine-tune the management of hrHPV-positive women according to the risk of present or incipient CIN3+ associated with individual genotypes or groups of genotypes ([Cheung et al., 2020](#); [Demarco et al., 2020](#)).

In addition to clinical purposes, HPV tests can also be used for epidemiological research and to evaluate the effects of HPV vaccination. To measure the effects of HPV vaccination in trials, high analytical sensitivity is required, whereas in clinical applications accuracy for clinically relevant outcomes is important (as discussed further below) ([WHO, 2010](#); [Dillner et al., 2011](#)). High-grade cervical lesions including CIN2+ (in particular, CIN3+) and AIS, and cervical SCC and adenocarcinoma of the cervix are all relevant clinical outcomes ([Herbert et al., 2008](#)).

HPV tests are typically performed on cervical specimens taken by health-care workers, but they can also be performed on self-collected vaginal samples or urine and on tissue specimens. This section focuses on the use of HPV tests in cervical cancer screening using cervical samples taken by a health professional. The use of HPV testing in other settings is described elsewhere: HPV genotyping in triage of hrHPV-positive women in Section 4.4.7 and hrHPV testing on self-collected samples and the use of HPV RNA testing in Sections 4.4.5 and 4.4.6, respectively.

In primary screening, hrHPV tests should yield results that are informative about the risk of having or developing cervical precancer or cancer and should have a balanced clinical sensitivity and specificity. Infections with low concentrations of virus, in particular infections with less carcinogenic hrHPV types that usually clear spontaneously, should ideally not be detected by a screening test ([Snijders et al., 2003](#); [Eklund et al., 2014](#)).

#### (i) Principles of HPV test validation

In 2009, an international team of virologists and clinical epidemiologists defined the minimum requirements that HPV assays should fulfil for them to be accepted for use in cervical cancer screening ([Meijer et al., 2009](#)). Two tests were accepted as standard comparator tests: Hybrid Capture 2 (HC2) and GP5+/6+ PCR enzyme immunoassay (EIA). Four large

population-based RCTs, conducted in Europe, have provided consistent evidence that screening with these assays provides better protection against future CIN3 or cancer compared with good-quality cytology ([Arbyn et al., 2012](#); [Ronco et al., 2014](#)). However, to validate other hrHPV DNA assays, it is not required to set up RCTs with long-term follow-up. It is deemed sufficient that three criteria ([Table 4.21](#)) are fulfilled to accept another hrHPV DNA test for use in primary cervical cancer screening. The given hrHPV DNA test (the index test) should have non-inferior cross-sectional sensitivity and specificity for CIN2+ compared with one of the comparator assays (HC2 or GP5+/6+ PCR EIA) ([Meijer et al., 2009](#)). The agreed benchmarks (index test divided by standard comparator test) are 0.90 for relative sensitivity and 0.98 for relative specificity. The paired statistical test for non-inferiority will be significant when the lower bound of the 90% confidence interval around the relative sensitivity or relative specificity is greater than or equal to the benchmark ([Tang et al., 2003](#)). A representative set of cervical samples (at least 60 CIN2+ cases and at least 800 < CIN2 cases) derived from a population-based screening cohort should be selected ([Meijer et al., 2009](#)). Moreover, the new test should show high intralaboratory and inter-laboratory reproducibility, with a lower bound of the 95% confidence interval of at least 87% or a kappa of at least 0.5 ([Meijer et al., 2009](#)). The recommended sample size for the reproducibility assessment is at least 500 with an hrHPV prevalence of 30% as established with a standard comparator test ([Table 4.21](#)). These guidelines apply only to hrHPV DNA testing. For screening tests using targets other than hrHPV DNA (e.g. HPV RNA, methylation markers, protein markers, or other test systems), additional longitudinal criteria are needed. For HPV DNA tests, these longitudinal data are not needed because the longitudinal safety (low 5-year risk of cancer after an earlier negative test result) is established through RCTs and supported by observational



**Table 4.21 International validation criteria for high-risk human papillomavirus (hrHPV) DNA tests acceptable for use in primary cervical cancer screening, based on the relative accuracy for detection of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) of an index HPV test compared with a standard comparator test<sup>a</sup>**

Criteria	Study population needed	Target
1. Relative sensitivity <sup>b</sup>	≥ 60 samples from women with CIN2+	<i>P</i> for non-inferiority < 0.05 <sup>c</sup> (accepting 0.90 as benchmark) The lower bound of the 90% CI should be ≥ 0.90
2. Relative specificity <sup>b</sup>	≥ 800 samples from women with < CIN2	<i>P</i> for non-inferiority < 0.05 <sup>c</sup> (accepting 0.98 as benchmark) The lower bound of the 90% CI should be ≥ 0.98
3. Intralaboratory and interlaboratory reproducibility	≥ 500 samples from a screening population with an hrHPV prevalence of 30% (as established with a standard comparator test)	Lower bound of the 95% CI ≥ 87% Kappa ≥ 0.5

CI, confidence interval; CIN2, cervical intraepithelial neoplasia grade 2; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; hrHPV, high-risk human papillomavirus.

<sup>a</sup> Standard comparator tests: Hybrid Capture 2 and GP5+/6+ polymerase chain reaction (PCR) enzyme immunoassay (EIA). These two tests have been validated through randomized controlled trials that demonstrated lower incidence of cervical cancer compared with good-quality cytology.

<sup>b</sup> Relative accuracy of the index hrHPV DNA test compared with the standard comparator test for the outcome CIN2+.

<sup>c</sup> One-sided non-inferiority test for paired data accepting a power of 90% and a confidence level of 95% (Tang et al., 2003). Because this statistical test is one-sided, the equivalent confidence level for the lower bound of the CI (two-sided expression) should be 90%.

Compiled from Meijer et al. (2009).

longitudinal studies. However, for other molecular targets, a high cross-sectional sensitivity does not provide sufficient evidence that the lead-time gain (time span between detectability of a neoplastic lesion and when it becomes clinically manifest) is similar to that for HPV DNA and that use of the same screening interval as that proposed for hrHPV DNA screening tests (usually 5 years or longer) can be accepted as safe.

### (ii) Updating and extension of HPV test validation guidelines

The international validation criteria (Meijer et al., 2009) are for hrHPV DNA testing on cervical samples. Currently, new criteria are being developed that will include HPV genotyping and HPV testing on alternative specimens (self-collected vaginal samples or urine) and may involve standard comparator tests other than HC2 and GP5+/6+ PCR EIA (Arbyn & Hillemanns, 2018). Recent meta-analyses indicated that HPV tests based on a principle of signal amplification (e.g. HC2 or *careHPV*) are less sensitive and specific

for the detection of CIN2+ on self-collected vaginal samples than on clinician-collected cervical samples. RNA-based HPV assays are less sensitive on self-collected samples. However, PCR-based hrHPV DNA assays, validated on cervical specimens, seem to be as sensitive and nearly as specific on vaginal samples as they are on cervical samples (Arbyn et al., 2014, 2018).

### (iii) Assays that detect molecules other than hrHPV DNA

An HPV RNA assay targeting E6/E7 transcripts of only five HPV types (HPV types 16, 18, 31, 33, and 45) was significantly less sensitive but more specific than the standard comparator hrHPV DNA tests (Arbyn et al., 2015). Another RNA HPV assay targeting E6/E7 transcripts of 14 hrHPV types in bulk fulfils the three international cross-sectional validation criteria described in Table 4.21 (Arbyn et al., 2015). The assessment of its longitudinal performance and risk of CIN3+ after baseline testing with an RNA

test versus after testing with a validated DNA test is covered in Section 4.4.6.

(iv) *Other important factors that influence the choice of a screening test*

In addition to accuracy, other characteristics need to be taken into account when choosing a screening test, such as the availability of the assay, reagents, and disposables, the throughput capacity and turnaround time (time span between arrival of the specimen and communication of the result), costs, applicability on samples taken by the woman (self-collected vaginal samples or urine), the requirement for equipped laboratories, user-friendliness, the need for running water and electricity, the possibility of point-of-care testing, and the possibility of providing triage information (genotyping or viral load). A comprehensive overview of logistic, regulatory, managerial, training, and quality control aspects of the choice of HPV assays, procurement, sample collection, transport of specimens to the laboratory, pre-analytical handling, testing, and result communication was given in a recent WHO document ([WHO, 2020a](#)).

Most of the assays that have been validated to date for screening require a well-equipped laboratory to perform the HPV tests. Two hrHPV DNA assays, one using the hybrid capture principle and the other using a cartridge, are prequalified by WHO for hrHPV testing in field conditions in low-resource countries ([WHO, 2019](#)). Point-of-care hrHPV testing is particularly relevant for screen-and-treat strategies (see Section 5.1).

#### 4.4.2 Comparison of HPV DNA testing versus cytology

(a) *Introduction*

The evidence for HPV DNA testing as a modality for primary cervical screening has been accumulating for two decades. From first principles, molecular testing for the presence of HPV

provides a sensitive assessment of a woman's risk of currently harbouring, or in the future developing, a precancer or invasive cervical cancer, because nearly all cervical cancers are caused by HPV infection.

In the 2005 *IARC Handbook* on cervical cancer screening ([IARC, 2005](#)), the performance of HPV assays in the detection of precancerous lesions was compared with that of cytology. At the time, almost all of the evidence was from cross-sectional studies, and there was no prospective evaluation of the impact of primary HPV screening on invasive cervical cancer. Nevertheless, the *Handbook* concluded: "For primary screening of women older than 30 years of age, HPV testing yields on average about 10–20% greater sensitivity and 10% lower specificity than cytology (either conventional or liquid-based). In some studies, the combination of cytology and HPV testing (as independent or reflex testing) attained very high sensitivity and negative predictive values (approaching 100%). A testing combination with such a high negative predictive value could potentially allow screening intervals to be increased, e.g., from the minimum of three years up to five years or longer, depending on the population and risk profile. The drawback of this approach is the loss in specificity with respect to either test in isolation due to the excessive number of patients who would need to be referred for colposcopy."

Since the publication of the 2005 *IARC Handbook*, the evidence base on the sensitivity and NPV of HPV DNA testing versus cytology has become substantially larger, and direct evidence has become available on the protection provided by HPV-based and cytology-based screening against cervical cancer and death from cervical cancer. Furthermore, the screening process for CIN2+ and CIN3+ has been evaluated in the context of a combination of measures taken to increase specificity and minimize harms, including the appropriate use of triage of HPV-positive women (see Section 4.4.7 and

Section 4.4.8). The evidence base for the relative performance of HPV and cytology screening now includes: (i) cross-sectional diagnostic studies, which have been synthesized in meta-analyses to provide evidence on the relative sensitivity and specificity of HPV DNA testing versus cytology for the detection of CIN2 and CIN3; (ii) evidence from longitudinal RCTs, mainly in high-income countries, to evaluate whether the increased detection of CIN2+ with HPV testing results in a decrease in CIN2+ in the subsequent screening round; (iii) evidence from a major RCT of HPV DNA testing versus cytology versus VIA screening in India, with cervical cancer incidence and mortality outcomes, and evidence from individual data of four RCTs in Europe that were pooled to evaluate the effect on cancer incidence; (iv) randomized health services trials and national, regional, and pilot screening programmes, which provide information about the impact of HPV-based screening, sometimes with new, less-aggressive protocols, on the detection of CIN3+ and on resource consumption, and which will provide evidence about effectiveness, and (v) longitudinal studies of women screened by HPV testing and cytology, which are particularly relevant for defining risk-based screening intervals.

This experience, combined with well-validated modelling of the longer-term effects of scaled-up HPV testing, has supported the increased use of HPV testing as the sole primary screening test (or, in a few settings, as a co-test with cytology) in high-income countries and the recommendation to support HPV testing in the 2020 WHO strategic plan for the elimination of cervical cancer as a public health problem ([WHO, 2020b](#)). Since 2017, several high-income countries have transitioned from cytology screening to primary HPV screening programmes at screening intervals of 5 years or longer, and this is increasingly also providing evidence on the real-world experience with HPV screening.

### (b) *Diagnostic studies*

A Cochrane review published in 2017 compared the accuracy of HPV testing and cervical cytology for the detection of CIN2+ and CIN3+ in women who were participating in cervical cancer screening and who were not being followed up for previous cytological abnormalities ([Koliopoulos et al., 2017](#)). This systematic review and meta-analysis searched for articles published between 1992 and 2015. The review focused on studies in which all women received both HPV testing and cervical cytology. A combination of colposcopy and histology was used as the reference standard. If at least one of the screening tests was positive, women underwent colposcopy with directed biopsy of abnormal areas and histological verification. Women did not know their disease status at the time of recruitment. Of the 40 eligible studies, which included more than 140 000 women, 29 studies conducted head-to-head comparison of HPV DNA testing by signal amplification or target amplification versus conventional cytology or LBC (Pap) testing using a threshold of ASC-US for the detection of CIN2+ or CIN3+.

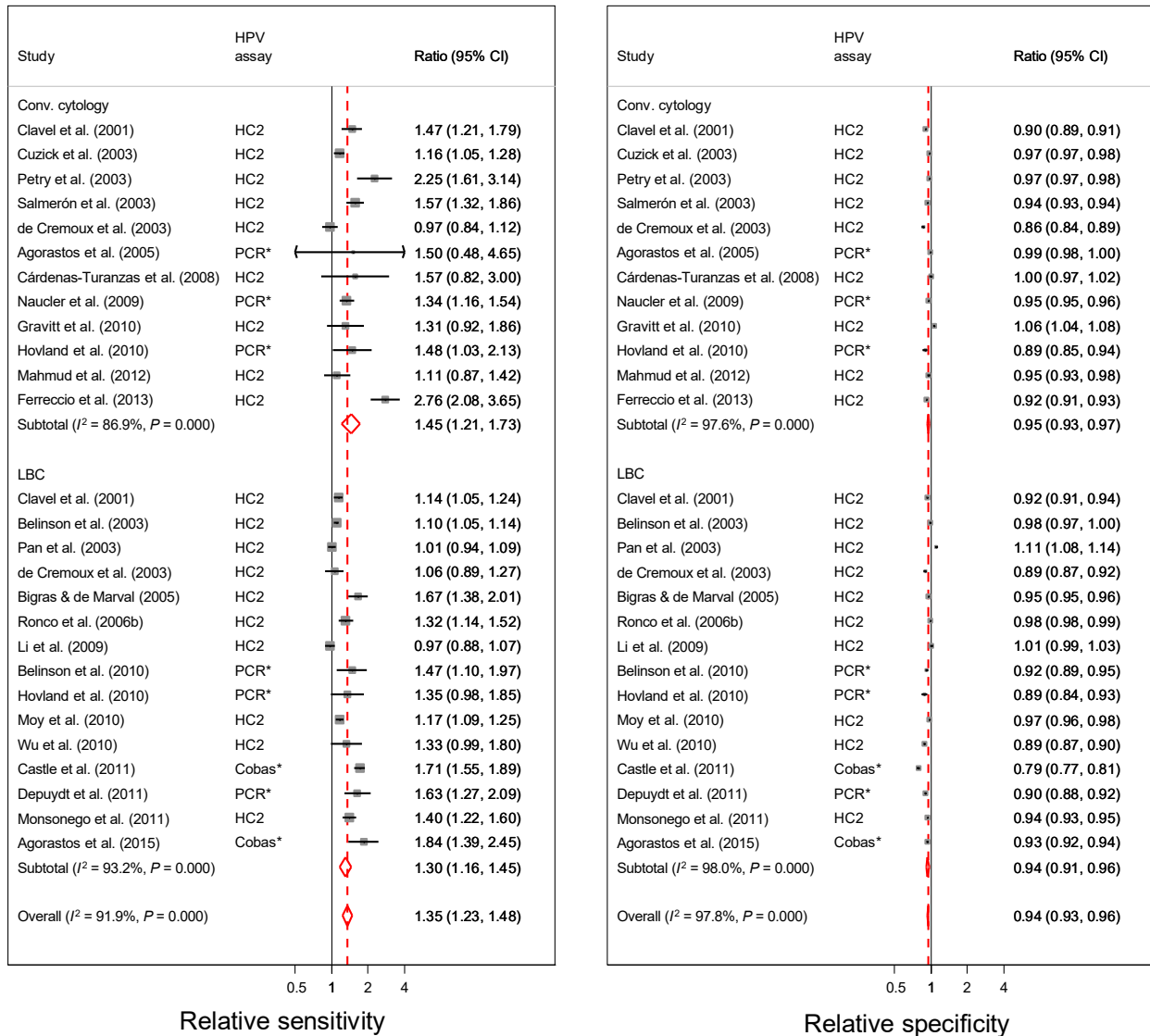
For the detection of CIN2+, the sensitivity of HPV DNA-based tests was higher than that of cytology methods (pooled relative sensitivity, 1.35; 95% CI, 1.23–1.48) and the specificity was lower (pooled relative specificity, 0.94; 95% CI, 0.93–0.96) ([Fig. 4.2](#)). For the detection of CIN3+, the pooled relative sensitivity was 1.37 (95% CI, 1.20–1.55) and the pooled relative specificity was 0.95 (95% CI, 0.94–0.97) ([Fig. 4.3](#)).

### (c) *RCTs*

#### (i) *Description*

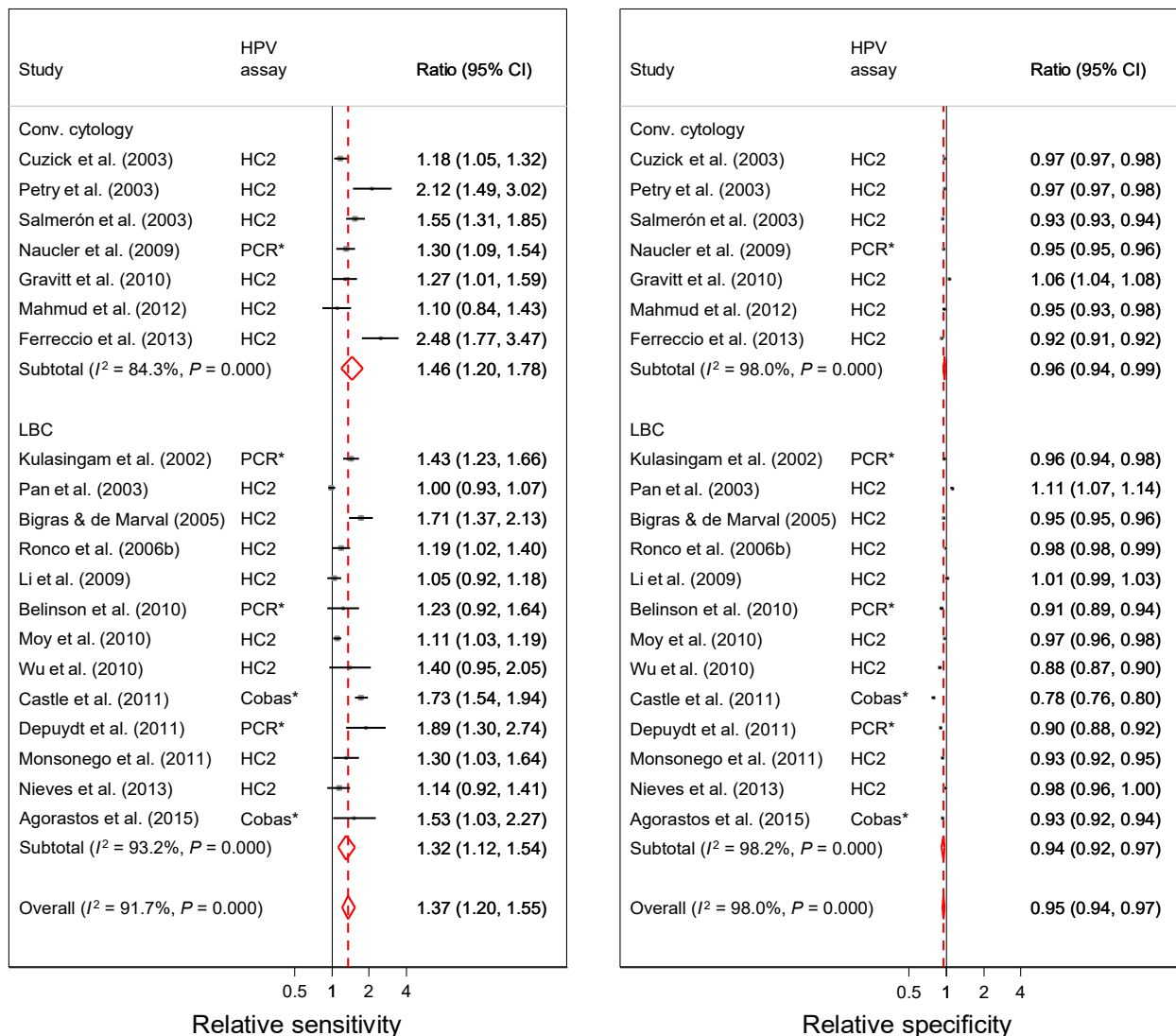
When the 2005 *IARC Handbook* was published, large RCTs of HPV testing in primary cervical cancer screening were in progress but had not yet reported longitudinal outcomes. Since then, eight major RCTs comparing HPV DNA-based screening with cytology-based

**Fig. 4.2 Relative sensitivity (left) and relative specificity (right) of hrHPV testing compared with cytology at a threshold of ASC-US+ for the detection of CIN2+**



ASC-US+, atypical squamous cells of undetermined significance or worse; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; Cobas\*, cobas 4800; Conv., conventional; HC2, Hybrid Capture 2; hrHPV, high-risk human papillomavirus; LBC, liquid-based cytology; PCR\*, polymerase chain reaction-based assay targeting at least 13 carcinogenic HPV types. Created by the Working Group with data from [Koliopoulos et al. \(2017\)](#).



**Fig. 4.3 Relative sensitivity (left) and relative specificity (right) of hrHPV testing compared with cytology at a threshold of ASC-US+ for the detection of CIN3+**

ASC-US+, atypical squamous cells of undetermined significance or worse; CI, confidence interval; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; Cobas\*, cobas 4800; Conv., conventional; HC2, Hybrid Capture 2; hrHPV, high-risk human papillomavirus; LBC, liquid-based cytology; PCR\*, polymerase chain reaction-based assay targeting at least 13 carcinogenic HPV types.  
 Created by the Working Group with data from [Koliopoulos et al. \(2017\)](#).

screening have reported results. An important goal of the RCTs was to evaluate whether the excess CIN2+ detected by HPV DNA-based screening represented clinically relevant persistent disease. For this purpose, women were randomly assigned to HPV DNA-based testing or cytology-based screening at enrolment, and it was investigated whether an increase in detection of CIN2+ in the intervention arm versus the control arm in the first round was followed by a decrease in the second round. In addition, to avoid bias, in the second round in most studies the same screening methodology was applied in both arms. RCTs have also been used to study the benefits of combined HPV DNA testing and cytology (co-testing) compared with primary HPV DNA testing. Those analyses are reviewed in Section 4.4.4. Brief descriptions of the characteristics of the eight major RCTs are given here.

Five RCTs were conducted in European countries, all within organized screening programmes in which the target population was actively invited to primary screening and, if needed, triage testing and treatment. These programmes routinely recorded the numbers of women invited, screened, and treated.

The New Technologies for Cervical Cancer Screening (NTCC) trial was conducted at nine participating centres in Italy and enrolled a total of 94 370 women aged 25–60 years over two implementation phases in 2002–2004. In the intervention arm, co-testing with HPV (HC2) testing and LBC was applied in the first phase (45 174 women enrolled in 2002–2003) and stand-alone HPV testing was applied in the second phase (49 196 women enrolled in 2002–2004). In the first phase, participants in the intervention arm younger than 35 years were referred for colposcopy if they were ASC-US+ or if they were HPV-positive and/or ASC-US+ after 1 year. Women aged 35 years and older were referred for colposcopy if they were HPV-positive and/or ASC-US+. In the second phase, all HPV-positive women were immediately referred for colposcopy, irrespective of

age. In the control arm, women were screened using conventional cytology alone. In the second round, all women were screened using conventional cytology, and no further HPV testing was done. Results from the first two rounds of screening, with a 3-year interval (total follow-up period, 7 years), have been published ([Ronco et al., 2006a, b, 2008, 2010](#)).

The Population Based Screening Study Amsterdam (POBASCAM) trial was conducted in the Greater Amsterdam region in the Netherlands. Women aged 29–61 years were recruited in 1999–2002. A total of 44 102 women were enrolled and randomized either to co-testing with HPV DNA (GP5+/6+ PCR EIA) testing and conventional cytology or to stand-alone conventional cytology in the first round. In the second round in both arms, HPV testing and cytology were performed on all participants 5 years later. Women with HSIL cytology were immediately referred for colposcopy, and women with ASC-US or LSIL cytology were offered repeat testing after 6 months and 18 months and then referred for colposcopy if they were cytology-positive. In the intervention arm, HPV-positive women with NILM cytology were also offered repeat testing followed by colposcopy if the second HPV test was positive ([Bulkmans et al., 2004](#)). Data were initially published on the first two screening rounds, with a 5-year interval, for about half of the cohort ([Bulkmans et al., 2007](#)) and then for the entire cohort ([Rijkaart et al., 2012a](#)). Further analyses have examined long-term risks ([Dijkstra et al., 2016](#)) and additional specific hypotheses on management of different screening results with different combinations of test results over one or two screening rounds ([Veldhuijzen et al., 2017](#); [Polman et al., 2019a](#)).

The Randomized Controlled Trial of Human Papillomavirus Testing in Primary Cervical Cancer Screening (SwedeScreen) trial was conducted in five cities in Sweden. A total of 12 527 women aged 32–38 years were enrolled and randomized either to co-testing with HPV

DNA (GP5+/6+ PCR EIA) testing and conventional cytology or to conventional cytology alone ([Naucler et al., 2007](#)). Women with ASC-US+ were referred for colposcopy. In the intervention arm, HPV-positive women with NILM cytology received repeat HPV testing after 12 months and were referred for colposcopy if the HPV test result was positive. In the second screening round, all women were screened with conventional cytology. The initial analysis included two screening rounds with an average of 4 years of follow-up per woman. Subsequent analyses have included long-term follow-up data ([Elfström et al., 2014](#); [Elfgren et al., 2017](#)).

The A Randomised Trial In Screening To Improve Cytology (ARTISTIC) trial was conducted in Greater Manchester, United Kingdom. A total of 24 510 women aged 20–64 years were enrolled in 2001–2003. Women were randomized 3:1 either to co-testing with HPV DNA (HC2) testing and LBC or to LBC alone. The management of screen-positive women in both arms was similar to that in the POBASCAM trial. The screening protocol for the second round was the same as that for the first round. Data from the first two screening rounds, 3 years apart, were initially reported ([Kitchener et al., 2009a, b](#)). Further analyses have reported on the long-term follow-up of this trial ([Kitchener et al., 2011](#)).

The Finnish trial was conducted in Finland in 2003–2008 ([Leinonen et al., 2012](#)) and enrolled 132 194 women aged 25–65 years. Participants were randomized either to primary screening with HPV DNA (HC2) testing, with conventional cytology triage if HPV-positive (intervention arm) or to conventional cytology alone (control arm). The follow-up period was limited to one screening round with follow-up after 5 years for cumulative detection of CIN, AIS, and invasive cervical cancer. Women in the intervention arm who were HPV-positive and with LSIL or worse (LSIL+) cytology and women in the control arm who were LSIL+ were referred for colposcopy,

and women who were HPV-positive and with less than LSIL cytology (intervention arm) or with ASC-US (control arm) were followed up with repeat testing.

The HPV For Cervical Cancer Screening (HPV FOCAL) trial was conducted in Canada in 2008–2016 ([Ogilvie et al., 2017, 2018](#); [Coldman et al., 2020](#)). A total of 19 009 women aged 25–65 years attending routine screening were randomized 1:1:1 into one of three groups: primary HPV DNA screening (stand-alone) with LBC triage of HPV-positive women (intervention arm), primary HPV DNA screening (stand-alone) with LBC triage of HPV-positive women and a 2-year safety check (safety arm), and LBC screening with HPV DNA triage of women with an ASC-US result (control arm) and colposcopy for women with LSIL+. In the intervention arm, HPV-negative women were recalled for exit screening with both LBC and HPV testing at 4 years. In the safety arm, HPV-negative women were recalled for exit screening with LBC at 2 years. In the control arm, women with NILM LBC were recalled for screening with LBC at 2 years and then again for exit screening with both LBC and HPV testing at 4 years.

The Hong Kong Special Administrative Region (Hong Kong SAR) trial was conducted at seven clinics in Hong Kong SAR, China, in 2010–2014 ([Chan et al., 2020](#)). A total of 15 955 women aged 30–60 years attending routine screening were randomized either to co-testing with HPV testing and LBC (intervention arm) or to LBC with HPV DNA triage of women with an ASC-US+ result (control arm). Women were referred for colposcopy if they were HPV-positive and/or had LSIL+. If the co-testing result was HPV-negative and ASC-US, repeat testing was offered. There were two rounds of screening, with a 3-year interval, and all women were screened with LBC in the second round.

The Compass trial, in Australia, is the first prospective RCT of primary HPV screening compared with cytology to be conducted in a

population with high coverage of HPV vaccination. Women aged 25–64 years were enrolled in 2015–2019 (Canfell et al., 2018). Participants were randomized 1:2 either to 2.5-yearly LBC with HPV triage of low-grade LBC (control arm) or to 5-yearly primary HPV testing (intervention arm). In the intervention arm, women who are positive for HPV16 or HPV18 are directly referred for colposcopy, and women who are positive for other (non-HPV16/18) carcinogenic HPV types undergo secondary randomization 1:1 to either LBC or dual-stain cytology (p16<sup>INK4a</sup> and Ki-67). In addition, 10% of women in the intervention arm who test negative for HPV will be recalled at 2.5 years for screening with LBC, for safety monitoring purposes. To date, data on the baseline and 12-month follow-up in 4995 women enrolled in 2013–2014 in the Compass pilot trial have been published (Canfell et al., 2017).

The only RCT to evaluate the effect of a single round of screening on cervical cancer incidence and associated mortality was conducted in Osmanabad District in India. This cluster RCT included 131 746 women aged 30–59 years from 52 village clusters randomly assigned to four groups in 2000–2003 (Sankaranarayanan et al., 2009). The groups were randomly assigned to undergo screening with HPV testing (34 126 women), conventional cytology (32 058 women), or VIA (34 074 women) or to receive standard care without screening (31 488 women; control group). Women who had positive results on screening underwent colposcopy and directed biopsies, and those with cervical precancerous lesions or cancer received appropriate treatment. The main results were reported with follow-up until 2007.

Efficacy results from RCTs comparing HPV-based screening with cytology-based screening have been compiled in systematic reviews and meta-analyses (Arbyn et al., 2012; Melnikow et al., 2018). Results per trial are presented in Table 4.22 and in Fig. 4.4. Relative risks and 95% confidence intervals were

recalculated by the Working Group. A normal distribution for the logarithm of the estimated relative risk was used to calculate confidence intervals. The NTCC first phase and second phase were pooled, and only NTCC participants aged 35 years and older were included in the analyses. Pooled meta-analytic estimates of the relative risks were calculated by the Working Group assuming a random-effects model and applying restricted maximum-likelihood estimation.

### (ii) Detection of CIN2+ and CIN3+

In the eight RCTs comparing primary HPV DNA testing alone or co-testing with HPV DNA testing and cytology (intervention arm) with cytology (control arm), there was consistent evidence that the detection rates of CIN2+ and CIN3+ were higher in the HPV DNA testing arm than in the cytology arm in the first round of screening (Fig. 4.4). In the eight RCTs, the relative risk for the detection of CIN2+ by HPV DNA testing compared with cytology ranged from 1.13 (95% CI, 0.94–1.37) in the ARTISTIC trial (Kitchener et al., 2009b) to 10.95 (95% CI, 1.51–79.34) in the Compass trial (Canfell et al., 2017), and the relative risk for the detection of CIN3+ ranged from 0.97 (95% CI, 0.75–1.25) in the ARTISTIC trial (Kitchener et al., 2009b) to 7.46 (95% CI, 1.02–54.66) in the Compass pilot trial (Canfell et al., 2017). Although the relative risks shown in Fig. 4.4 varied considerably across studies, seven of the eight RCTs reported a relative risk for the detection of CIN2+ with a lower bound of the 95% confidence interval between 1 and 2, and five of the eight RCTs reported a relative risk for the detection of CIN3+ with a lower bound of the 95% confidence interval between 1 and 2.

The risk of CIN2+ in the second round of screening was significantly lower in women who were randomized to HPV testing than in those in the cytology arm in the first round of screening (Fig. 4.4). The relative risk of CIN2+ ranged from

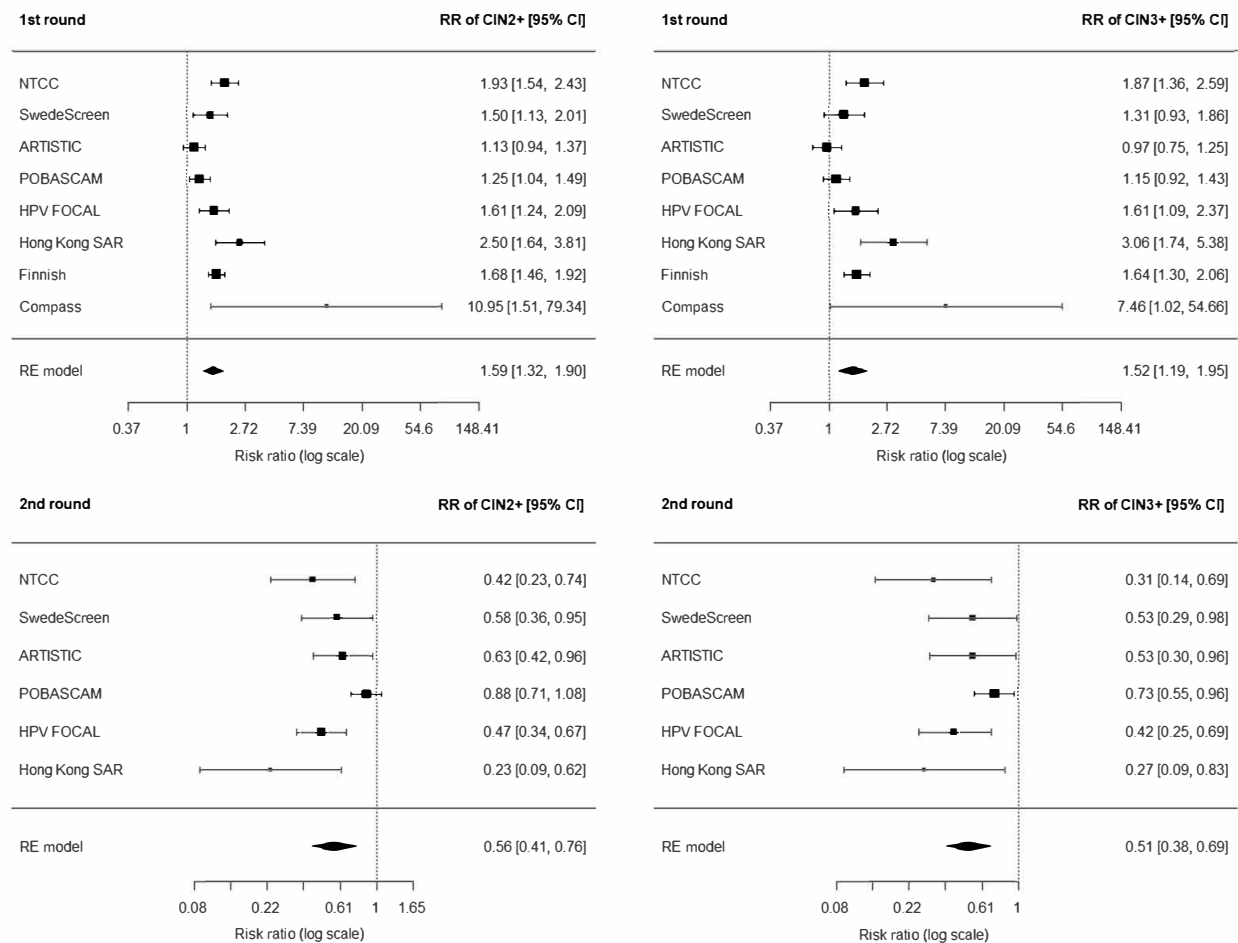


**Table 4.22 Randomized controlled trials with an HPV-based screening arm (intervention arm) and a cytology arm (control arm)**

Trial Country Reference	Age (years)	No. of screening rounds (interval, years)	Screening strategy in round 1: intervention vs control	No. of women in round 1	No. of colposcopy referrals (%)	No. detected (%)		PPV for CIN3+ (%)	No. of women for round 2 calculation	No. detected (%)	
						CIN2+	CIN3+			CIN2+	CIN3+
NTCC Italy <a href="#">Ronco et al. (2006b, 2008, 2010)</a>	35–60	2 (3)	Co-testing (phase 1) or hrHPV (phase 2)	34 430	2768 (8.0%)	213 (0.6%)	105 (0.3%)	3.8	33 733	16 (0.05%)	8 (0.02%)
			Cytology	34 405	928 (2.7%)	110 (0.3%)	56 (0.2%)	6.0	34 202	39 (0.1%)	26 (0.08%)
SwedeScreen Sweden <a href="#">Naucler et al. (2007)</a>	32–38	2 (3)	Co-testing	6257	265 (4.2%)	114 (1.8%)	72 (1.2%)	27.2	6257	25 (0.4%)	16 (0.3%)
			Cytology	6270	150 (2.4%)	76 (1.1%)	55 (0.9%)	36.7	6270	43 (0.7%)	30 (0.5%)
ARTISTIC United Kingdom <a href="#">Kitchener et al. (2009a)</a>	20–64	2 (3)	Co-testing	18 386	1247 (6.8%)	453 (2.5%)	233 (1.3%)	18.7	11 676	65 (0.6%)	29 (0.3%)
			Cytology	6124	320 (5.2%)	133 (2.2%)	80 (1.3%)	25.0	3866	34 (0.9%)	18 (0.5%)
Finnish Finland <a href="#">Leinonen et al. (2012)</a>	25–65	1 (5)	hrHPV	66 410	NR	540 (0.8%)	195 (0.3%)	NR	NR	NR	NR
			Cytology	65 784	NR	319 (0.5%)	118 (0.2%)	NR	NR	NR	NR
POBASCAM Netherlands <a href="#">Rijkaart et al. (2012a)</a>	29–56	2 (5)	Co-testing	19 999	NR	267 (1.3%)	171 (0.9%)	NR	19 579	160 (0.8%)	88 (0.5%)
			Cytology	20 106	NR	215 (1.1%)	150 (0.7%)	NR	19 731	184 (0.9%)	122 (0.6%)
Compass Australia <a href="#">Canfell et al. (2017)</a>	25–64	1 (5)	hrHPV	4000	154 (3.8%)	44 (1.1%)	30 (0.8%)	19.5	NR	NR	NR
			Cytology	995	27 (2.7%)	1 (0.1%)	1 (0.1%)	3.7	NR	NR	NR
HPV FOCAL Canada <a href="#">Ogilvie et al. (2018)</a>	25–65	2 (4)	hrHPV	9540	544 (5.7%)	147 (1.5%)	67 (0.7%)	12.3	9540	48 (0.5%)	22 (0.2%)
			Cytology	9408	290 (3.1%)	90 (9.6%)	41 (0.4%)	14.1	9408	100 (1.1%)	52 (0.6%)
Hong Kong Special Administrative Region trial China <a href="#">Chan et al. (2020)</a>	30–60	2 (3)	Co-testing	7931	738 (9.3%)	75 (1.0%)	49 (0.6%)	6.6	6018	5 (0.08%)	4 (0.07%)
			Cytology	7927	157 (2.0%)	30 (0.4%)	16 (0.2%)	10.2	6203	22 (0.4%)	15 (0.2%)

ARTISTIC, A Randomised Trial In Screening To Improve Cytology; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HPV, human papillomavirus; HPV FOCAL, HPV For Cervical Cancer Screening; NR, not reported; NTCC, New Technologies for Cervical Cancer Screening; POBASCAM, Population Based Screening Study Amsterdam; PPV, positive predictive value; RCT, randomized controlled trial; SwedeScreen, Randomized Controlled Trial of Human Papillomavirus Testing in Primary Cervical Cancer Screening; yr, year or years.

**Fig. 4.4 Randomized controlled trials comparing HPV-based screening versus cytology screening: relative risk of CIN2+ and CIN3+ in the first and second screening rounds**



Risk ratio (RR) of CIN2+ (left panel) or CIN3+ (right panel) at first (top) and second (bottom) cervical screening rounds comparing HPV testing with cytology in eight clinical trials.

ARTISTIC, A Randomised Trial In Screening To Improve Cytology; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HPV, human papillomavirus; HPV FOCAL, HPV For Cervical Cancer Screening; NTCC, New Technologies for Cervical Cancer Screening; POBASCAM, Population Based Screening Study Amsterdam; RE model, random-effects model; SAR, Special Administrative Region; SwedeScreen, Randomized Controlled Trial of Human Papillomavirus Testing in Primary Cervical Cancer Screening.

The pooled estimates were computed by the Working Group based on the data presented in [Table 4.22](#), using the restricted maximum-likelihood estimator method of the metafor library in R for random/mixed-effects models. Source: see [Table 4.22](#) for references.

0.23 (95% CI, 0.09–0.62) in the Hong Kong SAR trial ([Chan et al., 2020](#)) to 0.88 (95% CI, 0.71–1.08) in the POBASCAM trial ([Rijkaart et al., 2012a](#)), and the relative risk of CIN3+ ranged from 0.27 (95% CI, 0.09–0.83) in the Hong Kong SAR trial ([Chan et al., 2020](#)) to 0.73 (95% CI, 0.55–0.96) in the POBASCAM trial ([Rijkaart et al., 2012a](#)).

The ARTISTIC, POBASCAM, and SwedeScreen trials also reported the cumulative number of CIN2+ and CIN3+ cases detected in the first and second rounds and during extended follow-up beyond the second round, stratified by the HPV DNA testing and/or cytology result at baseline ([Kitchener et al., 2011](#); [Elfström et al., 2014](#); [Dijkstra et al., 2016](#)). In the ARTISTIC trial, the cumulative CIN3+ risk in women with a negative HPV test was 0.13% after two rounds of screening (with an interval of 3 years) and 0.28% after three rounds of screening, whereas the cumulative CIN3+ risk in women with normal cytology was 0.31% after two rounds and 0.63% after three rounds. In the POBASCAM and SwedeScreen trials, separate CIN3+ risks were calculated for the intervention arm and the control arm. In the POBASCAM trial, the cumulative CIN3+ risk in women from the intervention arm with a negative HPV test was 0.31% (95% CI, 0.24–0.41%) after two rounds of screening (with an interval of 5 years) and 0.56% (95% CI, 0.45–0.70%) after three rounds of screening, whereas the cumulative CIN3+ risk in women from the control group with normal cytology was 0.69% (95% CI, 0.58–0.82%) after two rounds and 1.20% (95% CI, 1.01–1.37%) after three rounds ([Dijkstra et al., 2016](#)). In the SwedeScreen trial, follow-up data were collected up to 13 years after enrolment and reported for specific time points. The cumulative CIN3+ risk in women from the intervention group with a negative HPV test was 0.04% after 3 years, 0.15% after 5 years, and 0.44% after 10 years, whereas the cumulative CIN3+ risk in women from the control group with normal cytology was 0.20% after 3 years, 0.51% after 5 years, and 0.97%

after 10 years ([Elfström et al., 2014](#)). The relative cumulative risk of CIN3+ in HPV-negative women compared with women with normal cytology ranged from 0.42 to 0.57 across trials and time points.

[The studies showed considerable variation in HPV and cytology testing technology, age ranges, and management in the HPV DNA testing intervention arms. Five of the eight RCTs evaluated co-testing with HPV testing and cytology compared with cytology alone. The trials also differed in their methods of disease ascertainment at exit testing. For example, in the NTCC and SwedeScreen trials the second round of screening was conducted with cytology, whereas in the POBASCAM and HPV FOCAL trials the second round of screening was conducted with co-testing with HPV testing and cytology, and in the ARTISTIC trial the screening protocols were the same in the first and second rounds. Furthermore, the definition of the second screening round varied across studies. In some trials (e.g. the POBASCAM and HPV FOCAL trials), the start of the second round was based only on time since enrolment, whereas some other trials also used criteria for the start of the second round that depended on the screening results in the first round. Despite design differences, most trials showed an increase in CIN3+ in the first round, and all trials with two screening rounds showed a decrease in CIN3+ in the second round.]

(iii) *Efficacy of screening for prevention of cervical cancer and associated death*

In the Osmanabad District trial ([Sankaranarayanan et al., 2009](#)), different screening strategies (HPV testing, conventional cytology, and VIA) were compared with standard care, but risk ratios for the comparison of HPV testing with cytology can be calculated from the tabulated number of cases and the person-years at risk. The risk ratios for the detection of advanced cancer (International Federation of Gynecology

and Obstetrics [FIGO] stage II or higher) and for cervical cancer mortality in the HPV testing group compared with the cytology group were 0.63 (95% CI, 0.41–0.96) and 0.59 (95% CI, 0.37–0.92), respectively. No reduction in all-cause mortality was observed for any screening intervention group compared with the standard-care control group.

[It is important to bear two issues in mind when interpreting the findings. First, the trial represented the findings of one round of screening in a previously unscreened population. Therefore, risk ratios for cervical cancer mortality are different from those in situations where women are repeatedly screened during their lifetime. Second, although active steps were taken to ascertain vital status and cause of death in the population, it is possible that in this setting there were some limitations in the processes of cancer registration and death ascertainment.]

A pooled analysis of four RCTs conducted in Europe compared the efficacies of HPV DNA testing and cervical cytology for the prevention of invasive cervical cancer ([Ronco et al., 2014](#)). This analysis was critical, because it examined an invasive cervical cancer end-point for the first time in a high-income country setting. The pooled analysis included 176 464 women aged 20–64 years who were randomly assigned to HPV-based screening (intervention arm) or cytology-based screening (control arm) in Italy (NTCC), the Netherlands (POBASCAM), Sweden (SwedeScreen), and the United Kingdom (ARTISTIC). Women were followed up for a median of 6.5 years, and during that time 107 invasive cervical carcinomas were detected. Cumulative detection of invasive cervical cancer was lower in the HPV testing arm than in the cytology arm during the study period (rate ratio, 0.60; 95% CI, 0.40–0.89), and no heterogeneity was detected between studies ( $P = 0.52$ ). Detection of invasive cervical carcinoma was similar between screening methods during the first 2.5 years of follow-up (rate ratio, 0.79; 95%

CI, 0.46–1.36) but was significantly lower in the HPV arm thereafter (rate ratio, 0.45; 95% CI, 0.25–0.81). In women with a negative screening test at entry (HPV-negative in the intervention arm and cytology-negative in the control arm), the rate ratio was 0.30 (95% CI, 0.15–0.60). The cumulative incidence of invasive cervical carcinoma in women with negative entry tests was 4.6 (95% CI, 1.1–12.1) per 100 000 women at 3.5 years and 8.7 (95% CI, 3.3–18.6) per 100 000 women at 5.5 years in the HPV testing arm and 15.4 (95% CI, 7.9–27.0) per 100 000 women at 3.5 years and 36.0 (95% CI, 23.2–53.5) per 100 000 women at 5.5 years in the cytology arm. The pooled rate ratio was lower for adenocarcinoma (0.31; 95% CI, 0.14–0.94) than for SCC (0.78; 95% CI, 0.49–1.25). The lowest rate ratios were observed in women aged 30–34 years (0.36; 95% CI, 0.14–0.94).

[The authors found no heterogeneity in efficacy between studies, which supports the pooling of data and the overall pooled findings. It should be noted that data from these trials are representative of women followed up for at least two rounds of screening, which may be different from long-term, steady-state effects of repeated rounds of screening with a particular screening test and management protocol in a population.]

#### (iv) Harms

Harms during the first round of screening were measured by the proportion of women referred for colposcopy after a positive screening test and by the PPV for CIN3+ (the proportion of CIN3+ detected in women referred for colposcopy). The number of colposcopy referrals includes women who were referred at baseline or after repeat testing within the same screening round. The proportion of colposcopy referrals was generally higher for HPV-based screening than for cytology-based screening ([Table 4.22](#)). The biggest differences in colposcopy referrals between the study arms were found in the NTCC trial (8.0% vs 2.7%) and the Hong Kong SAR trial (9.3% vs 2.0%), in which HPV-positive



women were not offered triage testing but were immediately referred for colposcopy. The PPV for CIN3+ was similar in the two study arms or higher in the cytology arm in all studies, with the exception of the Compass trial, in which the PPV was higher in the HPV-based testing arm (19.5%) than in the cytology arm (3.7%).

[The number of women with a positive screening test result and the number of colposcopies should be interpreted in relation to the number of CIN3+ detected. If the number of CIN3+ is proportional to the number of colposcopy referrals, then the harms per detected CIN3+ remain unchanged.]

A more complete picture of the harms of screening is obtained from the number of diagnostic procedures when measured over multiple rounds of screening. In the HPV FOCAL trial, the cumulative colposcopy referral rates were similar in the two study arms over two rounds of screening, and in the Hong Kong SAR trial, in which HPV-positive women were immediately referred for colposcopy, the cumulative colposcopy referral rate was higher in the HPV testing arm than in the cytology arm (relative colposcopy referral rate, 2.83; 95% CI, 2.47–3.24). Similar results on cumulative biopsy rates were observed in four RCTs conducted in Europe ([Ronco et al., 2014](#)). In the ARTISTIC, POBASCAM, and SwedeScreen trials, the cumulative biopsy rate over two rounds of screening was similar in the two study arms, whereas in the NTCC trial, in which HPV-positive women were immediately referred for colposcopy, the biopsy rate was higher in the HPV testing arm than in the cytology arm (relative biopsy rate, 2.24; 95% CI, 2.09–2.39).

An indication of overtreatment of cervical lesions can be obtained by comparing the cumulative detection of CIN2+ between the HPV testing arm and the cytology arm over two screening rounds. The relative risks of CIN2+ can be computed from the numbers in [Table 4.22](#). The relative risk of CIN2+ over two screening

rounds (as computed by the Working Group) was 1.01 (95% CI, 0.83–1.23) in the HPV FOCAL trial, 1.03 (95% CI, 0.87–1.23) in the ARTISTIC trial, 1.08 (95% CI, 0.94–1.24) in the POBASCAM trial, and 1.17 (95% CI, 0.92–1.49) in the SwedeScreen trial, suggesting that replacing cytology-based screening with HPV-based screening will lead to only a small increase in overtreatment. In the NTCC trial and the Hong Kong SAR trial, the estimated relative risks of CIN2+ over two screening rounds were 1.54 (95% CI, 1.25–1.89) and 1.54 (95% CI, 1.09–2.18), respectively, suggesting a moderate increase in overtreatment.

[A difference in the detection of CIN2+ between study arms over two screening rounds needs to be interpreted with care. It may indicate that the magnitude of overtreatment of CIN2+ differs between study arms, but it may also simply point at a difference in lead-time gain that is longer than the interval between two consecutive screens. In the POBASCAM and HPV FOCAL trials, in which women in both study arms received co-testing in the second screening round, so that differences in lead-time gain have become minimal after the second round, there was no marked difference in cumulative detection of CIN2+ between study arms over two screening rounds.]

#### (d) *Population-based cohorts*

##### (i) *Description*

Studies in Argentina ([Arrossi et al., 2019](#)), Denmark ([Thomsen et al., 2020](#)), Finland ([Veijalainen et al., 2019](#)), Italy ([Pasquale et al., 2015](#); [Maggino et al., 2016](#); [Passamonti et al., 2017](#); [Zorzi et al., 2017](#)), the Netherlands ([Aitken et al., 2019](#)), Sweden ([Lamin et al., 2017](#)), and the United Kingdom ([Rebolj et al., 2019](#)) have reported on the impact of primary HPV DNA screening in national, regional, or pilot screening programmes on precancer and cancer. In all cohort studies, HPV DNA-positive women were triaged with cytology to improve the balance between benefits

and harms. There was considerable variation with respect to the follow-up of HPV-positive women with NILM cytology, who were followed up with cytology in the Netherlands, with HPV testing in Argentina, Finland, and Italy, and with combined HPV testing and cytology in Denmark and the United Kingdom, and were re-invited at the next screening round in Sweden. The studies in Argentina, Finland, Italy, and the Netherlands compared primary HPV-based screening programmes with the cytology-based screening programmes that were offered before the implementation of HPV screening. The study in the United Kingdom compared a pilot HPV-based screening implementation cohort with a cytology-based programme running in the same period and region, and the studies in Denmark and Sweden conducted a randomized health services trial with a primary HPV-based screening arm and a cytology-based screening arm.

Co-testing with HPV testing and cytology has been implemented as a screening option in the USA. In 2003, Kaiser Permanente Northern California (KPNC), a large health maintenance organization, adopted screening based on co-testing, with a 3-year interval after a double-negative screening result. The KPNC cohort comprises about 1 million women aged 30–64 years who have received up to four rounds of co-testing ([Castle et al., 2019](#)). Co-testing has also been implemented as a pilot programme in the Wolfsburg region in Germany: the Wolfsburg Pilot Project for Better Prevention of Cervical Cancer with Primary HPV Screening (WOLPHSCREEN). By 2016, the WOLPHSCREEN programme had enrolled 26 624 women aged 30–70 years ([Horn et al., 2019](#)). The WOLPHSCREEN programme has a 5-year screening interval after a double-negative screening result. In 2019, women had completed up to three screening rounds. Co-testing cohorts do not have a control group, but comparisons between HPV testing and cytology screening

can be made on the basis of the co-testing results. These comparisons are particularly suitable for determining screening intervals ([Katki et al., 2011](#)). Further study features of the primary HPV testing and co-testing cohorts, such as study size, age range, and follow-up protocol for HPV DNA-positive women, are given in [Table 4.23](#).

Several other studies have been conducted with one round of co-testing followed by cytology screening in subsequent rounds. These include a pooled analysis of seven studies in European countries ([Dillner et al., 2008](#)), including 24 295 women followed up until 6 years after HPV testing who had at least one cervical cytology or histopathology examination during follow-up. Four other studies with a single round of co-testing are available: (i) the HPV in Addition to Routine Testing (HART) study, including 8735 women aged 30–60 years at five clinical centres in the United Kingdom, with a median follow-up of 6 years ([Mesher et al., 2010](#)); (ii) the Canadian Cervical Cancer Screening Trial (CCCaST) study, including 4400 women aged 30–69 years in Montreal, with a median follow-up of 1.5 years, and 5754 women aged 30–69 years in St. John's, with a maximum follow-up of 10 years ([Isidean et al., 2016](#)); (iii) the Vrije Universiteit Medical Centre-Saltro Laboratory Population-Based Cervical Screening (VUSA-Screen) study, including 25 871 women aged 29–61 years in Utrecht in the Netherlands, with a maximum follow-up of 3 years ([Rijkaart et al., 2012b](#)); and (iv) the Addressing the Need for Advanced HPV Diagnostics (ATHENA) study, including 41 955 women aged 25 years and older at 61 clinical centres in the USA, with a follow-up of 3 years ([Wright et al., 2015](#)).

#### (ii) *Detection of CIN2+ and CIN3+*

The results of the primary HPV screening cohorts with cytology triage for HPV DNA-positive women were consistent with those of the RCTs, because the detection rates of CIN2+ and CIN3+ were always at least as high

**Table 4.23 Population-based cohorts: comparison of screening with HPV DNA testing alone or with co-testing versus cytology**

Country Reference	Type of study	No. of screened subjects Age (years)	Colposcopy referral recommendation	HPV DNA+/co-test+ (%)	HPV versus cytology, RR <sup>a</sup> (95% CI)				
					Test-positive	Colposcopy referral	CIN2+	CIN3+	PPV for CIN3+
Argentina <a href="#">Arrossi et al. (2019)</a>	Primary HPV with cytology triage, regional programme (Jujuy)	49 565 30–60	ASC-US, HPV+ at 18 mo	13.6	3.42 (3.22–3.64)	2.69 <sup>b</sup> (2.42–2.99)	1.76 (1.52–2.03)	1.90 (1.61–2.24)	1.13 (1.00–1.29)
Denmark <a href="#">Thomsen et al. (2020)</a>	Primary HPV with cytology triage, randomized pilot implementation	11 339 30–59	ASC-US, HPV16/18+, HPV+ or ASC-US at 12 mo	8.8	3.84 (3.42–4.30)	1.81 <sup>b</sup> (1.58–2.07)	1.51 <sup>b</sup> (1.21–1.89)	1.40 <sup>b</sup> (1.07–1.82)	0.77 (0.62–0.97)
Finland <a href="#">Veijalainen et al. (2019)</a>	Primary HPV with cytology triage, regional programme (Tampere)	17 770 35–60	LSIL, HPV+ or LSIL at 12 mo	8.2	1.10 (1.02–1.19)	1.98 (1.75–2.24)	2.45 (1.76–3.41)	2.70 (1.75–4.17)	1.36 (0.90–2.06)
Germany <a href="#">Luyten et al. (2014)</a>	WOLPHSCREEN cohort. Co-testing, regional pilot programme (Wolfsburg)	19 795 30–70	HPV+ and ASC-US, ASC-US at 6 mo, HPV+ at 12 mo	7.5	2.76 (2.51–3.04)	3.22 (2.87–3.60)	2.50 (2.17–2.87)	2.25 (1.90–2.66)	0.70 (0.59–0.83)
Italy <a href="#">Pasquale et al. (2015)</a>	Primary HPV with cytology triage, regional programme (Valcamonica)	18 728 25–64	ASC-US, HPV+ at 12 mo	8.7	2.33 (2.14–2.54)	1.71 (1.56–1.88)	1.59 (1.23–2.07)	NR	NR
Italy <a href="#">Maggino et al. (2016)</a>	Primary HPV with cytology triage, regional programme (Venice)	89 217 25–64	ASC-US, HPV+ at 12 mo	6.8	2.35 (2.25–2.46)	1.78 (1.70–1.87)	2.23 (1.87–2.65)	NR	NR
Italy <a href="#">Passamonti et al. (2017)</a>	Primary HPV with cytology triage, regional programme (Perugia)	6272 25–64	ASC-US, HPV+ at 12 mo	6.3	4.19 (3.57–4.92)	4.00 (3.29–4.87)	2.65 (1.85–3.78)	NR	NR

**Table 4.23 (continued)**

Country Reference	Type of study	No. of screened subjects Age (years)	Colposcopy referral recommendation	HPV DNA+/co-test+ (%)	HPV versus cytology, RR <sup>a</sup> (95% CI)				
					Test-positive	Colposcopy referral	CIN2+	CIN3+	PPV for CIN3+
Italy <a href="#">Zorzi et al. (2017)</a>	Primary HPV with cytology triage, regional programme (Padua)	48 763 25–64	ASC-US, HPV+ at 12 mo	6.4	NR	NR	1.2 (0.9–1.7)	NR	NR
Netherlands <a href="#">Aitken et al. (2019)</a>	Primary HPV with cytology triage, national programme	454 573 29–61	ASC-US, ASC-US at 6 mo	9.1 <sup>c</sup>	1.89 (1.86–1.92)	1.97 (1.92–2.02)	1.34 (1.29–1.39)	1.28 (1.23–1.35)	0.65 (0.63–0.68)
Sweden <a href="#">Lamin et al. (2017)</a>	Primary HPV with cytology triage, randomized pilot implementation (Stockholm)	7325 56–60	ASC-US	5.5	2.69 (2.24–3.23)	1.18 (0.81–1.71)	1.07 (0.56–2.04)	1.02 (0.47–2.19)	0.86 (0.44–1.69)
United Kingdom <a href="#">Rebolj et al. (2019)</a>	Primary HPV with cytology triage, non-randomized pilot implementation	183 970 24–64	ASC-US, HPV+ and ASC-US at 12 mo, HPV+ at 24 mo	12.7	3.31 (3.25–3.38)	1.85 (1.80–1.89)	1.46 (1.40–1.52)	1.41 (1.34–1.48)	0.76 (0.73–0.80)
USA <a href="#">Castle et al. (2019)</a>	KPNC cohort. Co-testing, regional cohort (Northern California)	990 013 30–64	LSIL, HPV+ and ASC-US, HPV+ or ASC-US at 12 mo	8.0	1.30 (1.29–1.32)	NR	NR	1.36 (1.33–1.39)	NR

ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; HPV, human papillomavirus; KPNC, Kaiser Permanente Northern California; LSIL, low-grade squamous cell intraepithelial lesion; mo, month or months; NR, not reported; PPV, positive predictive value; RR, relative risk; WOLPHSCREEN, Wolfsburg Pilot Project for Better Prevention of Cervical Cancer with Primary HPV Screening.

<sup>a</sup> The relative risks, computed by the Working Group, are based on absolute numbers reported in the original publications. The 95% confidence intervals were calculated using a normal reference distribution for the logarithm of the estimated relative risk.

<sup>b</sup> Baseline only; no repeat testing information used.

<sup>c</sup> Absolute numbers were not available; based on proportions reported in the article.



with HPV screening as with cytology screening ([Table 4.23](#)). In studies that reported on both CIN2+ and CIN3+ cases, the relative risks of HPV testing versus cytology were similar for both end-points. The relative risks for the detection of CIN2+ varied from 1.07 (95% CI, 0.56–2.04) in the study in Sweden (restricted to women aged 56–60 years) to 2.65 (95% CI, 1.85–3.78) in the study in Perugia in Italy.

[In the studies in Argentina and Denmark, follow-up data for HPV-positive women with NILM cytology were incomplete. This may have led to an underestimation of the relative detection risk, because women with NILM cytology have a relatively low CIN2+ risk.]

Most countries implemented primary HPV screening with cytology triage in women older than 30 years, but in some regions in Italy and in the United Kingdom, HPV screening was also studied in women aged from 24 or 25 years to 29 years. In the areas of Padua, Valcamonica, and Venice in Italy, the risks of CIN2+ per screened woman were 1.0%, 2.1%, and 1.1%, respectively, in women younger than 30 years and 0.4%, 0.6%, and 0.4%, respectively, in women aged 30 years and older ([Pasquale et al., 2015](#); [Maggino et al., 2016](#); [Zorzi et al., 2017](#)). In the pilot implementation cohort in the United Kingdom, the risk of CIN2+ per screened woman was 6.6% in women younger than 30 years and 1.2% in women aged 30 years and older, and the risk of CIN3+ per screened woman was 4.0% in women younger than 30 years and 0.8% in women aged 30 years and older ([Rebolj et al., 2019](#)).

This risks of CIN2+ and CIN3+ in subsequent screening rounds were also studied in the cohorts in Italy. In the cohort in Padua ([Zorzi et al., 2017](#)), the CIN2+ risk in the second round after 3 years was 0.11% per screened woman and the CIN3+ risk was 0.03%. The relative risk of CIN2+ in the second round versus the first round was 0.24 (95% CI, 0.16–0.37), and the relative risk of CIN3+ was 0.14 (95% CI, 0.06–0.32). In the cohort in Perugia ([Passamonti et al., 2017](#)), the

risks of CIN2+ and CIN3+ in the second round after 3 years were 0.25% and 0.17%, respectively, and the relative risks of CIN2+ and CIN3+ were 0.25 (95% CI, 0.14–0.42) and 0.39 (95% CI, 0.20–0.79), respectively. In a study of three cohorts in Italy ([Del Mistro et al., 2019](#)), the relative risks of CIN2+ and CIN3+ in the second round versus the first round were found to be higher when an HPV infection was reported in the previous round, and also when the positive HPV test result was followed by a negative HPV test result during short-term repeat testing. This finding was also reported for the intervention arm of the POBASCAM trial ([Polman et al., 2017](#)).

[The low risks of CIN2+ and CIN3+ in the second primary HPV screening round support the use of intervals of longer than 3 years when the primary HPV test result in the previous round is negative.]

[Table 4.23](#) also shows the results of the cohorts in which co-testing with HPV testing and cytology has been implemented: the WOLPHSCREEN cohort in Germany and the KPNC cohort in the USA. For both studies, substantially higher CIN3+ risks were observed after a positive HPV test result than after abnormal cytology. In addition, in the KPNC cohort, the 5-year CIN3+ risk was 0.11% after a negative HPV test result and 0.25% after an NILM cytology result ([Castle et al., 2018](#)). In the WOLPHSCREEN cohort, the 5-year CIN3+ risk was 0.013% after a negative HPV test result and 0.071% after an NILM cytology result ([Horn et al., 2019](#)). Cohorts with only one round of co-testing followed by cytology follow-up yielded results that were in line with those from the KPNC and WOLPHSCREEN cohorts. In a pooled study of seven European cohorts ([Dillner et al., 2008](#)), the pooled 5-year CIN3+ risk was 0.27% after a negative HPV test result and 0.83% after an NILM cytology result. The VUSA-Screen study reported a 3-year CIN3+ risk of 0.06% after a negative HPV test result and 0.26% after NILM

cytology, and the ATHENA study reported a 3-year CIN3+ risk of 0.3% after a negative HPV test result and 0.8% after NILM cytology. The HART study and the CCCaST study reported risks only for the end-point CIN2+. In the HART study, the 3-year CIN2+ risk was 0.04% after a negative HPV test result and 0.21% after NILM cytology, and the 5-year CIN2+ risk was 0.15% after a negative HPV test result and 0.28% after NILM cytology. In the CCCaST study, the 3-year CIN2+ risk was 0.90% after a negative HPV test result and 1.40% after NILM cytology.

### (iii) Detection of cervical cancer

The two largest primary HPV screening cohorts, in the United Kingdom ([Rebolj et al., 2019](#)) and the Netherlands ([Aitken et al., 2019](#)), reported on cervical cancer detection over one round of screening and compared it with the cancer detection in a historical cytology screening cohort. In the cohort in the United Kingdom, cervical cancer detection over one round of screening was 0.05% for HPV DNA screening and 0.04% for cytology screening, and the adjusted odds ratio for cervical cancer detection was 1.27 (95% CI, 0.99–1.63) ([Rebolj et al., 2019](#)). In the cohort in the Netherlands, cervical cancer detection over one round was 0.04% for HPV DNA screening and 0.03% for cytology screening ([Aitken et al., 2019](#)).

In the KPNC co-testing cohort, the 5-year cancer risk was 0.5% after a positive HPV DNA test result and 0.5% after abnormal cytology ([Castle et al., 2019](#)). In the subgroup of women with a negative HPV test result ([Castle et al., 2018](#)), the 5-year cancer risk was 0.009%, which was about 40% lower than the 5-year cancer risk of 0.02% after an NILM cytology result. The cancer risk after a negative HPV test result further decreased after previous rounds of negative HPV testing: the 5-year cancer risk was 0.004% after two rounds of negative HPV DNA testing and 0.002% after three rounds of negative HPV DNA testing. The results from the

KPNC cohort were supported by the findings of the WOLPHSCREEN study, in which the risk of cancer in the first co-testing screening round was 0.10%, which further decreased to 0.03% in subsequent rounds ([Horn et al., 2019](#)).

[Together, the RCTs, the primary HPV screening cohorts, and the co-testing cohorts demonstrate that a negative HPV test result gives better reassurance against CIN3+ and cancer than does NILM cytology, and supports the use of longer screening intervals.]

### (iv) Harms

In the primary HPV screening cohorts, both the proportion of screen-positive women and the proportion of colposcopy referrals were higher than in cytology screening cohorts ([Table 4.23](#)). However, the proportions varied widely across studies. The relative proportion of screen-positive women varied from 1.10 (95% CI, 1.02–1.19) in the study in Finland to 3.84 (95% CI, 3.42–4.30) in the study in Denmark, and the relative proportion of colposcopy referrals varied from 1.18 (95% CI, 0.81–1.71) in the study in Sweden to 4.00 (95% CI, 3.29–4.87) in the study in Perugia in Italy. The proportion of CIN3+ per colposcopy referral (PPV for CIN3+) was below 1 in most settings (up to 35% lower in the Netherlands) but was higher in the studies in Argentina (RR, 1.13; 95% CI, 1.00–1.29) and in Finland (RR, 1.36; 95% CI, 0.90–2.06). In Italy, the studies in Perugia ([Passamonti et al., 2017](#)) and in Padua ([Zorzi et al., 2017](#)) also reported on the colposcopy referrals in the second HPV-based screening round. The proportion of colposcopy referrals per screened woman in the second round decreased by 10% (95% CI, –6% to 25%) in the Perugia cohort and by 51% (95% CI, 46–55%) in the Padua cohort compared with the first HPV-based screening round. The proportion of CIN3+ per colposcopy referral decreased by 58% (95% CI, 17–78%) in the Perugia cohort and by 71% (95% CI, 35–87%) in the Padua cohort.

[It must be recognized that the follow-up of HPV-positive women with NILM cytology was incomplete in the studies in Argentina and Denmark, and that in Sweden, HPV-positive women with NILM cytology did not receive short-term follow-up testing. This may influence the proportion of colposcopy referrals, which was lowest in Sweden. The high PPV for CIN3+ in the study in Finland is a direct consequence of the high relative detection rate of CIN3+ per screened woman in this study, which was the highest among the studies that reported on CIN3+ cases.]

Consistent with results from the primary HPV screening cohorts, the proportion of screen-positive women was higher for HPV testing than for cytology in the two co-testing cohorts (KPNC and WOLPHSCREEN). The WOLPHSCREEN cohort also reported that the number of colposcopy referrals in HPV-positive women was 3.22 (95% CI, 2.87–3.60) times that in women with abnormal cytology; the corresponding relative PPV for CIN3+ after colposcopy referral was 0.70 (95% CI, 0.59–0.83).

[Both triage testing of HPV-positive women and suitable follow-up management of HPV-positive women with NILM cytology results are important to achieve a good balance between screening benefits and harms. Nonetheless, the results from population-based cohorts indicated that an increase in the number of colposcopy referrals can be expected in the first round of HPV-based screening.]

#### 4.4.3 Comparison of HPV DNA testing versus VIA

##### (a) Introduction

No review was available that directly compared the impact of HPV DNA testing and VIA on cervical cancer incidence, mortality, and detection.

Evidence about diagnostic accuracy was extracted from eight reviews and meta-analyses

or pooled analyses across a wide range of geographical regions. Data were drawn from observational studies, and mostly cross-sectional studies; this may limit the strength of the evidence. In addition, the original studies included in the reviews and analyses had not necessarily compared HPV DNA testing and VIA directly. Thus, the pooled results may potentially be affected by multiple factors, including but not limited to (i) non-comparability of control groups, (ii) different screening participation rates across studies, and (iii) heterogeneity in quality assurance and monitoring methods. Moreover, the performance of VIA, which is a technique that is highly subjective and heavily dependent on the training and experience of providers, varied widely across different populations and research settings (see Sections 4.2.1–4.2.3). In addition, in many studies in which VIA was evaluated, colposcopy plus directed biopsy used as the reference were generally applied to women with a positive screening test result only, potentially leading to verification bias. Furthermore, colposcopy could miss up to 40% of prevalent precancers and is closely correlated with visual screening approaches (see Section 4.2.2); such potential outcome misclassification with VIA may greatly affect the estimates of the test accuracy. Given the above-mentioned limitations, in comparisons of HPV DNA testing with VIA, the results for accuracy parameters must be interpreted with caution.

The detection rate of cervical neoplasia and cancer was assessed mainly by two RCTs, a pooled analysis of two cohort studies, and three cross-sectional studies, one of which was applied in a real-world setting in China.

The incidence of and mortality from cervical cancer were assessed by an RCT in Osmanabad District in India, which was the only study available.

**Table 4.24 Accuracy of HPV DNA testing versus visual inspection with acetic acid (VIA)**

Reference Study population	Screening exposure Age of included subjects (years) End-point	Test positivity rates (%) (95% CI)	Sensitivity estimate, % (95% CI)		Specificity estimate, % (95% CI)		Relative sensitivity (95% CI)	Comments
			HPV	VIA	HPV	VIA	Relative specificity (95% CI)	
<a href="#">Arbyn et al. (2008)</a> Pooled analysis of > 58 000 women aged 25–64 yr recruited from 11 cross-sectional studies in urban settings in India and French- speaking countries in Africa in 1999–2003	HPV DNA test, VIA, VILI, VIAM, cytology (see comments) 25–64 CIN2+, CIN3+, cancer	VIA: 16.7; range, 6.0–27.4	CIN2+: 61.9 (56.2–67.7); range, 48.4–67.7 CIN3+: 68.4 (61.5–75.4); range, 62.3–73.5 Cancer: 72.1 (60.3–83.8); range, 61.5–85.7	CIN2+: 79.2 (73.3–85.0); range, 65.0–91.1 CIN3+: 82.9 (77.1–88.7); range, 58.3–94.6 Cancer: 88.7 (83.1–94.3); range, 66.7–100.0	CIN2+: 93.6 (92.4–94.8); range, 91.6–94.6 CIN3+: 93.4 (92.2–94.6); range, 91.4–94.4 Cancer: 93.0 (91.8–94.2); range, 91.4–94.0	CIN2+: 84.7 (80.7–88.0); range, 74.2–94.5 CIN3+: 84.2 (80.0–88.3); range, 73.8–94.3 Cancer: 83.6 (79.3–88.0); range, 73.1–94.1	HPV vs VIA: CIN2+: 0.883 (0.775–1.007) CIN3+: 0.956 (0.781–1.169) HPV vs VIA: CIN2+: 1.074 (1.051–1.097) CIN3+: 1.075 (1.051–1.099)	Evidence from observational studies. Not every study included had assessed the HPV DNA test and VIA concurrently. HPV DNA test (HC2) was applied in 4 studies in India, and VIA was used in all 11 studies in both Africa and India
<a href="#">Zhao et al. (2010)</a> Pooled analysis of individual patient data in 28 848 women from 17 population-based, cross-sectional cervical cancer screening studies in both urban and rural areas in 9 provinces in China in 1999–2008. The eligible women were sexually active, were not pregnant, had an intact uterus, and had no history of CIN or cervical cancer	HPV DNA test, VIA, cytology 17–59 CIN2+, CIN3+	HPV: 16.3 (4691 of 28 848 women) VIA: 10.8 (3122 of 28 815 women)	Uncorrected: CIN2+: 96.3 (94.9–97.4) CIN3+: 97.5 (95.7–98.7) Corrected: CIN2+: 95.1 (93.6–96.3) CIN3+: 97.6 (95.9–98.6)	CIN2+: 48.0 (42.1–53.9); range, 12.5–70.2 CIN3+: 54.6 (48.0–61.2); range, 14.3–85.7	Uncorrected: CIN2+: 86.4 (83.8–89.0) CIN3+: 85.1 (82.3–87.9) Corrected: CIN2+: 85.4 (85.0–85.8) CIN3+: 84.1 (83.7–84.5)	CIN2+: 90.4 (87.3–93.5); range, 70.0–98.2 CIN3+: 89.9 (86.8–93.0); range, 69.9–97.5	NR NR	Evidence from observational studies. Women included in the pooled analysis all concurrently received HPV DNA test, LBC, and VIA



**Table 4.24 (continued)**

Reference Study population	Screening exposure Age of included subjects (years) End-point	Test positivity rates (%) (95% CI)	Sensitivity estimate, % (95% CI)		Specificity estimate, % (95% CI)		Relative sensitivity (95% CI)	Comments
			HPV	VIA	HPV	VIA	Relative specificity (95% CI)	
<a href="#">Chen et al. (2012)</a> 101 299 apparently healthy women from 22 cross- sectional studies (99 972 women tested by VIA, 23 628 women tested by HPV DNA test). 6 common cervical screening strategies including VIA and HPV DNA test were assessed	HPV DNA test, VIA, VIAM, VILI, cytology (see comments) 16–70 CIN2+	NR	74 (69–78)	77 (75–78)	92 (92–93)	87 (87–88)	NR NR	Studies included in the review underwent quality assessment with QUADAS and STARD quality assessment criteria. Evidence from observational studies. Not every study included had assessed the HPV DNA test and VIA concurrently. Three types of HPV DNA test were involved (HC2, PCR, and <i>care</i> HPV), but only the HC2 assay with samples collected by health professionals was used to estimate the accuracy of HPV testing in this meta- analysis

**Table 4.24 (continued)**

Reference Study population	Screening exposure Age of included subjects (years) End-point	Test positivity rates (%) (95% CI)	Sensitivity estimate, % (95% CI)		Specificity estimate, % (95% CI)		Relative sensitivity (95% CI)	Comments
			HPV	VIA	HPV	VIA	Relative specificity (95% CI)	
<a href="#">Fokom-Domgue et al. (2015)</a> 8 studies in which the reference standard (colposcopy and colposcopy- directed biopsy) was performed in all women of the study population from sub- Saharan Africa were included. The study population was not at particular risk of cervical cancer (studies focusing on HIV- positive women or on women presenting with gynaecological symptoms were excluded). In total, 47 361 women were screened with VIA and 3950 women were screened with HPV DNA test	HPV DNA test, VIA, VILI 15–83 CIN2+	HPV: 25.8 (17.4–35.3); range, 12.5–42.8 VIA: 16.8 (11.0–23.6); range, 3.1–39.9	88.3 (73.1–95.5); range, 80.2–96.2	82.4 (76.3–87.3); range, 65.0–94.4	73.9 (50.7–88.7); range, 61.2–88.9	87.4 (77.1–93.4); range, 64.1–98.2	VIA vs HPV: 0.94 (0.82–1.16) VIA vs HPV: 1.17 (0.95–1.69)	Studies included were assessed as of moderate quality, based on the QUADAS-2 criteria. Evidence from observational studies. Not every study included had assessed the HPV DNA test and VIA concurrently. Test accuracy was assessed only among the studies in which the reference test (colposcopy and colposcopy- directed biopsy) was performed in all women (10 studies for VIA, 3 studies for HPV), which may avoid verification bias

**Table 4.24 (continued)**

Reference Study population	Screening exposure Age of included subjects (years) End-point	Test positivity rates (%) (95% CI)	Sensitivity estimate, % (95% CI)		Specificity estimate, % (95% CI)		Relative sensitivity (95% CI)	Comments
			HPV	VIA	HPV	VIA	Relative specificity (95% CI)	
<a href="#">Bobdey et al. (2015)</a> 16 studies conducted in India in 1990–2013 were included. Pooled data of 89 461 women in the VIA arm from 14 studies and 23 244 women in the HPV test arm from 8 studies were analysed	HPV DNA test, VIA, VIAM, VILI, cytology NA NR	NR	75.04; range, 45.70–97.10	68.76; range, 31.60–100.00	91.66; range, 84.20–94.60	84.02; range, 53.30–91.23	NR NR	No quality assessment criteria were applied in the 2 reviews. The age range of included participants and disease end-points of assessment, and the 95% CI of the pooled results on accuracy were not reported. Evidence from observational studies. Not every study included had assessed the HPV DNA test and VIA concurrently. Some included studies were conducted in the health clinics including gynaecologically symptomatic women. Thus, the pooled results of accuracy in the reviews consisted of both asymptomatic and symptomatic participants, which may limit the generalizability to healthy women
<a href="#">Bobdey et al. (2016)</a> 11 studies conducted in India in 1990–2015 were included. Pooled number of women in the VIA arm was 57 225 and in the HPV DNA test arm was 25 575	HPV DNA test, VIA, VIAM, VILI, cytology NA NR	NR	77.81	67.65	91.54	84.32	NR NR	

**Table 4.24 (continued)**

Reference Study population	Screening exposure Age of included subjects (years) End-point	Test positivity rates (%) (95% CI)	Sensitivity estimate, % (95% CI)		Specificity estimate, % (95% CI)		Relative sensitivity (95% CI)	Comments
			HPV	VIA	HPV	VIA	Relative specificity (95% CI)	
<a href="#">Mustafa et al. (2016)</a> 5 cross-sectional studies with a total of 8921 non-pregnant women not previously diagnosed with cervical neoplasia were included	HPV DNA test, VIA, cytology ≥ 18 CIN2/3	HPV: 17.6 VIA: 14.1	95 (84–98); range, 64–97	69 (54–81); range, 41–87	84 (72–91); range, 56–93	87 (79–92); range, 76–95	NR NR	All the included studies underwent quality assessment with QUADAS criteria. Evidence from observational studies. Women included in the studies had all concurrently received HPV DNA test and VIA
<a href="#">Holt et al. (2017)</a> Data of 2757 postmenopausal women were extracted from the 17 population-based studies in <a href="#">Zhao et al. (2010)</a> for further analysis	HPV DNA test, VIA, cytology 17–59 CIN2+, CIN3+	HPV: 17.2 (15.9–18.7) VIA: 6.2 (5.3–7.1)	CIN2+: 82/84, 97.6 (92.4–99.6) CIN3+: 47/48, 97.9 (90.2–99.9)	CIN2+: 26/84, 31.0 (21.8–41.4) CIN3+: 20/48, 41.7 (28.4–55.9)	CIN2+: 2280/2673, 85.3 (83.9–86.6) CIN3+: 2281/2709, 84.2 (82.8–85.5)	CIN2+: 2529/2673, 94.6 (93.7–95.4) CIN3+: 2559/2709, 94.5 (93.6–95.3)	NR NR	This is a further stratification analysis after the pooled analysis of 17 cross-sectional studies described in <a href="#">Zhao et al. (2010)</a>

CI, confidence interval, CIN, cervical intraepithelial neoplasia; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HC2, Hybrid Capture 2; HPV, human papillomavirus; LBC, liquid-based cytology; mo, month or months; NR, not reported; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; STARD, Standards for Reporting of Diagnostic Accuracy Studies; VIA, visual inspection with acetic acid; VIAM, visual inspection with acetic acid using low-level magnification; VILL, visual inspection with Lugol's iodine.

*(b) Accuracy of HPV DNA testing versus VIA*

Studies comparing the accuracy of HPV DNA testing versus VIA are presented in [Table 4.24](#). Most of the reviews reported a higher pooled sensitivity for HPV DNA testing compared with VIA, and the clinical performance of VIA varied greatly across different geographical areas and studies, which highlighted the difficulties in achieving reliable performance of VIA ([Arbyn et al., 2008](#); [Zhao et al., 2010](#); [Chen et al., 2012](#); [Bobdey et al., 2015, 2016](#); [Fokom-Domgue et al., 2015](#); [Mustafa et al., 2016](#)). The sensitivity of HPV DNA testing for detection of CIN2+ varied from 61.9% with HC2 test data pooled from studies in India ([Arbyn et al., 2008](#)) to 96.3% in the pooled analysis in China ([Zhao et al., 2010](#)); the sensitivity of VIA for detection of CIN2+ varied from 48.0% in the pooled analysis in China ([Zhao et al., 2010](#)) to 82.4% in the meta-analysis in sub-Saharan Africa ([Fokom-Domgue et al., 2015](#)), and VIA positivity rates were variable across studies. The specificity of HPV DNA testing for CIN2+ ranged between 84% and 93.6% in all reviews and analyses, except in the meta-analysis in sub-Saharan Africa (73.9%) ([Fokom-Domgue et al., 2015](#)); the specificity of VIA for CIN2+ varied from 84% in India ([Bobdey et al., 2015](#)) to 90.4% in China ([Zhao et al., 2010](#)).

In the pooled analysis of [Zhao et al. \(2010\)](#), a large proportion of participants had received directed biopsies and random biopsies under colposcopy, whereas in the meta-analysis of [Fokom-Domgue et al. \(2015\)](#), colposcopy and directed biopsies performed in all women occurred in only a few of the studies analysed. [Careful consideration is needed when interpreting the accuracy of VIA across different study settings.]

HPV DNA testing has been shown to be superior to VIA as a primary screening technique in detecting cervical neoplasia in postmenopausal women. The study of [Holt et al. \(2017\)](#) found that the sensitivity of HPV DNA testing for both

CIN2+ and CIN3+ remained stable near 98%, whereas the corresponding sensitivity of VIA decreased significantly, to 31.0% for CIN2+ and 41.7% for CIN3+.

However, in the study of [Arbyn et al. \(2008\)](#), the pooled sensitivity of HPV DNA testing for CIN2+ was substantially lower than that of VIA (61.9% vs 79.2%), although this difference was not statistically significant (relative sensitivity of HPV vs VIA, 0.883; 95% CI, 0.775–1.007). Several potential explanations for the relatively low sensitivity of HC2 testing have been discussed, including sample contamination or deterioration, limited scope of the hrHPV DNA probe, and misclassification of the outcome, which may result in overestimation of the sensitivity of VIA and underestimation of the sensitivity of HPV DNA testing. [Arbyn et al. \(2008\)](#) reported a relatively high correlation (0.61) between results of VIA and the reference standard (colposcopy), compared with the low correlation (0.13) between results of HC2 testing and colposcopy. [The Working Group noted that VIA and colposcopy were often performed at the same time by health workers who had been trained just before the study began. Potential bias may occur in favour of a test when the test is verified with an imperfect reference standard and results of the two techniques are correlated (e.g. similar inspection after application of acetic acid for both VIA and colposcopy).]

[There is also a potential issue concerning the correlation of reported pooled results, given the overlap between studies being included in different reviews. For example, the study of [Sankaranarayanan et al. \(2004\)](#) has been included in five reviews ([Arbyn et al., 2008](#); [Chen et al., 2012](#); [Bobdey et al., 2015, 2016](#); [Fokom-Domgue et al., 2015](#)).] This study was conducted in India and included 18 085 apparently healthy, asymptomatic women aged 25–65 years who were screened with HPV DNA testing, cytology, VIA, and VILI concurrently. The study reported a relatively low sensitivity for both HPV testing



and VIA at some study sites (e.g. in Kolkata, the sensitivity of HPV testing for CIN2/3 was 45.7%, and the sensitivity of VIA was 54.4%). Potential reasons were discussed by the authors, such as the variable expertise of screening providers in specimen collection, unsatisfactory specimens, or DNA losses during HC2 testing ([Sankaranarayanan et al., 2004](#)). [The Working Group noted that when studies with such large sample sizes are included, the potential impact on the pooled results in the reviews must be considered.]

(c) *Detection rate of cervical neoplasia and cancer with HPV DNA testing versus VIA*

Two cluster RCTs in India and South Africa, three cross-sectional studies in China and India, and a pooled analysis of two cohort studies in eastern Europe and Latin America have compared the detection rates of cervical precancer and cancer according to HPV DNA testing and VIA results ([Denny et al., 2005, 2010](#); [Sankaranarayanan et al., 2005, 2009](#); [Sarian et al., 2010](#); [Asthana & Labani, 2015](#); [Basu et al., 2015](#); [Zhao et al., 2018](#)). These studies are presented in [Table 4.25](#) and below.

Overall, HPV DNA testing yielded higher detection rates of high-grade cervical lesions compared with VIA.

The RCT conducted in Osmanabad District in India involved 131 746 women aged 30–59 years from October 1999 to November 2003. Clusters, consisting of villages, were randomized into four groups: HPV DNA testing (HC2), VIA, cytology, and a control group that received only health education but no screening at baseline. Immediate colposcopy was offered and directed biopsies were taken from abnormal areas for women in the VIA group. In the other screening groups, colposcopy appointments were made for women who tested positive, and punch biopsy specimens were taken if abnormal findings were present. The HPV testing, VIA, and cytology groups had positivity rates of 10.3%, 13.9%, and

7.0%, respectively, and colposcopy compliance rates of 89.1%, 98.7%, and 87.9%, respectively ([Sankaranarayanan et al., 2005, 2009](#)). According to the colposcopy and biopsy findings at baseline, the detection rates were 0.9% for CIN2/3 and 0.3% for cervical cancer in the HPV arm; the detection rates in the VIA arm were similar, at 0.7% for CIN2/3 and 0.3% for cervical cancer.

The other RCT was conducted in South Africa from June 2000 to December 2002. A total of 6555 women aged 35–65 years were recruited, and HPV DNA testing (HC2) was compared with VIA in a screen-and-treat strategy ([Denny et al., 2005, 2010](#)). All the participants were screened with HPV DNA testing and VIA at baseline and subsequently randomized to either HPV-and-treat or VIA-and-treat, or to a control group with evaluation delayed for 6 months. Women with a positive test result in both the HPV-and-treat and VIA-and-treat groups underwent cryotherapy. In the HPV DNA testing group, 467 of 2163 women (22%) underwent cryotherapy; in the VIA group, 482 of 2227 women (22%) underwent cryotherapy. At 6 months after randomization, colposcopy was performed by a physician blinded to the group assignment and clinical information for all women. Biopsies were taken for all acetowhite lesions, and appropriate treatment was given for women with CIN2+. At 6 months, the prevalence of CIN2+ was 0.80% (95% CI, 0.40–1.20%) in the HPV-and-treat group, 2.23% (95% CI, 1.57–2.89%) in the VIA-and-treat group, and 3.55% (95% CI, 2.71–4.39%) in the control group. The efficacy of each screen-and-treat approach was presented as the percentage difference in CIN2+ attributable to the approach [(control group – treatment group)/control group]. At the 6-month evaluation, there was a 77% reduction in prevalent CIN2+ in the HPV-and-treat group and a 37% reduction in the VIA-and-treat group compared with the control group. All women with positive HPV DNA or VIA results at enrolment, plus a subset of women who were both HPV DNA-negative and VIA-negative and were

**Table 4.25 Detection rates of cervical neoplasia and cancer with HPV DNA testing versus visual inspection with acetic acid (VIA)**

Reference Country	Study description	Detection rates for different disease end-points (%) (95% CI), n/N		Comments
		HPV	VIA	
<a href="#">Denny et al. (2005, 2010)</a> South Africa	RCT design. 6555 unscreened non-pregnant Black women aged 35–65 yr in Khayelitsha, South Africa, were recruited in 2000–2002. All women were screened using HPV DNA test and VIA at baseline, and subsequently randomized to HPV-and-treat ( <i>n</i> = 2163), VIA-and-treat ( <i>n</i> = 2227), or control arm ( <i>n</i> = 2165) with delayed evaluation. All were recalled for colposcopy and biopsy confirmation at 6 mo. In addition, 2708 of them, who were free of CIN2+ at 6 mo, who were HPV DNA-positive or VIA-positive at baseline, plus a subset of women who were both HPV DNA-negative and VIA-negative, were followed up at 12 mo and 36 mo	CIN2+: At 6 mo: 0.80 (0.40–1.20) At 12 mo: 1.42 (0.87–1.97) At 36 mo: 1.50 (NA)	CIN2+: At 6 mo: 2.23 (1.57–2.89) At 12 mo: 2.91 (2.12–3.69) At 36 mo: 3.80 (NA)	Landmark study focusing on HPV DNA testing versus VIA as primary screening methods for screen-and-treat strategy, which fits the situation of low-resource settings. The cumulative detection rates are reported here for each follow-up
<a href="#">Sankaranarayanan et al. (2005, 2009)</a> India	Cluster-RCT design. More than 130 000 healthy women, married but not pregnant, aged 30–59 yr with an intact uterus and no past history of cervical neoplasia, previously unscreened, in rural communities of Osmanabad District, India, were recruited in 1999–2003 and followed up until 2007. Recruited women were randomly assigned to HPV DNA test, VIA, cytology, or control group	CIN2/3: 0.9 (0.6–1.4), 245/27 192 Cervical cancer: 0.2 (0.1–0.4), 73/27 192 CIN2+: 1.2, 318/27 192	CIN2/3: 0.7 (0.3–1.5), 195/26 765 Cervical cancer: 0.3 (0.0–0.7), 82/26 765 CIN2+: 1.0, 277/27 192	Both articles provided the baseline results. Given that <a href="#">Sankaranarayanan et al. (2009)</a> provided more comprehensive information, the main results presented here are based on this article

Table 4.25 (continued)

Reference Country	Study description	Detection rates for different disease end-points (%) (95% CI), <i>n/N</i>		Comments
		HPV	VIA	
<a href="#">Sarian et al. (2010)</a> Eastern Europe and Latin America	Data were pooled from both the NIS cohort ( <i>n</i> = 3187) and the LAMS ( <i>n</i> = 12 114). Women in the NIS cohort attended 6 outpatient clinics in the Russian Federation, Belarus, and Latvia in 1998–2002, and had a mean age of 32.6 yr (range, 15–85 yr). All women underwent Pap testing and HPV DNA testing (HC2). Women in the LAMS cohort had a mean age of 37.9 yr (range, 14–67 yr) and were examined by cytology and VIA, VILI, cervicography, and HPV DNA test (HC2) at 4 clinics in Brazil and Argentina	CIN2+: 2.3, 169/7498	CIN2+: 0.7, 83/12 093	
<a href="#">Asthana &amp; Labani (2015)</a> India	Cross-sectional design. 4658 ever-married women aged 30–59 yr with no history of CIN or cervical cancer, hysterectomy, or the presence of any associated condition were recruited from rural areas in Uttar Pradesh, India, in 2011–2012. All women were screened with HPV DNA test with self-collected sample, HPV DNA test with clinician-collected sample, cytology, and VIA. All screen-positive women were referred for colposcopy and directed biopsy	CIN2+: Self-collected: 2.7 (1.2–4.2) per 1000 women screened Clinician-collected: 3.6 (1.8–5.4) per 1000 women screened CIN3+: Self-collected: 1.5 (0.37–2.6) per 1000 women screened Clinician-collected: 2.4 (0.97–3.8) per 1000 women screened	CIN2+: 1.5 (0.37–2.6) per 1000 women screened CIN3+: 0.21 (–0.21 to 0.63) per 1000 women screened	
<a href="#">Basu et al. (2015)</a> India	Cross-sectional design. 39 740 apparently healthy women aged 30–60 yr from rural districts adjacent to the metropolitan city of Kolkata in eastern India were recruited in 2010–2014. All women were screened with HPV DNA test and VIA	CIN2+: 5.1 per 1000 women screened CIN3+: 3.8 per 1000 women screened	CIN2+: 4.8 per 1000 women screened CIN3+: 2.8 per 1000 women screened	

**Table 4.25 (continued)**

Reference Country	Study description	Detection rates for different disease end-points (%) (95% CI), n/N		Comments
		HPV	VIA	
<a href="#">Zhao et al. (2018)</a> China	Cross-sectional study design. 33 823 women aged 35–64 yr, with an intact uterus and with no history of cervical neoplasia or cervical cancer, who were not pregnant and had no suspicious symptoms, and who understood the process and were willing to participate were recruited from rural areas across 7 large geographical regions in China in 2015–2018. In rural areas, women were randomized to initial screening with HPV test ( $n = 15\,577$ ), cytology ( $n = 7089$ ), or VIA ( $n = 11\,157$ )	CIN2+: 0.61, 95/15 577	CIN2+: 0.49, 55/11 157	This study is based on real-world data generated from both rural areas ( $n = 33\,823$ ) and urban areas ( $n = 30\,108$ ) across 7 large geographical regions in China. The results presented here only represent the data from rural areas, because VIA was not applied in urban areas. Women were initially randomized with a 1:1:1 ratio to the 3 arms; however, cytology was not applicable for some rural areas, so VIA was used instead, resulting in more VIA-screened women than HPV-screened and cytology-screened women

CIN, cervical intraepithelial neoplasia; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HC2, Hybrid Capture 2; HPV, human papillomavirus; LAMS, Latin American Screening Study; mo, month or months; NA, not available; NIS, New Independent States; VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol's iodine; yr, year or years.

free of CIN2+ at 6 months were followed up at 12 months and 36 months. At the 12-month follow-up, the cumulative prevalence of CIN2+ was 1.42% (95% CI, 0.87–1.97%) in the HPV-and-treat group, 2.91% (95% CI, 2.12–3.69%) in the VIA-and-treat group, and 5.41% (95% CI, 4.32–6.50%) in the control group in the 2708 women examined. This corresponds to a reduction of 74% in the HPV-and-treat group and of 46% in the VIA-and-treat group compared with the control group ([Denny et al., 2005](#)). At the 36-month follow-up, the cumulative detection rate of CIN2+ was lower in the HPV-and-treat group (1.5%) than in the VIA-and-treat group (3.8%), whereas the rate was 3.6% in the control group. This corresponds to a reduction of 72.5% (95% CI, 60.1–85.0%) in CIN2+ in the HPV-and-treat group and a reduction of 32.0% (95% CI, 11.1–52.8%) in CIN2+ in the VIA-and-treat group compared with the control group at 36 months ([Denny et al., 2010](#)). In addition, the incidence of CIN2+ detected more than 12 months after enrolment was 0.3% (95% CI, 0.05–1.02%) in the HPV-and-treat group, which was significantly less than in the VIA-and-treat group (1.3%; 95% CI, 0.8–2.1%) and in the control group (1.0%; 95% CI, 0.5–1.7%) ( $P = 0.003$ ) ([Denny et al., 2010](#)).

A study involving 33 823 women living in rural areas across seven large geographical regions in China reported detection rates of CIN2+ of 0.61% (95 of 15 577) with HPV DNA testing (*careHPV*, cobas 4800, or Liferiver hrHPV genotyping) and 0.49% (55 of 11 157) with VIA or VILI ([Zhao et al., 2018](#)).

In a cross-sectional study in rural India, 4658 eligible women were screened with HPV DNA testing (*careHPV*) with clinician-collected and self-collected samples, VIA, and cytology. For HPV DNA testing with clinician-collected samples, detection rates of CIN2+ were 3.6 (95% CI, 1.8–5.4) per 1000 women screened and detection rates of CIN3+ were 2.4 (95% CI, 0.97–3.8) per 1000 women screened. For HPV DNA testing on self-collected samples, detection rates of CIN2+

were 2.7 (95% CI, 1.2–4.2) per 1000 women screened and detection rates of CIN3+ were 1.5 (95% CI, 0.37–2.6) per 1000 women screened. For VIA, detection rates of CIN2+ were 1.5 (95% CI, 0.37–2.6) per 1000 women screened and detection rates of CIN3+ were 0.21 (95% CI, –0.21 to 0.63) per 1000 women screened ([Asthana & Labani, 2015](#)).

A demonstration project in eastern India reported detection rates of CIN2+ of 5.1 per 1000 women screened with HPV DNA testing and 4.8 per 1000 women screened with VIA. For CIN3+, the detection rate with HPV DNA testing (3.8 per 1000 women screened) was significantly higher ( $P = 0.016$ ) than that with VIA (2.8 per 1000 women screened) ([Basu et al., 2015](#)).

In a pooled analysis focused on studies in eastern Europe and Latin America, the estimated detection rate of CIN2+ was 2.3% (169 of 7498) in the HPV DNA testing group and 0.7% (83 of 12 093) in the VIA group ([Sarian et al., 2010](#)).

#### (d) *Changes in cervical cancer incidence and mortality rates*

Only the RCT in Osmanabad District in India has assessed the effect of a single round of HPV DNA testing and VIA as primary screening methods on cervical cancer incidence and mortality rates ([Sankaranarayanan et al., 2005, 2009](#)) ([Table 4.26](#)). During a follow-up of 8 years, a total of 127 cases of cervical cancer were diagnosed in the HPV DNA testing arm (age-standardized incidence rate [ASIR], 47.4 per 100 000 person-years), compared with 157 cases in the VIA arm (ASIR, 58.7 per 100 000 person-years). A single round of screening with HPV DNA testing also dramatically reduced the incidence of cervical cancer of FIGO stage II or higher compared with VIA screening. The burden of cervical cancer of stage II or higher was reported as 39 cases in the HPV DNA testing arm (ASIR, 14.5 per 100 000 person-years), compared with 86 cases in the VIA arm (ASIR, 32.2 per 100 000 person-years). Fewer cases of cervical cancer



**Table 4.26 Age-standardized incidence and mortality rates of cervical cancer with HPV testing versus visual inspection with acetic acid (VIA)**

Reference Country	Study description	Age-standardized incidence rate of all cervical cancer (per 100 000 person-years)		No. of cases of cervical cancer of stage II or higher/total no. of cases of cervical cancer (%)		Age-standardized incidence rate of cervical cancer of stage II or higher (per 100 000 person-years)		No. of cases of invasive cervical cancer among screening-negative women/total no. of screening-negative women		Deaths from cervical cancer/total no. of cases of cervical cancer (%)		Age-standardized mortality rate of cervical cancer (per 100 000 person-years)	
		HPV	VIA	HPV	VIA	HPV	VIA	HPV	VIA	HPV	VIA	HPV	VIA
<a href="#">Sankaranarayanan et al. (2005, 2009)</a> India	See <a href="#">Table 4.25</a>	47.4	58.7	39/127 (30.7%)	86/157 (54.8%)	14.5	32.2	8/24 380 (0.033%)	25/23 032 (0.109%)	34/127 (26.8%)	56/157 (35.7%)	12.7	20.9

HPV, human papillomavirus; VIA, visual inspection with acetic acid.

developed in HPV DNA-negative women (8 cases in 24 380 women; ASIR, 3.7 per 100 000 person-years) than in VIA-negative women (25 cases in 23 032 women; ASIR, 16.0 per 100 000 person-years). Lower cervical cancer-related mortality was also observed in the HPV DNA testing arm. There were 34 deaths in the HPV DNA testing arm (age-standardized mortality rate [ASMR], 12.7 per 100 000 person-years), compared with 56 deaths in the VIA arm (ASMR, 20.9 per 100 000 person-years) ([Sankaranarayanan et al., 2009](#)).

#### (e) Harms

Diagnostic harms can be inferred by the colposcopy referral rates and the PPVs of the screening tests. Details of studies reporting colposcopy referral rates and/or PPVs for HPV DNA testing and VIA are given in [Table 4.27](#). For HPV DNA testing compared with VIA, the different studies did not consistently report a higher or lower proportion of colposcopy referrals or a larger number of colposcopies needed to detect one CIN2+ or CIN3+ case. PPVs were generally higher with HPV DNA testing than with VIA.

### 4.4.4 Comparison of HPV DNA testing alone versus co-testing

#### (a) Introduction

Co-testing as a primary screening modality consists of analysing samples for both cytology and HPV at the same time, regardless of the corresponding test result. The analyses can be conducted on the same sample in the case of LBC, where the residual sample can be tested for HPV, or on separate samples taken in sequence at the same visit. The clinical decision about follow-up and/or referral is then made on the basis of the combination of the test results.

The introduction and broader use of LBC since the 2005 *IARC Handbook* has facilitated the use of co-testing in guidelines and routine practice. The technical implementation of co-

testing follows the use of cytology and HPV testing as previously described (see Sections 4.3.1 and 4.4.1, respectively). A range of test technologies and analysis platforms exist for both HPV testing and cytology. The interoperability of these sampling methods and platforms enables co-testing but varies across settings and manufacturers.

Studies examining co-testing range from classic RCTs to implementation studies and retrospective analyses of screening test results before precancer and cancer diagnosis. The time perspective for these studies varies: some studies look at the first round of screening results for detection rates and test performance, whereas others present longitudinal evidence for the comparison of cumulative incidence by baseline test results. The early RCTs that compared HPV testing with cytology enabled analyses of co-testing because cytology was done in every participant. In the main results reported by these trials, HPV testing alone was compared with cytology, but the follow-up data provided comparisons between cytology, HPV testing, and co-testing screening strategies ([Bulkmans et al., 2004](#); [Naucler et al., 2007](#); [Ronco et al., 2007a](#); [Kitchener et al., 2009a](#)).

In this review, meta-analyses and joint analyses of cohort studies were examined, as well as studies that directly evaluated disease outcomes or test performance of HPV testing alone compared with co-testing as a primary screening modality. Modelling studies, cost-effectiveness analyses, and studies that evaluated co-testing as a follow-up strategy or in conjunction with other biomarkers were excluded. Studies that examined co-testing in specific populations (e.g. non-attenders), as a test of cure, or as a screening programme exit test were also excluded.

**Table 4.27 Comparison of potential diagnostic harms of HPV DNA testing versus VIA**

Reference	Study description	Colposcopy referrals Referral rate (%) (95% CI), n/N		PPV for different disease end-points (%) (95% CI), n/N	
		HPV	VIA	HPV	VIA
<a href="#">Sankaranarayanan et al. (2009)</a>	See <a href="#">Table 4.25</a>	10.3, 2812/27 192	13.9, 3733/26 765	CIN2/3: 11.3, 318/2812 Cancer: 2.6, 73/2812	CIN2/3: 7.4, 277/3733 Cancer: 2.2, 82/3733
<a href="#">Longatto-Filho et al. (2012)</a>	LAMS cohort study. > 12 000 women at 4 clinics in Brazil and Argentina. Large sample size with both cross-sectional and prospective cohorts, which covered regions with different cervical cancer incidence rates. All women were screened with cytology, VIA, VILI, HPV DNA test (HC2) with self-collected sample and clinician-collected sample. Women with a positive screening test result were referred for colposcopy	NA	NA	CIN2+: Self-collected: 9.1 (3.0–22.6) Clinician-collected: 7.9 (6.0–10.1)	CIN2+: 6.1 (4.9–7.6)
<a href="#">Zhao et al. (2013)</a>	START-UP project. 7421 women aged 25–65 yr in 3 counties of China (Yangcheng, Xinmi, and Tonggu) were recruited and tested with <i>care</i> HPV, HC2, HPV E6, and VIA using both self-collected and clinician-collected samples. Women with a positive screening test result were referred for colposcopy with directed biopsy. In addition, a randomly selected 10% of women with a negative test result for all the tests also underwent colposcopy	<i>care</i> HPV: Self-collected: 14.5 Clinician-collected: 14.4 HC2: Self-collected: 17.9 Clinician-collected: 14.5	7.3	CIN2+: <i>care</i> HPV: Self-collected: 11.1 (9.3–13.1) Clinician-collected: 13.0 (11.1–15.2) HC2: Self-collected: 10.0 (8.4–11.7) Clinician-collected: 12.9 (10.9–15.0) CIN3+: <i>care</i> HPV: Self-collected: 7.7 (6.2–9.5) Clinician-collected: 9.1 (7.4–10.9) HC2: Self-collected: 6.8 (5.5–8.3) Clinician-collected: 9.0 (7.3–10.8)	CIN2+: 12.7 (10.0–15.9) CIN3+: 9.4 (7.0–12.2)

**Table 4.27 (continued)**

Reference	Study description	Colposcopy referrals Referral rate (%) (95% CI), n/N		PPV for different disease end-points (%) (95% CI), n/N	
		HPV	VIA	HPV	VIA
<a href="#">Asthana &amp; Labani (2015)</a> ; <a href="#">Labani &amp; Asthana (2016)</a>	See <a href="#">Table 4.25</a>	Self-collected: 2.4 (2.0–2.8), 111/4658 Clinician-collected: 2.9 (2.9–3.4), 136/4658	5.5 (4.9–6.2), 257/4658	CIN2+: Self-collected: 11.7 (6.3–19.1) Clinician-collected: 12.5 (7.4–9.1) CIN3+: Self-collected: 6.3 (2.6–12.6) Clinician-collected: 8.1 (4.1–13.9)	CIN2+: 2.7 (1.1–5.5) CIN3+: 0.4 (0.0–2.2)
<a href="#">Holt et al. (2017)</a>	Postmenopausal women (see <a href="#">Table 4.24</a> for details)	17.2 (15.9–18.7), 475/2757	6.2 (5.3–7.1), 170/2757	CIN2+: 17.3 (14.1–20.9), 82/475 CIN3+: 9.9 (7.4–12.8), 47/475	CIN2+: 15.3 (10.5–21.3), 26/170 CIN3+: 11.8 (7.5–17.3), 20/170
<a href="#">Wang et al. (2019)</a>	Cross-sectional design. 2668 women aged ≥ 18 yr in Inner Mongolia, China, were screened with HPV DNA test and VIA concurrently. Women with a positive test result were referred for colposcopy	17.5 (16.1–19.0), 467/2668	8.1 (7.1–9.2), 216/2668	CIN2+: 5.6 (3.8–8.0), 26/467	CIN2+: 6.0 (3.6–10.0), 13/216

CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HC2, Hybrid Capture 2; LAMS, Latin American Screening Study; PPV, positive predictive value; START-UP, Screening Technologies to Advance Rapid Testing for Cervical Cancer Prevention–Utility and Program Planning; VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol’s iodine; yr, year or years.

*(b) Screening performance*

A joint database analysis of HPV screening studies included seven studies in six European countries ([Dillner et al., 2008](#)) and aimed to estimate the long-term predictive values of HPV-based screening for CIN3+. This analysis included 24 295 women who were screened with HPV testing and cytology at baseline and had at least one additional cervical cytology or histopathology examination during follow-up. The studies differed with respect to the ages of women included, the HPV tests used, and the setting. The cumulative incidence of CIN3+ over 72 months of follow-up was examined by baseline test results, and the test characteristics were reported for cytology, HPV testing, and co-testing with cytology and HPV testing (at least one positive). The cumulative incidence of CIN3+ at 72 months for HPV-negative women was 0.27% (95% CI, 0.12–0.45%), which was similar to that for co-test-negative women at the same time point. At 72 months, the sensitivity of HPV testing for CIN3+ was 90% (95% CI, 80–95%) and the specificity was 88.28% (95% CI, 87.83–88.70%) [recalculated by the Working Group using absolute values without any adjustment; this was erroneously given in the publication]. The corresponding values at 72 months for co-testing with cytology and HPV testing were 92% (95% CI, 84–96%) and 87% (95% CI, 81–93%), respectively.

In a meta-analysis, co-testing with cytology and HC2 testing produced higher detection of CIN2+ (42%; 95% CI, 36–48%) and CIN3+ (33%; 95% CI, 29–37%) compared with cytology alone, and the specificity for the same outcomes was 6% (95% CI, 6–7%) and 8% (95% CI, 7–9%) lower, respectively. When cytology was added to HC2 testing and compared with HPV testing alone, the average sensitivity increased by 5% (95% CI, 4–7%) for CIN2+ and by 2% (95% CI, 1–3%) for CIN3+, and the specificity decreased significantly (ratio for CIN2+, 0.95; 95% CI,

0.94–0.96 and ratio for CIN3+, 0.93; 95% CI, 0.92–0.95). The pooled estimates from the trials showed a non-significant increase in sensitivity for co-testing compared with HPV alone (detection rate ratio for CIN2+, 1.06; 95% CI, 0.97–1.16 and detection rate ratio for CIN3+, 1.04; 95% CI, 0.92–1.17) ([Arbyn et al., 2012](#)). [The studies outlined below, which have been conducted since this meta-analysis was completed, used different HPV and cytology platforms but came to broadly the same conclusion.]

*(c) Effectiveness**(i) RCTs*

RCTs examining the performance of co-testing are outlined in [Table 4.28](#).

Four RCTs in Europe were identified that compared hrHPV co-testing with cytology alone: the NTCC trial in Italy ([Ronco et al., 2007a, 2010, 2014](#)), the POBASCAM trial in the Netherlands ([Bulkmans et al., 2004; Rijkaart et al., 2012a; Dijkstra et al., 2016](#)), the SwedeScreen trial in Sweden ([Naucler et al., 2007; Elfström et al., 2014](#)), and the ARTISTIC trial in the United Kingdom ([Kitchener et al., 2009a, b, 2014](#)). The primary results of these trials are reviewed in Section 4.4.2, and long-term follow-up data from these studies have been pooled and provide evidence on the comparison of testing methods and the effectiveness against invasive cervical cancer as an outcome ([Arbyn et al., 2012; Ronco et al., 2014](#)).

Both [Dijkstra et al. \(2016\)](#) and [Elfström et al. \(2014\)](#) examined the cumulative incidence of high-grade lesions (CIN2+ or CIN3+). [Dijkstra et al. \(2016\)](#) concluded that the difference between hrHPV testing and hrHPV co-testing with cytology became less pronounced as follow-up time increased, and [Elfström et al. \(2014\)](#) concluded that the difference was minimal over time. [Elfström et al. \(2014\)](#) also calculated the test performance over different follow-up periods (3, 5, 8, and 10 years) and found that although the



**Table 4.28 Randomized controlled trials and cohort studies comparing co-testing versus HPV DNA testing**

Reference	Study population	Screening exposure Age of included subjects (years)	End- point	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Detection rate	Incidence
<i>Randomized controlled trials</i>							
<a href="#">Mayrand et al. (2007)</a>	10 154 women who sought screening tests for cervical cancer in any of 30 clinics in Montreal and St. John's, Canada	HPV DNA test and cytology 30–69 Pap test result of ASC-US+, or HPV test result of $\geq 1$ pg HPV DNA/mL	CIN2+	100.0	92.5	NA	NA
<a href="#">Elfström et al. (2014)</a>	12 527 women who attended the organized cervical screening programme in Sweden. 13-year follow-up of the SwedeScreen RCT of primary HPV screening	HPV DNA test and cytology 32–38	CIN2+	Co-testing: 3-yr: 96.69 (90.25–98.93) 5-yr: 91.22 (84.84–95.07) 8-yr: 82.67 (75.79–87.91) 10-yr: 77.19 (70.16–82.97) HPV testing: 3-yr: 92.23 (84.58–96.25) 5-yr: 86.40 (79.21–91.37) 8-yr: 77.30 (69.95–83.29) 10-yr: 72.45 (65.17–78.71)	Co-testing: 3-yr: 90.32 (89.54–91.05) 5-yr: 90.73 (89.97–91.45) 8-yr: 90.98 (90.22–91.69) 10-yr: 91.10 (90.34–91.81) HPV testing: 3-yr: 94.05 (93.42–94.63) 5-yr: 94.47 (93.85–95.03) 8-yr: 94.69 (94.08–95.24) 10-yr: 94.82 (94.22–95.37)	NA	Cumulative incidence (%) (95% CI) at 13-yr follow-up (no difference between co-testing and HPV testing): CIN2+: 1.63 (1.11–2.32) in the intervention arm CIN3+: 0.84 (0.48–1.47) in the intervention arm

**Table 4.28 (continued)**

Reference	Study population	Screening exposure Age of included subjects (years)	End- point	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Detection rate	Incidence
<a href="#">Dijkstra et al. (2016)</a>	Of 44 938 women enrolled in the Netherlands, 22 420 were randomized to the intervention group (managed by co-testing results) and 22 518 to the control group (managed only by cytology result)	HPV DNA test and cytology 29–61	CIN3+ and cancer	NA	NA	NA	Incidence ratio (95% CI) (intervention vs control): CIN3+: Cytology-negative and/or HPV-negative: 0.86 (0.63–1.17) Cytology-negative and/or HPV-positive: 0.95 (0.71–1.28) Cytology-positive and/or HPV-negative: 0.62 (0.28–1.37) Cancer: Cytology-negative and/or HPV-negative: 0.58 (0.23–1.48) Cytology-negative and/or HPV-positive: 0.29 (0.10–0.87) Cytology-positive and/or HPV-negative: 5.97 (0.30–119.22)
<a href="#">Han et al. (2020)</a>	182 119 women screened in the primary health-care facilities of 9 districts in Beijing, China, from January 2014 to March 2015	HPV DNA test and cytology 35–64	CIN2+	NA	NA	Co-testing: 5.06 for CIN2+ 1.63 for CIN3+ HPV testing: 3.35 for CIN2+ 2.10 for CIN3+	NA

**Table 4.28 (continued)**

Reference	Study population	Screening exposure Age of included subjects (years)	End- point	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Detection rate	Incidence
<i>Cohort studies</i>							
<a href="#">Cuzick et al. (2003)</a> <a href="#">Mesher et al. (2010)</a> [6-year follow-up] <sup>b</sup>	Multicentre screening study of 11 085 women in the United Kingdom associated with 5 referral centres	HPV test and cytology 30–60	CIN2+	Baseline: Co-testing: <sup>b</sup> 100.0 (96.0–100.0) HPV testing (≥ 2 pg/mL): 96.0 (89.7–98.5)	Baseline: Co-testing: <sup>b</sup> 94.0 (93.4–94.5) HPV testing (≥ 2 pg/mL): 94.4 (93.9–95.0)	NA	6-yr cumulative incidence (%): Co-test-negative: 0.21 HPV-negative: 0.28
<a href="#">Petry et al. (2003)</a> <sup>a</sup>	8466 women attending routine cervical cancer screening in Germany	HPV test and cytology ≥ 29	CIN2+ and CIN3+	CIN2+: Co-testing: 100.0 (93.7–100.0) HPV testing: 97.8 (86.3–99.7) CIN3+: Co-testing: 100.0 (93.7–100.0) HPV testing: 97.3 (83.2–99.6)	CIN2+: Co-testing: 93.8 (91.8–95.3) HPV testing: 95.3 (93.5–96.6) CIN3+: Co-testing: 94.9 (93.1–96.2) HPV testing: 95.2 (93.4–96.5)	NA	NA
<a href="#">Katki et al. (2011)</a>	331 818 women enrolled in co-testing at KPNC starting in 2003–2005 (and with adequate enrolment co-test results) and followed up to 31 December 2009	HPV test and cytology ≥ 30	CIN3+	NA	NA	NA	5-yr cumulative incidence (per 100 000 women per year): Co-test-negative: 3.2 HPV-negative: 3.8

**Table 4.28 (continued)**

Reference	Study population	Screening exposure Age of included subjects (years)	End- point	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Detection rate	Incidence
<a href="#">Rijkaart et al. (2012b)<sup>c</sup></a>	VUSA-Screen study. 25 871 women in the Netherlands offered both cytology and hrHPV testing	HPV test and cytology 29–61	CIN2+ and CIN3+	NA <sup>c</sup>	NA <sup>c</sup>	NA	3-yr cumulative risk of CIN2+ (%) (95% CI): Co-test-negative: 0.24 (0.12–0.64) HPV-negative: 0.26 (0.14–0.69) 3-yr cumulative risk of CIN3+ (%) (95% CI): Co-test-negative: 0.05 (0.01–0.42) HPV-negative: 0.06 (0.02–0.46)
<a href="#">Wright et al. (2015)</a>	42 209 women in the USA who underwent cytology and hrHPV testing	HPV test and cytology ≥ 25	CIN3+	NA	NA	NA	3-yr cumulative incidence (%) (95% CI): Co-test-negative: 0.3 (0.1–0.6) HPV-negative: 0.3 (0.1–0.7)
<a href="#">Choi et al. (2016)</a>	922 women who visited the gynaecology clinic at the Korea University Ansan Hospital, Seoul, Republic of Korea, for routine screening or follow-up during an 18-mo period	HPV test and cytology 17–86 (median, 44.7)	CIN2+ and CIN3+	CIN2+: Co-testing: 72.1 HPV testing: 71.3 CIN3+: Co-testing: 59 HPV testing: 61.7	CIN2+: Co-testing: 96.7 HPV testing: 88.1 CIN3+: Co-testing: 100 HPV testing: 98.5	NA	NA

ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; KPNC, Kaiser Permanente Northern California; LSIL, low-grade squamous intraepithelial lesion; mo, month or months; NA, not applicable; RCT, randomized controlled trial; yr, year or years.

<sup>a</sup> The follow-up time was not clearly mentioned in the article.

<sup>b</sup> Positive test results defined as cytology ≥ mild (LSIL) or HPV ≥ 2 pg/mL.

<sup>c</sup> Test characteristics for HPV and cytology were reported separately, not as combined test results, and are therefore not noted here.

sensitivity of co-testing was higher than that of HPV testing alone, the specificity was lower for all follow-up periods. In the long-term follow-up of these two trials, the absolute difference in cumulative incidence between co-testing and HPV testing alone remained constant over time and was minimal.

The CCCaST study in Canada randomized 10 154 women aged 30–69 years to either screening with a focus on the HPV testing result or screening with a focus on the cytology result (both tests were performed in both arms). CIN2+ outcomes were reported by screening results (individual and joint HPV and cytology results and HPV genotype-specific results). The test characteristics reported for HPV testing alone and for co-testing with CIN2+ as the outcome were as follows: the sensitivity of HPV testing alone for CIN2+ was 94.6% (95% CI, 84.2–100%) and the specificity was 94.1% (95% CI, 93.4–94.8%) (using a threshold of 1 pg HPV DNA/mL, i.e. 5000 copies of HPV genome per test), and the sensitivity of co-testing for CIN2+ was 100% and the specificity was 92.5%, where the definition of a positive result was ASC-US+ cytology or an HPV test result of 1 pg HPV DNA/mL or above. These estimates were corrected for verification bias and were based on confirmation of the lesion in an excisional specimen ([Mayrand et al., 2006, 2007](#)).

In a quasi-RCT implemented in primary health-care facilities, [Han et al. \(2020\)](#) compared cytology with two intervention arms: (i) hrHPV testing alone with cytology triage and (ii) co-testing; the randomization to the intervention arms was done by district. The overall primary outcome was detection rates of CIN2+ by screening strategy; further outcomes included PPV by strategy for CIN2+ and biopsy rates. Detection rates were 5.06‰ for CIN2+ and 1.63‰ for CIN3+ for co-testing, 3.35‰ for CIN2+ and 2.10‰ for CIN3+ for hrHPV testing alone, and 2.47‰ for CIN2+ and 1.24‰ for CIN3+ for cytology. In this study, referral was

based on partial genotyping. In the co-testing arm, women who were positive for carcinogenic HPV types other than HPV16 or HPV18 and cytology-negative were referred for repeat testing after 1 year, instead of being deemed negative, as they were in the HPV testing arm.

Taken together, the comparison of co-testing versus HPV DNA testing as examined in these RCTs shows a marginally higher sensitivity for outcomes of CIN2+ and CIN3+ with co-testing than with HPV testing alone. The specificity of co-testing was lower than that of HPV testing alone. The cumulative incidence of high-grade lesions by baseline HPV test-negative women or co-test-negative women showed minor differences over time. Co-test-negative women had a slightly lower cumulative incidence of high-grade lesions, but the difference was not significant ([Table 4.28](#)).

#### (ii) Cohort studies

Cohort studies examining the performance of co-testing are outlined in [Table 4.28](#). They include the Hanover and Tübingen (HAT) study in Germany ([Petry et al., 2003](#)), the HART study in the United Kingdom ([Cuzick et al., 2003, Mesher et al., 2010](#)), the KPNC cohort in the USA ([Katki et al., 2011](#)), and the ATHENA study in the USA ([Wright et al., 2015](#)), as well as two studies embedded in routine screening, the VUSA-Screen study in the Netherlands ([Rijkaart et al., 2012b](#)) and a study in the Republic of Korea ([Choi et al., 2016](#)).

The HAT study included 7908 women aged 30 years and older from routine screening in two cities in Germany in 1998–2000 ([Petry et al., 2003](#)). Two samples were taken at baseline; one was analysed with conventional cytology and the other with HPV testing. One round of screening was included, and women were followed up depending on the combination of test results at baseline. Test characteristics were estimated for combinations of baseline test results and the outcomes of CIN2+ and CIN3+. For HPV testing



alone, the sensitivity for CIN2+ was 97.8% (95% CI, 86.3–99.7%) and the specificity was 95.3% (95% CI, 93.5–96.6%). For co-testing (with a cytology threshold of ASC-US+, including unsatisfactory results or any hrHPV positivity), the sensitivity was 100.0% (95% CI, 93.7–100.0%) and the specificity was 93.8% (95% CI, 91.8–95.3%). In the co-testing analysis, positivity in either test resulted in referral. For the outcome of CIN3+, the estimates were similar.

The HART study enrolled 11 085 women aged 30–60 years from routine screening in five cities in the United Kingdom in 1998–2001. As in the HAT study, two samples were taken and analysed with conventional cytology and with HPV testing (Cuzick et al., 2003). Comparisons of the performance of HPV testing alone and co-testing were presented both in the baseline results after one round of screening (Cuzick et al., 2003; test characteristics) and in the long-term follow-up based on an average of 6 years of follow-up (Mesher et al., 2010; cumulative incidence of CIN2+ by baseline test result). At baseline, the sensitivity of HPV testing alone (using a threshold of 2 pg/mL) for CIN2+ was 96.0% (95% CI, 89.7–98.5%) and the specificity was 94.4% (95% CI, 93.9–95.0%), whereas the sensitivity of co-testing, in which the definition of a positive result was mild (similar to LSIL) or worse in cytology or  $\geq 2$  pg/mL by HPV testing, was 100.0% (95% CI, 96.0–100.0%) and the specificity was 94.0% (95% CI, 93.4–94.5%) (Cuzick et al., 2003). The long-term follow-up of the cohort (Mesher et al., 2010) showed the cumulative incidence of CIN2+ in non-overlapping categories of baseline test results, including HPV-negative women and co-test-negative women; 0.28% of women who were HPV-negative at baseline were diagnosed with CIN2+ during follow-up, and 0.21% of women who were co-test-negative (i.e. HPV-negative and cytology-negative) at baseline developed CIN2+ during follow-up.

KPNC adopted a co-testing strategy in 2003. Data from this large cohort including 331 818

women were reported by Katki et al. (2011) and reflect routine clinical practice. Over 5 years of follow-up, the cumulative incidence of cancer was higher for hrHPV-negative women (3.8 per 100 000 women per year) than for co-test-negative (i.e. hrHPV-negative and cytology-negative) women (3.2 per 100 000 women per year). In a further analysis of the KPNC cohort data (Gage et al., 2014), specific proposed screening strategies in the USA were examined; hrHPV testing alone and co-testing at different intervals were compared with respect to risks of CIN2+, CIN3+, and cancer. The main comparison of interest was the risk of CIN3+ or cancer at 3 years for hrHPV-negative women versus the risk at 5 years for co-test-negative women. The risk of CIN3+ was significantly lower in hrHPV-negative women at 3 years than in co-test-negative women at 5 years (0.069% vs 0.11%;  $P < 0.0001$ ). The risk of cancer was also lower in hrHPV-negative women at 3 years than in co-test-negative women at 5 years (0.011% vs 0.014%), although this difference was not statistically significant. Schiffman et al. (2018) also used the KPNC cohort to examine the relative contribution of the cytology component to co-testing, and concluded that the increased sensitivity of co-testing versus HPV testing alone for detection of treatable precancers and early curable cervical cancers affects very few cases.

In the context of the population-based screening programme in the Netherlands, the VUSA-Screen study (Rijkaart et al., 2012b) examined the effectiveness of co-testing with cervical cytology and hrHPV testing. A total of 25 658 women with adequate baseline samples for cytology and HPV testing were included. Histological results stratified by the baseline screening test result were reported. The 3-year cumulative risk of CIN3+ was 0.06% (95% CI, 0.02–0.46%) for HPV-negative women and 0.05% (95% CI, 0.01–0.42%) for both cytology-negative and hrHPV-negative women. Therefore, adding cytology to hrHPV testing was interpreted to have minimal impact on

evaluating the risk of CIN3+. Test characteristics for hrHPV testing and cytology were reported separately, not as combined test results, and are therefore not given here.

The ATHENA study aimed to evaluate hrHPV testing as a primary screening modality in women aged 25 years or older recruited from routine cervical screening ([Wright et al., 2015](#)). The screening strategies examined included hrHPV testing alone (with referral for colposcopy for women who were HPV16- and/or HPV18-positive or ASC-US+ in reflex cytology) and a co-testing strategy that corresponded to United States screening recommendations (cytology alone for women younger than 30 years and co-testing for women aged 30 years or older). The cumulative risks of CIN2+ and CIN3+ were measured over 3 years. The cumulative incidence rate of CIN3+ in HPV-negative women was 0.3% (95% CI, 0.1–0.7%), which was the same as in women who were both HPV-negative and cytology-negative (0.3%; 95% CI, 0.1–0.6%).

In a large cohort trial, the clinical performance of primary HPV screening plus LBC co-testing was compared with that of HPV screening alone and LBC alone at a hospital in Seoul, Republic of Korea, in women aged 17–86 years ([Choi et al., 2016](#)). For CIN2+, the sensitivity of primary HPV testing alone was 71.3% and of co-testing was 72.1%; the specificity was 88.1% and 96.7%, respectively. For CIN3+, the sensitivity of HPV testing alone was 61.7% and of co-testing was 59%; the specificity was 98.5% and 100%, respectively.

In recent years, a series of retrospective cohort studies have been conducted that examined the screening history of selected screening cohorts and cohorts of women diagnosed with CIN3+, AIS, or cancer. In a laboratory-based study, [Blatt et al. \(2015\)](#) conducted a retrospective cohort analysis examining the co-test results of 256 648 women aged 30–65 years who had complete results for cytology and HPV testing in 2005–2011 and a follow-up cervical biopsy within 1 year of the index test. Test characteristics for

CIN3+ were calculated and reported as follows: the sensitivity of HPV testing alone was 94.0% (95% CI, 93.3–94.7%), and the sensitivity of co-testing was 98.8% (95% CI, 98.6–99.2%). The inclusion criteria required that women had undergone colposcopy and biopsy within 1 year of the index test. By including only women with a follow-up biopsy and limiting the follow-up time to within 1 year, the study excluded a significant percentage of HPV-positive and cytology-negative women who returned for rescreening after more than 1 year; this biased the results in favour of strategies that include cytology at baseline ([Castle, 2015](#); [Giorgi Rossi et al., 2016](#)).

[Kaufman et al. \(2020\)](#) took a comparable retrospective approach to analysing co-test results before diagnosis. They examined a total of 13 633 071 co-test results in women aged 30 years or older. Women were included in the analysis if they had at least one LBC and HPV co-test result before a histopathologically confirmed diagnosis of CIN3, AIS, or cancer; 1615 co-tests before 1259 cancer diagnoses and 11 164 co-tests before 8048 CIN3 or AIS diagnoses were included. The results were reported as the proportion of positive results by testing modality before the different diagnoses (cancer was analysed overall and by histopathology), overall and stratified by within 12 months of diagnosis or more than 12 months before diagnosis. In the analysis of test results within 12 months of diagnosis of a cancer, 77.5% of the women were HPV-positive, 85.1% were LBC-positive, and 94.1% were positive on either test. In contrast, the results for more than 12 months before diagnosis show minimal differences between testing modalities. [The focus on test performance within 12 months of a diagnosis presents a significant limitation in the interpretation and application of the results. The authors did not distinguish between screening tests and clinical tests undergone because of symptoms. Tests undergone within a short period of cancer diagnosis often represent tests undergone in the diagnostic workup of a cancer rather than

screening tests; therefore, they are not as indicative of the performance of the testing modality for screening purposes.]

Overall, the performance of HPV testing alone and co-testing in the cohort studies summarized above followed a pattern similar to the results presented in the RCTs: higher sensitivity for co-testing than for HPV testing alone, but lower specificity. The cohort studies presented further data on the risk of high-grade lesions by baseline test result (HPV-negative or co-test-negative). These results confirmed the results of the RCTs and showed little or no difference in cumulative risk between HPV-negative and co-test-negative women over time.

### (iii) Harms

In the RCTs reviewed, the PPV for CIN2+ was higher for HPV testing alone than for co-testing. In the long-term follow-up of the SwedeScreen trial, the PPV for CIN2+ was 19.51%, 25.63%, 29.02%, and 31.12% for HPV testing alone at 3, 5, 8, and 10 years, respectively, compared with 13.32%, 17.53%, 20.21%, and 21.56% for co-testing at the same intervals ([Elfström et al., 2014](#)). In the CCCaST study, the PPV for CIN2+ was 7.0% for HPV testing alone and 5.5% for co-testing; the colposcopy referral was 6.1% for HPV testing alone and 7.9% for co-testing ([Mayrand et al., 2007](#)).

The PPV for HPV testing alone was consistently higher than that for co-testing, although the differences were small. In the joint database analysis of HPV screening studies, the PPV for CIN3+ was 17.1% (95% CI, 12.7–21.4%) for HPV testing alone and 14.7% (95% CI, 9.9–19.0%) for co-testing ([Dillner et al., 2008](#)). In the HAT study, the PPV for CIN2+ was 10.9% (95% CI, 8.2–14.2%) for HPV testing alone and 8.6% (95% CI, 6.5–11.3%) for co-testing. The proportion of women referred for colposcopy was 5.2% for HPV testing alone and 6.8% for co-testing ([Petry et al., 2003](#)). In the HART study, the PPV for CIN2+ was 15.0% (95% CI, 12.2–18.34%) for

HPV testing alone (using a threshold of 2 pg/mL) and 14.4% (95% CI, 11.8–17.5%) for co-testing (using a threshold of mild [similar to LSIL] or worse in cytology or  $\geq 2$  pg/mL by HPV testing) ([Cuzick et al., 2003](#)). In the ATHENA study, there was no significant difference in the PPV for CIN2+ between HPV testing alone (20.2%; 95% CI, 18.3–22.0%) and co-testing (19.5%; 95% CI, 17.6–21.4%) ([Wright et al., 2015](#)). The proportion of women referred for colposcopy was higher for co-testing than for HPV testing alone.

### 4.4.5 HPV testing on self-collected versus clinician-collected samples

#### (a) Diagnostic accuracy

The diagnostic accuracy of HPV-based testing for detection of CIN2+ and CIN3+ on specimens collected by self-sampling needs to be assessed separately. Clinician-collected cervical specimens have been the reference standard for detection of CIN2+, because exfoliated cells are more likely to be sampled from the target site than with self-sampling, which may include cells from the vagina. Self-sampling is being considered as an alternative to clinician sampling because it is more convenient for women and there are potential cost savings for the health-care system ([Campos et al., 2017, 2020](#)). Using a self-sampling device, a woman can collect a sample at home or at a specific collection point; this avoids a speculum examination and leaves the cervix undisturbed, which may improve visual triage of screen-positive women if this is performed on the same day.

[Arbyn et al. \(2014\)](#) evaluated 36 studies, including 154 556 women, on the accuracy of self-collected samples versus clinician-collected samples when used for HPV testing. In the context of screening, HPV testing on self-collected samples detected, on average, 76% (95% CI, 69–82%) of CIN2+ and 84% (95% CI, 72–92%) of CIN3+. The pooled absolute specificity was 86%

**Table 4.29 Relative sensitivity and relative specificity of hrHPV assays on self-collected samples versus clinician-collected samples, by sampling device and storage medium<sup>a</sup>**

Covariate	Number of studies	Relative sensitivity (95% CI)	Relative specificity (95% CI)
<i>Sampling device</i>			
hrHPV assay based on signal amplification			
Brush	13	0.84 (0.78–0.90)	0.93 (0.91–0.96)
Swab	7	0.85 (0.78–0.91)	0.93 (0.90–0.95)
Lavage	2	0.84 (0.69–1.04)	0.74 (0.55–0.98)
Tampon	1	0.86 (0.78–0.96)	1.02 (1.00–1.03)
hrHPV assay based on polymerase chain reaction			
Brush	12	0.98 (0.95–1.02)	0.95 (0.91–0.99)
Swab	4	0.98 (0.93–1.03)	0.93 (0.89–0.98)
Lavage	4	0.95 (0.87–1.04)	1.09 (0.91–1.30)
Tampon	0	NA	NA
<i>Storage medium</i>			
hrHPV assay based on signal amplification			
Cell-preserving <sup>b</sup>	3	0.84 (0.78–0.90)	0.93 (0.91–0.96)
Virological <sup>b</sup>	15	0.86 (0.81–0.91)	0.95 (0.92–0.98)
Dry samples	0	NA	NA
Other	1	0.90 (0.71–1.13)	0.92 (0.71–1.21)
hrHPV assay based on polymerase chain reaction			
Cell-preserving	6	1.00 (0.96–1.04)	0.92 (0.88–0.97)
Virological	3	0.97 (0.91–1.04)	0.94 (0.89–0.99)
Dry samples	7	0.96 (0.90–1.02)	1.01 (0.94–1.10)
Other	1	0.95 (0.80–1.13)	1.05 (0.69–1.58)

CI, confidence interval; hrHPV, high-risk human papillomavirus; NA, not available.

<sup>a</sup> Relative values were computed using a bivariate normal model, separating studies using an hrHPV assay based on signal amplification or an hrHPV assay based on polymerase chain reaction. Pooling was performed using a bivariate normal model.

<sup>b</sup> When the bivariate model containing covariates did not fit or when the number of studies was < 4, a separate pooling of the relative sensitivity and relative specificity using a model for ratios of proportions was run.

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(95% CI, 83–89%) for CIN2+ and 87% (95% CI, 84–90%) for CIN3+ ([Arbyn et al., 2014](#)).

An updated analysis was performed ([Arbyn et al., 2018](#)) that included 56 diagnostic accuracy studies up to April 2018 ([Table 4.29](#)). Studies were included if the following criteria were met: information was provided on a vaginal sample collected by the woman herself (self-collected sample) followed by a cervical sample collected by a clinician (clinician-collected sample); the same hrHPV assay was performed on both samples; all HPV tests evaluated had been clinically validated according to the Meijer guidelines ([Meijer et al., 2009](#)); and the presence or

absence of CIN2+ was verified by colposcopy and biopsy in all enrolled women or in women with one or more positive test results. Studies with cytology follow-up for women with negative colposcopy results at baseline assessment were also included but were indexed for sensitivity analyses. Standard methods were used for pooling diagnostic test accuracy ([Harbord et al., 2007](#); [Harbord & Whiting, 2009](#)). Indicators included the relative accuracy of tests on self-collected samples versus clinician-collected samples, estimated by incorporating assay category as a covariate in the model. The variation of the accuracy was also evaluated according to the



clinical setting (screening population, high-risk population, follow-up for previous abnormalities, and monitoring after treatment), assay, self-sampling device, and storage medium. [Although the pooled absolute sensitivity and specificity for outcomes CIN2+ and CIN3+ varied by clinical setting, relative values were considered adequate for comparison and were presented first for a screening situation and then for a combination of all clinical settings using only relative indicators.] The relative accuracy of hrHPV assays on self-collected samples versus clinician-collected samples did not vary substantially by clinical setting. The overall relative pooled sensitivity was 0.85 (95% CI, 0.80–0.89) for CIN2+ and 0.86 (95% CI, 0.76–0.98) for CIN3+, and the relative pooled specificity was 0.96 (95% CI, 0.93–0.98) for CIN2+ on self-collected samples versus clinician-collected samples. A higher test positivity and lower PPVs tended to be observed for self-collected samples compared with clinician-collected samples when assays based on signal amplification were used. This was not observed when PCR-based assays were used. PCR-based hrHPV assays were equally sensitive (ratio, 0.99; 95% CI, 0.97–1.02) and slightly less specific (ratio, 0.98; 95% CI, 0.97–0.99) for CIN2+ on self-collected samples versus clinician-collected samples, with similar test positivity and non-significantly lower PPVs.

*(b) Additional studies*

Since the review by [Arbyn et al. \(2018\)](#), additional studies have been identified that evaluated the accuracy of hrHPV testing for the detection of CIN2+ with vaginal samples and with cervical samples. [El-Zein et al. \(2018\)](#) reported on the Cervical And Self-Sample In Screening (CASSIS) study, which recruited 1217 women aged 21–74 years in Montreal, Canada, attending colposcopy clinics because of an abnormal cytology result. Participants provided three consecutive samples: two different self-collected samples, using the HerSwab device and the

cobas 4800 HPV swab, and a clinician-collected sample. The self-collection devices are designed to be anatomically comfortable to enable women to self-collect a sample of exfoliated cervicovaginal cells; the clinician-collected sample was collected with either a swab or a simple brush. [The Working Group did not find the relevant information to confirm whether the clinician collection was performed with a brush or a swab.] The order of the self-sampling devices was assigned randomly. Of 1076 women with complete information (per-protocol population), HPV positivity was high and comparable between the three devices, ranging from 47.4% to 50.5%. Overall, 152 cases of CIN2+ were detected in the per-protocol analysis and 166 in the intention-to-treat analysis.

The relative sensitivity and the relative specificity of self-sampling with the HerSwab device versus clinician sampling for ASC-US+ were 0.94 and 1.07, respectively. The relative sensitivity and the relative specificity of self-sampling with the cobas swab versus clinician sampling for ASC-US+ were 0.94 and 1.02, respectively; the differences were not statistically significant. [The Working Group noted that all women in the study were referred because of an abnormal test result; this may indicate that most women were likely to have a high HPV viral load, and thus the study population may not be suitable for an evaluation of accuracy between tests applied to screening settings.]

In a randomized non-inferiority trial, [Polman et al. \(2019b\)](#) evaluated the diagnostic accuracy of HPV testing on self-collected samples versus clinician-collected samples for the detection of CIN2+ and CIN3+ in a screening population of women aged 29–61 years in the Netherlands. Samples were tested for carcinogenic HPV types using GP5+/6+ PCR EIA. Of the 187 473 women invited to participate, 8212 were randomly allocated to self-sampling first (group A) and 8198 to clinician sampling first (group B) [The response rate was very low,



because self-sampling was an opt-in option of how to be screened.] A total of 7643 women were included in group A and 6282 in group B. A total of 569 (7.4%) self-collected samples and 451 (7.2%) clinician-collected samples tested positive for HPV (RR, 1.04; 95% CI, 0.92–1.17). The sensitivity and specificity of HPV testing for CIN2+ and CIN3+ did not differ between self-collected and clinician-collected samples: for CIN2+, the relative sensitivity was 0.96 (95% CI, 0.90–1.03) and the relative specificity was 1.00 (95% CI, 0.99–1.01), and for CIN3+, the relative sensitivity was 0.99 (95% CI, 0.91–1.08) and the relative specificity was 1.00 (95% CI, 0.99–1.01). [Note that HPV-positive women in both groups were cross-retested with the other collection method, which was done before colposcopy, but the HPV cross-testing results were not disclosed to study participants and were not used for screening management. Although the study had low participation in regular users of screening, the sample size was high in both arms and the study design was powerful.]

In a small cross-sectional study in 104 women aged 25 years or older in Manchester, United Kingdom, attending a colposcopy clinic for management of abnormal cervical screening, [Sargent et al. \(2019\)](#) evaluated the diagnostic accuracy on self-collected vaginal samples and urine and clinician-collected cervical samples for the detection of CIN2+. Vaginal samples and cervical samples were tested using the cobas 4800 and RealTime HPV assays. CIN2+ was detected in 18 women. The sensitivity for detection of CIN2+ was similar for vaginal samples and cervical samples with both HPV assays [relative sensitivity, 1.01] (RealTime assay: 89%, 16 of 18; cobas 4800 assay: 88%, 15 of 17).

#### (c) *Longitudinal evaluation of self-sampling*

In the Shanxi Province Cervical Cancer Screening Study I, in China, 1997 non-pregnant women aged 35–45 years with no history of cervical cancer or hysterectomy were enrolled

in 1999 via cluster sampling ([Zhang et al., 2018](#)). At enrolment, all the women underwent HPV testing on a self-collected sample and a clinician-collected sample. All the women had histologically confirmed results at baseline. HPV testing was done using a signal amplification test (HC2). The relative sensitivities for CIN2+ in clinician-collected samples versus self-collected samples were 1.17 (95% CI, 1.07–1.29) at baseline and 1.15 (95% CI, 1.07–1.25) at 6 years. The values of specificity were identical at baseline and at 6 years (RR, 0.99; 95% CI, 0.97–1.00). Data at 16 years provided similar values.

Issues related to the acceptability of and participation in self-sampling are reviewed in Section 3.3.2.

[Aitken et al. \(2019\)](#) reported on the nationwide implementation of hrHPV-based screening in the Netherlands. In this programme, women receive an invitation to have a cervical sample taken by the provider, but they can also opt for self-sampling at home. Data from the first 18 months of the hrHPV-based screening programme were compared with the previous, cytology-based programme with respect to participation, referral, and detection of CIN. About 8% (36 295 of 454 573) of the women had opted for the use of a self-sampling device. Although no increase in participation could be related to self-sampling, CIN2+ detection was higher in self-collected samples than in clinician-collected samples (1.4% vs 1.1%;  $P < 0.001$ ).

#### (d) *Use of HPV RNA tests on vaginal self-collected samples*

The 2018 meta-analysis that assessed the relative accuracy of HPV tests on self-collected versus clinician-collected samples also included three studies in which HPV testing was done with an RNA test (Aptima) ([Arbyn et al., 2018](#)). The sensitivity of HPV RNA testing for CIN2+ was significantly lower on self-collected samples than on clinician-collected samples (relative sensitivity, 0.69; 95% CI, 0.52–0.92), whereas the

specificity for CIN2+ was similar in both specimens (relative specificity, 0.97; 95% CI, 0.92–1.02).

Two additional studies evaluated the use of an HPV RNA test (Aptima) on vaginal self-collected samples. [Senkomago et al. \(2018\)](#) studied 350 female sex workers aged 18–50 years in 2009–2013 and compared HPV RNA detection on clinician-collected samples versus self-collected samples. A total of 22 cases with confirmed CIN2+ were detected over a period of 24 months; 18 (82%) were HPV RNA-positive on the clinician-collected samples, and 17 (77%) were HPV RNA-positive on the self-collected samples at baseline [relative sensitivity, 0.85 (95% CI, 0.41–1.76)]. [Note that the referral for biopsy and histological confirmation was done solely on the basis of cytology results, not by HPV test results.] [Islam et al. \(2020\)](#), from the same group, published additional data on HPV RNA testing (Aptima) on dry and wet self-collected samples and found similar performance [the outcome was cytology-confirmed HSIL+].

#### 4.4.6 Comparison of HPV RNA testing versus HPV DNA testing

##### (a) Use of HPV RNA tests in primary cervical cancer screening

A 2015 review ([Arbyn et al., 2015](#)) evaluated the sensitivity and specificity for the detection of CIN2+ and CIN3+ of diverse HPV DNA and RNA assays applied in primary cervical cancer screening and compared them with those of reference HPV DNA tests (HC2 and GP5+/6+ PCR EIA). Six studies that included populations from primary screening were identified that used a 14-HPV type target RNA test (Aptima) and one study that used a 5-HPV type RNA test (PreTect HPV-Proofer). There was no indication that the sensitivity for CIN2+ of the 14-HPV type RNA test was different from that of the comparator HPV DNA test, but it had a higher specificity; the relative sensitivity was 0.98 (95% CI, 0.95–1.01) and the relative specificity was 1.04 (95% CI,

1.02–1.07). The 5-HPV type RNA test was found to be less sensitive but more specific than the comparator HPV DNA test; the relative sensitivity for CIN2+ was 0.74 (95% CI, 0.63–0.88) and the relative specificity was 1.12 (95% CI, 1.10–1.13).

Since that 2015 systematic review, additional studies have been identified that compared the clinical cross-sectional accuracy of an HPV RNA test (Aptima) ([Iftner et al., 2015](#); [Maggino et al., 2016](#); [Muangto et al., 2016](#); [Cook et al., 2017](#)) in cervical screening with that of clinically validated hrHPV DNA tests. Other studies aimed to evaluate the longitudinal NPV ([Cook et al., 2018](#); [Forslund et al., 2019](#); [Iftner et al., 2019](#); [Zorzi et al., 2020](#)).

In the study of [Iftner et al. \(2015\)](#), 10 040 women aged 30–60 years from the routine cervical cancer screening population of three German centres, in Tübingen, Saarbrücken, and Freiburg, were invited to participate, and 9451 of them were included in the analysis. The study detected 90 cases of CIN2+ and 43 cases of CIN3+. There was no evidence of a difference in the sensitivity for the detection of CIN2+ between the HPV RNA test (Aptima) (87.8%; 95% CI, 80.2–95.5%) and the HPV DNA test (HC2) (93.2%; 95% CI, 87.1–99.2%) [relative sensitivity, 0.94], but the specificity for the detection of CIN2+ of the HPV RNA test was significantly higher than that of the HPV DNA test. For the detection of CIN3+, the sensitivity values were 90.9% for the RNA test and 100.0% for the DNA test [relative sensitivity, 0.90]. For the detection of CIN2+, the specificity values were 96.1% for the RNA test and 94.9% for the DNA test [relative specificity, 1.01]. Women with negative screening test results at baseline were invited to a second round of screening in 2019, and 3295 of them (82.4%) attended follow-up ([Iftner et al., 2019](#)). In the second round, 3057 women (92.8%) tested negative by all three screening tests (DNA, RNA, and cytology). A total of 140 women (4.6%) had at least one positive test result at follow-up, and

115 (82%) of those women underwent a colposcopic examination. The 6-year cumulative risks of CIN2+ were 0.62% (95% CI, 0.24–1.59%) for HPV RNA-negative women and 0.47% (95% CI, 0.27–0.81%) for HPV DNA-negative women, and the 6-year cumulative risks of CIN3+ were 0.31% (95% CI, 0.17–0.57%) for HPV RNA-negative women and 0.22% (95% CI, 0.10–0.49%) for HPV DNA-negative women. In women who tested negative by both HPV tests at baseline, the cumulative risk of CIN3+ was 0.17% (95% CI, 0.04–0.75%). The relative sensitivity for the detection of CIN3+ of the HPV RNA test compared with the HPV DNA test was 0.91 [95% CI, 0.8–1.03]. [The Working Group noted that the relative risk of CIN3+ between the two cohorts was not provided, and it was estimated to be 1.43, with the 95% confidence interval including unity.]

[Cook et al. \(2017, 2018\)](#) evaluated an HPV RNA test (Aptima) against an HPV DNA test (HC2) within the HPV FOCAL trial. The screening efficacy in women aged 25–65 years of an HPV DNA test (HC2) with LBC triage of all HPV DNA-positive women was compared with LBC screening with HPV DNA triage of women with an ASC-US result. HPV RNA and HPV DNA tests were compared at the baseline screen (3473 women). With HPV DNA as the comparator test, the relative sensitivity of the HPV RNA test for the detection of CIN2+ was 0.96 and for the detection of CIN3+ was 1.00, and the relative specificity was 1.01. In an updated follow-up at 48 months, HPV RNA and HPV DNA tests were compared within the intervention arm (women who tested positive with the HC2 test were triaged with LBC) at baseline and at 48 months for the detection of CIN2+. Women with < CIN2 irrespective of the HPV DNA test result at 48 months were screened with the HPV RNA test, the HPV DNA test, and LBC. At 48 months, 4.8% were HPV RNA-positive and 5.2% were HPV DNA-positive, and the relative sensitivity was close to 1 for both CIN2+ and

CIN3+ outcomes. The relative specificity was 1.005. At 48 months, in the 3226 women who were HPV RNA-negative at baseline, 12 of 2858 (0.4%) had CIN2+; in the 3184 women who were HPV DNA-negative at baseline, 13 of 2821 (0.5%) had CIN2+. There was no difference in the detection of CIN2+ at 48 months between the HPV RNA-negative and HPV DNA-negative women at baseline, and accuracy estimates at 48 months were similar.

[Forslund et al. \(2019\)](#) studied a population-based cohort of 95 023 women in Sweden with available cervical samples collected between May 2007 and January 2012 and frozen at –80 °C. Registry linkages identified that 1204 of these women had CIN3+ after 4 months to 7 years since enrolment. Baseline samples were analysed with an HPV RNA test (Aptima) and an HPV DNA test (cobas 4800), and results from both tests were obtained for 1172 women. Both for women younger than 30 years and for women aged 30 years or older, the HPV RNA and HPV DNA tests had similar sensitivities for the detection of CIN3+. In women aged 30 years or older, the longitudinal sensitivities for CIN3+ occurring during the 2-year period 5–7 years after enrolment were lower for the HPV RNA test, with a relative sensitivity of 0.92 and a relative longitudinal NPV of 1.

[Maggino et al. \(2016\)](#) and [Zorzi et al. \(2020\)](#) published the baseline data and the 5-year follow-up data for two cohorts in two neighbouring areas in Italy, one tested with an HPV RNA test (Aptima) and the other with an HPV DNA test (HC2). Women in both cohorts who tested negative at baseline (22 338 women in the RNA cohort and 68 695 women in the DNA cohort) were followed up. The study reports on the 5-year risk of CIN2+ and CIN3+ and the performance parameters at the 3-year rescreening of a negative HPV RNA test compared with those of a negative HPV DNA test in the two cohorts. The Veneto Cancer Registry was checked to search for invasive cancers and CIN3 diagnosed

up to 5 years after the negative baseline test. The baseline data showed that the proportion of positive Pap tests in HPV-positive women and the cumulative referral rate for colposcopy were both higher (52.8% vs 38.2%,  $P < 0.0001$ ; 4.8% vs 4.5%,  $P = 0.04$ ) in the HPV RNA cohort than in the HPV DNA cohort. The ratio of positive HPV tests, of referral for colposcopy, and of detection of CIN2+ in the RNA cohort compared with the DNA cohort were as follows: HPV prevalence ratio, 1.08 (95% CI, 0.99–1.17); referral ratio, 1.06 (95% CI, 0.95–1.18); and CIN2+ detection ratio, 0.85 (95% CI, 0.54–1.33). The relative 5-year cumulative risks of CIN2+ in the RNA cohort and the DNA cohort were 1.1 and 1.5 per 1000 women, respectively (ratio, 0.74; 95% CI, 0.45–1.16), and the risks of cancer were 4.5 and 8.7 per 100 000 women, respectively (ratio, 0.51; 95% CI, 0.01–4.22). [The study has a major caveat, because the comparison was not performed within the same study population but compared two cohorts in parallel.]

[An important issue relating to HPV RNA tests has been the difficulty of estimating the length of time for which a baseline test has negative predictive value. Given the overall slightly lower sensitivity of the HPV RNA tests, the safety of intervals between screening rounds of longer than 5 years remains uncertain. The studies reporting on longer than 5 years are those of [Iftner et al. \(2019\)](#) and [Forslund et al. \(2019\)](#), who reported on women with negative results at baseline. Although [Iftner et al. \(2019\)](#) did not detect a statistically significant difference between HPV RNA tests and HPV DNA tests, [Forslund et al. \(2019\)](#) found a higher longitudinal sensitivity for the HPV DNA test that was evaluated. The lower sensitivity of HPV RNA tests applied in screening settings may affect the longitudinal NPV at 5 years.]

(b) *Use of HPV RNA tests in triage of women with minor abnormal cervical cytology*

[Ovestad et al. \(2011\)](#) evaluated two HPV RNA tests – a 5-HPV type RNA test (PreTect HPV-Proofer) and a 14-HPV type RNA test (Aptima) – and two HPV DNA tests – Amplicor and cobas 4800 – for the triage of women with ASC-US or LSIL cytology results. The study included 528 women in Norway selected from a consecutive population-based follow-up of LBC samples for the diagnosis of CIN2/3. [The study has several limitations. One is that the population is a referral population for abnormal results and may not be the most suitable to compare screening tests with a lower HPV viral load. Furthermore, the two RNA tests that were evaluated targeted different sets of HPV types. The 14-HPV type RNA test was significantly more specific than the Amplicor DNA test (ratio, 2.14; 95% CI, 1.23–2.73) and was more sensitive than the 5-HPV type RNA test (ratio, 1.91; 95% CI, 1.43–2.56) but less specific (ratio, 0.47; 95% CI, 0.34–0.63).]

[Arbyn et al. \(2013b\)](#) performed a meta-analysis of studies reporting on an HPV RNA test (Aptima) compared with an HPV DNA test (HC2) for the triage of women with ASC-US or LSIL cytology results. Eight studies were retrieved, which included 1839 ASC-US cases and 1887 LSIL cases. The outcome was histological detection of CIN2+ or CIN3+. All of the women included had undergone a colposcopic evaluation (this may not imply that all of the women had had a biopsy); a negative colposcopy was considered as ascertainment for the absence of disease when no biopsies were taken. [Table 4.30](#) summarizes the relative accuracy of the HPV RNA test compared with the HPV DNA test for CIN2+ or CIN3+ at a threshold of abnormal cytology of ASC-US or LSIL. The sensitivity of the HPV RNA test was not significantly different from that of the HPV DNA test for either of the outcomes measured, but the specificity of the



**Table 4.30 Pooled relative sensitivity and specificity of HPV RNA testing compared with HPV DNA testing**

Baseline outcome	Outcome after triage	Parameter	Ratio (HPV RNA/HPV DNA) (95% CI)
ASC-US	CIN2+	Sensitivity	1.01 (0.97–1.06)
ASC-US	CIN2+	Specificity	1.19 (1.08–1.31)
ASC-US	CIN3+	Sensitivity	1.01 (0.96–1.06)
ASC-US	CIN3+	Specificity	1.18 (1.08–1.29)
LSIL	CIN2+	Sensitivity	0.96 (0.92–1.03)
LSIL	CIN2+	Specificity	1.37 (1.22–1.54)
LSIL	CIN3+	Sensitivity <sup>a</sup>	0.98 (0.91–1.06)
LSIL	CIN3+	Specificity <sup>a</sup>	1.35 (1.11–1.66)

ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion.

<sup>a</sup> The SAS macro MetaDAS failed to converge. Therefore, the pooled relative sensitivity and specificity were computed separately as ratios. Reproduced with permission from [Arbyn et al. \(2013b\)](#). Copyright 2013, John Wiley & Sons.

HPV RNA test was significantly higher both for CIN2+ and for CIN3+. [The study is robust, because the overall analysis was not heterogeneous and the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) evaluation did not identify major issues.]

The meta-analysis of [Verdoodt et al. \(2013\)](#) compared the diagnostic accuracy of two HPV RNA tests (PreTect HPV-Proofer and NucliSENS EasyQ), both of which target five HPV types, with that of an HPV DNA test (HC2) for the detection of CIN2+ and CIN3+ in women with ASC-US or LSIL. In women with ASC-US or LSIL, HPV RNA testing was significantly more specific than HPV DNA testing for the detection of CIN2+ (ratio 1.98; 95% CI, 1.7–2.3) or CIN3+ (ratio, 3.36; 95% CI, 2.82–4.0), but was significantly less sensitive for the detection of CIN2+ (ratio, 0.80; 95% CI, 0.73–0.87) and CIN3+ (ratio, 0.74; 95% CI, 0.69–0.80). [The comparison between the HPV RNA tests and the HPV DNA test is expected to be limited because of the difference in the HPV types targeted; the HC2 test targets 13 hrHPV types, whereas both RNA tests that were evaluated target five hrHPV types.]

As a part of the Clinical Evaluation of Aptima mRNA (CLEAR) study, [Stoler et al. \(2013\)](#)

evaluated HPV RNA testing for the triage of 939 women with ASC-US cytology for colposcopy referral. A cervical specimen in liquid cytology medium was used to test in a blinded fashion for HPV DNA (cobas 4800), for HPV RNA (Aptima), and for RNA type-specific HPV16, HPV18, and HPV45 for those samples that were HPV RNA-positive. The final diagnoses were based on a consensus panel review of the histology of the biopsy specimen. For detection of CIN2+, the HPV RNA test and the HPV DNA test were equally sensitive (ratio, 1.0; 95% CI, 0.91–1.10), and the HPV RNA test was more specific than the HPV DNA test (ratio, 1.13; 95% CI, 1.04–1.21). Risk stratification using partial HPV genotyping was similar for the two assays. [The CLEAR study had been included in the previous meta-analysis by [Gen-Probe \(2011\)](#), in which data were extracted from a report published by the United States FDA.]

[Cook et al. \(2017\)](#) evaluated an HPV RNA test (Aptima) against an HPV DNA test (HC2) within the HPV FOCAL trial (described above). In addition to the main strategy, further triage strategies to refer women for colposcopy were compared in HPV DNA-positive or HPV RNA-positive women as follows:



**Table 4.31 Colposcopy referral rates and CIN2+ and CIN3+ detection rates by baseline and triage strategies**

Primary test result	Triage strategy result	Number of women screened	Colposcopy referral rate (%) (95% CI)	Detection rate (per 1000 women screened) (95% CI)	
				CIN2+	CIN3+
Baseline HPV DNA+	ASC-US+	125	36.0 (30.3–42.7)	11.2 (8.2–15.3)	4.0 (2.4–6.8)
Baseline HPV DNA+	Persistent HPV DNA+ and/or ASC-US+	86	24.8 (20.1–30.5)	3.2 (1.8–5.7)	1.2 (0.4–3.0)
Baseline HPV RNA+	ASC-US+	107	30.8 (25.6–37.1)	10.9 (8.0–15.0)	4.0 (2.4–6.8)
Baseline HPV RNA+	HPV16/18/45+	67	19.3 (15.2–24.4)	7.8 (5.4–11.3)	3.5 (2.0–6.0)
Baseline HPV RNA+	ASC-US+, or NILM and HPV16/18/45+	133	38.3 (32.4–45.2)	12.4 (9.2–16.6)	4.6 (2.8–7.5)

ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HPV, human papillomavirus; NILM, negative for intraepithelial lesion or malignancy.

Reprinted with permission from [Cook et al. \(2017\)](#). Copyright 2017, Elsevier.

(i) HPV DNA-positive and ASC-US+, (ii) HPV DNA-positive with 12-month HPV persistence and/or ASC-US+, (iii) HPV RNA-positive and ASC-US+, (iv) HPV RNA-positive and HPV16/18/45-positive, and (v) HPV RNA-positive and ASC-US+, or HPV RNA-positive and NILM and HPV16/18/45-positive. [Genotyping was performed with an HPV RNA (Aptima) HPV16/18/45 genotyping assay.] [Table 4.31](#) shows the accuracy results of the different triage strategies. [The Working Group noted that women who were HPV DNA-negative but HPV RNA-positive were not referred for colposcopy; this could lead to an underestimate of an added value of the HPV RNA test, although this should be minimal, given the slightly lower sensitivity of HPV RNA tests compared with HPV DNA tests.] Compared with the triage strategy of immediate referral for colposcopy of women who were HPV DNA-positive with abnormal cytology at baseline and those with 12-month HPV persistence (60.8 per 1000 women screened), the colposcopy referral rate was significantly lower (38.3 per 1000 women screened;  $P < 0.001$ ) in the strategy in which HPV RNA-positive women with abnormal LBC or HPV16/18/45 positivity were referred at baseline.

#### 4.4.7 Triage of women with a positive primary HPV screening test result

Testing for the presence of HPV (in the absence of triage) is inherently limited in terms of its specificity for the presence of histologically confirmed CIN2+ and CIN3+ ([Arbyn et al., 2012](#)). Although hrHPV positivity predicts an increased risk of the future development of CIN2+ and CIN3+ (even if disease is not present at the time of the index screening test) ([Katki et al., 2011](#)), the lower cross-sectional specificity nevertheless implies that some screen-positive women might be followed up unnecessarily. Therefore, appropriate triage testing, management, and follow-up of HPV-positive women is of critical importance to optimize the balance of benefits and harms of primary HPV screening. The general principle is to refer for diagnostic workup women who are at a higher risk of having a current or incipient precancer, to return to routine screening women who are at low risk, and to keep under surveillance women who are at intermediate risk ([Arbyn et al., 2017](#)).

*(a) Methods*

For this *Handbook*, the Working Group updated a previous meta-analysis on the accuracy of six tests or combinations of tests used to triage hrHPV-positive women identified at screening for the detection of underlying cervical precancer (HAS, 2019). Literature retrieval was extended up to 31 January 2020. The Working Group drafted the review question in PICOS form (population, intervention, comparator, outcome, and studies) to determine the inclusion and exclusion criteria for the studies. PICOS components of the research question are summarized in Box S1 (Annex 1; web only; available from <https://publications.iarc.fr/604>). Studies were eligible if (i) cross-sectional and/or longitudinal outcome data were available for women with a positive hrHPV screening test result triaged with an index test, and (ii) verification with the reference standard (colposcopy and targeted biopsy, possibly complemented with random biopsies and/or endocervical curettage) was performed on all women or on women with at least one positive triage test result. Normal satisfactory colposcopy without biopsy was accepted as ascertainment of the absence of CIN2+. The methodological quality of the selected studies was assessed using the QUADAS-2 checklist (Whiting et al., 2011).

The current review was limited to one-time (reflex) triage strategies for women with a positive hrHPV test result on a clinician-collected cervical specimen using the following tests: (i) cytology at a threshold of ASC-US+, (ii) genotyping for HPV16/18, (iii) p16/Ki-67 immunocytochemistry (dual staining), (iv) VIA, (v) the combination of HPV16/18 genotyping and cytology, and (vi) the combination of HPV16/18 genotyping and VIA. Strategies involving other triage tests or combinations and two-time triage strategies (including surveillance of women who were reflex triage-negative) and triage of women with an HPV-positive self-collected sample are not included here.

The numbers of true positives and false positives and true negatives and false negatives were extracted from each primary study to compute the sensitivity, specificity, PPV, NPV, the complement of NPV (i.e.  $1 - \text{NPV}$  [cNPV]), the test positivity rate, and the underlying prevalence of CIN2+ and CIN3+. Standard statistical procedures for pooling diagnostic accuracy data were used (Leeftang et al., 2008). The results were displayed graphically in forest plots and summary ROC (sROC) curves. For each triage approach, the relative sensitivity and specificity compared with reflex cytology at a threshold of ASC-US+ was also assessed. Finally, to illustrate the principle of triage as it applies in a specific local setting, the implied performance of CIN3+ risk-based stratification was considered for each triage approach, given examples of potentially acceptable local risk thresholds for either return to routine screening or referral for colposcopy. The numbers of false-positive and true-positive and false-negative and true-negative results were calculated for a population of 1000 triaged hrHPV-positive women, as were the PPV and cNPV for CIN3+. In addition, the proportion of triage-positive women who would be referred for colposcopy was calculated, together with the number of women who must be referred for colposcopy to detect one case of CIN3+ ( $= 1/\text{PPV}$ ). For this exercise, three background situations were simulated in terms of the underlying risk of CIN3+: (i) a low-risk situation, with a prevalence of CIN3+ of 5% (corresponding to the 10th percentile of the distribution of observed prevalence throughout the meta-analysis); (ii) an intermediate-risk situation, with a prevalence of CIN3+ of 8% (corresponding to the median prevalence); and (iii) a high-risk situation, with a prevalence of CIN3+ of 17% (corresponding to the 90th percentile of the distribution of observed prevalence throughout the meta-analysis).

*(b) Results*

Overall, 93 studies were included in the meta-analysis; the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is shown in Fig. S1 (Annex 1; web only; available from <https://publications.iarc.fr/604>). Most QUADAS-2 items for the included studies were assessed as satisfactory or borderline; see Fig. S2 (Annex 1; web only; available from <https://publications.iarc.fr/604>). The summary results of all the meta-analyses are presented in Table 4.31. The detailed results are presented in Figs. S3–S5, and Table S1 (Annex 1; web only; available from <https://publications.iarc.fr/604>).

*(i) Triage with cytology at a threshold of ASC-US+*

The pooled sensitivity for CIN2+ in 39 studies was 72% (95% CI, 65–77%) and for CIN3+ in 28 studies was 78% (95% CI, 69–84%), and the pooled specificity for < CIN2 was 75% (95% CI, 69–80%) (see Fig. 4.5, Fig. S3 [Annex 1; web only; available from <https://publications.iarc.fr/604>], Table 4.32). The pooled relative sensitivity for the detection of CIN2+ was higher (ratio, 1.22; 95% CI, 1.04–1.44) and the specificity was lower (ratio, 0.75; 95% CI, 0.64–0.88) in the group of studies in which the cytologists were aware of the HPV status compared with the group of studies in which the cytologists were blinded to the HPV status; for the sROC curves stratified by the cytologists' knowledge of the HPV status, see Fig. S4B (Annex 1; web only; available from <https://publications.iarc.fr/604>). For the detection of CIN3+, the impact of the cytologists' knowledge of the HPV status was smaller (detailed results not shown). There were no significant differences in accuracy for detection of CIN2+ or CIN3+ between conventional cytology and LBC methods used in triage of HPV-positive women when ASC-US+ was used as the threshold (detailed results not shown). However, the accuracy of cytology at a threshold of ASC-US+ for

CIN2+ was higher in HPV16/18-positive women than in HPV16/18-negative women (detailed results not shown).

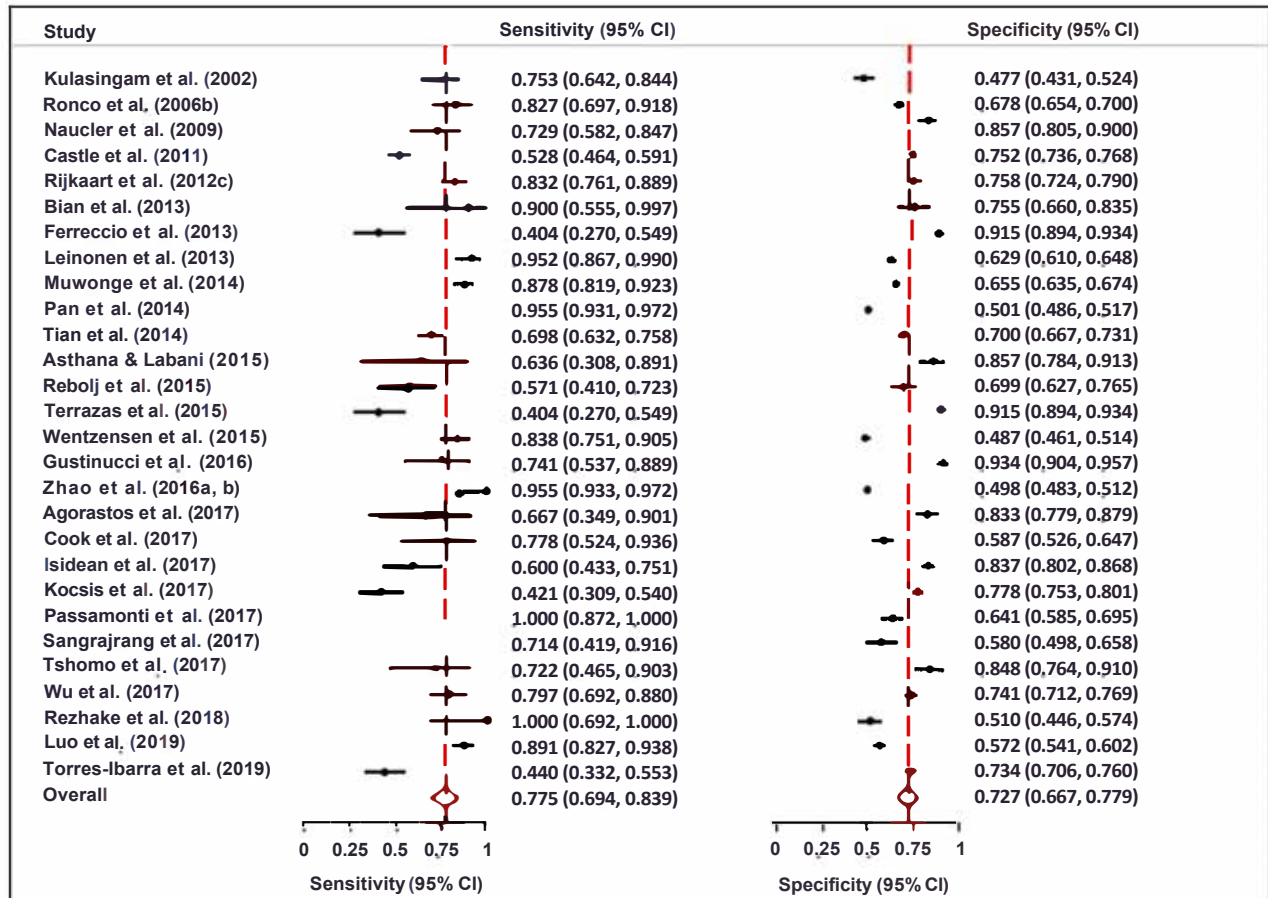
*(ii) Triage with VIA*

Fig. 4.6 shows a forest plot for the meta-analysis of the absolute sensitivity and specificity of triage of hrHPV-positive women with VIA for the detection of CIN3+. The sensitivity was extremely heterogeneous between studies, varying from 6% (Asthana & Labani, 2015) to 100% (Almonte et al., 2020) for CIN2+ and from 7% to 100% for CIN3+ (Fig. 4.6). Exclusion of these two extreme observations yielded a pooled sensitivity of 64% (95% CI, 56–72%) for CIN2+ and of 69% (95% CI, 61–75%) for CIN3+, and a pooled specificity for < CIN2 of 79% (95% CI, 73–84%) (Table 4.32). The relative accuracy estimates (VIA compared with cytology) did not differ from unity; the sensitivity ratio was 1.15 (95% CI, 0.76–1.83) for CIN2+ and 1.01 (95% CI, 0.70–1.45) for CIN3+, and the specificity ratio for < CIN2 was 0.82 (95% CI, 0.58–1.16) (detailed results not shown). Very wide interstudy variation in the relative sensitivity and specificity was observed ( $I^2 > 97%$ ; data not shown).

*(iii) Triage with HPV16/18 genotyping*

The pooled sensitivity of HPV16/18 genotyping to triage hrHPV-positive women was 53% (95% CI, 50–56%) for CIN2+ and 61% (95% CI, 57–65%) for CIN3+, and the pooled specificity for < CIN2 was 75% (95% CI, 70–79%) (Table 4.32, Fig. S4 and Fig. S5 [Annex 1; web only; available from <https://publications.iarc.fr/604>]). For the detection of CIN2+, HPV16/18 genotyping was less sensitive (ratio, 0.85; 95% CI, 0.75–0.96) but similarly specific (ratio, 1.03; 95% CI, 0.95–1.12) compared with cytology at a threshold of ASC-US+. For the detection of CIN3+, there was no significant difference in accuracy between triage with HPV16/18 genotyping and reflex cytology at a threshold of ASC-US+.

**Fig. 4.5 Meta-analysis of the absolute sensitivity and specificity of triage of hrHPV-positive women with reflex cytology at a threshold of ASC-US+ for the detection of CIN3+**



ASC-US+, atypical squamous cells of undetermined significance or worse; CI, confidence interval; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; hrHPV, high-risk human papillomavirus.

Created by the Working Group.

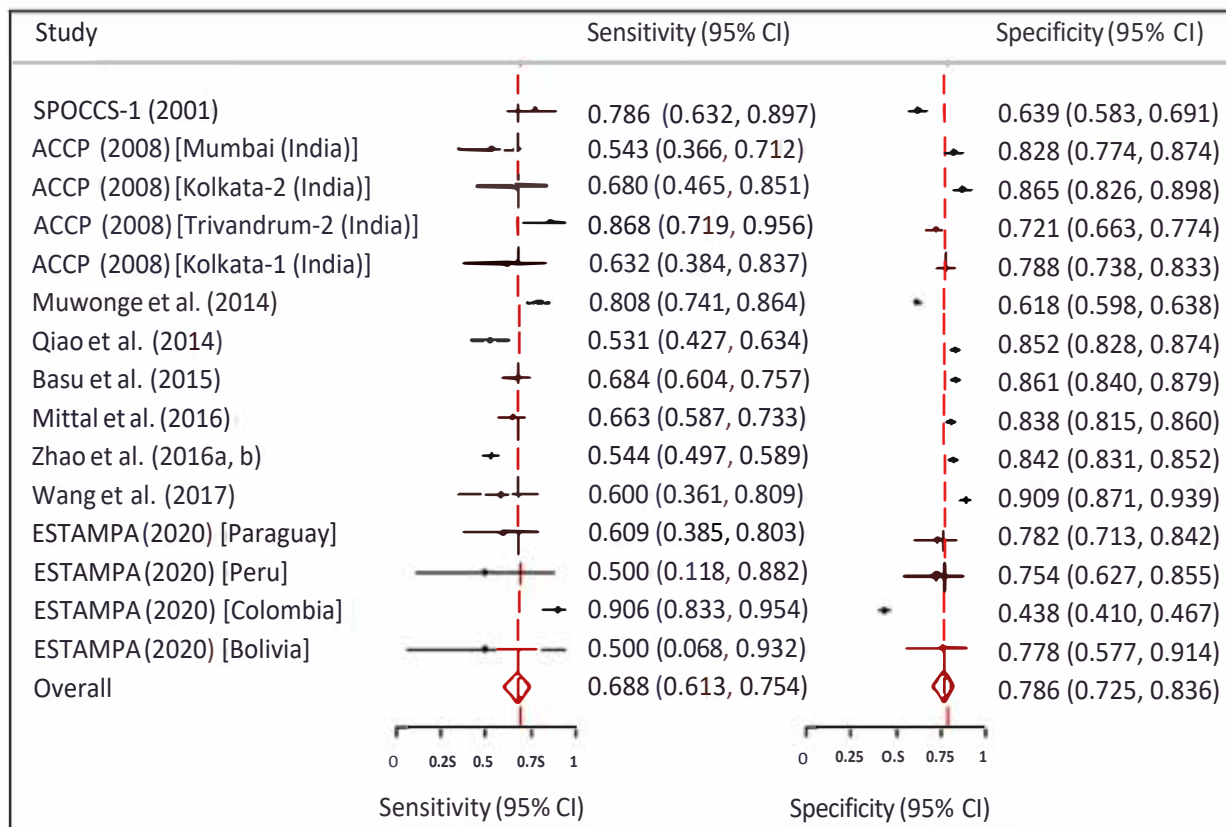
(iv) *Triage with immunocytochemistry (dual staining) for p16/Ki-67*

Dual staining for p16/Ki-67 was more sensitive than reflex cytology at a threshold of ASC-US+, but the difference was significant only for CIN2+ (81% vs 72%; ratio, 1.12; 95% CI, 1.01–1.25) and not for CIN3+ (Table 4.32, Fig. S4 and Fig. S5 [Annex 1; web only; available from <https://publications.iarc.fr/604>]). The specificity of dual staining for < CIN2 was similar to that of cytology at a threshold of ASC-US+ (69% vs 75%).

(v) *Triage with HPV16/18 genotyping combined with cytology or VIA*

HPV16/18 genotyping is usually not used as a stand-alone method to triage hrHPV-positive women. A combined strategy in which HPV16/18-positive women are directly referred for colposcopy and women who are positive only for other carcinogenic HPV types are further triaged with cytology, with referral for colposcopy when cytology shows ASC-US+, had a sensitivity of 83% (95% CI, 79–86%) for CIN2+ and 86% (95% CI, 72–84%) for CIN3+, and the specificity



**Fig. 4.6** Meta-analysis of the absolute sensitivity and specificity of triage of hrHPV-positive women with VIA for the detection of CIN3+

ACCP, Alliance for Cervical Cancer Prevention; CI, confidence interval; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; hrHPV, high-risk human papillomavirus; SPOCCS, Shanxi Province Cervical Cancer Screening Study; VIA, visual inspection with acetic acid.

ACCP (2008): main reference is [Arbyn et al. \(2008\)](#); ESTAMPA (2020): main reference is [Almonte et al. \(2020\)](#); SPOCCS-1 (2001): main reference is [Belinson et al. \(2001\)](#).

Note: Unpublished data were provided by IARC from the ESTAMPA study ([Almonte et al., 2020](#)).

Created by the Working Group.

for < CIN2 was 55% (95% CI, 48–62%). Only two studies provided data for the combination of HPV16/18 genotyping and VIA ([Table 4.32](#), [Fig. S4](#) and [Fig. S5](#); Annex 1; web only; available from <https://publications.iarc.fr/604>).

(vi) *Utility of triage based on the post-test risk of CIN3+*

[Fig. 4.7](#) is an example pre-test–post-test probability plot showing the risk of CIN3+ through the triage pathway applied to hrHPV-positive women starting with partial genotyping (i.e.

HPV16/18-positive). Women who are positive only for other hrHPV types receive a secondary triage with cytology at a threshold of ASC-US+. In [Fig. 4.7](#), a median underlying risk (8%) of CIN3+ in hrHPV-positive women (notionally representing, for example, a population in a middle-income or high-income country) is assumed. Triage with HPV16/18 genotyping enables post-test separation of the population of women into those who are positive for HPV16/18, with a higher risk (almost 20%) of CIN3+, and those who are negative for HPV16/18, with a

**Table 4.32 Pooled cross-sectional sensitivity and specificity of selected tests used to triage hrHPV-positive women to detect CIN2+ or CIN3+**

Triage test	Outcome	Number of studies	Referral rate (%) (IQR or range) <sup>a</sup>	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
ASC-US cytology (all)	CIN2+	39	33.8 (28.9–43.8) <sup>a</sup>	71.5 (65.2–77.1)	74.7 (69.2–79.5)
VIA	CIN2+	17	22.4 (19.3–35.3) <sup>a</sup>	64.2 (56.1–71.5)	79.2 (73.0–84.2)
HPV16/18 genotyping	CIN2+	16	30.7 (20.2–34.3) <sup>a</sup>	52.9 (50.2–55.7)	74.9 (70.3–79.0)
p16/Ki-67 dual staining	CIN2+	5	36.5 (29.4–46.0)	80.8 (74.5–85.8)	69.0 (61.1–75.9)
HPV16/18 genotyping, ASC-US+ cytology if positive for other hrHPV types	CIN2+	12	53.5 (44.6–68.8) <sup>a</sup>	82.6 (79.2–85.5)	55.4 (48.2–62.4)
HPV16/18 genotyping, VIA if positive for other hrHPV types	CIN2+	2	45.3 (43.3–49.4)	87.2 (78.4–92.8)	59.9 (56.2–63.4)
ASC-US cytology (all)	CIN3+	28	<sup>b</sup>	77.5 (69.4–83.9)	72.7 (66.7–77.9)
VIA	CIN3+	15	<sup>b</sup>	68.8 (61.3–75.4)	78.6 (72.5–83.6)
HPV16/18 genotyping	CIN3+	10	<sup>b</sup>	61.2 (57.2–65.2)	74.9 (68.7–80.2)
p16/Ki-67 dual staining	CIN3+	4	<sup>b</sup>	85.1 (77.4–90.5)	63.8 (55.6–71.2)
HPV16/18 genotyping, ASC-US+ cytology if positive for other hrHPV types	CIN3+	9	<sup>b</sup>	85.8 (72.1–84.2)	67.5 (60.1–72.4)
HPV16/18 genotyping, VIA if positive for other hrHPV types	CIN3+	2	<sup>b</sup>	91.5 (79.4–96.8)	57.6 (54.0–61.0)

ASC-US+, atypical squamous cells of undetermined significance or worse; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; IQR, interquartile range; VIA, visual inspection with acetic acid.

<sup>a</sup> Referral rate is the percentage of hrHPV-positive women with a positive triage test result. IQR if  $\geq 8$  studies; range if  $< 8$  studies.

<sup>b</sup> Referral rate is not given for the CIN3+ outcome, because it should be the same as for the CIN2+ outcome.

lower risk (about 3%). This latter group can be further triaged with cytology to resolve their risks of CIN3+ to 6.5% (ASC-US+ cytology) and  $< 2\%$  (cytology-negative). [The triage process can effectively risk-stratify women for the presence of underlying CIN3+. This example effectively illustrates context sensitivity and how the risk stratification inherent in the triage process must ultimately consider the underlying burden of disease as well as the local acceptability of various levels of risk.]

Table S1 (Annex 1; web only; available from <https://publications.iarc.fr/604>) shows the post-test risks of CIN3+ in triage-positive women (PPV) and in triage-negative women (cNPV) for all six triage strategies in low-risk, intermediate-risk, and high-risk situations. The green shading indicates, as an example, the decision thresholds chosen for risk of CIN3+ at  $> 10\%$  for

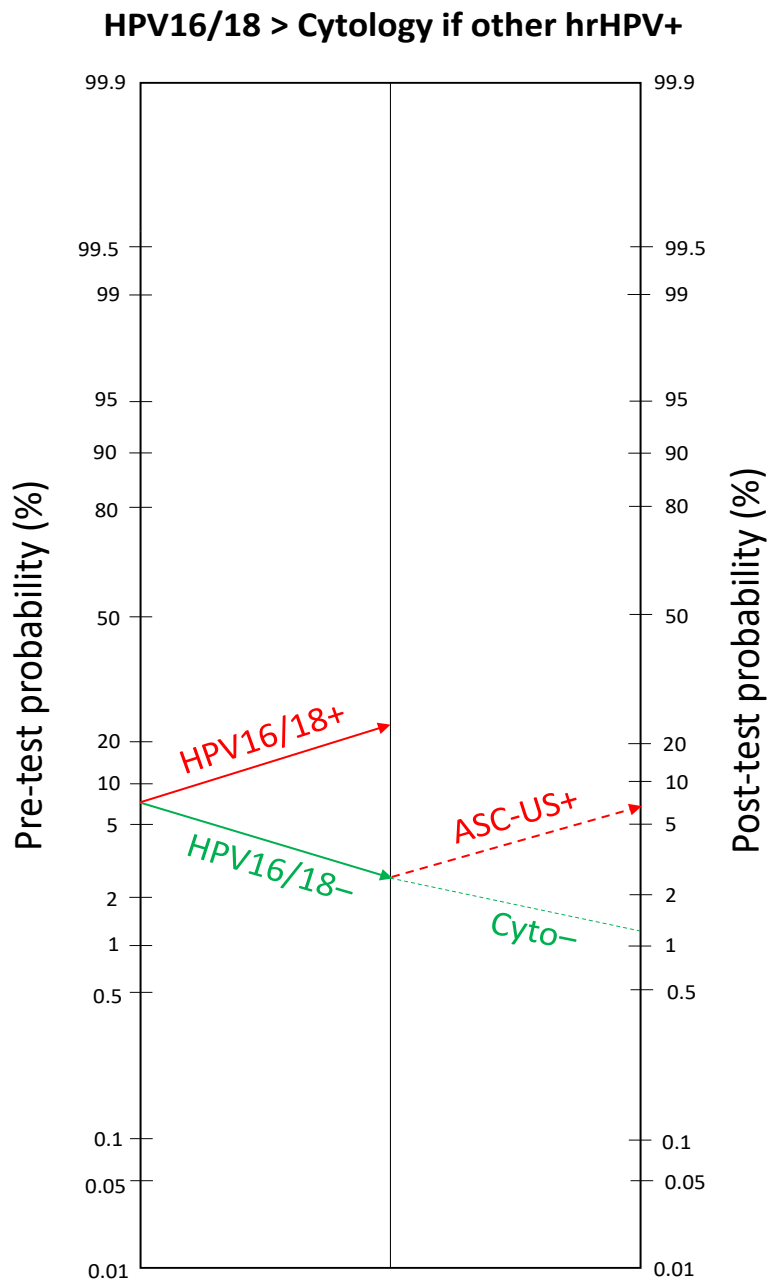
referral and  $< 1\%$  for return to routine screening. [It should be noted that each local programme should choose its own decision thresholds in the context of locally acceptable risks. More complex algorithms than those assessed here can be considered to fine-tune management, particularly in relation to the management of an intermediate-risk group who are hrHPV-positive but have a negative triage test result at the index test, for whom surveillance (i.e. two-time triage testing) is an option ([Arbyn et al., 2020](#)).]

#### 4.4.8 Harms of HPV testing

The harms of HPV testing consist of the psychosocial impact of screening and of a positive HPV test result, and the physical and psychosocial harms of the sampling procedure and of diagnostic follow-up procedures and



**Fig. 4.7 Pre-test–post-test probability plot, showing the risk of CIN3+ through the triage pathway applied to hrHPV-positive women, computed from pooled accuracy estimates applied in a given pre-test risk situation**



Triage with HPV16/18 genotyping followed by colposcopy if HPV16/18-positive. Women who are positive only for other hrHPV types are further triaged with cytology and referred for colposcopy if ASC-US+.

The first triage is applied to a median-risk situation with a pre-test risk of 8% (see left vertical axis). Applying HPV16/18 genotyping stratifies the risk to 19.5% if HPV16/18-positive and to 2.8% if positive only for other hrHPV types. Applying cytology to women who are positive only for other hrHPV types stratifies the risk to 6.5% if ASC-US+ and to 1.3% if cytology is normal.

ASC-US+, atypical squamous cells of undetermined significance or worse; CI, confidence interval; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; Cyto, cytology; hrHPV, high-risk human papillomavirus; VIA, visual inspection with acetic acid.

Created by the Working Group.

treatments. The psychosocial impact of a positive HPV test result is potentially greater than that of an abnormal cytology result, because HPV is sexually transmitted. Qualitative information about psychosocial harms collected by focus groups and in-depth interviews ([Anhang et al., 2004](#); [Kahn et al., 2005](#); [McCaffery et al., 2006](#); [Waller et al., 2007](#); [Daley et al., 2010](#); [O'Connor et al., 2014](#); [Patel et al., 2018](#)) has revealed that a positive HPV test result may cause anxiety and distress and may lead to concerns about the association between HPV and cervical cancer. It may also evoke feelings of stigma and shame and influence sexual relationships by leading to feelings of blame or guilt towards previous or current sexual partners.

The psychosocial impact of HPV testing in cervical screening programmes has been estimated by questionnaire surveys. These include studies that measured harms of HPV testing as a primary screening test ([McCaffery et al., 2004](#); [Kitchener et al., 2008](#); [Hsu et al., 2018](#); [Andreassen et al., 2019](#); [McBride et al., 2020](#)) and studies that measured harms of HPV testing in women with ASC-US ([Maissi et al., 2004](#); [McCaffery et al., 2010](#); [Kwan et al., 2011](#); [Wang et al., 2011](#); [Garcés-Palacio et al., 2018](#)). To understand what type of information should be included in HPV screening invitation letters, in leaflets, and on websites in order to minimize psychosocial harms, several studies have examined whether the psychological harms experienced are influenced by a woman's knowledge about HPV ([Waller et al., 2007](#); [Papa et al., 2009](#); [Burger et al., 2014](#); [Markovic-Denic et al., 2018](#); [Patel et al., 2018](#)).

The harms associated with collection of samples may be different for clinician collection and sample collection at home using a self-sampling device. The experience with self-sampling has been assessed in questionnaire surveys ([Nelson et al., 2017](#)) containing items on the preference for self-sampling compared with clinician collection, and sometimes also items

on the physical and/or psychosocial harms of the collection procedure.

Finally, the magnitude of the harms of HPV testing, diagnostic workup, and treatment of high-grade lesions in cervical screening can be represented by the numbers of screen-positive women, referrals for colposcopy, and treatments, and may be higher for HPV-based screening than for VIA or cytology-based screening because of the relatively high HPV test positivity rate in screening ([Arbyn et al., 2012](#)). The proportions of screen-positive women, referrals for colposcopy, and treatments have been reported in meta-analyses of diagnostic HPV screening studies, RCTs, and implementation studies of HPV screening. The magnitude of diagnostic and treatment harms of HPV DNA-based programmes compared with cytology-based and VIA-based programmes was presented in Sections 4.4.2 and 4.4.3, respectively.

(a) *Psychosocial harms of HPV testing as a primary screening test*

The first study on the psychosocial impact of HPV testing as a primary test in cervical screening was conducted in the United Kingdom in 271 women (mean age, 32 years) who received HPV testing and cytology testing ([McCaffery et al., 2004](#)). Anxiety was measured by the short form of the STAI-6 ([Marteau & Bekker, 1992](#)) and distress by the Cervical Screening Questionnaire (CSQ; [Wardle et al., 1995](#)), and results were collected within 1 month. Among women with normal cytology, anxiety and distress were higher in HPV-positive women than in HPV-negative women. A similar pattern was observed in women with abnormal or unsatisfactory cytology, but the variability of the estimates was high because the stratum size was only 40 women. In addition, more HPV-positive women than HPV-negative women felt worse about their current partner and about previous and future partners, and this effect was similar for women

with normal cytology and those with abnormal or unsatisfactory cytology.

Psychosocial outcomes in women with normal cytology were also measured in a substudy of the ARTISTIC trial ([Kitchener et al., 2008, 2009a](#)), a population-based randomized screening trial in the United Kingdom. Women with normal or mildly abnormal cytology recruited in the ARTISTIC trial were randomized either to cytology with revealed HPV testing or to cytology with concealed HPV testing. The women in the HPV-revealed arm received the results of their HPV test with their baseline cytology result; the women in the HPV-concealed arm were informed of only the cytology result. Anxiety, distress, and sexual satisfaction were assessed in 705 participants after about 2 weeks. Anxiety was measured by the STAI-6, distress was measured by the GHQ ([Bridges & Goldberg, 1986](#)), and sexual satisfaction was measured by the Sexual Rating Scale ([Garratt et al., 1995](#)). When the analysis was restricted to women who were aware of the HPV test result (the revealed arm) and who were cytology-negative, higher levels of anxiety and distress were reported in women who were HPV-positive than in women who were HPV-negative (41% vs 29%; OR, 1.70; 95% CI, 1.33–2.17). However, there was no evidence of a higher level of anxiety or distress in the revealed arm compared with the concealed arm (OR, 0.99; 95% CI, 0.81–1.21). A significant 7% difference on the Sexual Rating Scale was observed in HPV-positive women with normal cytology compared with the group of women with normal cytology and no revealed HPV test result.

A randomized implementation study of primary HPV screening versus cytology screening in Norway measured anxiety and depression by means of the Patient Health Questionnaire-4 (PHQ-4) ([Kroenke et al., 2009](#)) in 1007 screened women ([Andreassen et al., 2019](#)) randomized to either HPV testing every 5 years (followed by cytology if HPV-positive) or cytology testing every 3 years (followed by HPV testing if

low-grade cytology was detected). Compared with women who were screened with cytology, women screened with an HPV test were not more likely to have mild, moderate, or severe anxiety and depression scores. Moreover, no differences in mean anxiety and depression levels were found when comparing HPV-positive women with normal cytology from the HPV screening group with women with normal cytology from the cytology group. [A possible explanation for the absence of an effect on psychosocial outcomes in the study in Norway is that women answered the questionnaire 4 months to 2 years after having received their last screening result, and elevations in anxiety and depression levels may have been temporary and levels may already have returned to normal. There was also considerable variation among participants in anxiety and depression levels, with some participants showing moderate or severe anxiety and depression levels.]

An inventory of the psychosocial harms in primary HPV screening implemented in a middle-income setting was conducted by [Arrossi et al. \(2020\)](#). In 163 HPV-positive women participating in the regional primary HPV screening programme in Jujuy, Argentina, psychosocial impact was measured by means of the Psycho-Estampa Scale, which was designed and validated for use in Latin American women. The Psycho-Estampa Scale consists of five domains: (i) an emotional domain, related to feelings about having a sexually transmitted infection; (ii) a sexuality domain, related to attitude and practice in sexual relationships; (iii) an uncertainty of information domain; (iv) a domain pertaining to the impact on family members; and (v) a worries domain, covering worries about HPV, cancer, and treatment. In the study population, the mean levels were highest for worries about HPV, cancer, and treatment but were also elevated for the other domains. The scores were higher in women with abnormal cytology triage than in women with normal cytology.

A systematic review of 25 studies on the effect of a positive HPV test on psychosexual outcomes ([Bennett et al., 2019](#)) considered overall psychosexual impact, sexual satisfaction and pleasure, frequency of sex, interest in sex, and feelings about partners and relationships. The studies included were very heterogeneous, which made it difficult to draw conclusions about the psychosexual impact of HPV testing, but in general women were concerned about transmitting HPV to a partner and about where the infection came from.

The longitudinal pattern of psychosocial outcomes was studied in England in a questionnaire survey in 1127 women aged 24–65 years who were screened at one of the primary HPV screening pilot centres; the study included a control group with negative cytology who were not tested for HPV ([McBride et al., 2020](#)). Elevated anxiety (STAI-6) and distress (GHQ) scores were recorded in HPV-positive women compared with women with negative cytology in the first 3 months after the test result had been received. However, after 12 months, anxiety and distress levels had returned to normal levels, irrespective of the HPV test result at 12 months. With respect to disease-related concerns, a positive HPV test result at baseline and at 12 months contributed to worry about cancer, and HPV clearance at 12 months contributed to reassurance. [The observation that a positive HPV test result at 12 months did not lead to an increase in the mean levels of anxiety and distress but was associated with worry about cancer suggests that although a positive HPV test result gives rise to disease-related concern initially, it is not disruptive of daily functioning when repeated.]

The observation that distress levels decrease over time was confirmed in a smaller study of 70 HPV-positive women in Taiwan, China, who were followed up until 12 months after a positive HPV test result ([Hsu et al., 2018](#)).

(b) *Psychosocial harms of HPV testing as triage after an abnormal cytology result*

One of the first studies that evaluated the psychosocial harms of HPV testing in women with an abnormal cytology result was a pilot study embedded in routine cytology screening in England, which recruited 1376 women with a normal or BMD cytology result (ASC-US/LSIL); 867 of the women with ASC-US/LSIL also had an HPV test ([Maissi et al., 2004](#)). The 536 women with a positive HPV test result were compared with the 331 women with a negative HPV test result and the 509 women who were not tested for HPV. Women with a positive HPV test result had the highest level of anxiety as measured by the STAI-6, the highest level of distress as measured by the GHQ, and the largest concern about the test result compared with the other groups. Women with an abnormal cytology result, whether tested for HPV or not, were less likely to know what their results meant compared with women with a normal cytology result; 26% of women with a positive HPV test result stated that they did not know what this meant for their health. Levels of anxiety, distress, and concern were similar in women with a negative HPV test result and in women who were not tested for HPV. [Because the study was cross-sectional, it did not provide information about the duration of elevated levels of anxiety and distress.] After a 6-month follow-up assessment ([Maissi et al., 2005](#)), mean levels of anxiety and distress were lower and did not differ between the three groups. The level of concern about a positive HPV test result was still elevated after 6 months compared with the level of concern after a negative HPV test result or no HPV test, but the level of concern had decreased from the baseline level. Worries about sexual health were measured for the first time after 6 months, and they were also higher in the group with a positive HPV test result.

An association between psychosocial harms and HPV testing does not necessarily imply that HPV triage has a negative effect on psychosocial outcomes in women with ASC-US. For example (as mentioned above) in the ARTISTIC trial, HPV-positive and HPV-negative women had different levels of psychosocial outcomes, but there were no significant differences in mean levels between the cytology and HPV randomization arms. To address this for women with ASC-US, in a pragmatic, randomized screening study in Australia of 314 women with an ASC-US test result, women were randomized to HPV testing, repeat cytology testing after 6 months, or an informed choice of either test supported by a decision tool ([McCaffery et al., 2010](#)). In the informed-choice arm, 61 (64%) women chose HPV testing and 35 (36%) chose repeat cytology testing. Psychosocial outcomes were measured after 2 weeks and after 3, 6, and 12 months. After 2 weeks, no mean effect of HPV testing was observed on anxiety as measured by the STAI-6 or on distress as measured by the CSQ ([Wardle et al., 1995](#)), although HPV testing was associated with 57% of women having intrusive thoughts in the HPV testing arm, compared with 32% in the repeat cytology testing arm and 43% in the informed-choice arm. However, after 1 year, most of the women in the HPV testing arm did not report residual intrusive thoughts, and distress was highest in the repeat cytology testing arm.

The temporary nature of anxiety, as observed in the studies in England and Australia described above, was confirmed in a study of 299 ethnic Chinese women in Hong Kong SAR with an ASC-US test result who received adjunct HPV testing ([Kwan et al., 2011](#)). Baseline differences in the mean level of anxiety (STAI-6) between HPV-negative and HPV-positive women had disappeared after 6 months. The effect of HPV testing on the HPV Impact Profile (HIP) was also examined. The HIP scale is a combined, multi-dimensional scale ([Mast et al., 2009](#)) with seven

dimensions: worries and concerns, emotional impact, sexual impact, self-image, partner issues and transmission, interactions with physicians, and health control and impact on daily living. HIP scores were different for HPV-positive and HPV-negative women at baseline and at 6 months, although the differences were smaller at 6 months.

A hospital-based survey in China in 2605 women who had visited the hospital in the previous 3 months ([Wang et al., 2011](#)) confirmed that HIP scores were elevated in women with an HPV-positive ASC-US test result compared with women with an HPV-negative ASC-US test result or women with normal cytology. A pragmatic trial in Colombia compared psychosocial outcomes in 675 women ([Garcés-Palacio et al., 2020](#)) randomized to repeat cytology testing, HPV testing, or colposcopy after an ASC-US test result. The study found that anxiety measured by a long-form 20-item version of the Spielberger anxiety scale (STAI-20) and the HIP was higher in HPV-positive women than in HPV-negative women at 2 months, but that the differences in mean levels had disappeared after 1 year. There were no significant differences between the different randomization groups.

A strength of the randomized trials in Australia ([McCaffery et al., 2010](#)) and Colombia ([Garcés-Palacio et al., 2020](#)) is that the direct causal effect of HPV testing on psychosocial harms in the screening population is measured. This causal effect of learning about the HPV test result on psychosocial outcomes cannot be concluded from a comparison of psychosocial outcomes in HPV-positive and HPV-negative women, because HPV-positive women may have different levels of harms than HPV-negative women before the HPV test result is revealed. This conjecture was examined by a study in 2842 women in the United Kingdom ([Johnson et al., 2011](#)) participating in the TOMBOLA trial ([Cotton et al., 2006](#)). Psychosocial outcomes were measured before the HPV test result was



revealed. Anxiety was measured by the HADS ([Zigmond & Snaith, 1983](#)). In White women, there were no baseline differences in anxiety and cancer worries, but in non-White women, anxiety was lower in HPV-positive women than in HPV-negative women. In non-smokers, cancer worry was more common in HPV-positive women than in HPV-negative women; the opposite association was observed in ex-smokers.

[This suggests that the effect on psychosocial outcomes of knowing the HPV test result may be somewhat confounded by baseline differences between HPV-positive and HPV-negative women.]

(c) *Psychosocial harms and knowledge about HPV*

Mass education about HPV can prevent anxiety and psychological distress associated with HPV testing ([Anhang et al., 2004](#)). Focus group interviews ([Anhang et al., 2005](#)) identified that women desire detailed information about HPV, including susceptibility, risk of cervical cancer, and the effect of preventive interventions on this risk. The studies described here aimed to estimate the association between knowledge of HPV and psychosocial harms.

[Waller et al. \(2007\)](#) conducted a web-based survey in the United Kingdom in 811 female students. The participants were asked to imagine that they had had a positive HPV test result, and the study assessed the impact of their knowledge that HPV is sexually transmitted and about the high prevalence of HPV infection on stigma, shame, and anxiety by withholding pieces of information from some participants. Knowledge of the high prevalence was associated with lower levels of stigma, shame, and anxiety, whereas knowledge that HPV is sexually transmitted was associated with higher levels of stigma and shame but not anxiety. Women who knew that HPV is sexually transmitted but not that it is highly prevalent had the highest scores for stigma and shame.

The findings of this study were supported by a structured interview study in 46 women in the United Kingdom, which indicated that lack of knowledge enhances anxiety after a positive HPV test result ([Patel et al., 2018](#)), and a study of 324 women in Serbia with an abnormal cytology result ([Markovic-Denic et al., 2018](#)), which found that awareness of a positive HPV test result increases anxiety and perceived risk of cancer and concern, but that knowledge about HPV decreased anxiety and concern. Slightly different results were obtained by a small educational intervention study in the USA in 50 women aged 30 years and older ([Papa et al., 2009](#)), which indicated that education may not alleviate the concern about developing cancer, and a randomized web-based survey in 3540 women in Norway ([Burger et al., 2014](#)), which indicated that a switch to HPV screening does not increase anxiety, irrespective of whether additional information about HPV is provided.

[The study outcomes suggest that awareness that HPV is sexually transmitted increases levels of anxiety, stigma, and shame, but that low levels can be retained by creating awareness of the high prevalence of HPV. Implementation of HPV testing should be accompanied by a well-designed education and communication strategy to explain what a positive HPV test result means.]

(d) *Diagnostic harms of HPV testing as triage after an ASC-US or LSIL test result*

The magnitude of the diagnostic harms of HPV testing as triage is indicated by the clinical specificity for the absence of CIN2+ and the number of referrals for colposcopy. Pooled estimates were calculated in a meta-analysis of 39 studies in women with ASC-US and 24 studies in women with LSIL in whom HPV triage was conducted by HC2 testing; the women subsequently underwent colposcopy and colposcopy-directed biopsies for histological verification ([Arbyn et al., 2012, 2013a](#)). The pooled specificity of HPV triage testing after an ASC-US result



for detection of CIN2+ was 58.3% (95% CI, 53.6–62.9%). There was considerable variation across the studies, with specificities ranging from 27% to 79%. The pooled specificity of HPV triage testing for the management of LSIL for detection of CIN2+ was only 27.8% (95% CI, 23.8–32.1%) and varied from 16% to 58% across studies. The proportion of referrals for colposcopy was 48.2% (95% CI, 43.7–52.6%) for ASC-US and 76.9% (95% CI, 73.5–80.2%) for LSIL.

Three well-documented studies in the meta-analyses that were large enough to enable comparison of different age cohorts were the Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS) trial ([Sherman et al., 2002](#)), the NTCC trial ([Ronco et al., 2007b](#)), and the KPNC cohort ([Castle et al., 2010](#)). In women with ASC-US, the proportions of colposcopy referrals with HPV triage were 54% in the ALTS trial, 30% in the NTCC trial, and 35% in the KPNC cohort. In women with LSIL, the proportions of colposcopy referrals with HPV triage were 85% in the ALTS trial, 55% in the NTCC trial, and 84% in the KPNC cohort. In all three studies, the proportions of colposcopy referrals with HPV triage were dependent on age. In the ALTS trial, the proportion of women referred in the ASC-US subgroup decreased from 71% in women aged 18–22 years to 31% in women aged 29 years or older, whereas the referral proportion in the LSIL subgroup decreased only from 87% in women aged 18–22 years to 75% in women aged 29 years or older. In the NTCC trial, the referral proportions in the ASC-US subgroup were 46% in women aged 25–34 years and 25% in women aged 35–60 years, whereas the referral proportions in the LSIL subgroup were 72% in women aged 25–34 years and 41% in women aged 35–60 years. In the KPNC cohort, the referral proportions in the ASC-US subgroup decreased from 52% in women aged 30–34 years to 28% in women aged 60–64 years, and the referral proportions in the LSIL subgroup decreased

from 89% in women aged 30–34 years to 74% in women aged 60–64 years.

(e) *Psychosocial and physical harms of self-collection versus clinician collection*

HPV testing can be performed on a self-collected sample, and this may decrease the physical and psychosocial harms of the sample collection process. Several studies have collected information about the impact of the sample collection method on the acceptability and harms of HPV testing. A systematic review of 20 studies that assessed the acceptability of self-sampling, preferences, and experience with self-sampling ([Huynh et al., 2010](#)) indicated that discomfort and pain were not experienced in general. Most women in the studies also had a positive attitude towards self-sampling as a part of future screening. A concern observed in multiple studies was that women were unsure whether they had followed the testing procedure correctly and had greater confidence in the accuracy of the clinician collection. The preference for self-sampling was also observed in a larger systematic review and meta-analysis of 37 studies published in 1986–2014 that included more than 18 000 women in North America, South America, Europe, Africa, and Asia ([Nelson et al., 2017](#)). Most of the studies were in countries in North America, South America, and Europe; six studies were in Asian countries, and five studies were in African countries. Nine studies involved self-sampling at home. The pooled estimate of women reporting a preference for self-collection over clinician collection was 59% (95% CI, 48–69%). Reasons for preferring self-collection were that it is easy to use and that it is private, not embarrassing, convenient, and comfortable. Some women reported that they disliked self-collection because it was painful or physically uncomfortable, because it led to anxiety, or because of uncertainty about whether the sampling was done correctly. Some women indicated that they did not like touching themselves. One study in women in India,

Nicaragua, and Uganda also reported that most women surveyed (78%) preferred self-sampling; 75% reported that it was easy, although 52% were initially concerned about hurting themselves and 24% were worried about not getting a good sample. The acceptability of self-sampling was higher when providers prepared the women through education, when providers allowed women to examine the collection brush, and when providers were present during the self-collection process ([Bansil et al., 2014](#)).

Since the two systematic reviews were conducted, several studies have been published in which women invited for HPV screening were asked about their experiences and/or harms of self-sampling. Most of those studies were pilot implementation studies evaluating home-based self-sampling, sometimes with the involvement of a community health worker. An overview of recent studies is given here. A study of home-based HPV self-sampling in 746 non-responders to the screening programme in Australia randomized women to self-collection for HPV testing or a repeat invitation letter for a cervical cytology test at the clinic ([Sultana et al., 2015](#)). More than 90% of the women considered self-collection to be easier, more convenient, less embarrassing, and less uncomfortable; however, similar to studies in the meta-analyses, most women were unsure about the reliability of the HPV self-sampling test result. Most women (88%) preferred self-sampling at home because it was simple and did not require an appointment at the clinician's office. Similar findings were reported in a study of home-based self-sampling with involvement of a community health worker in 200 underscreened Aboriginal women in rural and remote communities in Australia, more than 90% of whom indicated that they were highly satisfied with the HPV self-sampling kit and the process involved ([Dutton et al., 2020](#)). Two large studies in Latin America – a study in 2616 women in Argentina invited for regular screening ([Arrossi et al., 2016](#)) and a study in 1867 underscreened women

in El Salvador ([Maza et al., 2018](#)) – assessed the attitude towards home-based self-sampling, both with involvement of a community health worker. Both studies reported that saving time was an additional reason to prefer self-sampling, in addition to the reasons that self-sampling is easy to perform and more comfortable and less embarrassing than clinician sampling. [Maza et al. \(2018\)](#) reported that feeling empowered was a reason for choosing self-sampling. [Arrossi et al. \(2016\)](#) reported, based on 433 women who chose clinician sampling instead of self-sampling, that the main reasons for not choosing self-sampling were trust in the clinician and the woman's fear of hurting herself. Another large self-sampling study included about 13 000 women in rural regions in Greece, who were recruited through a nationwide network of midwives ([Chatzistamatiou et al., 2020](#)). Women conducted self-sampling at home or at a general practitioner (GP) clinic and indicated minimal pain or discomfort and preference for self-collection when the test result is reliable. Testing at home was also preferred to self-sampling at a GP clinic. Positive experience of home-based self-sampling was also reported in other, smaller studies, including in women in rural Canada ([Duke et al., 2015](#)), Kenya ([Oketch et al., 2019](#)), Nigeria ([Modibbo et al., 2017](#)), and the United Republic of Tanzania ([Bakiewicz et al., 2020](#)), and in women in Japan with limited experience of tampon use ([Hanley et al., 2016](#)).

The role of home-based self-sampling in programmatic, regular screening is currently being discussed in several countries. In two recent studies, in the Netherlands ([Polman et al., 2019c](#)) and Sweden ([Hermansson et al., 2020](#)), HPV self-sampling was evaluated as a primary instrument in the setting of HPV-based screening without the use of an additional test for women with a negative HPV self-sampling result. In the study in the Netherlands ([Polman et al., 2019c](#)), experience was measured in routine screening in which women were randomized to HPV testing

on a self-collected versus clinician-collected sample. Responses were collected from 3835 women. Self-collection scored substantially lower on discomfort, pain, nervousness, and shame and higher on privacy compared with clinician collection. Trust in the test result was high with both self-collected and clinician-collected samples for HPV testing, irrespective of the HPV test result, although it was slightly higher for clinician sampling; 77% of the women reported that they preferred self-sampling for future screening. In the study in Sweden ([Hermansson et al., 2020](#)), in 868 women aged 60 years or older who had a positive HPV self-sampling result, 59% reported a preference for self-sampling versus 17% for clinician sampling. The main reasons for preferring self-sampling were that it is easy to perform and less embarrassing and less time-consuming than clinician sampling.

Information from non-responders and from clinicians can help to gain further insights into attitudes towards self-sampling. A study in underscreened women in the USA ([Malone et al., 2020](#)) compared attitudes in self-sampling kit returners (116 of 272 women invited) and non-returners (119 of 1083 women invited) and found no difference in attitude towards screening. The most common reason for non-return was low confidence in the woman's ability to correctly use the kit ([Malone et al., 2020](#)). In both groups, trust in the preventive effect of HPV screening against cancer was low. A randomized trial of HPV self-sampling in women in the USA that assessed attitudes in screened women and in clinicians ([Mao et al., 2017](#)) indicated that both screened women and clinicians expressed concerns about trust in the self-sampling test and valued the opportunity to discuss other health concerns with the clinician at the time of sampling.

Several individual studies compared attitudes and experiences with multiple sampling devices. In a study in non-responders in the Netherlands, the experiences of almost 10 000 women, to whom either a brush or lavage was offered, were

compared ([Bosgraaf et al., 2014](#)). The experience of using the devices did not differ with respect to shame, feeling at ease, stress, discomfort, and pain, with levels similar to those observed in earlier studies. In a similarly designed study in Finland ([Karjalainen et al., 2016](#)), low discomfort and pain levels were reported for both devices. In a study in the KwaZulu-Natal region of South Africa in young women aged 16–22 years attending rural high schools ([Mbatha et al., 2017](#)), a choice between home-based self-sampling with a swab or a brush and clinician sampling was offered to all women. Most women expressed a preference for self-sampling (56%) compared with clinician sampling (44%). Pain was reported less often for the swab than for the brush, and the swab was preferred to the brush by most women who favoured self-sampling. However, in a study in Norway in women with a positive clinician-based hrHPV test, in which home-based self-sampling with a swab and a brush was subsequently offered to all women ([Leinonen et al., 2018](#)), both the swab and the brush were rated very positively, but the brush was reported as slightly easier to use and more comfortable.

[This indicates that although the experience was in general very positive, the preferred self-sampling method may vary across populations.]

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