COURSE: Evidence-Based Approaches to HPV Screening implementation

Module 3. Tests for primary screening for cervical cancer

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CONTENTS

INTRODUCTION AND LEARNING OBJECTIVES

The improved understanding of the natural history of cervical carcinogenesis, and the near-universal role of HPV in the carcinogenic process, has transformed our approach to cervical cancer screening. Furthermore, multiple epidemiological, molecular, and clinical studies have enabled the identification of those HPV infections associated with precancerous and cancerous lesions, making their detection a highly accurate disease marker.

Cytology has been used as the primary cervical cancer screening test for the past 70 years and has helped reduce cervical cancer rates in many countries. However, it has failed to effectively reduce the cervical cancer burden in others, for reasons discussed in this module. As a result, cytology-based screening is no longer the primary recommended screening method by international agencies such as the World Health Organization (WHO), and many countries have switched—or are in the process of switching—from cytology to HPV testing.

After this module, participants will be able to:

- Describe the characteristics of a test suitable for primary cervical cancer screening.
- Compare the advantages of HPV testing over cytology and co-testing.
- Evaluate HPV tests that meet clinical validity criteria for screening.
- Respond to the commonly mentioned concerns of the transition to HPV-based screening.
- Assess the feasibility of HPV screening tests in low-resource settings

UNIT 1. PRIMARY SCREENING OF CERVICAL CANCER

There are several tests available that target different stages of the cervical carcinogenesis process. This module restricts discussion to those tests suitable for primary screening (i.e., the initial test used to screen the asymptomatic population).

As described in **MODULE 2**, primary screening aims to identify those women with a higher risk of cervical cancer. Tests should ideally have high sensitivity (identify the disease of interest, if present, with a positive test result) and high specificity (not mislabel healthy patients without the disease with a positive test result). However, no test achieves the ideal of 100% sensitivity and 100% specificity. Therefore, these two parameters (sensitivity and specificity) need to be balanced in order to maximize effectiveness and minimize the cost and harm of treatment and of secondary tests.

For a first-line screening test, high sensitivity is preferred over high specificity to minimise the number of false negatives. However, to reduce unnecessary referral for final diagnosis and/or treatment (false positives) in populations screened with a primary test with limited specificity, those that test positive are tested again with a confirmatory test. This step is called TRIAGE and may be embedded within the primary test itself.

EXAMPLE

In cervical cancer, a common strategy consists of an HPV test that provides pooled results for positivity to the HPV types targeted by the test and use cytology as a triage test (two separate tests). Alternatively, some assays provide specific genotype information for selected HPV types with the highest risk of cervical cancer, such as the highest risk types HPV16 and HPV18, and the remaining types are grouped together (other HPV). This distinction allows to prioritize those positive for HPV16 or 18 for colposcopy.

This module examines primary cervical cancer screening with HPV testing as the currently recommended primary screening test. A brief summary of cervical cytology is presented to understand the advantages of HPV testing further.

ACTIVITY

Read the following statements about primary screening and decide if they are TRUE or FALSE.

1. Its aim is to detect the precancerous cervical lesions that would progress to cancer if untreated.
2. High specificity of the screening test is preferred over high sensitivity.
3. When using a test with a moderate specificity, positive cases need to be triaged, i.e., tested again with a confirmatory test.

The correct answers are:

1 True, 2 False, 3 True.

UNIT 2. CYTOLOGY

2.1 Characteristics

Cytology is also known as the Papanicolaou test, Pap test, Pap smear, cervical smear or cervical cytology.

To obtain and interpret a cervical cytology, a healthcare provider collects cells from the ecto and endocervix. The cells are smeared and fixed over a glass slide. After staining the cells using haematoxylin and eosin, morphological changes associated with precancerous or cancerous lesions can be detected. In some settings, particularly in Eastern Europe, Romanowsky dye is used to stain the smeared cells but only those stained by haematoxylin and eosin, as proposed by Papanicolaou are named as Pap test or Pap smear. Recently, the International Agency for Research on Cancer, after an extensive bibliographical search, has been unable to support the Romanowsky dye as the staining procedure for cervical cytology in cervical cancer screening due to limited available evidence (IARC 2022).

2.2 Strengths and limitations

Cytology was the most common and longest standing cervical cancer screening method in numerous high-resource countries for the past 70 years. Its implementation through high-quality organised programmes with high coverage rates has undoubtedly reduced cervical cancer incidence and mortality.

In such high-resource settings, cytology was successful despite its generally moderate sensitivity for detecting precancerous lesions and limited longitudinal predictive value, which was mitigated by repeating the test approximately every three years (increased frequency of screening).

Visual detection of morphological cellular changes enables the diagnosis of precancerous lesions, but the interpretation of these changes is observer-dependent. Training, prevalence of disease and the quality of the sample resulted in a wide range of cytology sensitivity values for detecting HSIL+ ranging from 50% to >80% (Cuzick et al. 2006). Consequently, in the USA, 32% of cervical cancer cases diagnosed between

1995 and 2000 occurred in women who had been screened with cytology and incorrectly labelled as negative (Leyden et al. 2005).

NOTE: *The 32% value above is an attributable fraction (i.e, the proportion of cases attributable or caused by a risk factor, in this case a negative cytology result), and they must be interpreted cautiously due to its dependence on time and place. For instance, in country A where no screening has ever been done, there won't be any previous negative result and the attributable fraction of a false negative test will be zero. In a country B, where all women are screened in a regular manner, most cases will be attributable to failure in screening although a portion of them might be cancers that developed between screening rounds and progress too rapidly to be detected in time.*

Nordic countries began screening in the late-60s and were an example of a successful cytology-based screening programme. **Figure 1** shows the decline in age-specific cervical cancer incidence at increasing calendar year (lines). For example, there were 64 cervical cancer cases per 100,000 women aged 40-44 in 1965, compared with 17 cervical cancer cases per 100,000 women in 2005.

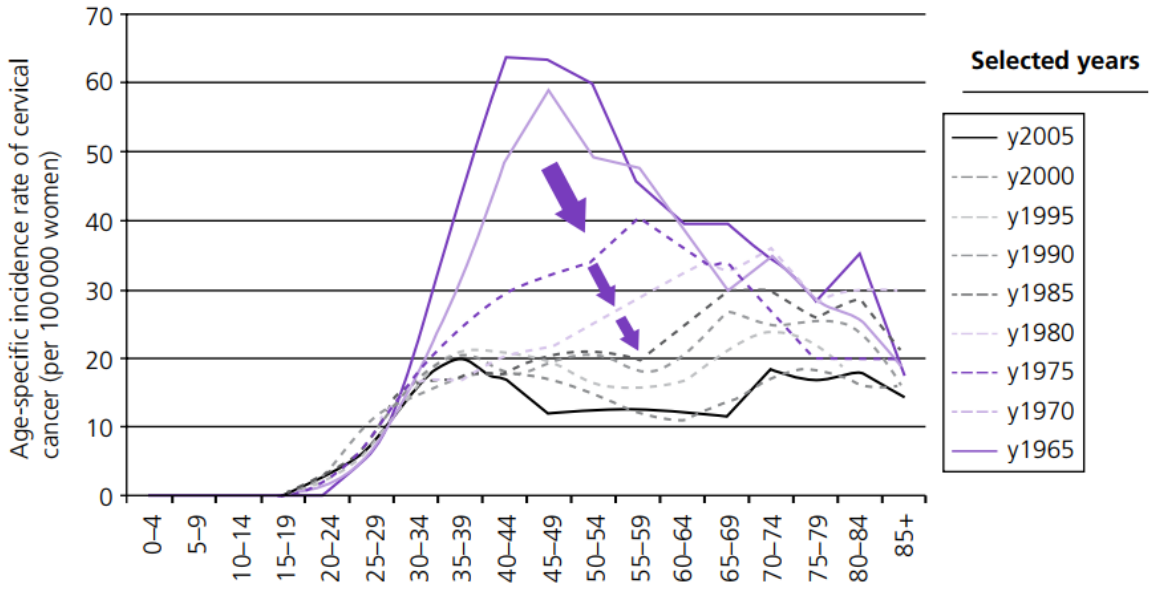


Figure 1. Age-specific incidence of cervical cancer in Scandinavian countries from 1965 and 2005 using data from the NORDCAN database (Danckert et al. n.d.). Graphic source: Laia Bruni.

However, against these historical reductions, these countries have recently observed an increase in cervical cancer incidence in young women up to the age of 49 with an estimated annual change of +1.8% In Sweden, the incidence of cervical cancer has increased only in women that were screened and had a negative cytology result (Wang et al. 2020). Systematic re-review of all smears taken before the diagnosis of a cervical cancer identified an increasing trend over time of false negative cytologies (Edvardsson et al. 2021). The reason for the declining performance of cytology is not known but is assumed to be related to losing its prominent space in cervical screening. Reasons for the increased incidence in other Nordic countries have not been elucidated.

Furthermore, incidence rates of cervical adenocarcinoma have been increasing over recent years, with an annual percent change ranging from 0.5% and >3% depending on the country (Bray et al. 2005).

Cytology has reached a limit in terms of prevention. In countries with a wide use of cytology as a primary screening approach, there is no further decrease in cervical cancer incidence due to its subjectivity. Furthermore, cytology has a lower sensitivity for detecting glandular precursor lesions at the endocervix compared with lesions of the squamous columnar epithelium at the ectocervix. Therefore, it is less capable of detecting adenocarcinomas than squamous cell carcinomas.

However, despite its limitations as primary screening test, cytology has a **specificity with values above 90%** in European and North American studies, as observed in **Figure 2.**

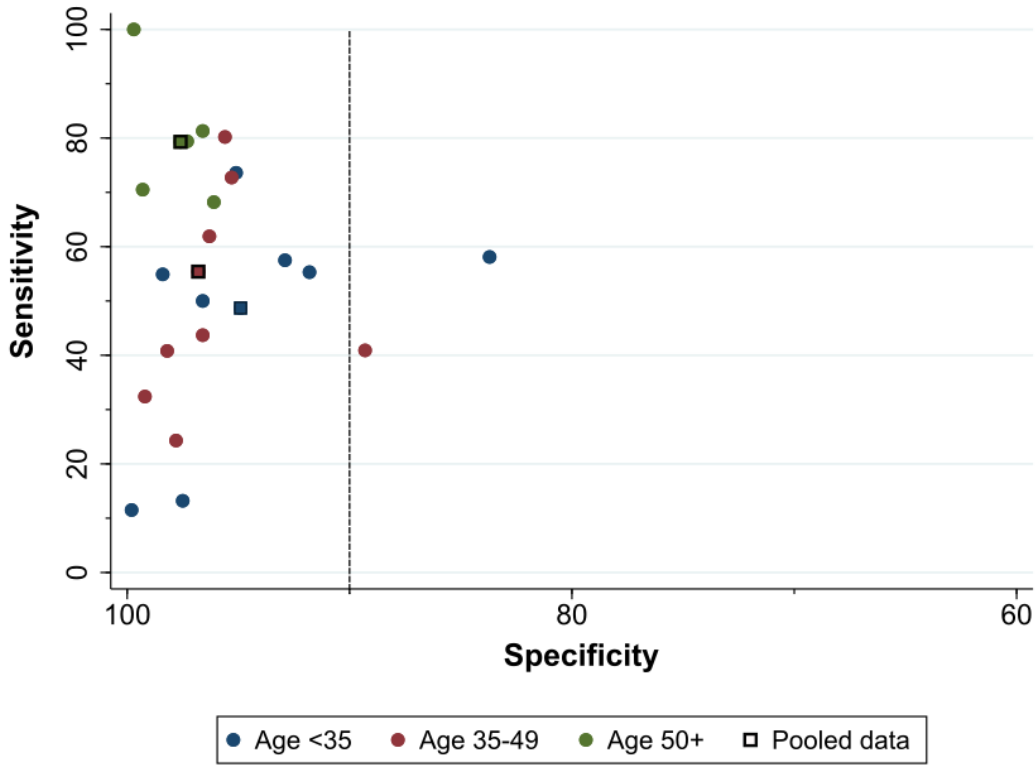


Figure 2. Sensitivity versus specificity of cytology by age range from several studies conducted in Europe and North America (Cut-off used to define cytology as abnormal is ASCUS+) (Cuzick et al. 2006)

NOTE: *The ideal primary screening test would be the one with the highest sensitivity and specificity. Therefore, the best-performing tests in* ***Figure 2*** *are those plotted at the top left corner.*

Liquid-based cytology (LBC) was developed to improve the low sensitivity of conventional cytology. Instead of smearing the cells on a glass slide immediately after sample collection, in an LBC approach the collected cervical cells are transferred into a vial containing a preservative fluid for semi-automated production of slides at the laboratory. However, it does not result in higher sensitivity.

A meta-analysis of published studies (Arbyn et al. 2008) estimated the absolute and relative sensitivity and specificity for CIN2+ of both conventional and LBC for the disease thresholds HSIL+, LSIL+ or ASCUS+ (**Table 1**).

Table 1. Absolute and relative sensitivity and specificity for CIN2+ of conventional and liquid-based cytology (Arbyn et al. 2008)

	Absolute measures (95%CI)				Relative measures (95%CI)
	Liquid-based cytology		Conventional cytology		
Sensitivity					
HSIL+	57.1	(46.3–67.2)	55.2	(45.5–64.7)	1.05 (0.95–1.16)
LSIL+	79.1	(70.1–86.0)	75.6	(66.5–83.0)	1.03 (0.96–1.11)
ASC-US+	90.4	(82.5–95.0)	88.2	(80.2–93.2)	1.03 (0.97–1.09)
Specificity					
HSIL+	97	(93.8–98.6)	96.7	(95.6–97.5)	0.99 (0.98–1.01)
LSIL+	78.8	(69.8–85.7)	81.2	(71.9–88.0)	0.97 (0.94–1.01)
ASC-US+	64.6	(50.1–76.8)	71.3	(58.3–81.6)	**0.91 (0.84–0.98)**

The analysis shows no evidence of relevant differences between the two methods except for the lower specificity of LBC at ASC-US threshold, requiring HPV-based triage of low-grade cytological lesions

NOTE: *A meta-analytical approach compiles information from a selected set of studies that meet specific inclusion criteria. A quality assessment of each study is structured to guide the interpretation of potential biases and the reliability of the estimates. In screening, data from well-conducted meta-analyses can assist decision-making when evaluating different screening tests or strategies. However, the potential heterogeneity across studies requires careful evaluation when interpreting results and may limit the use of pooled estimates.*

RULE OF THUMB

Meta-analysis of screening tests can be performed to estimate relative accuracy estimates to compare one screening test versus another. The confidence intervals for the relative measurements enable an assessment of the statistical difference between two tests. If the confidence intervals include unity, the observed values are of no statistically significant difference; thus, the two compared tests are comparable for the indicator evaluated.

Even with similar performance, LBC offers the following practical and economic improvements over conventional cytology.

- Up to 9% fewer inadequate or unsatisfactory samples (standardised slide preparation).
- Removal of 'noise' (artifacts, red blood cells, etc.) to facilitate slide interpretation.
- Shorter interpretation time and therefore higher throughput.
- Reduction in manual labour and its associated costs.
- Sampling in liquid medium allows for multiple subsequent testing with the same sample (also known as reflex testing) even after processing for cytology, i.e it is unnecessary to recall women with an abnormal result for new sampling. Thus, liquid medium can be used in co-testing approaches where cytology and HPV tests (DNA or RNA-based) are conducted in all screening visits or used for triage after a positive HPV test or an abnormal cytology result. Samples in liquid medium can also be used for detecting other biomarkers such as methylation assays.

The switch from conventional cytology to liquid media samples that can be both for HPV testing and cytology has to take the following into account:

- The transport medium adds to the cost, though may result in lower overall costs when managing a high volume of samples.
- Laboratory staff will need to be specifically trained.
- Additional supplies and equipment will be required.
- Transport medium need to be validated for its performance.

2.3 Failure in resource-constrained settings

Many resource-constrained settings that implemented regional or national programmes with cytology showed limited or no impact on cervical cancer mortality. The reasons for failure can be divided into two types:

Reasons related to cytology:

- Cytology performance depends on trained cytotechnologists and pathologists to collect, prepare, and interpret samples but many low-resource settings face shortages of such skilled professionals.
- Requires well-equipped laboratories, reliable electricity, quality control systems, and transportation of specimens that are often lacking or inconsistent in low-resource regions.
- Cytology has a higher false positive rate compared to HPV testing. This leads to missed cases (sensitivity) and requires frequent testing every 3 years (negative predictive value), which can be logistically and financially burdensome.
- Typically involves several visits: for sample collection, receiving results, and follow-up care. In settings where travel is difficult or expensive, this leads to high loss to follow-up and reduced program effectiveness.
- Delays in reporting (i.e diagnosis) due to cytology being more labour intense than HPV testing can affect optimal follow-up and reduce timely treatment.

NOTE: *For a given prevalence of precancerous lesions, the lower sensitivity of cytology compared to other primary screening tests like HPV, will inevitably result in a lower negative predictive value.*

Reasons related to lack of organised population-based programmes:

- Poor coverage due to the absence of a call and recall system to a defined target population to ensure participation.
- Absence of fail-safe mechanisms for colposcopy and treatment.
- Absence of trained personnel: pathologists, cytotechnologists or gynecologists.
- Absence of infrastructure for treatment.
- Absence of free health service provisions.
- Poor investment in preventive approaches.

NOTE: *For more information on how to organise a screening programme, the infrastructure required, and how to assess its performance, please refer to* ***MODULE 8****.*

A successful screening programme requires high invitational coverage of the target population, high test coverage or participation, adequate interval between tests, adequate management of screen positives and robust quality assessment. Well organized programmes, even when using long intervals between tests like in the Netherlands with HPV testing, have shown to considerably reduce the incidence of cervical cancer. In low resource settings, where 1 or 2 lifetime screening approaches are being considered as a minimal intervention, a robust test combined with adequate management of women with positive results are expected to reduce the cervical cancer burden provided there is a high coverage (70%).

Alternative screening strategies for resource-limited settings are provided at the end of this module.

ACTIVITY

Read the following statements and decide if they are associated to conventional (CC) or liquid-based cytology (LBC) or both.

1. It has been the most common and longest standing cervical cancer screening method.
2. Cervical cells are collected into a vial containing a preservative fluid, and later smeared on a glass slide.
3. Collected cells are smeared on a glass slide immediately after sample collection.
4. It results in fewer inadequate or unsatisfactory samples.
5. It allows to run additional tests using the same sample.
6. The interpretation of the morphological changes in the smeared cells is observer-dependent.

The correct answers are:

1 CC, 2 LBC, 3 CC, 4 LBC, 5 LBC, 6 Both.

UNIT 3. HPV TESTING

3.1 Characteristics

HPV testing for cancer screening generally involves the identification of DNA or RNA of oncogenic HPV types in the anogenital mucosa.

Did you know?

HPV detection in other media (urine or blood) is being explored for potential use as primary screening tests for cervical cancer. For more information, please refer to the review by Poljak et al. (2023 **RISCC**).

Most HPV tests used for screening detect the 12 types classified by IARC as carcinogenic for humans in group 1 or 2A (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) – the recommended set of HPV types to be detected by WHO (World Health Organization 2024). Many also include a probable carcinogen like HPV 68). Fewer tests include HPV66 (an HPV type with only a "possible" carcinogenic potential) and a few also add HPV 53.

As of 2023, there are over 250 (n=264) commercially available HPV tests. They differ in terms of whether they target DNA or RNA, which specific HPV types are detected, and whether they provide information on overall or genotype specific detection, as well as the detection method used (signal amplification hybridisation vs. PCR). More information on HPV tests validated for use in screening can be found in section 3.3.3 of this module.

3.2 HPV DNA tests: strengths and limitations

Excellent sensitivity and high specificity

One of the first HPV DNA tests, used in many studies worldwide, is Hybrid Capture 2 (HC2), a signal amplification test that identifies 13 oncogenic HPV types. The number of laboratories using HC2 has been declining progressively being now close to zero.

A meta-analysis of published studies (Arbyn et al. 2015; Bosch et al. 2016) estimated the pooled absolute and relative sensitivity and specificity for CIN3+ of cytology (ASC-US+ threshold), HPV testing (HC2) and both test combined. HC2 showed a 95% sensitivity for CIN3+, which is around 30% higher than cytology. About HC2 specificity for CIN3+, it was reported to be around 89% which was not statistically different than cytology (**Table 2**).

Table 2. Absolute and relative sensitivity and specificity for CIN3+ of cytology (ASCUS+ as cut-off), HPV testing and both combined (Arbyn et al. 2015; Bosch et al. 2016)

Screening test	N° of studies	Sensitivity (95%CI)	Specificity (95%CI)
ABSOLUTE DATA			
Cytology (ASC-US+)	21	0.75 (0.66-0.84)	0.92 (0.90-0.94)
HC2	22	0.95 (0.93-0.97)	0.89 (0.87-0.91)
Co-testing (HC2 and cytology ASC-US+)	12	0.97 (0.94-0.99)	0.83 (0.77-0.89)
RELATIVE DATA			
HC2 vs Cytology (ASCUS+)	26/22	1.32 (1.15-1.51)	0.98 (0.97-1.00)
Co-testing (ASC-US+) vs HC2	10/7	1.04 (1.03-1.06)	0.94 (0.92-0.95)
Co-testing (ASC-US+) vs cytology (ASC-US+)	10/9	1.33 (1.29-1.37)	0.93 (0.92-0.93)

RULE OF THUMB

*When the confidence intervals of two estimates do not overlap, it means that they are statistically different. However, when they do overlap (such as co-testing and HC2 in **Table 2**) we cannot state that they differ.*

HPV tests other than HC2 show a better performance

HC2 has a detection limit of 100 IU/µl for HPV16/18 whereas other HPV tests detect 10 IU/µl, resulting in a lower sensitivity (Hortlund et al. 2021; Yilmaz et al. 2023 **RISCC**).

Pooled sensitivity and specificity values for specific PCR-based HPV tests that detect more than 12 HPV types have reported values of 95% and 92% for CIN2+, and 94% and 87% for CIN3+, respectively (Koliopoulos et al. 2017).

In the table above, co-testing showed higher sensitivity but lower specificity than both cytology or HC2 alone, as expected for double testing, which considerably increases costs.

NOTE: *Do not confuse co-testing, where all women are tested with both methods and referred to colposcopy if either is positive with the term triage, where only women who test positive on the primary test receive the second test.*

However, the evaluation led by the IARC (IARC 2022) on co-testing states that:

> *"**The benefits of co-testing do not outweigh the harms**. There is a minimal increase in sensitivity with co-testing; however, this gain is small and the impact on cancer incidence is unclear. Furthermore, this difference in sensitivity affects very few cases, suggesting that the relative contribution of the cytology component of co-testing is limited. Over longer follow-up, the cumulative risks of CIN2+ and CIN3+ for co-test-negative women differ minimally from those for HPV-negative women."*

Be careful when interpreting co-testing results. Women with an HPV16/18 positive result and normal cytology, which could be interpreted as a transient infection without cellular changes, show a 5-year cumulative cancer risk of 1.3%

As explained in **MODULE 2**, the predictive values as well as the sensitivity and specificity of tests are affected by the disease prevalence, yet HPV tests behave differently. Most screening tests detect disease-related changes (for example, atypia associated to high-grade lesions in cervical cancer screening). However, HPV testing detects HPV infections which are the cause of the disease instead of disease-related changes.

In young women, HPV tests specificity is low due to the high prevalence of HPV infections that are likely to be transient. However, the HPV type-specific PPV remains quite unaffected. Therefore, despite the increased number of colposcopy referrals in high-prevalence populations (i.e. 30-50%), the number of referrals to colposcopy to detect one high-grade lesion (i.e. 1/PPV) is maintained (Giorgi-Rossi et al., 2012).

The initiation of HPV-based screening is recommended after age 30 as it is more cost-effective due to the higher probability of detecting a persistent rather than transient infection and a higher prevalence of precancerous lesions.

Despite the consistent PPV of HPV testing for high-grade lesions irrespective of HPV prevalence, screening with HPV testing of young unvaccinated women may lead to overdiagnosis of high-grade lesions that will not progress to cancer. However, data comparison between the NTCC (New Technologies for Cervical Cancer) trial and other HPV trials in Europe suggests that overdiagnosis may be avoided if triage of HPV positive women is applied.

NOTE: *For information on how to overcome the lower specificity of HPV tests using different types of triage, and the clinical management options for the possible combinations, please refer to* ***MODULE 4.***

KEY IDEA

HPV testing and co-testing detect more precancerous lesions than cytology alone. However, the lower specificity of these strategies, particularly at younger ages in countries where young women have not been offered vaccination, requires subsequent triaging.

Did you know?

In vaccinated birth cohorts, the PPV of the screening test is expected to decrease. The PPV depends on the progression probability of HPV infections to high-grade lesions. In unvaccinated girls, a high prevalence of HPV infections correlates with a high prevalence of disease. In vaccinated girls, a positive HPV result is more likely to be related to an HPV type

with a lower oncogenic potential (non HPV16/18) and therefore a lower prevalence of disease is expected (Giorgi-Rossi et al. 2012). There are no clear guidelines on the optimal primary test in vaccinated birth cohorts.

NOTE: *For more information on the impact of vaccination on screening, please refer to* ***MODULE 6****.*

HPV testing has better negative predictive value (reassurance after a negative result) for current and future precancerous lesions and invasive cancer

HPV tests have a high negative predictive value for present and subsequent disease, i.e. very few women with virus infection are incorrectly labelled as negative (false negative). Women with a negative HPV result are unlikely to develop cervical disease in the five to 10 years after the test – at least two years more than the protection offered by a negative cytology result.

In a landmark study (Dillner et al. 2008), data from several European screening programmes were pooled to evaluate the use of HPV testing compared with cytology. The study revealed that 50 per 10,000 women with a normal cytology at baseline developed CIN3+ within the next 3 years (**blue arrow**). In contrast, only around 10 women per 10,000 with a negative HC2 test at baseline developed a CIN3+ lesion (**grey arrow**).

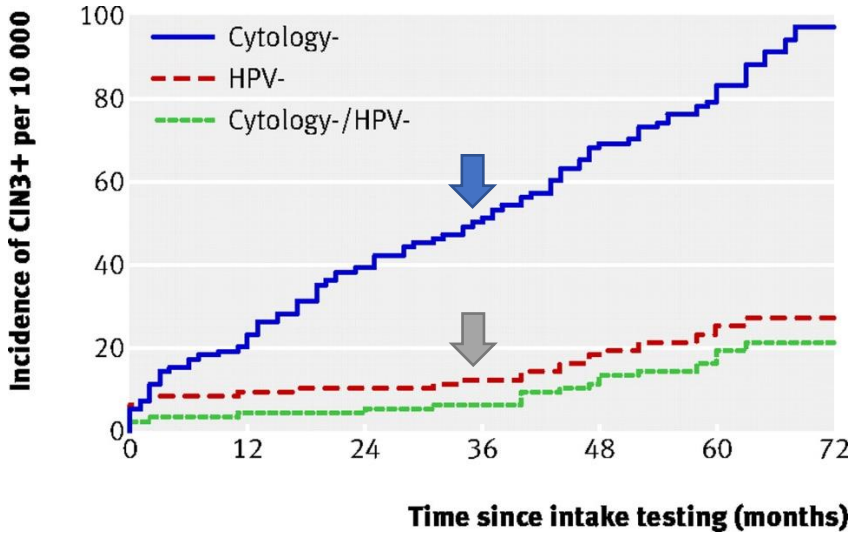


Figure 3. Cumulative incidence of CIN3+ up to 72 months after a negative baseline result for cytology (blue), HPV testing (red) or both (green)

HPV-based screening provides 60-70% more protection against cervical cancer than cytology (Ronco et al. 2014). A negative HPV test result provides a longer safety period.

The individual data of four European randomised clinical trials (Ronco et al. 2014) evaluating the performance of cytology versus HPV testing in screening settings were pooled (**Figure 4**). The outcome of this analysis was a diagnosis of invasive cervical cancer. The analysis showed that in the first three years after a negative cytology (**pink**) or a negative HPV test (**blue**) result, the detection of cervical cancer cases in each arm was extremely low and non-differential. After this timepoint, the number of cases in the cytology arm started to increase whereas in the HPV arm these remained significantly lower throughout the 8-year study period. Very few cases were detected in the HPV arm in the first 5 years, providing strong evidence for a safety window (screening interval) of at least 5 years.

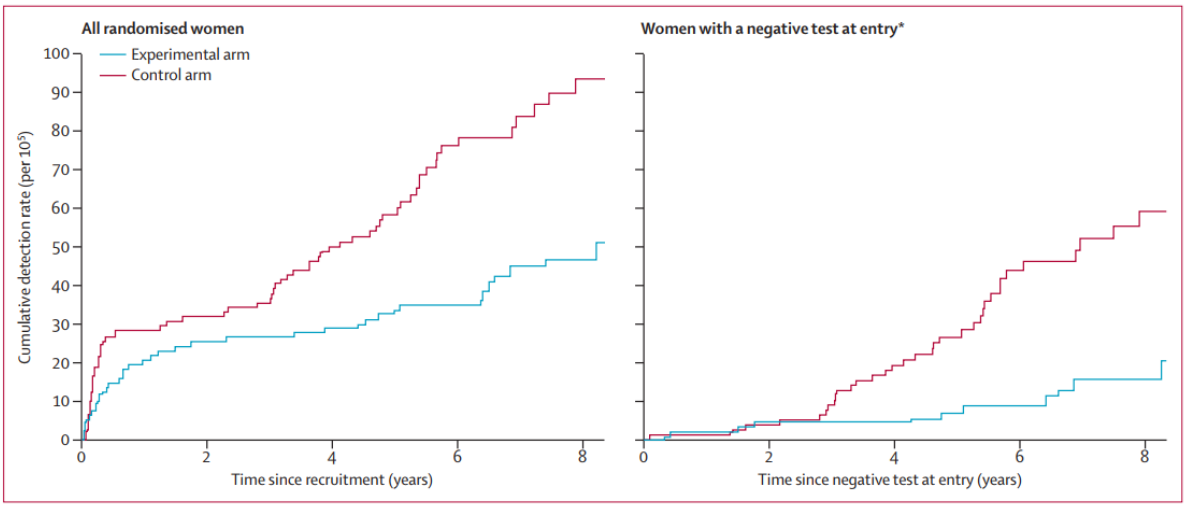


Figure 4. Cumulative detection of cervical cancer (Ronco et al. 2014)

The WHO guidelines (World Health Organization 2021) recommend the use of DNA-based HPV tests at 5-10 year screening intervals.

The use of HPV testing in screening programmes results in increased detection of treatable precancerous lesions in the first screening round, but fewer lesions detected in the second screening round of women initially screened with HPV compared with cytology. The additional lesions detected at the first round with HPV test were likely to include persistent infections to progress (i.e. were of clinical relevance) that probably would have been detected in the second round in the cytology arm. Therefore, early management of HPV-positive lesions in women over 30 does not lead to overtreatment but rather early treatment of precancerous lesions.

KEY IDEA

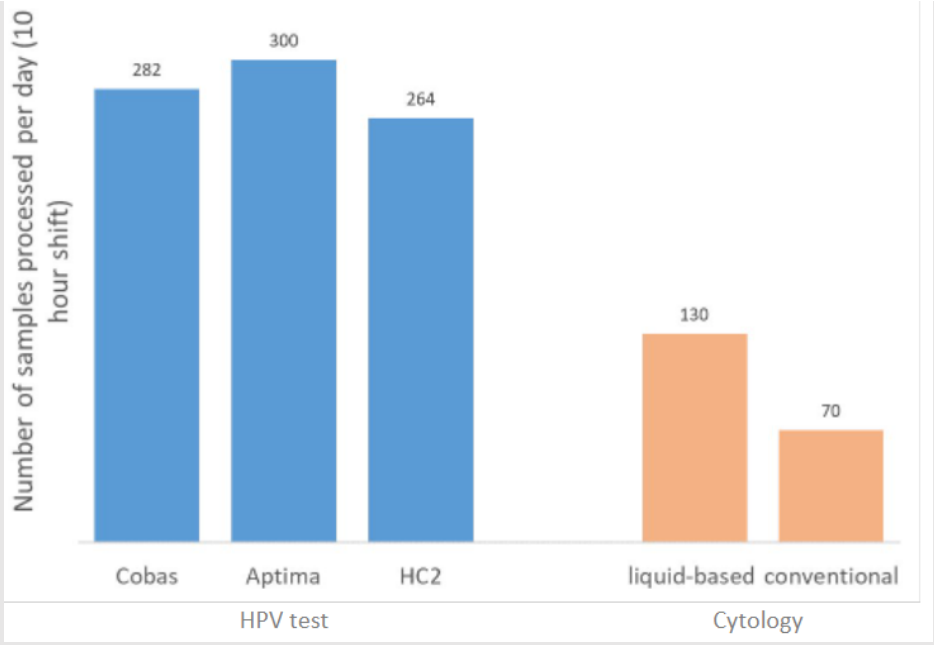
A negative HPV is associated with a lower immediate and longitudinal risk of cervical neoplasia. This means that 5 years after a negative HPV result, the risk of developing cancer is lower than the risk in the three years after a negative cytology.

HPV processing: automated, high throughput and reproducibility

Many of the HPV tests dedicated to screening programmes can be processed using automated platforms with very few manual manipulations. This facilitates high throughput, avoids contamination and provides results in digital files allowing for checking and reducing errors. Such tests are used in organised settings with high sample volumes.

EXAMPLE

A recent study (Loonen et al. 2020) compared the performance of three HPV platforms. Depending on the HPV test, 60-94 samples can be processed in runs of 3-5 hours whereas 7 conventional or 13 liquid-based cytology slides can be screened per hour (Davey et al. 2007). Therefore, in a daily shift of up to a maximum of 10 hours, more than double the number of samples can be processed.



Given the subjectivity of cytology, maintaining high accuracy requires constant training and quality control assessment. This can be somewhat mitigated by incorporating automated reading of slides, but these technologies are not widespread in cytopathology laboratories (Rezende 2021). On the other hand, HPV tests are performed by robotic systems and result in high reproducibility not only within the same laboratory (intralaboratory) but between laboratories (interlaboratory) (Arbyn et al. 2021 **RISCC**; Yilmaz et al. 2023 **RISCC**).

Despite the use of automated platforms and high reproducibility, HPV screening programmes will still require a quality assurance programme.

NOTE: *For more information on quality control, please refer to* ***MODULE 8.***

KEY IDEA

HPV testing enables faster sample processing and more reproducible results.

HPV testing provides an objective outcome

It provides an objective result (positive/negative) based on the quantity of viral material detected. Some HPV tests provide detailed information on the genotype(s) detected.

KEY IDEA

HPV primary screening is more likely to provide unambiguous results that do not depend on reader subjectivity.

HPV testing is more cost-effective than cytology and co-testing

Simulation models for cost-effectiveness analyses enable a projection of the health gains associated with a screening test (reduced cervical cancer incidence and mortality) versus the costs associated with screening, triage and diagnostic tests as well as treatment.

In most economic evaluations assessing the use of different primary screening tests, HPV alone is more cost-effective (more effective at the same or lower cost, or more costly and more effective where the latter justifies the cost) than cytology alone. When compared with co-testing, HPV alone is more cost-effective (similar performance but without the costs associated with cytology).

An HPV testing programme can be more cost-effective (Mendes et al. 2015) based on

- reduced test cost by using high-volume centralised laboratories,
- the commercial HPV test used (performance data and sampling method), and
- the assumed impact of a positive HPV result on women's quality of life

However, the main determinant of cost-effectiveness is the negative predictive value that allows for the extension of the screening interval to 5 years (Dillner 2013).

KEY IDEA

HPV testing is more cost-effective than cytology and co-testing.

HPV testing can be performed on either cervical or vaginal samples

A major game-changer in the screening scenario is the possibility of using molecular tests such as HPV testing on samples of vaginal exudates taken by women themselves (i.e. self-sampling) particularly if a highly sensitive test is used like those that are PCR-based. However, self-samples are not suitable for evaluating morphological changes. If the triage test is performed with a morphology test like cytology, an additional sample needs to be taken whereas HPV genotyping or viral load can be done in the same sample (Lei et al. 2024). The potential use of dual-staining as triage of HPV-positive self-samples is being explored as its interpretation is based on immunostaining results rather than cellular morphology (Toliman et al. 2020).

NOTE: *For more information on self-collected samples, please refer to* ***MODULE 5.***

KEY IDEA

HPV screening programmes can use self-sampling to improve coverage and increase convenience for women.

HPV tests can be conducted using liquid-based cytology (LBC)

In unvaccinated women aged 25-29, cytology is used to overcome the specificity of HPV tests (i.e. for reducing the high number of HPV infections observed that will rarely lead to cancer). If LBC is used, the same processed sample can be used for triage of women with an abnormal cytology result, thus avoiding recall. Likewise, LBC reflex triage can be used for HPV-positive samples collected in liquid media.

KEY IDEA

Settings using liquid-based cytology can benefit from reflex cytology for HPV-positive samples or reflex HPV testing for low-grade cytology results.

HPV testing is expected to have high sensitivity to detect adenocarcinoma in situ and adenocarcinomas

Cytology has low sensitivity for detecting adenocarcinomas and their precursors. Potential explanations include sampling issues (focal and small lesions, often located in the endocervical canal) and the difficulty in differentiating the cytological and colposcopic features of adenocarcinoma in situ from the normal columnar

epithelium. HPV tests, on the other hand, have demonstrated a higher sensitivity to these lesions.

EXAMPLE

A pooled analysis of four large randomised trials in Europe (Ronco et al. 2014) showed a 70% reduction in the adenocarcinoma rate among women screened with HPV testing compared with those screened with cytology (rate ratio: 0.31; 95%CI: 0.14-0.69).

KEY IDEA

The increasing incidence rates of adenocarcinoma observed in recent years could be reversed by implementing HPV screening.

ACTIVITY

Read the following statements about HPV testing and decide if they are TRUE or FALSE.

1. HPV testing has a similar sensitivity for CIN3+ than cytology.
2. The long-term cumulative risks of CIN2+ of HPV-negative women are similar to those of co-test negative women.
3. The lower specificity for CIN3+ of HPV testing over cytology can be overcome by triage testing.
4. Cytology has a better negative predictive value (reassurance after a negative result) than HPV testing.
5. In a daily shift, more than the double number of samples can be processed by HPV testing when compared to cytology reading.
6. HPV testing is more reproducible due to its objective outcome and the automated processing.
7. Co-testing is more cost-effective than HPV testing alone due to its higher sensitivity for CIN3+.
8. HPV testing in a self-collected sample allows for cytology triage.
9. HPV testing detects a larger number of cervical adenocarcinomas.

The correct answers are:

1 False, 2 True, 3 True, 4 False, 5 True, 6 True, 7 False, 8 False, 9 True.

3.3 HPV DNA genotyping

Some HPV assays include ***partial or extended genotyping*** either as primary screening or as triage for HPV positive women. The most common format involves providing separate results for HPV16 and/or HPV18 versus the remaining HPV types detected by the HPV test.

This HPV type differentiation is important as different oncogenic HPV types have different risks of progression to cervical neoplasia. HPV16 has the highest cancer risk and is the most common type in invasive cervical cancers. HPV18 and HPV45 rank second and third most oncogenic HPV types for cancer and they are particularly common in adenocarcinomas (IARC 2022).

EXAMPLE

A meta-analysis of women with normal cytology but a positive HPV test result (i.e. positive for any or several oncogenic types) estimated a CIN3+ incidence rate of 8 per 1000 woman-years. When stratified by HPV type, the incidence rate changed to:

- 21 per 1000 woman-years for HPV16/18
- 3 per 1000 woman-years for other HPV types, respectively

Therefore, in one year, 21 per 1000 women with normal cytology and positive HPV 16 or 18 infections will develop CIN3 versus only 3 per 1000 women with normal cytology and an HPV infection other than 16 or 18 (Malagón et al. 2020).

Some countries are screening using **extended *genotyping***, i.e. separate results for six, eight or 13 HPV types either grouped or individually to facilitate more tailored management of women infected with HPV types.

In this study from the United States (**Figure 5**), HPV16 and HPV33 showed the highest risk of progression to CIN3+, followed by HPV types 18, 58, 35, 31 45 and 52. Among the remaining HPV types, HPV39 showed a slightly higher immediate risk than the others, though all showed a stable risk after three years of follow-up.

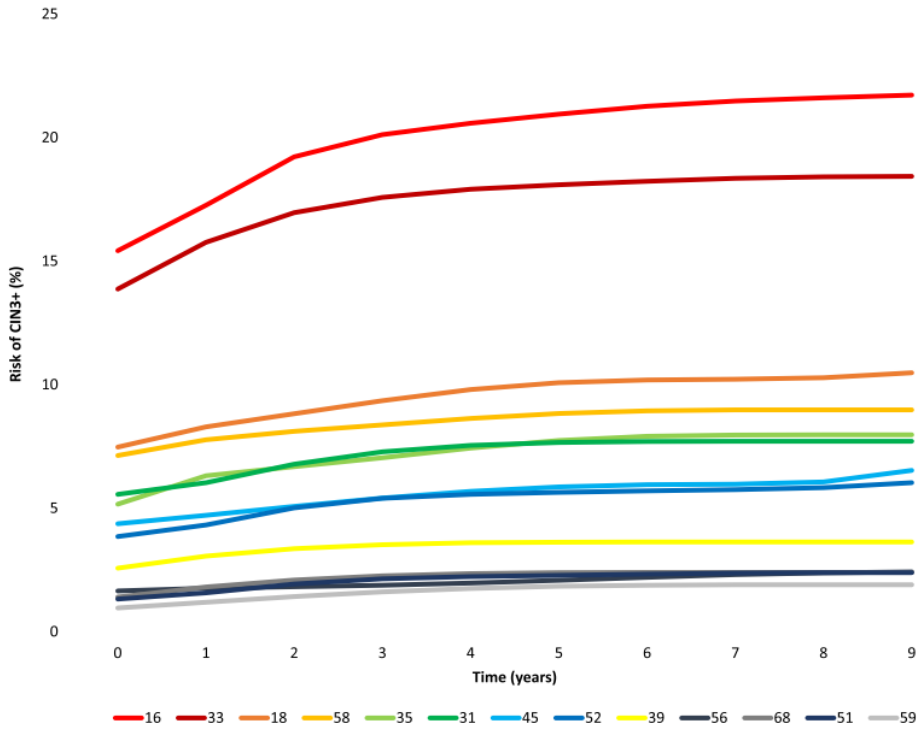


Figure 5. Immediate and subsequent risk of CIN3+ by HPV type over 9 years of follow-up (Demarco et al. 2020).

These differences in risk have a direct impact on the screening programme performance and efficiency (Wang et al., 2023 **RISCC**): To prevent one cervical cancer case caused by HPV16, approximately 5,500 women need to be screened whereas over 1,300,000 women need to be screened to prevent a single case caused by HPV59. Furthermore, follow-up of 147 women positive for HPV16 would prevent one cancer case, while for HPV59, this number increases to 4,389.

When available, genotyping information of HPV tests should be used to improve the programme efficiency.

In some countries oncogenic HPV types are categorised into two-four tiers with different cancer risk, which is relevant for current management options (immediate referral, triage or surveillance at different timepoints) based on the type-specific immediate and longitudinal risk of CIN3+ although preferably on the risk of invasive cervical cancer (Bonde et al. 2020; Demarco et al. 2020; Sundström and Dillner 2020),

to determine the screening interval and to facilitate the clinical management of screened women.

NOTE: *For more information on the accuracy of HPV tests with partial or extended genotyping, please refer to* ***MODULE 4A****.*

There is sound information on the HPV type-specific attributable risk for invasive cervical cancer and these data should inform about the most relevant HPV types that require specific immediate or delayed management because of their high, moderate or very low risk to progress. Longitudinal data from follow-up cohorts on HPV type-specific progression and regression rates are extensive for CIN3, but more limited for invasive cancer (Hortlund et al. 2021).

Additional considerations about the HPV type-specific information include:

- WHO has developed target product profiles (TPP) for HPV screening tests in the laboratory and at the point of care for funders and manufacturers. These profiles set the minimal and preferred characteristics that these technologies need to meet with the aim to prioritize areas for development of new technologies or improvement of existing ones. These TPPs recommend against the identification of HPV66 and HPV68 due to their low carcinogenic risk (World Health Organization 2024).
- HPV35 is especially relevant in women of African descent and therefore is upgraded to intermediate risk in a United States study (Demarco et al. 2020). Although most HPV tests include HPV 35, this type is not included in the existing vaccines.

Did you know?

Sweden and Denmark have already incorporated extended genotyping in their cervical cancer screening programs.

- Sweden classifies and manages women according to the following 3 groups: HPV16/18/45, HPV31/33/52 and 58, or HPV35/39/51/59/66/68 (National Quality Register for Cervical Cancer Prevention (NKCx) 2024).
- Denmark stratifies in 2 groups: HPV16/18/45/31/33/52 or HPV35/39/51/58/59/66/68 (Bonde et al. 2022).

NOTE: *For more information on different screening strategies based on extended genotyping data, please refer to the protocols above for Sweden and Denmark as well as the guidelines from the United States (Massad et al. 2024).*

3.4 HPV mRNA tests

HPV RNA tests detect oncogenic viral proteins, while HPV DNA tests detect genomic presence of the virus. As a result, it has been suggested that RNA tests might be a more targeted marker of the involvement of HPV in cervical carcinogenesis although it has not been demonstrated.

Around 5% of commercially available tests detect transcripts or mRNA of the HPV oncogenes E6 and E7. This section focuses on Aptima®, which has been more widely studied, that targets mRNA **for 14 high-risk HPV types** although it has a variant that genotypes separately only for HPV16 mRNA and HPV 18/45 mRNA.

The Aptima® HPV Assay has shown similar sensitivity for CIN2+ and CIN3+ but slightly higher specificity for less than CIN2 in comparison with validated hrHPV DNA assays.

A meta-analysis of published studies (Arbyn et al., 2022 **RISCC**) estimated the relative sensitivity and specificity for CIN2+ and CIN3+ of Aptima® compared to HC2 or GP5/6+. Compared to high-risk HPV DNA tests, Aptima® demonstrated similar sensitivity for CIN2+ and CIN3+ but slightly higher specificity for <CIN2 (**Table 3**).

Table 3. Pooled and relative sensitivity for CIN2+ and CIN3+ and specificity of Aptima versus HC2 or GP5/6+ tests (Arbyn et al. 2022 **RISCC**)

Outcome	N° of studies	Relative sensitivity (95%CI)	Relative specificity (95%CI)
CIN2+	8	0.98 (0.95-1.01)	1.03 (1.02-1.04)
CIN3+	5	0·98 (0.95-1.01)	

NOTE: *APTIMA shows a lower sensitivity for both CIN2+ and CIN3+ than validated HPV tests on self-collected vaginal samples (pooled relative sensitivity of 84% and 64%, respectively). Therefore, it is not recommended in self-collected samples in its actual form (APTIMA's manufacturer is adapting the test to improve its performance in self-collected samples). For more information on the use of HPV tests in self-collected samples, please refer to* ***MODULE 5.***

Because RNA positivity is supposed to occur later, longitudinal data on CIN2+ incidence after a negative RNA test result (NPV) is needed to safely extend the screening interval as per HPV DNA tests. The long term duration of the NPV of RNA tests for CIN2+ has been shown to be similar to that of DNA tests although still based on limited longitudinal data (Forslund et al. 2019; Iftner et al. 2018; Strang et al. 2021; Zorzi et al. 2020).

The WHO guidelines (World Health Organization 2021) recommend the use of mRNA-based HPV tests for primary screening in clinician-based samples at screening intervals no longer than 5 years.

The decision to screen at intervals no longer than 5 years while DNA-based can be used at 10-year intervals is based on the heterogeneous and limited evidence regarding comparative longitudinal data between both types of HPV tests.

3.5 Validation of HPV tests for screening

Any test to be used as the primary screening test in a screening programme should be of clinical value, easy to perform, rapid, reproducible and affordable.

Expert consensus guidelines were developed in 2009 for the validation of HPV tests relative to screening women above age 30 (Meijer et al. 2009). The guidelines, commonly known as Meijer's guidelines and later modified under the VALGENT protocol (Arbyn et al. 2016), state that HPV tests should have:

- Clinical sensitivity to CIN2+ non-inferior to the 90% clinical sensitivity of HC2;
- Clinical specificity for CIN2+ non-inferior to the 98% clinical specificity of HC2;
- Intra and interlaboratory agreement (i.e. concordance between samples processed twice in the same or different laboratories) with a lower confidence interval non-inferior to 87%.

Did you know?

The original guidelines used HC2 or GP5/6+ as referent technology. Since then, several validated tests, especially those PCR-based: RealTime High Risk HPV Test *(Abbott, Wiesbaden, Germany)*, Cobas 4800 HPV Test *(Roche Molecular System, Pleasanton, USA)*, Onclarity HPV Assay *(BD Diagnostics, Sparks, USA)*; and Anyplex II HPV HR Detection *(Seegene, Seoul, South Korea)*, have shown a higher sensitivity than HC2 and can be used as referent to validate new assays (Arbyn et al., 2024 **RISCC**).

Out of 264 commercially available HPV tests (Poljak et al., 2024 **RISCC**), in 2023 only 56 (21% HPV tests had data to assess that their clinical and/or analytical performance characteristics were in line with agreed standards within the HPV community.

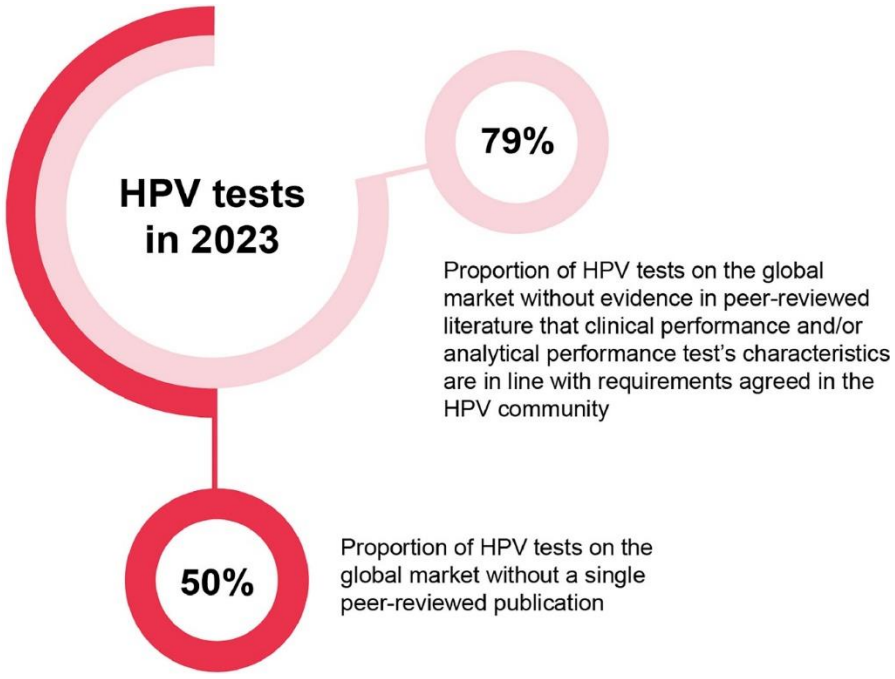


Figure 6. Proportion of HPV tests according to their concurrence with agreed standards and availability of analytical and/or clinical data (Poljak et al., 2024 **RISCC**)

Of the 56 HPV tests assessed, those that met the international validation criteria by July 2024 were further reduced to 19 (Arbyn et al., 2024 **RISCC**; Arbyn et al., 2023 **RISCC**; Arbyn et al., 2021 **RISCC**).

As expected, among validated HPV tests, the long-term safety (longitudinal sensitivity and negative predictive values) is similar. Therefore, the choice of an HPV validated test to be used in a screening programme should focus on other criteria such as its ability for partial, extended, or full genotyping, automation capability, throughput capacity, hands-on time, and cost (Oštrbenk Valenčak et al., 2024 **RISCC**).

Once implemented, proper quality controls need to be in place (Cuschieri et al., 2023 **RISCC**; Prétet et al., 2024 **RISCC**). Among these, participation in proficiency studies of HPV testing used in HPV-based cervical screening programmes is recommended (Yilmaz et al. 2023 **RISCC**).

ACTIVITY

Read the following statements and decide if they are TRUE or FALSE.

1. HPV screening might include partial or extended genotyping.
2. The interest in extended genotyping relies in the difference in risk of progression by HPV-types.
3. To avoid missing any cervical cancer case, all HPV tests must include all oncogenic HPV types.
4. The WHO recommends the use of mRNA testing for primary screening at a maximum of 5-year intervals.
5. All commercially available HPV tests can be used for primary screening.

The correct answers are:

1 True, 2 True, 3 False, 4 True, 5 False.

3.6 Common concerns around HPV screening implementation

As described previously, **there are many reasons why HPV testing alone, instead of co-testing, should replace cytology**.

That said, there are still some concerns regarding its implementation. Accordingly, we provide below the most frequent arguments against implementation of HPV testing and their counterarguments (Tota et al. 2017):

Argument 1. There is no need for change, since cervical cancer rates have remained low with cytology screening.

Though somewhat true, the costs of maintaining quality assurance programmes for cytology and the need for frequent screening have resulted in inefficient programmes in many settings. Those countries that were successfully using cytology, such as the Nordic countries, have observed that incidence rates of cervical cancer have reached a plateau or even increased due to the increase in adenocarcinomas, which are poorly identified by cytology.

Furthermore, cervical cancer incidence rates in many parts of the world may be low but, when translated to absolute numbers, many cases could be prevented. For example, Germany has an age-standardised cervical cancer mortality rate of 2.2 per 100,000 women. However, in a population of around 83 million, this means that around 2,000 women died from the disease in 2020, i.e. 5 women per day. If highly accurate preventive measures were consistently applied, a considerable proportion of these deaths could be avoided.

Argument 2. Changes will be costly, since HPV testing is more expensive than Pap cytology.

In small laboratories, one HPV test may have a higher upfront cost than a cytology test, but high-volume processing in centralised laboratories can save costs. In settings with tender procedures in place, HPV tests have been purchased at lower cost than cytology (Inturrisi & Berkhof, 2022 **RISCC**).

Despite the potential initial higher costs of HPV-based screening programmes, the extended interval between two visits for HPV-negative women and the better test performance generally result in a better cost-effectiveness for HPV testing. For example, within a 15-year interval, in line with the recommendations, using cytology every 3 years equals a woman screened five times, whereas using HPV testing every 5 years equals only three screenings.

Argument 3. HPV-based screening will lead to excess colposcopy referrals, thus increasing the costs of the screening programme.

In an HPV-based screening programme, the strategy of referring all screen positives to colposcopy is likely to increase colposcopy referrals but will also result in a higher detection of high-grade lesions. Furthermore, this effect has been consistently observed only in the first round of screening.

Most HPV-based screening programs use some form of triaging before referring a screen-positive woman, such as extended HPV genotyping.

UNIT 4. PRIMARY SCREENING TESTS IN LOW-RESOURCE SETTINGS

In low-resource settings, visual inspection with acetic acid and iodine (VIA/VILI) by naked eye has been the most common primary screening test. It arose because of the absence or suboptimal performance of traditional screening methods used in high-income countries (cytology followed by colposcopy) in low-resource settings.

The main advantages of VIA are its low cost and the immediate availability of results, facilitating a screen and treat approach. However, it is highly subjective and consequently has variable sensitivity and specificity to detect precancers across different settings. A large variability has been observed in referral rates for treatment when using VIA as primary screening. Ensuring adequate training, supervision, and ongoing quality assurance can be challenging. VIA programs are unlikely to have histology confirmation limiting a quality control assessment.

WHO (World Health Organization 2021) recommends HPV-based screening approaches over cytology or visual inspection with acetic acid (VIA) in all-resource settings.

This recommendation is largely based on consistently improved performance to detect precancerous lesions using an HPV test, its much higher positive predictive value and a very high negative predictive value leading to longer intervals for those with negative results.

However, resource-constrained settings are confronted with several other challenges to implement HPV testing:

- Immediate costs of tests and equipment to start a programme and its sustainability.
- Need of a laboratory infrastructure, trained personnel and quality control systems that may vary in complexity based on the screening assay.

- Point-of-care option(s). In many settings, the lack of fail-safe mechanisms results in women with a positive test result can result in loss of follow-up for subsequent testing, diagnosis or treatment Tests that facilitate screen and treat strategies on the same day (point-of-care) are highly recommended although, to date, no assay can provide immediate results.
- High HPV prevalence and high burden of disease.
- Need for triage options (because of the low specificity for CIN3+ of HPV tests). In high resources settings, triage is accessible through genotyping, colposcopy, and biopsy. In low-resource settings, VIA is the most commonly used test to decide upon treatment of screened HPV positive women. However, this approach has poor accuracy, and therefore, some settings are opting for immediate treatment with no triage if eligible for ablation whereas others are exploring the use of extended genotyping embedded within the same screening test.

The WHO has included HPV tests in their list of priority medical devices for cancer management. To ensure that good quality products are procured and distributed, in vitro diagnostics such as the HPV test can undergo a WHO systematic 'Prequalification' process to determine the capacity of a manufacturer to produce a product of consistent quality in accordance with international standards and WHO/UNFPA specifications. This is an important credential that facilitates national regulatory approvals. By 2025 only four tests had been prequalified (WHO | Public reports of WHO prequalified IVDs (HPV virological technologies) n.d.) although additional tests may be available depending on national regulatory frameworks:

CareHPV Test Kit (Qiagen, China in collaboration with CARE Inc, USA)

Developed by CARE (Cooperative for Assistance and Relief Everywhere, Inc.) for resource-limited settings, and manufactured and marketed by Qiagen GmbH. The test detects 14 high-risk HPV types (no genotyping data provided) and requires around 2.5 hours of processing time. It requires a skilled laboratory technician, as there are several manual processing steps required for batch processing using 96 well plates.

The test is an adaptation of HC2. It does not require running water, air conditioning or complex laboratory infrastructure. Processing is relatively easy to learn (though inconsistent experiences have been reported) and the expected cost is around 5-7 euros.

It is not a point-of-care test, and at least 90 samples should be run per batch for optimal processing and to minimize waste. In some settings, a considerable percentage of invalid plates have been reported due to technician error, power outages or test system malfunction. Well-to-well contamination has occasionally been observed.

The careHPV assay has been CE-marked since 2010 and received WHO prequalification in 2018. Multiple settings have been using careHPV in China, Central America, Burkina Faso and South Africa.

Did you know?

Previous studies have reported up to a 30% of false positive HC2 results for the targeted HPV types in the test (i.e, no true presence of high-risk HPV types) (Gillio-Tos et al. 2013; Sargent et al. 2008). As an adaptation of HC2, careHPV may have the same limitation.

Xpert HPV (Cepheid, USA)

A single disposable cartridge-based test for each sample run on GeneXpert, a real-time PCR system validated for tuberculosis diagnosis, HIV diagnosis, HIV viral load and hepatitis C virus viral load and other applications, requiring no manual intervention.

The test is performed in less than one hour and can be run on any of Cepheid's GeneXpert platforms, already available in many resource constrained countries, all of which require reliable electricity and are operated through a laptop or desktop computer. It detects 14 high-risk HPV types, among which HPV 16 and HPV 18/45 are individually typed.

The Xpert HPV assay has been CE-marked since 2014, received WHO prequalification in 2017 and has been validated within the VALGENT protocol.

Did you know?

The positivity cut-off can be adapted to increase specificity – particularly relevant for HIV-positive women– with a small reduction in sensitivity (Kuhn et al. 2020).

Despite its numerous strengths, the main disadvantage of the test is its high cost and limited throughput which hampers its use in large-scale programmes. Concerns have also been raised around waste and disposal.

Abbott RealTime High Risk HPV (Abbott GmbH, Germany) **and Cobas HPV** (Roche Molecular Systems Inc., Switzerland)

These two are PCR-based qualitative in vitro tests for detecting DNA from 14 high-risk HPV types among which HPV16 and HPV18 are individually typed. Both assays are used as benchmark assays and have been implemented in both high- and low-resource settings such as Guatemala or Tanzania.

In addition to WHO prequalification, both are CE-marked and have been validated within the VALGENT protocol. Cobas HPV is also FDA approved. Their test cost may not be suitable for resource-constrained settings but an optimal tender process could substantially reduce its costs.

Did you know?

The ScreenFire RS HPV assay is an isothermal amplification test for detecting DNA from HPV16, HPV18/45, HPV31/33/35/52/58, and HPV39/51/56/59/68 (extended genotyping results in 4 risk-based groups) that requires around 2 hours of processing time.

The isothermal amplification technique allows to reduce the complexity of HPV testing without impacting its sensitivity. The test can be batched testing adapted to the number of samples to be tested (no reagents waste) and it has been specially designed to prevent contamination (only basic pipetting skills required with no previous DNA extraction needed).

It is a relatively affordable test (likely to be <10 euros) and is compatible with dry self-samples.

It can be used as a very informative primary screening test thus avoiding a triage step, as proposed in South Africa.

For more information please see Inturrisi et al., 2024 and Hou et al., 2024.

The use of a qualified or nationally approved test does not guarantee adequate proficiency by the testing laboratory.

For an overview of the HPV tests used in 208 laboratories worldwide and their proficiency results by HPV assay, check the table below. Annual proficiency reports can be found in the International Human Papillomavirus Reference center website

HPV assay	Number of data sets	No. of proficient data sets				
		100 % proficient	99-90 % proficient	89-80 % proficient	<80 % proficient	Not proficient
All assays	**208**	**197**	**0**	**0**	**3**	**8**
Cobas 4800 (Roche)	39	37	0	0	1	1
37 HPV GenoArray (Hybribio)	19	18	0	0	0	1
21 HPV GenoArray (Hybribio)	18	18	0	0	0	0
Genotyping with Real-time PCR (Hybribio)	18	18	0	0	0	0
14 High-risk (Hybribio)	17	17	0	0	0	0
HPV Direct FlowChip (Master Diagnostica)	18	18	0	0	0	0
Abbott m2000 HPV	9	9	0	0	0	0
Onclarity/COR (BD)	8	8	0	0	0	0
Abbott Alinity m (Abbott)	8	7	0	0	0	1
Allplex HPV HR (Seegene)	6	5	0	0	0	1
Allplex HPV 28 (Seegene)	5	5	0	0	0	0
AmpFire HPV Screening 16/18/HR (Atila)	3	3	0	0	0	0
14 Real-TM Quant (SACACE)	3	1	0	0	0	2
Cobas 6800 (Roche)	3	3	0	0	0	0
In-house Realtime PCR	2	1	0	0	0	1
Anyplex II HPV28 (Seegene)	2	2	0	0	0	0
Xpert HPV (Cepheid)	2	2	0	0	0	0
Aptima (Hologic)	2	1	0	0	1	0
Cobas 5800 (Roche)	2	1	0	0	0	1
Anyplex II HPV (Seegene)	2	2	0	0	0	0
In-house Luminex	2	2	0	0	0	0
In-house PCR-Sequencing	2	2	0	0	0	0
Other commercial assays[a]	18	17	0	0	1	0

[a]*In the other commercial assays category, the following assay types are included: Alias: Harmonia HPV, LyoHarmonia HPV, Alias: Venus HPV, LyoVenus HPV, Liferiver Genotyping23, QIAscreen HPV, OncoPredict HPV SCR, OncoPredict HPV QT, HybridCapture2, Sansure 13-HPV assay, Sansure HPV Genotype, Screenfire, INNO-LiPA, NeoPlex HPV HR, MehrViru HPV, Standard M10 Hr HPV, Biotech Discovery HR HPV, Chapter Dx*

Irrespective of the HPV test used, a considerable number of women have an HPV infection that will never progress to cervical cancer. Therefore, adequate clinical management strategies for HPV-positive women are to be implemented as detailed in **MODULE 4A**.

ACTIVITY

Read the following statements and decide if they are TRUE or FALSE.

1. The World Health Organization recommends HPV-based screening approaches over cytology or visual inspection with acetic acid in resource-constrained settings.
2. HPV tests can be implemented worldwide without the need of additional infrastructure or costs.
3. Any HPV test can be used in resource-constrained settings if the cost is low.

The correct answers are:

1 True, 2 False, 3 False.

SUMMARY

- HPV testing offers several advantages over cytology: it is more sensitive, allows for larger screening intervals, is objective and highly reproducible, is more cost-effective, can be used on self-collected samples, allows for reflex triage testing without recall, and is more accurate in detecting adenocarcinoma. However, it has lower specificity if used without genotyping, which needs to be addressed by triage tests.
- HPV testing has been shown to reduce the incidence of invasive cervical cancer in randomised clinical trials.
- HPV testing for screening should include only those high-risk types involved in cervical carcinogenesis. The tests can be based on DNA or mRNAs. Some assays provide partial or complete genotype information.
- Despite the widespread commercial availability of HPV tests, only around 10% of tests have been clinically validated for use in a screening programme.
- The introduction of self-sampling and an HPV-based screening strategy is likely to impact screening coverage significantly

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ADDITIONAL MATERIAL / REVIEWS

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