# COURSE: Evidence-Based Approaches to HPV Screening implementation

## Module 4A. Screening management - Follow-up of HPV-positive women


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# INTRODUCTION AND LEARNING OBJECTIVES

The transition to HPV-based screening is a major step forward in cervical cancer prevention, but it also presents new challenges such as the effective triage of HPV-positive women to decide who requires treatment or follow-up. Risk-based management offers a tailored approach by incorporating factors such as screening history, vaccination status, and other risk indicators in addition to triage results to guide clinical decisions.

This module outlines the potential strategies for managing HPV-positive women, with a focus on risk-based approaches. It reviews WHO-recommended triage options, compares their performance, and provides criteria for selecting the most appropriate test. It also covers the management of precancerous lesions and follow-up recommendations.

At the conclusion of this module, participants will be able to:

- Understand the principles of risk-based management of HPV-positive women.
- Interpret risk based on screening history, vaccination status, and patient-derived factors.
- Assess the use and limitations of the WHO-recommended triage methods (partial genotyping, cytology, dual staining, colposcopy and visual inspection with acetic acid) and compare their diagnostic performance.
- Explore the use and limitations of emerging triage technologies such as extended genotyping, viral load measurements, E6/E7 oncoprotein detection, mRNA and methylation markers
- Describe the follow-up of HPV-positive triage-negative women.
- Evaluate the criteria to select the appropriate triage test
- Understand treatment options for precancerous lesions and follow-up algorithms.

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# UNIT 1. MANAGEMENT OF hrHPV POSITIVE WOMEN

Although hrHPV positivity predicts an increased risk of the future development of CIN2+ and CIN3+ even if the disease is not present at the time of the index screening test (Katki et al., 2011), its moderate specificity implies that some screen-positive women are followed up unnecessarily.

To limit the potential harm of HPV screening, several strategies can be used:

- Use only validated HPV tests for carcinogenic types
- Consider increasing the screening interval
- Use triage tests

Triage of hrHPV positive women can limit the burden of follow-up, over-diagnosis, and over-treatment by increasing the global specificity and positive predictive value (PPV) of hrHPV testing. Some triage tests can be performed on the specimen collected for screening. However, often triage passes over multiple cycles of retesting. In some settings, its implementation might not be feasible when multiple visits are needed particularly when loss to follow-up is a major concern.

Therefore, two approaches can be used to decide upon the management of hrHPV positive women:

### A) A Screen-and-Treat approach

Screen positives are referred to immediate treatment by ablation of the cervical lesions unless contra-indications are present. Ablation means that the transformation zone of hrHPV-positive women is destroyed without further histological assessment. If the transformation zone is not visible or there is a suspicion of cancer the woman is referred for additional evaluation. In settings where triage is embedded within the primary screening test, such as partial or extended genotyping, treatment can be restricted to triage-positive women.

This Screen-and-Treat strategy likely results in overtreatment and is mainly implemented in settings with limited resources where triage options are not available.

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Yet, this approach aims to remove any lesion as well as the most susceptible tissue to HPV infection and therefore does not treat the infection per se.

**Did you know?**

In women living with HIV, WHO recommends a screen, triage and treat approach due to the higher hrHPV test positivity in these women

***NOTE:*** *For more information on screening of women living with HIV or those with other immunosuppressed conditions, please see MODULE 7.*

### B) A Screen, Triage, and Treat approach

In this strategy, the decision to treat is based on a positive hrHPV screening test followed by a positive triage result.

Triage classifies women depending on their risk of developing cervical disease leading to a reduction in the number of unnecessary colposcopy referrals and overtreatment of low-risk women, while also identifying higher-risk women and offering them timely, suitable treatment. Therefore, clinical management of women with cervical cancer screening results is progressively more acceptable to be based on risk thresholds that are the determinants of action (i.e, risk-based management approach) instead of treating exclusively based on a test result.

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# UNIT 2. RISK-BASED MANAGEMENT APPROACH

## 2.1 The concept of risk-based management

A risk-based management approach focuses on individuals at high risk of developing cancer, aiming to achieve several key objectives:

- To offer or adapt screening selectively, such as providing lung cancer screening only to those at higher risk (current heavy smokers) or initiating breast cancer screening at an earlier age for women with a genetic predisposition.
- To selectively refer for diagnostic procedures following a positive triage result, thereby reducing unnecessary tests.
- To treat precancerous lesions selectively, minimizing the risk of overtreatment.

***A risk-based screening approach ensures that screening and management are adapted to the risk of having or developing cervical (pre-)cancer. This not only benefits the individual woman but results in better use of resources, improving the performance and efficiency of the screening programme.***

In **cervical cancer** screening, a risk-based approach is mainly used to refine the management of screen-positive women. Yet, it can also be used to decide on subsequent screening for screen-negative women or the clinical management when CIN2 or CIN3 is detected.

EXAMPLE

In Sweden, a local (Wang et al., 2021 RISCC) and a nationwide (Arroyo Mühr et al., 2024 RISCC) implementation trials on risk-based cervical cancer screening were conducted. Women at increased risk of cervical cancer without sufficient follow-up were offered self-sampling via text message. Invitations were sent gradually, prioritised according to the specific risk level of each group, as follows:

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- In 2020, among those with inadequate follow-up, women with a previous AGC cytology result and those aged 65-70 with abnormal cytology after age 50 years.
- In 2021, never attenders between 40-70 and, among those with inadequate follow-up, women aged 35-64 Women with HSIL or HPV16/18 positive LSIL and women aged 30-80 with a HPV16 or HPV18 positive result.

A risk-based management approach has three main components:

- 1) Population risks
- 2) Risk thresholds or levels of action
- 3) Clinical actions

In a very simplified way, the risk of disease is estimated to classify participants within the risk gradient. Based on predefined risk thresholds, the clinical action associated with the risk levelis applied (**Figure 1**)

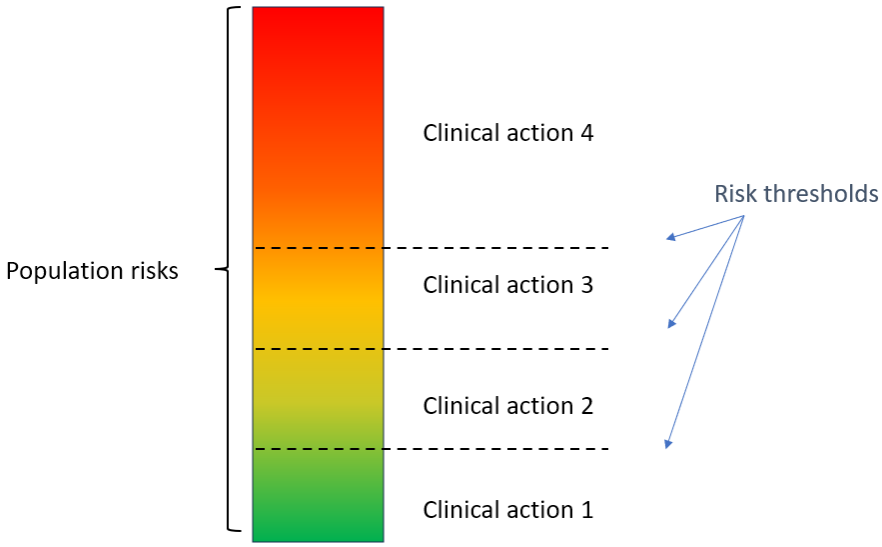


**Figure 1. Visual representation of a risk-based management approach**

Usually, risk-based cervical cancer screening uses the **precancer risk** (CIN3+) level to decide the appropriate management. This way, the clinical management can be tailored to the woman´s risk of pre-cancer (e.g. colposcopy referral when the immediate risk of CIN3+ is 10% or higher). Adjusting the various components of the screening strategy to the different risk levels, optimizes the benefit-harm balance of screening.

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***The risk of CIN3+ depends on test results but also on:***

***Previous screening history, HPV vaccination status and other patient-derived factors (age, immune status, etc.).***

***NOTE:*** *When we say that* ***the immediate risk of CIN3+ is 10% or higher,*** *it means that at least 10% (10 in 100 women) in these circumstances will have CIN3 or worse whereas a maximum of 90% (90 in 100) women will be disease-free.*

Risk-based management differs from results-based management. The latter usually involves one-size-fits-all solutions based on the test result (e.g. all hrHPV positive with abnormal cytology referred to colposcopy) regardless of other factors that influence the risk level. However, the increasing number of test options (cytology, HPV DNA, HPV genotyping, dual staining, HPV RNA, etc) is leading to many potential combinations which can be managed by using well designed flow-charts together with apps to obtain a final risk score that will direct management.

**Did you know?**

**Risk-based Screening for Cervical Cancer (RISCC)** is an EU-funded project that has developed a risk-based policy for cervical cancer screening in Europe. Researchers have estimated the risks of pre-cancer using not just screening and follow-up results but also the woman's vaccination status and other patient-derived factors such as age or immune status. To find out more, see **https://www.riscc-h2020.eu.**

Some of the main results have been incorporated into this and other modules. Look for **RISCC** in the references to identify them.

Each risk level needs a specific clinical action associated with it, which is determined based on the risk of having or developing a precancerous lesion or cancer according to the information available. The same clinical action is then applied to all patients at any particular risk level. In other words, "**Equal Management of Equal Risk**" (Schiffman et al., 2020).

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Current action thresholds are based on those previously established for cytology-based cervical cancer screening. As Katki et al. (2013) explained, "*risk estimates [for each abnormal test result] were not known when screening and management guidelines were created, but there was an underlying understanding of which screening results carried the greatest risk of clinically important outcomes, such as CIN3 and cancer. As a result, different abnormal Pap and biopsy results were managed with interventions of different aggressiveness depending on the implicit risk they carried (e.g., immediate colposcopy, return for repeat Pap testing in 6–12 months, or repeat routine screening in 3 years). When risk exceeded a given threshold, implicitly, guidelines triggered a corresponding management option*".

***Risk stratification is only useful when it translates into different clinical actions.***

The clinical action will depend on the purpose of the risk-based management approach. Potential options include whether to prioritize screening / recall of women at higher risk, follow-up options in screen-positive women or who to treat in case of a detected lesion.

In the management of hrHPV positive women, the general principle (Arbyn et al., 2017) based on their risk of current or incipient precancer is:

- Women at high risk - Referral for diagnostic workup and/or treatment
- Women at low risk - Return to routine screening
- Women at intermediate risk - To keep under surveillance with varying intensity (1 to 3 or more years).

***Each country should consider its epidemiological situation, resources, and acceptance of risk among its population to reach its consensus on the number of risk levels and their associated clinical actions.***

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**Did you know?**

The IARC / JRC working group responsible for the upcoming update of the EU quality assurance guidelines on cervical cancer screening is preparing a survey for experts to define the most appropriate risk thresholds.

As an example, **Table 1** outlines the main reference risk levels used to guide the clinical management of women with an abnormal screening result in the United States. Since several different triage strategies can determine the same level of risk, using *equal management for equal risk* principle, the resulting clinical action in those cases is the same.

**Table 1. Example of a classification of risk levels used to guide clinical management based on cytology and HPV test results**

| Categorisation of the risk for CIN3+ | Examples of situations | Clinical action |
|---|---|---|
| **Very high** | HSIL+ HPV16pos (*64%) | Colposcopy (plus treatment if needed) |
| **High** | HSIL+ hrHPVpos (*49%)<br>HSIL+ hrHPVneg (*25%) | |
| **Moderate-high** | ASC-US hrHPVpos (*4.5%-10%) | |
| **Moderate-low** | Lower risk than ASC-US hrHPVpos but greater than hrHPVneg (*0.25-4.5%) | Follow-up with triage tests (without colposcopy) at different intervals |
| **Low** | Negative cytology (0.25% at 5 years*) | Return to routine screening at different intervals |
| | hrHPVneg (0.15% at 5 years*) | |

*ASCCP risk levels

***NOTE:*** *Risk estimations in the scientific literature vary depending on the study population or the methodology used.*
*For example, in the United Kingdom, women with hrHPV-positive ASC-US had a 10% risk of developing CIN3+ within 3 years (Gilham et al., 2020), while in the United States, women with hrHPV-positive ASC-US showed an immediate risk of CIN3+ of 5% and a five-year risk of 7.3% (Egemen et al., 2020).*

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## 2.2 Risk based on screening data

It includes not only the current screening results but also the previous screening.

### Screening history

There are several factors, related to the screening history, that affect the risk of precancer:

**Participation to screening**

Whether they have or not attended before (Andrae et al., 2008) and the adherence to the recommended screening interval (Gök et al., 2012; Ibáñez et al., 2015).

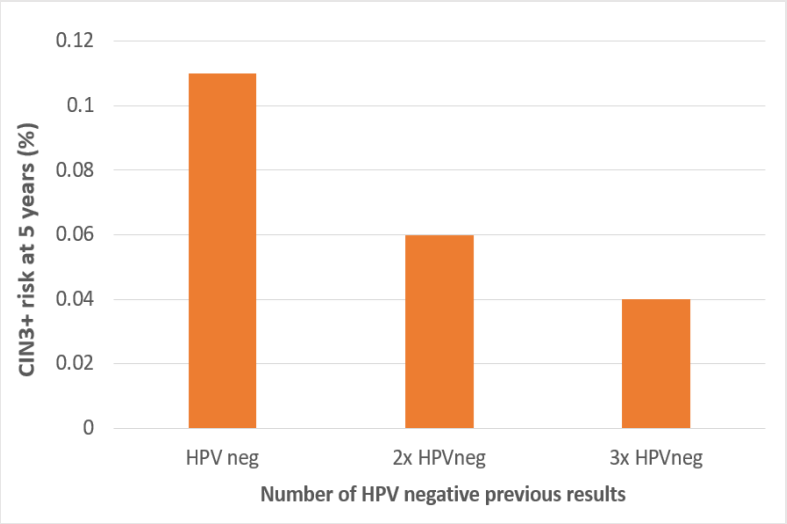
**Primary screening test used in the previous screening round.**

As described in **MODULE 3**, the negative predictive value of hrHPV testing is higher than that of cytology. Therefore, at a certain time after a negative screening result, the risk of cervical cancer is lower in those with a negative hrHPV result in comparison to those with normal cytology (Ronco et al., 2010).

**Number of previous rounds of hrHPV testing with a negative result.**

EXAMPLE

In the United States (Castle et al., 2018), follow-up of a large cohort of women has shown that the 5-year risk of CIN3+ after a negative hrHPV test decreases with an increasing number of hrHPV negative results in previous screening rounds.

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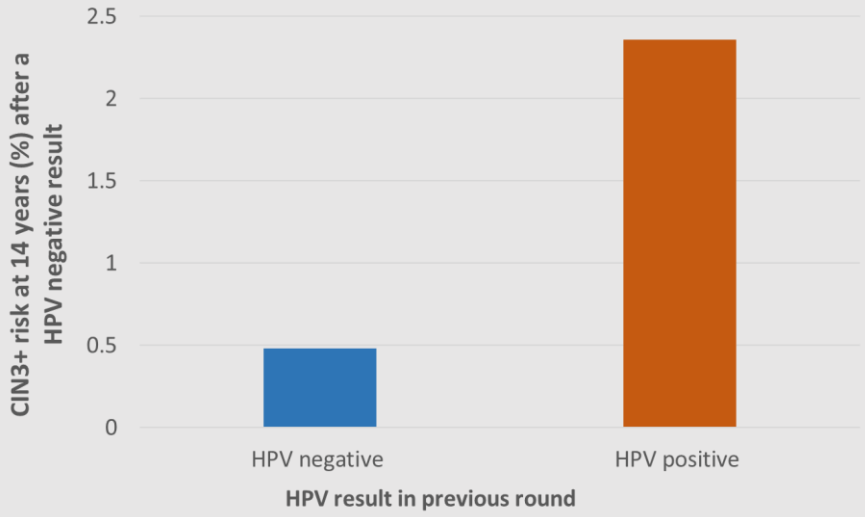
### A previous hrHPV positive result.

EXAMPLE

In the Netherlands (Inturrisi, et al., 2022 RISCC), follow-up of a large cohort of women has shown that the 14-year risk of CIN3+ after a negative hrHPV test increases from 0.48% to 2.4% when the hrHPV-negative result was preceded by an hrHPV-positive result five years earlier.




The long-term low risk of CIN3+ after a negative hrHPV result in comparison with cytology supported policy makers in the Netherlands to extend the screening interval from five to ten years for hrHPV-negative women aged 40 and 50 and to re-invite hrHPV-positive women with negative triage results after five years. However, hrHPV-negative women at age 45 or 55 with a positive hrHPV screening result in the previous round are re-invited after five years.

***Screening history plays an important role in the current risk of CIN3+, which requires that screening algorithms take this information into account to make screening more effective.***

## Current screening

It refers to the screening test results but also those obtained in the triage step, which further refines the risk of screen-positive women.

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EXAMPLE

Not all women with hrHPV-positive ASC-US have the same risk of developing CIN3+ (Arbyn et al., 2017):

- Women with ASC-US cytology and positive for HPV16/18 have an estimated average CIN3+ risk of 18%.
- Women with ASC-US cytology and positive for other hrHPV types have an estimated average CIN3+ risk of 4.5%.

***Triage allows to focus on the smaller subset of screened women at the highest risk, thereby minimizing unnecessary interventions and treatments.***

The risk based on the current screening results is further detailed in this module, specifically in the following unit on triage of women with abnormal screening results.

## 2.3 Risk based on vaccination status

The risk of women depends on whether they have been vaccinated but also the vaccination strategy implemented in their settings (girls-only versus gender-neutral vaccination and whether catch-up campaigns were done) and the HPV vaccination coverage achieved.

Further data on these risks and their implications in screening management are detailed in **MODULE 6**.

## 2.4 Risk based on other patient-derived factors

As described in Module 1, several factors have been associated with an increased risk of progression to cancer in hrHPV-infected women. Among these, the most relevant factors that could be used for further risk-stratification are:

- HIV status.
- Smoking – Increasing risk with intensity and duration.

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- Parity – Increasing risk with increased number of full-term pregnancies.
- Infection with Chlamydia trachomatis.

**KEY IDEA**

Risk-based screening is a new approach that ensures logic, safe, and consistent management in the face of the increasing complexity of multiple combinations of available tests. It sets out clinical management explicitly, based on risks that were previously implicit in clinical algorithms but were not quantified.

**ACTIVITY**

Read the following statements about risk-based management approach and decide if they are TRUE or FALSE.

1. It can only be used to refine the management of screened women with abnormal results.
2. It is based on the concept of "equal management of equal risk".
3. It uses internationally agreed thresholds to decide upon the most appropriate clinical action.
4. The risk of CIN3+ is estimated based on the screening history, vaccination status and/or patient-derived factors.

The correct answers are:

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

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# UNIT 3. TRIAGE OF HRHPV POSITIVE WOMEN

In cervical cancer screening, triage methods can be divided into three large groups:

- ***Morphololologic tests.*** These tests aim to observe morphological cell changes, which require a microscope. Therefore, their interpretation depends on the observant (i.e. subjective).

  Examples: Cytology and p16 and/or Ki-67 staining of cytology slides (cyto-immunochemistry).

- ***Molecular tests.*** These tests are based on the presence or quantification of molecules such as viral components or molecular changes in women caused by hrHPV. Therefore, their interpretation is objective.

  Examples: HPV DNA and RNA HPV tests, partial or extended genotyping, viral load, protein markers (chemical detection of E6 and/or E7 oncoproteins, for instance by ELISA) and methylation.

- ***Visual inspection tests.*** These tests involve the direct observation of the cervix using a magnifying device or with the naked eye.

  Examples: Visual inspection with acetic acid (VIA) or lugol iodine (VILI).

These triage methods can be used alone or combined in a single triage event or with subsequent triage testing at 6 months - 1 year of those testing negative in the initial triage event.

***In settings planning to use a screen-triage-treat management approach, WHO recommends using partial genotyping, colposcopy, VIA, cytology or dual-stain cytology to triage women after a positive hrHPV test result.***

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***NOTE:*** *WHO recommendations of management of screen-positive women are part of living guidelines that are being updated in phases. Therefore, lack of recommendation does not necessarily imply that WHO recommends against its use.*

The present module focuses on the triage methods recommended by WHO and potential combinations although some information on other options such as extended genotyping, viral load, E6 and E7 oncoproteins, messenger RNA or viral/host methylation markers is also briefly provided.

## 3.1 WHO recommended triage options

### Partial genotyping

In high-resources settings, a highly used triage is partial genotyping (i.e., separate information for HPV16 and/or HPV18) although extended genotyping is being used in some countries. The advantages of this triage test are:

- The fact that it is embedded in many hrHPV assays and therefore does not require an additional sample to be tested.
- The result is objective and repeatable and more directly linked to the risk of CIN3+ than an ASC-US or LSIL cytological result.
- It can be applied on self-collected samples.
- It will be especially relevant to take into account the rapidly dropping prevalence of vaccine types in young women due to the population-level impact of HPV vaccination.

***HPV genotyping is rarely used as a standalone triage test.***

Women with hrHPV types infections other than HPV16 or HPV18 are usually subjected to further triage testing. The most common further triage test is cytology.

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Partial genotyping triage classifies women into those positive for HPV16/18 with a higher risk of CIN3+ (almost 20%) and those negative for HPV16/18 with a lower risk (about 3%). This latter group is usually further triaged with cytology although countries like Sweden and Denmark are currently using grouped extended genotyping embedded within the primary screening test. Further triage with cytology (**Figure 2**) results in CIN3+ risk of 6.5% for those with an ASCUS+ cytology and <2% for those with a normal cytology.

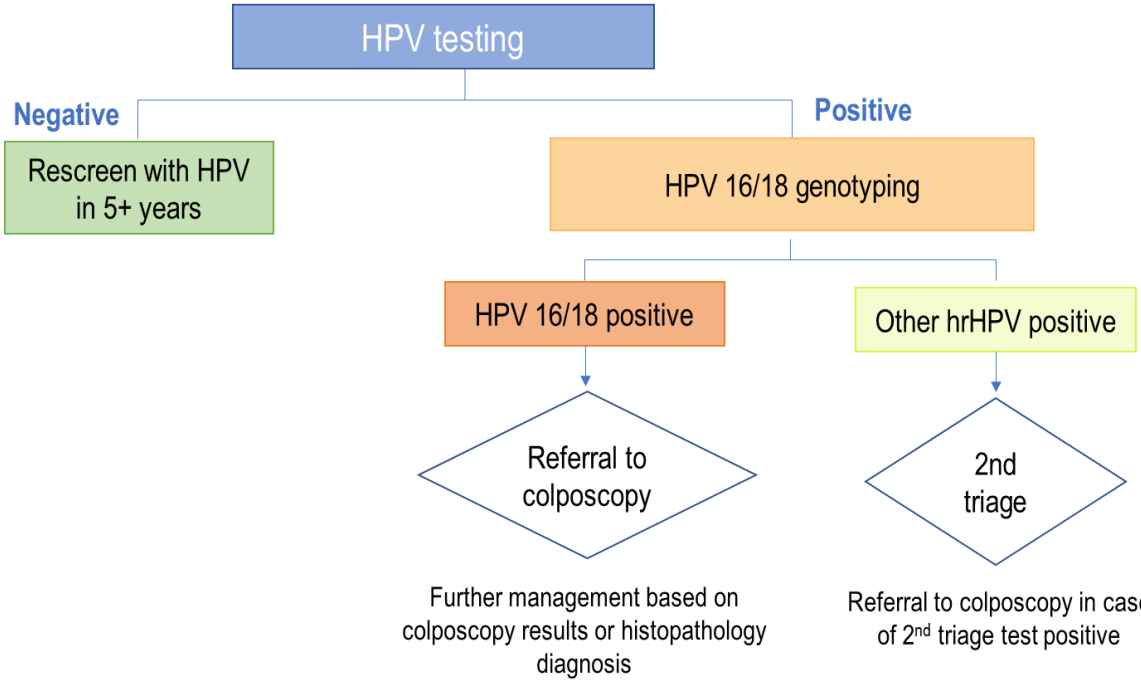


**Figure 2. Potential algorithm for the clinical management of hrHPV-positive women triaged with partial genotyping**

**Did you know?**

Women with an atypical glandular cells (AGC) cytology result show a high risk of CIN3+ when HPV16/18 positive but a very low risk of CIN3+ if hrHPV negative (Norman et al., 2022). These results suggest that partial genotyping in women with an AGC cytology can result in an improved detection of adenocarcinoma precursor lesions through direct referral to colposcopy.

## Cytology

Cytology is still one of the most used triage tests for hrHPV positive women:

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- Its specificity is high when an adequate threshold for positivity is set
- It can be performed on the same specimen used for screening if the specimen is stored in a cell-preserving medium (liquid-based cytology)
- In settings where a previous quality-assured cytology-program is in place, it allows for recycling of cytologists/technicians

Where cytology is used, the most common algorithm involves the referral to colposcopy of those above ASC-US+ as depicted in **Figure 3.**

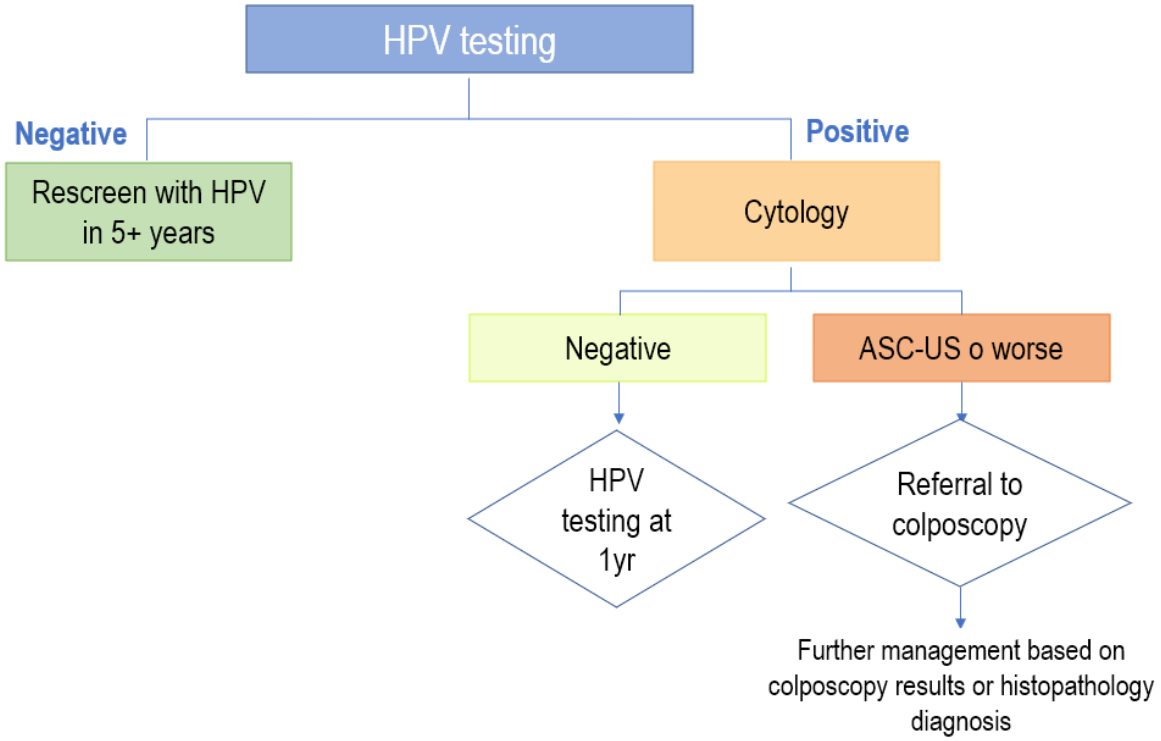


**Figure 3. Potential algorithm for clinical management of hrHPV-positive women triaged with cytology**

**Did you know?**

Approaches to automated cytology reading such as ThinPrep Imaging System *(Hologic®)*, FocalPoint GS Imaging System *(Becton Dickinson®)* and CytoProcessor *(Datexim®)* show statistically equal or better diagnostic performances than those of the manual method (Rezende et al., 2021).

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***Cytology triage requires a highly skilled workforce and significant investment in ongoing quality assurance to perform optimally.***

Quality assurance is possible in high-income countries with the relevant infrastructure. Yet, even in these settings, the shift to HPV primary screening will bring about sizeable reductions in the overall cytology workload. Adequate recruitment, training, and retention of cytology staff in an era of HPV primary screening may prove challenging and efforts to address this are required.

**Did you know?**

The absence of cells from the transformation zone or lack of endocervical cells in a cytology is not a criterion to repeat a cytology provided it is satisfactory (Arbyn et al., 2007).

## Dual staining

There is increasing evidence that p16/Ki-67 dual-staining (DS) cytology can be used as a surrogate biomarker of the HPV E6/E7 oncogenes expression.

p16INK4a, or p16, is a cellular protein which highlights disruption of the retinoblastoma (RB)/E2F pathway related to the activity of the HPV oncogene E7. The assay is performed using immunocytochemistry (or histochemistry), initially as a single marker and now as a dual stain with Ki67, a cell proliferation marker, which confers additional specificity (Cuschieri et al., 2018; Peeters et al., 2019; Wentzensen et al., 2019). The co-expression of p16 and Ki-67 suggests a deregulation of the cell cycle mediated by hrHPV infection and could assist in predicting the presence of high-grade cervical epithelial lesions (**Figure 4**).

**Did you know?**

p16 staining is also useful for disease stratification in lesions categorized as cervical intraepithelial grade 2 (see LAST classification in **MODULE 4B**).

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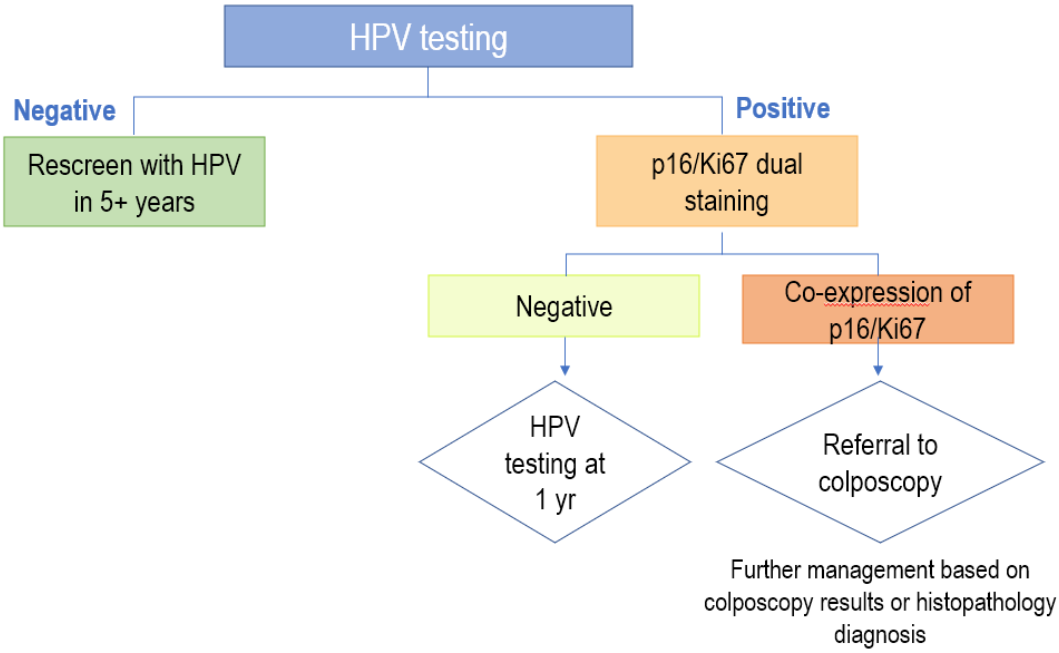


**Figure 4. Potential algorithm for clinical management of hrHPV-positive women triaged with dual staining**

## *Automated p16/Ki-67 dual staining shows promising results*

Automated p16/Ki-67 dual staining has recently been evaluated. An artificial intelligence-based automated algorithm to evaluate p16/Ki-67 dual stain (DS) (CYTOREADER) applies a whole-slide scan followed by a machine learning algorithm to detect and quantify p16/Ki-67 DS-positive cells. First results indicate a better performance than manual reading.

EXAMPLE

The diagnostic accuracy of the automated DS was compared with manual DS and conventional cytology for the detection of precancer among 602 women referred to colposcopy in the USA (Wentzensen et al., 2021). The automated DS algorithm had marginally lower positivity compared to manual DS (58% vs 63%, respectively, referred to colposcopy) with comparable sensitivity for CIN3+ (87% in both methods) and marginally higher specificity (46% vs 41%, respectively).

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## Colposcopy

Colposcopy involves the direct visualisation of the cervix, vagina and vulva through a colposcope that also allows, if appropriate, to collect tissue from abnormal areas for histological diagnosis. It is considered a minimally invasive technique and therefore is rarely used as a single triage test (**Figure 5**) but generally used subsequently after a positive result in a different triage test.

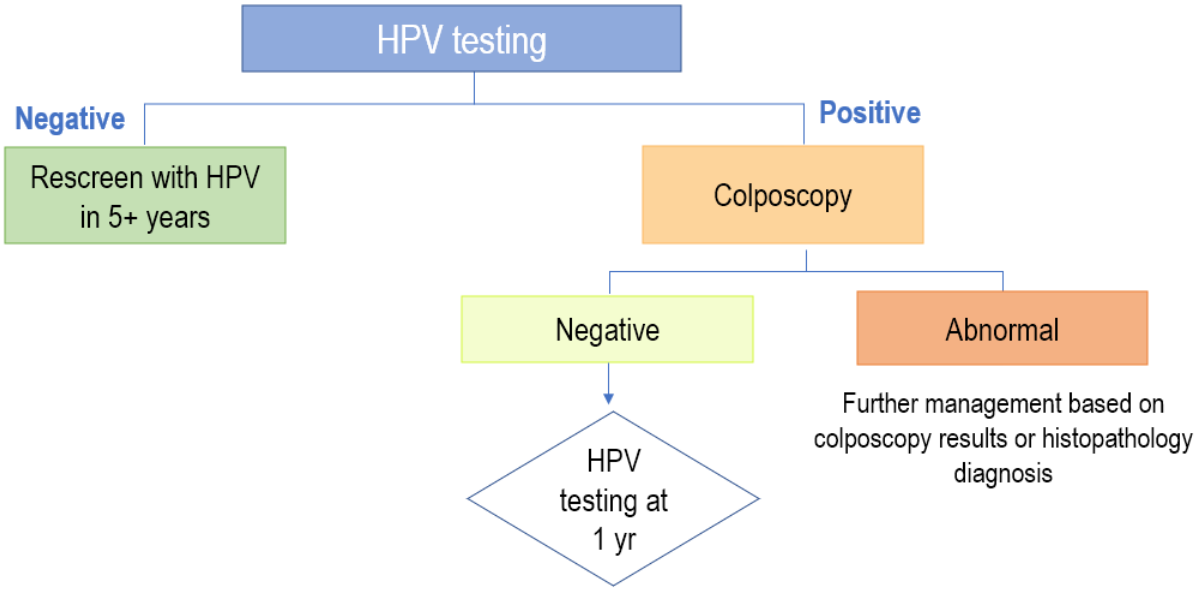


**Figure 5. Potential algorithm for clinical management of hrHPV-positive women triaged with colposcopy**

Given its characteristics and importance, see specific section on colposcopy within **MODULE 4B.**

## Visual inspection with acetic acid

Visual inspection of the cervix with acetic acid and iodine (VIA/VILI) by naked eye examination has been used as primary screening test in low-resource settings. Although no longer recommended by WHO for primary screening, it is recommended as a potential triage test for hrHPV positive women in these settings due to its low cost and the immediate availability of results, facilitating a *screen and treat* approach (**Figure 6**).

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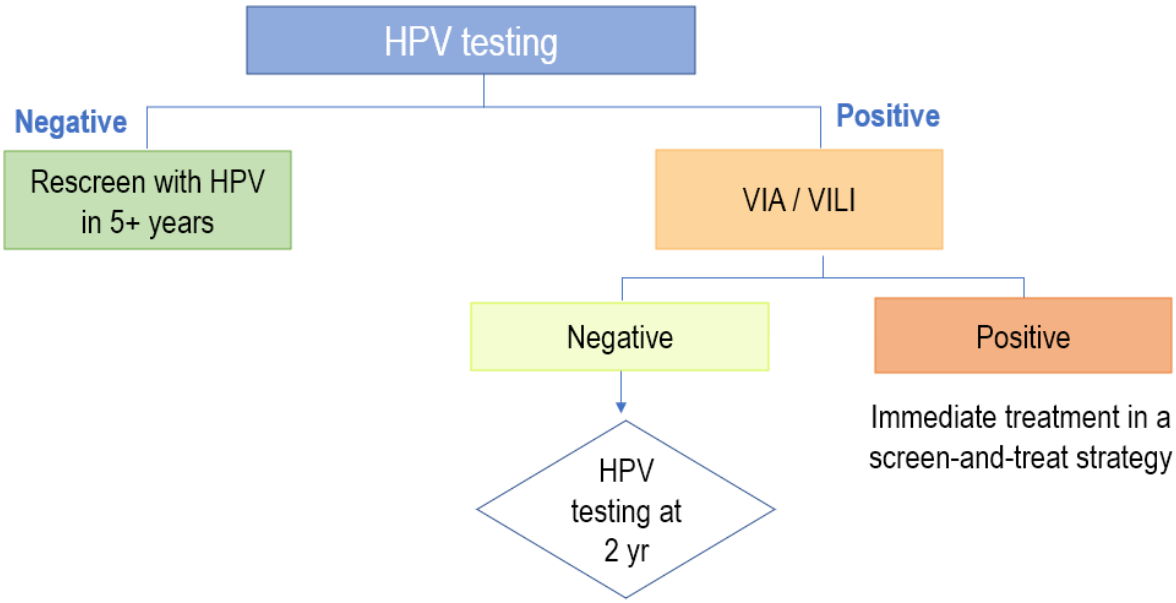


**Figure 6. Potential algorithm for clinical management of hrHPV-positive women triaged with VIA/VILI**

When VIA is used to triage hrHPV positive women, its subjectivity results in a large variability in referral rates for treatment. Ensuring adequate training, supervision, and continued quality assurance can be challenging and do not necessarily result in better performance. Furthermore, VIA programs are unlikely to have histology confirmation limiting the assessment by a reference standard.

**Did you know?**

To address the subjectivity in the interpretation of VIA and cytology, newer technologies based on Artificial Intelligence (AI) are being explored. Automated Visual Evaluation (AVE), incorporating digital imaging technology using electronic readers and smartphones, can be used to capture and interpret data, as has been successfully used for HIV and malaria (Befano et al., 2025; Peeling, 2015). Furthermore, it allows for point-of-care triage enabling complete assessment and treatment in one session, thus avoiding loss-to-follow-up due to multi-step triage.

For more information on using artificial intelligence, please check the relevant section within **MODULE 4B**.

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## 3.2 Triage test performance and comparison

The triage test performance included in this unit is based on the work done by Arbyn and colleagues within the RISCC project and partially included in other publications (IARC, 2022). It includes a comprehensive, unpublished report containing meta-analyses and summary data of different triage options in clinician-collected samples.

***NOTE:*** *This review includes literature published before February 2020. An updated review will be published with the upcoming new edition of the European guidelines for quality assurance in cervical cancer screening, including more and better documented triage with longer follow-up.*

Performance data is available for over 25 triage strategies, but here only those recommended by WHO are presented (**Table 2**):

**Table 2. Performance data of the WHO recommended triage tests for hrHPV positive women.**

| Strategy | Referral rate % (IQR) | Sensitivity CIN3+ % (95% CI) | Specificity <CIN2 % (95% CI) |
|---|---|---|---|
| **Cytology (ASC-US+)** | 33.8 (28.9-43.8) | 77.5 (69.4-83.9) | 72.7 (66.7-77.9) |
| **HPV16/18 genotyping** | 30.7 (20.2 -34.3) | 61.2 (57.2-65.2) | 74.9 (68.7-80.2) |
| **HPV16/18 genotyping & cytology ASCUS+ for other hrHPV** | 53.5 (44.6-68.8) | 85.8 (72.1-84.2) | 67.5 (60.1-72.4) |
| **Dual staining** | 36.5 (29.4-46.0)* | 82.3 (73.5-88.6) | 66.5 (57.9-74.2) |
| **Colposcopy** | Not applicable | 84.9 (74.8-91.4) | 64.1 (51.4-75.0) |
| **VIA**** | 22.4 (19.3-35.3) | 68.8 (61.3-75.4) | 78.6 (72.5-83.6) |

* Range in included studies (n=5) is provided instead of the IQR

** Accuracy measures estimated after exclusion of extreme values

**Did you know?**

Cytology performance is similar for both conventional and liquid-based cytology but improves when cytologists know the hrHPV status.

When compared with cytology at ASC-US+ cutoff (most used triage test so far), partial genotyping and dual staining showed a similar CIN3+ performance (no statistically significant differences).

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VIA also did not show different performance to cytology at ASC-US+ although large differences in VIA performance were observed between studies (sensitivity range: 6% to 100%).

The CIN3+ performance of colposcopy at major abnormality threshold was similar to cytology at ASC-US+ but when a minor abnormality threshold was used colposcopy was more sensitive but less specific.

The performance of partial genotyping with further cytology triage in other hrHPV positive women is more sensitive than cytology alone but less specific.

***NOTE:*** *Relative performance data generated in settings with well-established cytology programmes may not be representative of all settings. Consequently, in settings where quality of cytology is less certain, the relative performance of other triage tests may be better.*
*For more information on the limitations of cytology, please check* ***MODULE 3.***

Triage strategies may vary according to the threshold levels of the triage test of interest. For example, in a given setting there may be interest in obtaining a higher specificity of the screening strategy chosen at the expense of a lower sensitivity. For example, an increase in the cytology threshold at LSIL+, ASC-H+ or HSIL+. In comparison to cytology at ASC-US+, it results in 22%, 17% or 40% increase in specificity but a 15%, 25% or 49% reduction in CIN3+ sensitivity, respectively.

***The performance data above reflect findings where hrHPV screening is applied on clinician-collected cervical samples and are not translatable to self-collected samples.***

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**ACTIVITY**

Read the following statements about the WHO recommended triage options and decide if they are TRUE or FALSE.

1. Partial genotyping is rarely used as a standalone triage test. hrHPV types other than HPV16/18 are further triaged.
2. Visual inspection with acetic acid is recommended as triage test but not for primary screening by WHO.
3. Methylation is a triage test recommended by WHO.
4. The relative performance of any test versus cytology does not depend on the setting.
5. The performance of triage tests based on clinician-collected samples is not translatable to self-collected samples.

The correct answers are:

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

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## 3.3 Other approaches to triage

Other triage options may have a similar or superior performance to those mentioned above. Their evaluation requires considering their accuracy, and reproducibility.

### Extended genotyping:

We have already looked at the relevance of partial genotyping (identifying HPV16 and 18 separately) to stratify hrHPV-positive woman according to their risk of disease. However, as described in MODULE 3, accumulating data shows that the hrHPV types included within the "other hrHPV positive result" have different risk of CIN3+ among them. Therefore, extended genotyping has the same advantages described by partial genotyping combined with a better stratification of risk among hrHPV positive women for types other than HPV16/18 often already embedded within the primary screening test.

***WHO is about to include HPV extended genotyping in the list of recommended triage strategies (expected date: late 2025).***

Of the 14 hrHPV genotypes generally detected by HPV tests, HPV39, 51, 56, 59 and 68 have such a low potential for progression that they could be assumed to behave like the low-risk HPV genotypes. These HPV genotypes are detected in more than 20% of women with an HPV positive test, so that a more conservative management can improve the performance of the screening programme (reducing the number of unnecessary colposcopies, for example). As described in the previous module, HPV66 should not be detected.

EXAMPLE

The risk of CIN3+ at 9 years after a positive hrHPV result were assessed in women aged 30 or more classified in 4 risk groups depending on the HPV type detected at baseline (Oštrbenk Valenčak et al., 2024 RISCC). This grouping was decided based on the IARC hierarchical ranking (IARC, 2022).

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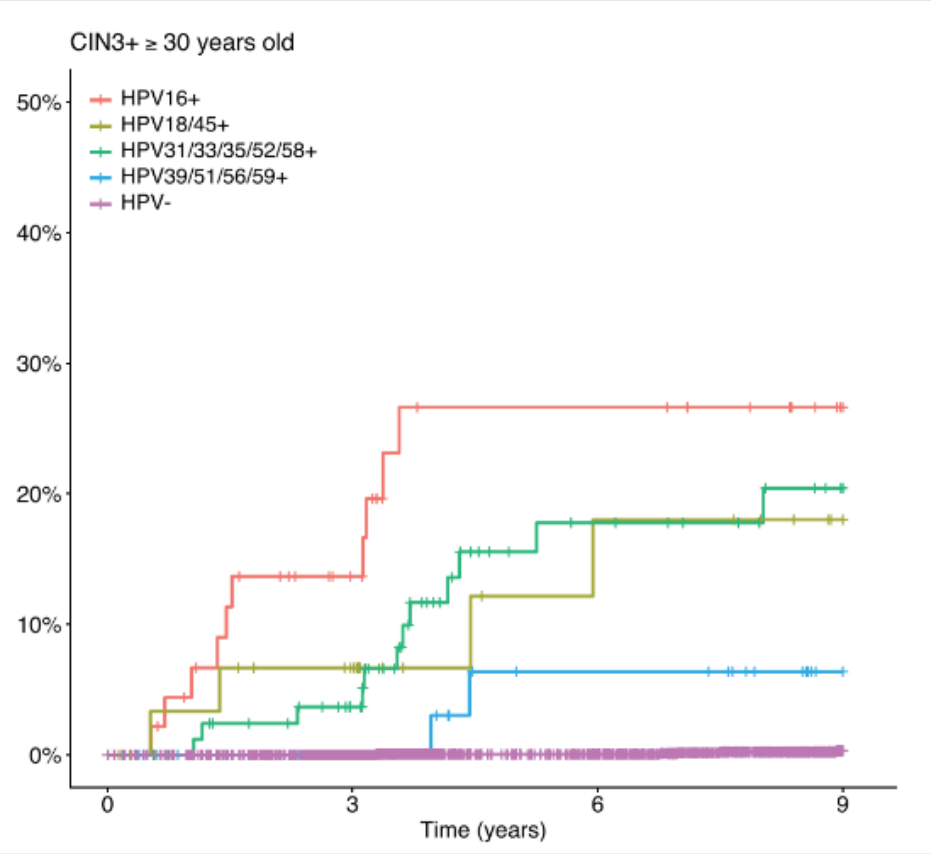


Data shows that HPV16 positive has the highest risk of CIN3+ (32%), groups HPV 18/45 and 31/31/35/52/58 show intermediate risks (25 and 27%) whereas HPV 39/51/56/59 show the lowest risk (8%).

***The CIN3+ risk of each HPV genotype varies between studies owing to differences in the study population characteristics, the follow-up period, or the HPV assays used. Whereas the hrHPV types most implicated in invasive carcinoma tend to be the same, geographic differences are noted in the type-specific CIN3+ risk due to the population prevalence.***

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One of the issues to be solved with extended genotyping relies on how to apply it in clinical management

- It can be used to group hrHPV-positive women into two or three risk categories to guide follow-up, as done in Sweden and Denmark.
- It can also be used to define HPV positivity based on a restricted selection of hrHPV types (Dun et al., 2024 **RISCC**). This has been suggested mainly for resource-constrained settings or populations with high HPV prevalence such as women living with HIV.

***NOTE:*** *The specific triage strategy using extended genotyping might require tailoring to the setting. HPV45 is usually classified among the highest risk groups of lesion in several continents due to its associated risk with cervical adenocarcinoma, but might not have an added value in certain other parts of the world, like China, where its prevalence in adenocarcinoma is relatively rare (Dun et al., 2024* ***RISCC****).*

**Did you know?**

Extended genotyping can also be helpful for the management of women with an AGC result. Among women with an AGC and hrHPV-positive for types other than HPV16/18, women positive for HPV31 and HPV33 had the highest risk of CIN3+ whereas HPV45 was the most commonly detected in subsequent cancer cases (Yilmaz et al., 2023 **RISCC**).

## Use of viral load

Many HPV test results are provided as a signal intensity (continuous data) that is then categorised as positive above a certain predefined threshold. These quantitative values are considered as surrogates of the viral load.

Persistent type-specific viral load, irrespective of hrHPV type, is associated with cancer. An increased viral load may reflect a reproductive infection, which subsequently may clear spontaneously, especially for infections not caused by HPV16. On the other hand,

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HPV16 viral load is correlated with severity of cervical lesions and cancer (Adcock et al., 2019; Gravitt et al., 2007; Schmitt et al., 2013).

EXAMPLE

In the ALTS study, women with an ASC-US diagnosis (Fu Xi et al., 2017) were followed to assess the association between CIN2/3 and the DNA load for specific hrHPV genotypes. In general, the increase in the cumulative risk of CIN2/3 per unit increase in the viral load (log10 transformed) was statistically significant for four of the alpha-9 HPV types:

- HPV31 (adjusted hazard ratio (HR)) = 1.32, 95% CI: 1.14-1.52)
- HPV35 (adjusted HR = 1.47, 95% CI: 1.23-1.76)
- HPV52 (adjusted HR = 1.14, 95% CI: 1.01-1.30)
- HPV58 (adjusted HR = 1.49, 95% CI: 1.23-1.82)

The association was marginally significant for HPV33 (species 9) and HPV45 (species 7) but not significant for other hrHPV types.

This study suggests that the CIN2/3 risk associated with a high viral load varies by HPV genotype and that the results are significant for four hrHPV genotypes associated with HPV16 (i.e. the alpha-9 species).

## E6 and E7 oncoproteins

Elevated expression of the E6 and E7 oncoproteins is associated with the development of pre-cancer.

A few tests are available for determining the expression of these oncoproteins, either by direct detection (OncoE6 Test™) or by detection of messenger RNA as a proxy of expression of the E6 and E7 oncogenes.

A meta-analysis of published studies (Downham et al., 2023 **RISCC**) analysed the performance of oncoprotein testing (E6 and/or E7) as triage of hrHPV positive women. In comparison to cytology at ASC-US+ and partial genotyping, oncoprotein triage testing showed a 10-15% lower sensitivity for CIN3+ but a 22-28% higher specificity.

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Specific detection of HPV 16 and 18 oncoproteins has provided more satisfactory results than broad detection of oncoproteins for up to eight hrHPV genotypes. This limits its usability as a triage test (Downham et al., 2024).

## mRNA

The accuracy of using mRNA tests for triaging hrHPV-positive women has been measured in tests detecting E6/E7 for 5 (Proofer test) or 14 (Aptima) hrHPV genotypes.

The 14-type HPV mRNA test is more widespread though mainly as a primary screening test.

As triage, sensitivity for both CIN2+ and CIN3+ is higher than cytology at ASC-US+ but specificities are lower. A limited genotyping mRNA test (identifying HPV16 and HPV18/45) could be used for triage of women testing positive by the 14-type HPV mRNA test.

## Methylation

DNA methylation changes are observed in many cancers, including cervical cancer.

Controlled DNA methylation is essential for regulating normal cell processes, such as embryonic development, chromosomal instability and protecting against viral DNA. Conversely, abnormal methylation of human genes and/or of the HPV viral genome can alter the functions of gene products that regulate tumour suppression, DNA repair, apoptosis, metastasis and invasion (Bowden et al., 2019; Lorincz, 2016; Steenbergen et al., 2014).

Although multiple studies have evaluated the accuracy of methylation tests for cervical cancer screening (Kelly et al., 2019), they are difficult to interpret because of significant variability in:

- Type of target gene (human or viral)
- CpG sites in the target gene

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- Cut-off values for test positivity or negativity
- Number of markers used
- Study design and study population (screening, triage, arbitrary convenience population)

DNA methylation shows promise for detecting CIN3+ in triage of hrHPV-positive women. Its performance sometimes is similar to that of cytology at ASC-US+ but with a higher specificity. Additionally, they can be used as reflex tests in both vaginal and urine self-collected samples.

However, different findings have been observed for particular methylation tests and to date no human or viral gene has been shown to have sufficiently high sensitivity as a unique marker. In fact, identifying the optimal combination of markers is an important area of research interest.

**Did you know?**

The RISCC consortium have assessed several methylation markers for triage of hrHPV positive women in self-samples (Verhoef et al., 2022 **RISCC**). Among them, the bi-marker panel ASCL1/LHX8 shows promising results often with a better sensitivity for CIN3+ and specificity than partial genotyping. However, when comparing methylation testing on self-collected samples with clinician-collected samples, methylation testing on self-collected samples shows a lower specificity at a similar sensitivity (Verhoef et al., 2023 **RISCC**) which requires of further optimisation of these markers.

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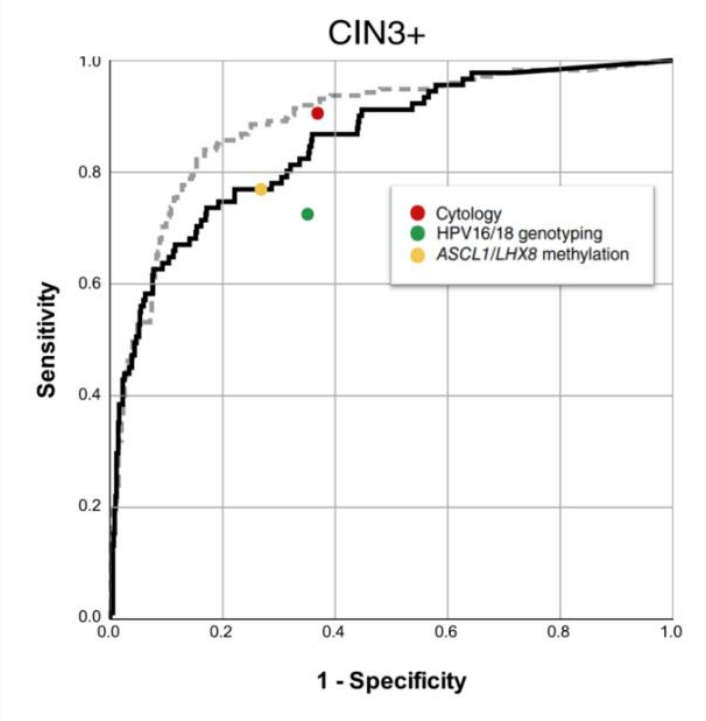


Before DNA methylation can be widely implemented, tests will need to be adapted in terms of affordability and automated / simplified processing as well as optimised for self-collected samples.

***NOTE:*** *For more information on DNA methylation, please check the technical meeting report from the HPV Prevention and Control Board, an independent group of experts aiming to provide guidance and reflection on strategic, technical, and policy issues regarding implementation and sustainability of HPV prevention and control programmes (Burdier et al., 2024).*

## 3.4 Management of triage negative women

Women with a positive screening result but a negative triage result should not be sent directly to regular screening as they might remain at risk of cervical disease, although lower depending on the triage strategy used. In these women, closer follow-up with additional testing at a predefined interval may be indicated based on the risk of developing a precancerous lesion.

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**Did you know?**

The concept "triage negative women" does not necessarily refer to women with a negative or normal result in the triage test but those with a triage result that do not indicate direct referral to colposcopy. For example, in the Netherlands and Australia, hrHPV positive women with a non HPV16/18 infection and an ASC-US / LSIL cytology result are the "triage-negative women", to be re-tested at 12 months.

Therefore, research is not only focusing on who should be referred to colposcopy at the initial screening event but also on the most optimal follow-up strategy for those not initially referred, which requires defining which test or combination of tests is to be offered and when.

In general, additional testing during follow-up provides a more sensitive strategy than a strategy without further follow-up (i.e., return to routine screening) but it usually results in a loss of specificity (i.e., more women are referred to unnecessary testing).

**Did you know?**

For hrHPV positive women with a normal cytology reflex-triage, the 2015 European guidelines recommend two different follow-up strategies (von Karsa et al., 2015): a second cytology at ASC-US+, or hrHPV testing at six to twelve months.

Increasing the follow-up time before assessing hrHPV persistence (24 versus 12-month follow-up) results in some detection loss but a greater proportion of transient infections cleared and could lead to greater efficiencies in identifying and referring at-risk women with persisting infections (Arbyn et al., 2020 **RISCC**).

There is little evidence of performance and effectiveness when more additional close follow-up visits are conducted (longitudinal performance), such as, for example, when women stay in a follow-up scheme as long as they are hrHPV-positive.

***Surveillance of triage outcomes from newly established HPV-based screening programmes will provide real-world evidence into the longitudinal performance of triage***

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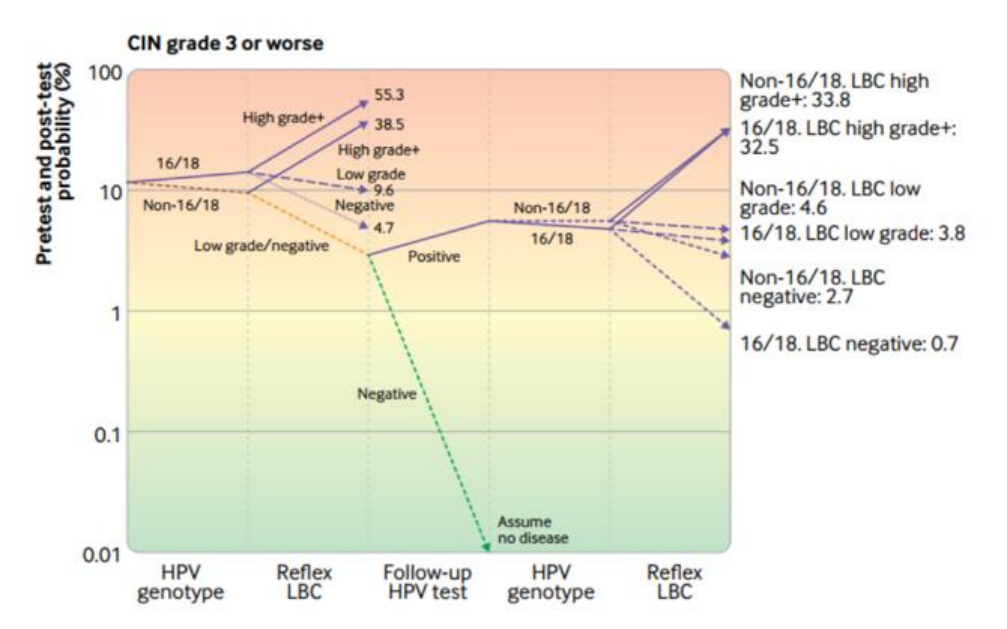
***strategies in the future to fine-tune the optimal follow-up time to assess clearance of hrHPV infections and the colposcopy referral criteria at follow-up.***

EXAMPLE

Australia started its HPV-based cervical cancer screening in 2017 with partial genotyping and cytology as triage strategy. hrHPV-positive women were referred to close follow-up at 1-yr if the HPV infection was caused by a hrHPV type other than HPV16/18 and cytology was either normal or low-grade. At 1-yr, all hrHPV-positive women, all women were referred to colposcopy (Smith et al., 2022 RISCC).

Follow-up data analysis shows that, at the 12-month follow-up, the highest proportion of women were those with non-HPV16/18 positive infections with a normal/ASC-US/LSIL cytology result. These women show a risk of CIN3+ at the 12-month follow up similar to non-HPV16/18 positive women with a normal/ASC-US/LSIL cytology result at the initial triage test (around 4.5%) suggesting that testing with cytology and partial genotyping at 24 month-follow-up is appropriate.

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## 3.5 Selection of triage tests

The ability of a test to classify women (i.e., its utility) based on their risk of disease can be visually represented in pre/post-test probability or *ppp* plots. These graphs show the CIN3+ risks before and after a triage test is applied (**Figure 7**).

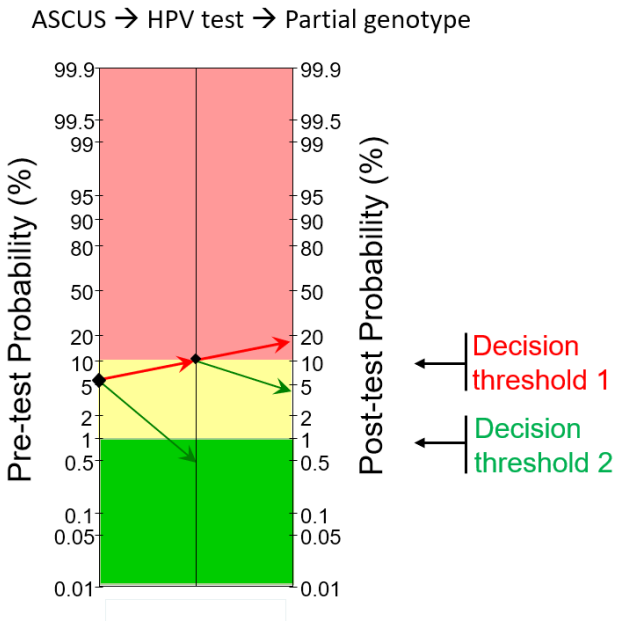


**Figure 7. Pre/post-test probability plot (ppp plot) of CIN3+ when using HPV testing and partial genotyping in women with an ASC-US cytology result** (Arbyn et al., 2020)

These graphs are especially useful when the decision threshold for clinical action has already been defined. When the pre/post-test probability of a given triage strategy are located in the same risk zone, the triage test is not clinically useful.

***Each setting needs to define its own decision thresholds based on its locally acceptable risks.***

There is no clear consensus on the criteria to decide whether a triage strategy is acceptable or not, but some parameters are commonly used to assess it:

**PPV for CIN3+ or post-test risk in women with a positive triage result.**

A CIN3+ risk of 10% is a common threshold in Europe for referral to colposcopy although it can vary from 4% in the United States (Perkins et al., 2020) to 20% in the Netherlands

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(Polman et al., 2019). It assesses the triage test efficiency as diagnostic work-up/treatment being justified in women with a triage positive result.

**cNPV for CIN3+ or post-test risk in women with a negative triage result.**

A CIN3+ risk under 1% is a common threshold in Europe to return to routine screening although 2% is informally accepted in the Netherlands It assesses the triage test safety for triage negative women.

**Number of colposcopies or women referred to colposcopy needed to detect one CIN3+ case (NNC)**

It is the same as the 1/PPV. The lower the NNC, the more efficient is the triage strategy.

***NOTE:*** *Besides the accuracy of the triage tests, the underlying prevalence of disease (pre-test probability) affects the predictive value of the triage algorithm. Therefore, an acceptable triage strategy in settings with a high prevalence of disease could not be acceptable in settings with a lower prevalence. The CIN3+ post-test risks can be computed from the accuracy estimates pooled in meta-analyses combined with local pre-test risks.*

The benefits, harms and programmatic costs of the recommended triage options by WHO are similar. Therefore, the choice of triage method depends on the following factors:

- **Feasibility:** Includes aspects such as access to and experience with the necessary equipment, infrastructure and the ability to reach target populations.
- **Training:** Needed to adequately perform, process, and possibly interpret triage tests.
- **Programme Quality Assurance:** Quality assurance mechanisms, such as standardized protocols and regular performance evaluations, can be required to maintain the reliability of the selected triage method.
- **Available Resources:** Includes costs, laboratory infrastructure, and technical support.

When selecting the most adequate triage strategy, other aspects to be considered include the possibility of embedded testing together with the primary HPV DNA test,

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potential testing in self-samples avoiding re-call of hrHPV positive women, and the complexity and duration of follow-up of triage-negative women. A high number of subsequent visits in triage-negative women can result in a certain degree of drop-out. Where the drop-out is significant, more sensitive initial reflex triage scenarios can be preferred.

**Did you know?**

The efficiency of different triage strategies can also be assessed through an incremental analysis similar to a cost-effectiveness analysis (Kroon et al., 2024 **RISCC**). In this example, the increased costs between different triage strategies (represented by the increased number of colposcopy referrals) were compared to the increased number of CIN3+ detected per each additional colposcopy referral (i.e, the marginal PPV).

***NOTE:*** *Several studies have assessed the performance of different triage strategies as single step or even as two or three-steps. For some examples, please see Stanczuk et al. (2021) based on real-world screening data from Scotland, Rezhake et al. (2020) using data from rural China or Kroon et al. (2024) using cost-effectiveness analysis.*

**ACTIVITY**

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

1. Extended genotyping allows for further risk stratification of hrHPV types other than HPV16/18, potentially embedded within the primary screening test.
2. Viral load refers to the number of hrHPV positive or negative results in previous screening rounds.
3. Methylation tests show similar performance results irrespectively of the target gene.
4. hrHPV positive women with a negative triage test have a risk of disease similar to those that are hrHPV negative at screening and therefore, they don't require close follow-up.
5. Given the similar benefits, harms and programmatic costs of the recommended triage tests by WHO, the choice of the triage method depends on its feasibility, training and programme quality assurance needs and the available resources.

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The correct answers are:

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

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# UNIT 4. MANAGEMENT OF PRECANCEROUS LESIONS

In countries with high-resources, women in a screen-triage-treat approach are generally referred to colposcopy, and if some conditions are met, biopsy samples are taken for histologic diagnosis. Further details on these actions are explained in **MODULE 4B** on visual techniques and diagnostic tests.

***NOTE:*** *Treatment of cervical cancer is not covered in this course.*

## 4.1 Treatment options

***While international and regional guidelines provide recommendations for managing hrHPV-positive women, it is essential to adhere to the local or national screening protocols.***

In general, the available options for management of precancerous lesions include:

### Ablative or destructive procedures

It involves the destruction of abnormal cells or tissue before it can progress to cancer. It can be done through freezing (cryotherapy), lasering (laser ablation) or burning (thermal ablation, also known as cold coagulation or thermocoagulation). Eligibility for ablative procedures needs to be assessed on a case-by-case basis through colposcopy or naked-eye visual inspection, both after application of acetic acid.

### Excisional Procedures

It involves the removal of the abnormal cells or tissue before it can progress to cancer. It can be done using a large loop powered by an electrosurgical unit (LLETZ, also known as LEEP) or using a surgical blade (cold-knife conization).

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***WHO recommends LLETZ over ablative procedures where LLETZ is available and accessible. Also recommends against the use of cold-knife conization in a screen and treat approach.***

**Did you know?**

The comparison of excisional treatments showed that more aggressive local treatments, such as cold-knife conization, were associated to a reduced risk of treatment failure than LLETZ but increased risk of preterm birth (Athanasiou et al., 2022 **RISCC**). Preterm birth risk also increases with cone length. Therefore, the choice of treatment should rely on woman's age, size and location of lesion, and desire to have children.

### Hysterectomy or trachelectomy

It involves the complete removal of the cervix, either alone (trachelectomy or cervix amputation) or together with the uterus (total hysterectomy) depending on the desire of future pregnancy.

### Observation and follow-Up

It involves close monitoring of women at shorter intervals, generally 6 month – 1 year, for further testing or colposcopy.

In general, all CIN3+ lesions need to be treated due to the risk of progression to invasive cancer but, as highlighted throughout the course, not all CIN2 lesions will progress and therefore do no not need to be treated. However, to date there is no clear biomarker to identify which CIN2 lesions might benefit from a more conservative approach although research in the field is ongoing.

Methylation may play a role in the conservative management of CIN2 lesions. Although longitudinal data is missing to assess whether high methylation levels are associated with more aggressive CIN2 lesions, promising results have been observed; in Finland, methylation was a better predictor of regression/progression than cytology or HPV16/18/31/33 genotyping (Louvanto et al., 2019) whereas in the Netherlands, a negative methylation result in combination with low-grade cytology or HPV16 negative

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at baseline was associated with a high regression rate of CIN2 lesions (Kremer et al., 2022 **RISCC**).

***NOTE:*** *For more information on the role of methylation in the management of CIN2 lesions, please see Dovnik & Poljak (2023 **RISCC**).*

***Treatment for precancerous lesions includes only those listed above. As of July 2025, no recommendations exist on the use of any kind of therapies to treat HPV infections.***

More information and resources can be found here:
https://essencialsalut.gencat.cat/en/detalls/Article/infeccio-vph-tractament

## 4.2 Management of treated women

Compared with the general population, women adequately treated for HSIL/CIN2-3 are at high risk of disease recurrence but are also at higher risk of cervical cancer in the long term (Melnikow et al., 2009; Soutter et al., 2006).

Disease recurrence can be caused by:

- Persistent hrHPV infection after treatment, with or without residual HSIL/CIN2-3 in the margins of the excised cone or due to insufficient ablation
- The acquisition of a new hrHPV infection.

***NOTE:*** *The difference between residual or recurrent (de novo) disease is not always clear. In general, lesions found within a year post-treatment are usually considered residual, while those detected later or after an observation of absent CIN2+ are defined as recurrent.*

To detect residual/recurrent lesions that might progress to cervical cancer, adequate follow-up after treatment is recommended (Perkins et al., 2020; Sand et al., 2018). Most recurrences occur within the first 1-2 years, so initial follow-up is generally

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recommended at 6 months post-treatment (Perkins et al., 2020; Torné et al., 2015) with HPV testing due to its higher sensitivity than cytology or margins of the excised cone (Arbyn et al., 2017; Bomans et al., 2025).

**Did you know?**

DNA methylation is being explored for posttreatment monitoring to help identify women with residual/recurrent CIN that might require re-treatment (Dick et al., 2023 **RISCC**).

Even after early monitoring, treated women remain at increased risk for up to 25 years, especially those over 50 (Rebolj et al., 2012; Kocken et al., 2011; Melnikow et al., 2009; Prendiville & Sankaranarayanan, 2017). Continued follow-up every 3-5 years is recommended, extending screening beyond the upper screening age limit if necessary (Perkins et al., 2020; Prendiville & Sankaranarayanan, 2017; Torné et al., 2015).

**Did you know?**

HPV vaccines might reduce the risk of recurrent CIN2+ disease in women undergoing treatment for high-grade lesions (Kechagias et al., 2022). However, large scale, high quality randomised controlled trials are required to establish the level of effectiveness and cost of HPV vaccination in these women.

## 4.3 Cervical cancer screening guidelines

The previous units aimed to provide some guidance on how to potentially manage hrHPV-positive women including the potential use of triage, risk-based screening or treatment options for precancerous lesions. However, each setting needs to define its own cervical cancer screening guidelines. Global organisations such as the European Federation of Colposcopy (EFC) or the International Federation of Gynecology and Obstetrics (FIGO) provide recommended actions based on extensive reviews and can be used as sources for additional information.

For reference and potential consultation, the table below includes the links to the local cervical cancer screening guidelines from several countries:

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| Country | Name of the instrument | Link |
|---|---|---|
| **Croatia** | Proposal for the Protocol of the First Phase of the Reorganized National Cervical Cancer Early Detection Program | https://www.hzjz.hr/wp-content/uploads/2019/12/Prijedlog_protokola_reorganiziranog_programa_DRAFT-2.pdf |
| **Denmark** | Screening for Cervical Cancer. Recommendations | https://www.sst.dk/da/Udgivelser/2018/Screening-for-livmoderhalskraeft |
| **Estonia** | Cervical cancer screening - Tervisekassa | https://www.tervisekassa.ee/partnerile/raviasutusele/haiguste-ennetus/emakakaelavahi-soeluuring |
| **Finland** | Cervical cancer screening – Finnish Cancer Registry | https://cancerregistry.fi/screening/cervical-cancer-screening/ |
| **France** | Evaluation of human papillomavirus (HPV) research in primary screening of precancerous and cancerous lesions of the cervix and the role of double immunolabeling p16/Ki67 | https://www.has-sante.fr/jcms/c_2806160/fr/evaluation-de-la-recherche-des-papillomavirus-humains-hpv-en-depistage-primaire-des-lesions-precancereuses-et-cancereuses-du-col-de-l-uterus-et-de-la-place-du-double-immuno-marquage-p16/ki67 |
| **Germany** | What is the situation on cervical cancer screening in Germany as an European example ? - Prof. Dr. Thomas Iftner (Universitat Tubingen) | https://www.cocir.org/fileadmin/Events_2021/Cervical_18_March/7_-_Thomas_Iftner_-_COCIR-DITTA_Webinar_18032021.pdf |
| **Greece** | Cervical cancer screening in Greece (2000) | https://www.sciencedirect.com/science/article/abs/pii/S0959804900003142 |
| **Iceland** | Screening for abnormal cells in the cervix – Embaetti landlaeknis | https://assets.ctfassets.net/8k0h54kbe6bj/5yPF8RuUKriZJJDq1lZfdA/72f74d3d5bbd6b2096e507e645fe0786/Skimun_vegna_frumubreytinga_i_leghalsi_baeklingur2021_LOK_EN.pdf |
| **Ireland** | HPV Primary Screening Algorithm | https://www.cervicalcheck.ie//_fileupload/Health-professionals/HPV_Primary_Screening_Algorithm.pdf |
| **Italy** | Shared guidelines for the prevention of cervical cancer – National Institute of Health (ISS) | https://www.iss.it/-/snlg-prevenzione-carcinoma-cervice-uterina |
| **Latvia** | Cervical cancer screening in Latvia: A brief history and recent improvements (2009–2011) | https://s3-eu-west-1.amazonaws.com/thejournalhub/10.15570/archive/acta-apa-13-1/4.pdf |

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| Country | Name of the instrument | Link |
|---|---|---|
| **Lithuania** | Bulleting of Clinical Coding – Coding of services provided in the Cervical Cancer early diagnosis program recommendations | https://ligoniukasa.lrv.lt/uploads/ligoniukasa/documents/files/KKB%202022%20kovas%20Nr_%2032%20Gimdos%20kaklelio%20v%C4%97%C5%BEio%20ankstyvosios%20diagnostikos%20programoje%20numatyt%C5%B3%20paslaug%C5%B3%20kodavimo%20rekomendacijos.pdf |
| **Luxembourg** | Plan National Cancer Luxembourg 2014-2018 - Directives pour la Prévention et le Dépistage du Cancer du Col de l'Utérus | https://conseil-scientifique.public.lu/content/dam/conseil_scientifique/publications/col-de-l'ut%C3%A9rus/PNC-Directives-prevention-et-depistage-cancer-col-uterus.pdf |
| **Malta** | Primary HPV-based cervical cancer screening in Europe: implementation status, challenges, and future plans (2020) | https://www.sciencedirect.com/science/article/pii/S1198743X19304914#:~:text=Malta,women%20over%2030%20%5B33%5D. |
| **Poland** | The Polish Society of Gynecological Oncology Guidelines for the Diagnosis and Treatment of Cervical Cancer (v2024.0) | https://www.mdpi.com/2077-0383/13/15/4351 |
| **Portugal** | Budget impact analysis of cervical cancer screening in Portugal: comparison of cytology and primary HPV screening strategies | https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-019-6536-4 |
| **Slovakia** | Cervical cancer screening in Slovakia | https://www.noisk.sk/files/2020/2020-10-01-skrining-rakoviny-krcka-maternice-na-slovensku.pdf |
| **Slovenia** | Guidelines for the comprehensive treatment of women with precancerous changes of the cervix<br><br>Procedures for detection and treatment of women with | https://zora.onko-i.si/fileadmin/user_upload/publikacije/strokovna_priporocila/2011_Smernice_web.pdf<br><br>https://zora.onko-i.si/fileadmin/user_upload/publikacije/strokovna_priporocila/2011_Postopki_web.pdf |

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| Country | Name of the instrument | Link |
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| | precancerous changes of the cervix | |
| **Spain** | Spanish Association of cervical pathology and colposcopy (AEPCC) Prevención secundaria del cancer de cuello del útero, 2022. Conducta clínica ante resultados anormales de las pruebas de cribado | https://www.aepcc.org/wp-content/uploads/2022/11/Guia-Prevencion-cancer-cervix-2022.pdf |
| **Sweden** | The Swedish Cervical Screening Cohort | https://www.nature.com/articles/s41597-024-03519-2#:~:text=Today%2C%20the%20new%20recommendation%20states,50%20and%20701%2C2. |
| **The Netherlands** | Programme characteristics of the cervical cancer screening programme | https://www.rivm.nl/en/cervical-cancer-screening-programme/professionals/programme-characteristics |
| **United Kingdom** | Guidance<br>Cervical screening care pathway | https://www.gov.uk/government/publications/cervical-screening-care-pathway/cervical-screening-care-pathway |

In the following tables some relevant guidelines that comply with international standards are highlighted:

| Country | *Name of the instrument* | *Link* |
|---|---|---|
| **World Health Organization (WHO) - Human reproduction programme (hrp)** | WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition | https://iris.who.int/bitstream/handle/10665/342365/9789240030824-eng.pdf?sequence=1 |
| **Australia** | Important changes to the National Cervical Screening Program's Clinical Guidelines pathway for women at intermediate risk | https://www.health.gov.au/news/important-changes-to-the-national-cervical-screening-programs-clinical-guidelines-pathway-for-women-at-intermediate-risk |
| **Canada (Gynecologic Oncology Society of Canada (GOC), Society of Colposcopists of** | Canadian Guideline on the Management of a Positive Human Papillomavirus Test | https://screeningforlife.ca/wp-content/uploads/SOGC-Guidelines-HPV-and-Specific-Populations.pdf |

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| Country | *Name of the instrument* | *Link* |
|---|---|---|
| **Canada (SCC), and the Canadian Partnership Against Cancer.)** | and Guidance for Specific Populations | |
| | 2023 Canadian Colposcopy Guideline: A Risk-Based Approach to Management and Surveillance of Cervical Dysplasia | https://www.mdpi.com/1718-7729/30/6/431 |
| **China (Branch of Cancer Prevention and Control, Chinese Preventive Medicine Association, Chinese Obstetrics and Gynecology Association Colposcopy and Cervical Neoplasia Committee, Chinese Society of Colposcopy and Cervical Pathology of China Health Birth Science Association, Beijing Medical Doctor (Technician) Society of Laboratory Medicine)** | Chinese expert consensus on human papillomavirus nucleic acid testing for cervical cancer screening (2022) | https://rs.yiigle.com/cmaid/1452731 |
| **India (Federation of Obstetric and Gynaecological Societies of India)** | Screening and Management of Preinvasive Lesions of Cervix and HPV Vaccination | https://www.fogsi.org/wp-content/uploads/2018/03/FOGSI-GCPR-March-2018-final.pdf |
| **New Zealand** | National Cervical Screening Programme: HPV Primary Screening Clinical Pathway to Introduce Self-Testing | https://consult.health.govt.nz/nsu/hpv-primary-screening-self-testing/supporting_documents/nationalcervicalscreeningprogrammhpvprimaryscreeningclinicalpathwayintroduceselftestingpublicconsultation.pdf |
| **Singapur** | MANAGEMENT GUIDELINES FOR CERVICAL SCREENING & PREINVASIVE DISEASE OF THE CERVIX | https://platform.who.int/docs/default-source/mca-documents/policy-documents/guideline/SGP-RH-47-01-GUIDELINE-2019-eng-Clinical-Management- |

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| Country | *Name of the instrument* | *Link* |
|---|---|---|
| | | Guidelines-Cervical-Screening.pdf |
| **South Africa (South African HPV Advisory Board)** | Guidelines for cervical cancer screening in South Africa | https://journals.co.za/doi/pdf/10.10520/EJC-9584c6bc7 |
| **United States (American Society of Clinical Oncology)** | Secondary Prevention of Cervical Cancer: ASCO Resource–Stratified Guideline Update | https://ascopubs.org/doi/10.1200/GO.22.00217 |

**ACTIVITY**

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

1. All screen-detected lesions need to be treated (i.e., destroyed or removed).
2. In the future, methylation markers could be used to identify those lesions more likely to regress and therefore that could benefit from a follow-up management approach.
3. Women with previous lesions, even if treated, have a higher risk of residual/recurrent disease and cancer.

The correct answers are:

1 False, 2 True, 3 True.

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# SUMMARY

- In a risk-based approach, women are classified along a risk gradient based on screening and management history, vaccination status, and other individual factors. Clinical actions are aligned with predefined risk thresholds to enable more personalized management.
- Each country or setting should define its own clinical decision thresholds according to local epidemiology, resources, and acceptable levels of risk.
- Triage of hrHPV-positive women improves specificity and positive predictive value (PPV), helping to reduce unnecessary follow-ups, over-diagnosis, and over-treatment.
- For screen-triage-treat strategies, WHO recommends partial genotyping, colposcopy, VIA, cytology, or dual-stain cytology as triage methods after a positive HPV test.
- The benefits, harms, and programmatic costs of WHO-recommended triage options are broadly similar. Selection should be based on feasibility, training requirements, quality assurance capacity, and resource availability.
- Emerging triage strategies—such as extended genotyping, type-specific viral load, E6/E7 oncoproteins, mRNA, and methylation—are promising but require further validation before routine use.
- hrHPV-positive women with a negative triage result still require follow-up, until their risk returns to a level comparable to that of hrHPV-negative women.
- Precancerous lesions can be managed using ablative or excisional (surgical) methods, or monitored through follow-up, depending on the case.
- Women treated for HSIL/CIN2–3 remain at increased risk of recurrence and long-term cervical cancer, underscoring the need for further surveillance.

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# BIBLIOGRAPHY


Adcock, R., Cuzick, J., Hunt, W. C., McDonald, R. M., & Wheeler, C. M. (2019). Role of HPV Genotype, Multiple Infections, and Viral Load on the Risk of High-Grade Cervical Neoplasia. *Cancer Epidemiology and Prevention Biomarkers*, *28*(11), 1816-1824. https://doi.org/10.1158/1055-9965.EPI-19-0239

Andrae, B., Kemetli, L., Sparén, P., Silfverdal, L., Strander, B., Ryd, W., Dillner, J., & Törnberg, S. (2008). Screening-preventable cervical cancer risks: Evidence from a nationwide audit in Sweden. *Journal of the National Cancer Institute*, *100*(9), 622-629. https://doi.org/10.1093/jnci/djn099

Arbyn, M., Herbert, A., Schenck, U., Nieminen, P., Jordan, J., Mcgoogan, E., Patnick, J., Bergeron, C., Baldauf, J.-J., Klinkhamer, P., Bulten, J., & Martin-Hirsch, P. (2007). European guidelines for quality assurance in cervical cancer screening: Recommendations for collecting samples for conventional and liquid-based cytology. *Cytopathology*, *18*(3), 133-139. https://doi.org/10.1111/j.1365-2303.2007.00464.x

Arbyn, M., Redman, C. W. E., Verdoodt, F., Kyrgiou, M., Tzafetas, M., Ghaem-Maghami, S., Petry, K.-U., Leeson, S., Bergeron, C., Nieminen, P., Gondry, J., Reich, O., & Moss, E. L. (2017). Incomplete excision of cervical precancer as a predictor of treatment failure: A systematic review and meta-analysis. *The Lancet. Oncology*, *18*(12), 1665-1679. https://doi.org/10.1016/S1470-2045(17)30700-3

Arbyn, M., Rezhake, R., Yuill, S., & Canfell, K. (2020). Triage of HPV-positive women in Norway using cytology, HPV16/18 genotyping and HPV persistence. *British Journal of Cancer*, *122*(11), 1-3. https://doi.org/10.1038/s41416-020-0787-9

Arbyn, M., Xu, L., Verdoodt, F., Cuzick, J., Szarewski, A., Belinson, J. L., Wentzensen, N., Gage, J. C., & Khan, M. J. (2017). Genotyping for Human Papillomavirus Types 16 and 18 in Women With Minor Cervical Lesions: A Systematic Review and Meta-analysis. *Annals of Internal Medicine*, *166*(2), 118-127. https://doi.org/10.7326/M15-2735

Arroyo Mühr, L. S., Wang, J., Hassan, S. S., Yilmaz, E., Elfström, M. K., & Dillner, J. (2024). Nationwide registry-based trial of risk-stratified cervical screening. *International Journal of Cancer*. https://doi.org/10.1002/ijc.35142


*CC BY-NC-SA 4.0 – © 2025 The RISCC project consortium*

Athanasiou, A., Veroniki, A. A., Efthimiou, O., Kalliala, I., Naci, H., Bowden, S., Paraskevaidi, M., Arbyn, M., Lyons, D., Martin-Hirsch, P., Bennett, P., Paraskevaidis, E., Salanti, G., & Kyrgiou, M. (2022). Comparative effectiveness and risk of preterm birth of local treatments for cervical intraepithelial neoplasia and stage IA1 cervical cancer: A systematic review and network meta-analysis. *The Lancet Oncology*, *23*(8), 1097-1108. https://doi.org/10.1016/S1470-2045(22)00334-5

Befano, B., Kalpathy-Cramer, J., Egemen, D., Inturrisi, F., Jeronimo, J., Rodríguez, A. C., Campos, N., Cremer, M., Ribeiro, A., Ajenifuja, K. O., Goldstein, A., Haider, A., Yeates, K., Madeleine, M., Norris, T., Figueroa, J., Alfaro, K., Raiol, T., Adepiti, C., … PAVE Consortium. (2025). Initial evaluation of a new cervical screening strategy combining human papillomavirus genotyping and automated visual evaluation: The Human Papillomavirus-Automated Visual Evaluation Consortium. *Journal of the National Cancer Institute*, djaf054. https://doi.org/10.1093/jnci/djaf054

Bomans, L., Ramirez, A. T., Hillemanns, P., Gultekin, M., & Arbyn, M. (2025). Prediction of Treatment Failure After Excisional Treatment of Cervical Precancer: A Systematic Review and Meta-analysis. *Obstetrics and Gynecology*. https://doi.org/10.1097/AOG.0000000000005997

Bowden, S. J., Kalliala, I., Veroniki, A. A., Arbyn, M., Mitra, A., Lathouras, K., Mirabello, L., Chadeau-Hyam, M., Paraskevaidis, E., Flanagan, J. M., & Kyrgiou, M. (2019). The use of human papillomavirus DNA methylation in cervical intraepithelial neoplasia: A systematic review and meta-analysis. *EBioMedicine*, *50*, 246-259. https://doi.org/10.1016/j.ebiom.2019.10.053

Burdier, F. R., Waheed, D.-N., Nedjai, B., Steenbergen, R. D. M., Poljak, M., Baay, M., Vorsters, A., & Van Keer, S. (2024). DNA methylation as a triage tool for cervical cancer screening – A meeting report. *Preventive Medicine Reports*, *41*, 102678. https://doi.org/10.1016/j.pmedr.2024.102678

Castle, P. E., Kinney, W. K., Xue, X., Cheung, L. C., Gage, J. C., Zhao, F.-H., Fetterman, B., Poitras, N. E., Lorey, T. S., Wentzensen, N., Katki, H. A., & Schiffman, M. (2018). Effect of Several Negative Rounds of Human Papillomavirus and Cytology Co-testing on Safety Against Cervical Cancer: An Observational Cohort Study. *Annals of Internal Medicine*, *168*(1), 20-29. https://doi.org/10.7326/M17-1609

*CC BY-NC-SA 4.0 – © 2025 The RISCC project consortium*

Cuschieri, K., Ronco, G., Lorincz, A., Smith, L., Ogilvie, G., Mirabello, L., Carozzi, F., Cubie, H., Wentzensen, N., Snijders, P., Arbyn, M., Monsonego, J., & Franceschi, S. (2018). Eurogin roadmap 2017: Triage strategies for the management of HPV-positive women in cervical screening programs. *International Journal of Cancer*, *143*(4), 735-745. https://doi.org/10.1002/ijc.31261

Dick, S., Heideman, D. A. M., Mom, C. H., Meijer, C. J. L. M., Berkhof, J., Steenbergen, R. D. M., & Bleeker, M. C. G. (2023). Methylation testing for the detection of recurrent cervical intraepithelial neoplasia. *International Journal of Cancer*, *153*(12), 2011-2018. https://doi.org/10.1002/ijc.34678

Dovnik, A., & Poljak, M. (2023). The Role of Methylation of Host and/or Human Papillomavirus (HPV) DNA in Management of Cervical Intraepithelial Neoplasia Grade 2 (CIN2) Lesions. *International Journal of Molecular Sciences*, *24*(7), Article 7. https://doi.org/10.3390/ijms24076479

Downham, L., Jaafar, I., Rol, M. L., Nyawira Nyaga, V., Valls, J., Baena, A., Zhang, L., Gunter, M. J., Arbyn, M., & Almonte, M. (2023). Accuracy of HPV E6/E7 oncoprotein tests to detect high-grade cervical lesions: A systematic literature review and meta-analysis. *British Journal of Cancer*, 1-9. https://doi.org/10.1038/s41416-023-02490-w

Downham, L., Rol, M. L., Forestier, M., Romero, P., Mendoza, L., Mongelós, P., Picconi, M. A., Colucci, M. C., Padin, V. M., Flores, A. P., Zúñiga, M., Ferrera, A., Cabrera, Y., Crispín, M. F., Ramirez, A. T., Cele, L., Diop-Ndiaye, H., Samaté, D., Manga, P., … Almonte, M. (2024). Field experience with the 8-HPV-type oncoprotein test for cervical cancer screening among HPV-positive women living with and without HIV in LMICs. *International Journal of Cancer*. https://doi.org/10.1002/ijc.34953

Dun, C., Yuan, M., Zhao, X., Hu, S., Arbyn, M., & Zhao, F. (2024). Clinical evaluation of primary human papillomavirus (HPV) testing with extended HPV genotyping triage for cervical cancer screening: A pooled analysis of individual patient data from nine population-based cervical cancer screening studies from China. *Cancer Medicine*, *13*(11), e7316. https://doi.org/10.1002/cam4.7316

Egemen, D., Cheung, L. C., Chen, X., Demarco, M., Perkins, R. B., Kinney, W., Poitras, N., Befano, B., Locke, A., Guido, R. S., Wiser, A. L., Gage, J. C., Katki, H. A., Wentzensen, N., Castle, P. E., Schiffman, M., & Lorey, T. S. (2020). Risk Estimates Supporting the 2019 ASCCP Risk-Based Management Consensus Guidelines. *Journal of Lower*

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*Genital Tract Disease*, *24*(2), 132-143. https://doi.org/10.1097/LGT.0000000000000529

Fu Xi, L., Schiffman, M., Ke, Y., Hughes, J. P., Galloway, D. A., He, Z., Hulbert, A., Winer, R. L., Koutsky, L. A., & Kiviat, N. B. (2017). Type-dependent association between risk of cervical intraepithelial neoplasia and viral load of oncogenic human papillomavirus types other than types 16 and 18. *International Journal of Cancer*, *140*(8), 1747-1756. https://doi.org/10.1002/ijc.30594

Gilham, C., Sargent, A., & Peto, J. (2020). Triaging women with human papillomavirus infection and normal cytology or low-grade dyskaryosis: Evidence from 10-year follow up of the ARTISTIC trial cohort. *BJOG: An International Journal of Obstetrics & Gynaecology*, *127*(1), 58-68. https://doi.org/10.1111/1471-0528.15957

Gök, M., Heideman, D. A. M., van Kemenade, F. J., de Vries, A. L. M., Berkhof, J., Rozendaal, L., Beliën, J. A. M., Overbeek, L., Babović, M., Snijders, P. J. F., & Meijer, C. J. L. M. (2012). Offering self-sampling for human papillomavirus testing to non-attendees of the cervical screening programme: Characteristics of the responders. *European Journal of Cancer*, *48*(12), 1799-1808. https://doi.org/10.1016/j.ejca.2011.11.022

Gravitt, P., Kovacic, M. B., Herrero, R., Schiffman, M., Bratti, C., Hildesheim, A., Morales, J., Alfaro, M., Sherman, M., Wacholder, S., Rodríguez, A., & Burk, R. (2007). High load for most high risk human papillomavirus genotypes is associated with prevalent cervical cancer precursors but only HPV16 load predicts the development of incident disease. *International journal of cancer*. https://doi.org/10.1002/ijc.23012

IARC. (2022). *Cervical Cancer Screening* (Vol. 18). IARC Press. http://www.iarc.fr/en/publications/pdfs-online/prev/handbook10/

Ibáñez, R., Alejo, M., Combalia, N., Tarroch, X., Autonell, J., Codina, L., Culubret, M., Bosch, F. X., & de Sanjosé, S. (2015). Underscreened Women Remain Overrepresented in the Pool of Cervical Cancer Cases in Spain: A Need to Rethink the Screening Interventions. *BioMed Research International*, *2015*, 605375. https://doi.org/10.1155/2015/605375

Inturrisi, F., Rozendaal, L., Veldhuijzen, N. J., Heideman, D. A. M., Meijer, C. J. L. M., & Berkhof, J. (2022). Risk of cervical precancer among HPV–negative women in the

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Netherlands and its association with previous HPV and cytology results: A follow-up analysis of a randomized screening study. *PLOS Medicine*, *19*(10), e1004115. https://doi.org/10.1371/journal.pmed.1004115

Katki, H. A., Kinney, W. K., Fetterman, B., Lorey, T., Poitras, N. E., Cheung, L., Demuth, F., Schiffman, M., Wacholder, S., & Castle, P. E. (2011). Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: A population-based study in routine clinical practice. *The Lancet Oncology*, *12*(7), 663-672. https://doi.org/10.1016/S1470-2045(11)70145-0

Katki, H. A., Schiffman, M., Castle, P., Fetterman, B., Poitras, N., Lorey, T., Cheung, L., Raine-Bennett, T., Gage, J., & Kinney, W. (2013). Benchmarking CIN 3+ Risk as the Basis for Incorporating HPV and Pap Cotesting into Cervical Screening and Management Guidelines. *Journal of Lower Genital Tract Disease*, *17*, S28-S35. https://doi.org/10.1097/LGT.0b013e318285423c

Kechagias, K. S., Kalliala, I., Bowden, S. J., Athanasiou, A., Paraskevaidi, M., Paraskevaidis, E., Dillner, J., Nieminen, P., Strander, B., Sasieni, P., Veroniki, A. A., & Kyrgiou, M. (2022). Role of human papillomavirus (HPV) vaccination on HPV infection and recurrence of HPV related disease after local surgical treatment: Systematic review and meta-analysis. *BMJ (Clinical Research Ed.)*, *378*, e070135. https://doi.org/10.1136/bmj-2022-070135

Kelly, H., Benavente, Y., Pavon, M. A., De Sanjose, S., Mayaud, P., & Lorincz, A. T. (2019). Performance of DNA methylation assays for detection of high-grade cervical intraepithelial neoplasia (CIN2+): A systematic review and meta-analysis. *British Journal of Cancer*, *121*(11), 954-965. https://doi.org/10.1038/s41416-019-0593-4

Kocken, M., Helmerhorst, T. J. M., Berkhof, J., Louwers, J. A., Nobbenhuis, M. A. E., Bais, A. G., Hogewoning, C. J. A., Zaal, A., Verheijen, R. H. M., Snijders, P. J. F., & Meijer, C. J. L. M. (2011). Risk of recurrent high-grade cervical intraepithelial neoplasia after successful treatment: A long-term multi-cohort study. *The Lancet Oncology*, *12*(5), 441-450. https://doi.org/10.1016/S1470-2045(11)70078-X

Kremer, W. W., Dick, S., Heideman, D. A. M., Steenbergen, R. D. M., Bleeker, M. C. G., Verhoeve, H. R., van Baal, W. M., van Trommel, N., Kenter, G. G., Meijer, C. J. L. M., & Berkhof, J. (2022). Clinical Regression of High-Grade Cervical Intraepithelial Neoplasia Is Associated With Absence of FAM19A4/miR124-2 DNA Methylation

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(CONCERVE Study). *Journal of Clinical Oncology*, JCO.21.02433. https://doi.org/10.1200/JCO.21.02433

Kroon, K. R., Bogaards, J. A., Heideman, D. AM., Meijer, C. JLM., & Berkhof, J. (2024). Colposcopy referral and CIN3+ risk of human papillomavirus genotyping strategies in cervical cancer screening. *Cancer Epidemiology, Biomarkers & Prevention*. https://doi.org/10.1158/1055-9965.EPI-24-0046

Lorincz, A. T. (2016). Virtues and Weaknesses of DNA Methylation as a Test for Cervical Cancer Prevention. *Acta Cytologica*, *60*(6), 501-512. https://doi.org/10.1159/000450595

Louvanto, K., Aro, K., Nedjai, B., Bützow, R., Jakobsson, M., Kalliala, I., Dillner, J., Nieminen, P., & Lorincz, A. (2019). Methylation in Predicting Progression of Untreated High-grade Cervical Intraepithelial Neoplasia. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *70*(12), 2582. https://doi.org/10.1093/cid/ciz677

Melnikow, J., McGahan, C., Sawaya, G. F., Ehlen, T., & Coldman, A. (2009). Cervical intraepithelial neoplasia outcomes after treatment: Long-term follow-up from the British Columbia Cohort Study. *Journal of the National Cancer Institute*, *101*(10), 721-728. https://doi.org/10.1093/jnci/djp089

Norman, I., Yilmaz, E., Hjerpe, A., Hortlund, M., Elfström, K. M., & Dillner, J. (2022). Atypical glandular cells and development of cervical cancer: Population-based cohort study. *International Journal of Cancer*, *151*(11), 2012-2019. https://doi.org/10.1002/ijc.34242

Oštrbenk Valenčak, A., Kroon, K. R., Fabjan, D., Mlakar, J., Seme, K., Berkhof, J., & Poljak, M. (2024). Clinically validated HPV assays offer comparable long-term safety in primary cervical cancer screening: A 9-year follow-up of a population-based screening cohort. *International Journal of Cancer*. https://doi.org/10.1002/ijc.35200

Peeling, R. W. (2015). Diagnostics in a digital age: An opportunity to strengthen health systems and improve health outcomes. *International Health*, *7*(6), 384-389. https://doi.org/10.1093/inthealth/ihv062

Peeters, E., Wentzensen, N., Bergeron, C., & Arbyn, M. (2019). Meta-analysis of the accuracy of p16 or p16/Ki-67 immunocytochemistry versus HPV testing for the

*CC BY-NC-SA 4.0 – © 2025 The RISCC project consortium*

detection of CIN2+/CIN3+ in triage of women with minor abnormal cytology. *Cancer Cytopathology*, *0*(0). https://doi.org/10.1002/cncy.22103

Perkins, R. B., Guido, R. S., Castle, P. E., Chelmow, D., Einstein, M. H., Garcia, F., Huh, W. K., Kim, J. J., Moscicki, A.-B., Nayar, R., Saraiya, M., Sawaya, G. F., Wentzensen, N., Schiffman, M., & Committee, for the 2019 A. R.-B. M. C. G. (2020). 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. *Journal of Lower Genital Tract Disease*, *24*(2), 102-131. https://doi.org/10.1097/LGT.0000000000000525

Polman, N. J., Snijders, P. J. F., Kenter, G. G., Berkhof, J., & Meijer, C. J. L. M. (2019). HPV-based cervical screening: Rationale, expectations and future perspectives of the new Dutch screening programme. *Preventive Medicine*, *119*, 108-117. https://doi.org/10.1016/j.ypmed.2018.12.021

Prendiville, W., & Sankaranarayanan, R. (2017). Colposcopy and Treatment of Cervical Precancer. En *IARC Technical Report* (Vol. 45, Número 45). IARC Technical Publications; 45.

Rebolj, M., Helmerhorst, T., Habbema, D., Looman, C., Boer, R., Van Rosmalen, J., & Van Ballegooijen, M. (2012). Risk of cervical cancer after completed post-treatment follow-up of cervical intraepithelial neoplasia: Population based cohort study. *BMJ (Online)*, *345*(7882), 1-11. https://doi.org/10.1136/bmj.e6855

Rezende, M. T., Bianchi, A. G. C., & Carneiro, C. M. (2021). Cervical cancer: Automation of Pap test screening. *Diagnostic Cytopathology*, *49*(4), 559-574. https://doi.org/10.1002/dc.24708

Rezhake, R., Chen, F., Hu, S.-Y., Zhao, X.-L., Zhang, X., Cao, J., Qiao, Y.-L., Zhao, F.-H., & Arbyn, M. (2020). Triage options to manage high-risk human papillomavirus-positive women: A population-based cross-sectional study from rural China. *International Journal of Cancer*, *147*(8), 2053-2064. https://doi.org/10.1002/ijc.33001

Ronco, G., Giorgi-Rossi, P., Carozzi, F., Confortini, M., Dalla Palma, P., Del Mistro, A., Ghiringhello, B., Girlando, S., Gillio-Tos, A., De Marco, L., Naldoni, C., Pierotti, P., Rizzolo, R., Schincaglia, P., Zorzi, M., Zappa, M., Segnan, N., Cuzick, J., & New Technologies for Cervical Cancer screening (NTCC) Working Group. (2010). Efficacy of human papillomavirus testing for the detection of invasive cervical

*CC BY-NC-SA 4.0 – © 2025 The RISCC project consortium*

cancers and cervical intraepithelial neoplasia: A randomised controlled trial. *The Lancet. Oncology*, *11*(3), 249-257. https://doi.org/10.1016/S1470-2045(09)70360-2

Sand, F. L., Frederiksen, K., Munk, C., Jensen, S. M., & Kjær, S. K. (2018). Long-term risk of cervical cancer following conization of cervical intraepithelial neoplasia grade 3—A Danish nationwide cohort study. *International Journal of Cancer*, *142*(9), 1759-1766. https://doi.org/10.1002/ijc.31202

Schiffman, M., Wentzensen, N., Perkins, R. B., & Guido, R. S. (2020). An Introduction to the 2019 ASCCP Risk-Based Management Consensus Guidelines. *Journal of Lower Genital Tract Disease*, *24*(2), 87-89. https://doi.org/10.1097/LGT.0000000000000531

Schmitt, M., Depuydt, C., Benoy, I., Bogers, J., Antoine, J., Arbyn, M., Pawlita, M., & VALGENT Study Group. (2013). Multiple human papillomavirus infections with high viral loads are associated with cervical lesions but do not differentiate grades of cervical abnormalities. *Journal of Clinical Microbiology*, *51*(5), 1458-1464. https://doi.org/10.1128/JCM.00087-13

Smith, M. A., Sherrah, M., Sultana, F., Castle, P. E., Arbyn, M., Gertig, D., Caruana, M., Wrede, C. D., Saville, M., & Canfell, K. (2022). National experience in the first two years of primary human papillomavirus (HPV) cervical screening in an HPV vaccinated population in Australia: Observational study. *BMJ (Clinical Research Ed.)*, *376*, e068582. https://doi.org/10.1136/bmj-2021-068582

Soutter, W. P., Sasieni, P., & Panoskaltsis, T. (2006). Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. *International Journal of Cancer*, *118*(8), 2048-2055. https://doi.org/10.1002/ijc.21604

Stanczuk, G. A., Currie, H., Forson, W., Baxter, G., Lawrence, J., Wilson, A., Palmer, T., Arbyn, M., & Cuschieri, K. (2021). Self-sampling as the principal modality for population based cervical screening: Five-year follow-up of the PaVDaG study. *International Journal of Cancer*, *n/a*(n/a). https://doi.org/10.1002/ijc.33888

Steenbergen, R. D. M., Snijders, P. J. F., Heideman, D. A. M., & Meijer, C. J. L. M. (2014). Clinical implications of (epi)genetic changes in HPV-induced cervical

*CC BY-NC-SA 4.0 – © 2025 The RISCC project consortium*

precancerous lesions. *Nature Reviews Cancer*, *14*(6), 395-405. https://doi.org/10.1038/nrc3728

Torné, A., del Pino, M., Cusidó, M., Alameda, F., Andia, D., Castellsagué, X., Cortés, J., Granados, R., Guarch, R., LLoveras, B., Lubrano, A., Martínez-Escorizal, J., Ordi, J., Puig-Tintorén, J., Ramírez, M., de Sanjosé, S., Torrejón, R., Bosch, X., Piris, M., … Comino, R; Lailla, JM; Ponce, J. (2015). AEPCC-Guía: Prevención del cáncer de cuello de útero 2014. *Publicaciones AEPCC*, 1-55.

Verhoef, L., Bleeker, M. C. G., Polman, N., Steenbergen, R. D. M., Ebisch, R. M. F., Melchers, W. J. G., Bekkers, R. L. M., Molijn, A. C., Quint, W. G., Van Kemenade, F., Meijer, C. J. L. M., Berkhof, J., & Heideman, D. A. M. (2023). Evaluation of DNA methylation biomarkers ASCL1 and LHX8 on HPV-positive self-collected samples from primary HPV-based screening. *British Journal of Cancer*, *129*(1), Article 1. https://doi.org/10.1038/s41416-023-02277-z

Verhoef, L., Bleeker, M. C. G., Polman, N., Steenbergen, R. D. M., Meijer, C. J. L. M., Melchers, W. J. G., Bekkers, R. L., Molijn, A. C., Quint, W. G., van Kemenade, F. J., Berkhof, J., & Heideman, D. A. M. (2022). Performance of DNA methylation analysis of ASCL1, LHX8, ST6GALNAC5, GHSR, ZIC1 and SST for the triage of HPV-positive women: Results from a Dutch primary HPV-based screening cohort. *International Journal of Cancer*, *150*(3), 440-449. https://doi.org/10.1002/ijc.33820

von Karsa, L., Arbyn, M., De Vuyst, H., Dillner, J., Dillner, L., Franceschi, S., Patnick, J., Ronco, G., Segnan, N., Suonio, E., Törnberg, S., & Anttila, A. (2015). European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. *Papillomavirus Research*, *1*, 22-31. https://doi.org/10.1016/j.pvr.2015.06.006

Wang, J., Elfstrom, K., Borgfeldt, C., & Dillner, J. (2021). A pilot study of risk-stratified cervical cancer screening [version 2; peer review: 2 approved]. *Open Research Europe*, *1*(84). https://doi.org/10.12688/openreseurope.13398.2

Wentzensen, N., Clarke, M. A., Bremer, R., Poitras, N., Tokugawa, D., Goldhoff, P. E., Castle, P. E., Schiffman, M., Kingery, J. D., Grewal, K. K., Locke, A., Kinney, W., & Lorey, T. S. (2019). Clinical Evaluation of Human Papillomavirus Screening With p16/Ki-67 Dual Stain Triage in a Large Organized Cervical Cancer Screening Program. *JAMA Internal Medicine*. https://doi.org/10.1001/jamainternmed.2019.0306

*CC BY-NC-SA 4.0 – © 2025 The RISCC project consortium*

Wentzensen, N., Lahrmann, B., Clarke, M. A., Kinney, W., Tokugawa, D., Poitras, N., Locke, A., Bartels, L., Krauthoff, A., Walker, J., Zuna, R., Grewal, K. K., Goldhoff, P. E., Kingery, J. D., Castle, P. E., Schiffman, M., Lorey, T. S., & Grabe, N. (2021). Accuracy and Efficiency of Deep-Learning-Based Automation of Dual Stain Cytology in Cervical Cancer Screening. *Journal of the National Cancer Institute*, *113*(1), 72-79. https://doi.org/10.1093/jnci/djaa066

Yilmaz, E., Lagheden, C., Ghaderi, M., Wang, J., Dillner, J., & Elfström, K. M. (2023). Assessment of Human Papillomavirus Non-16/18, Type-Specific Risk for Cervical Intraepithelial Neoplasia Grade 3 or Worse Among Women With Cervical Atypical Glandular Cells. *Obstetrics & Gynecology*, *142*(3), 679. https://doi.org/10.1097/AOG.0000000000005286

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