WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition: use of mRNA tests for human papillomavirus (HPV)

Web Annex. Evidence-to-decision framework for mRNA testing for HPV
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## Evidence-to-decision table

### Population, intervention, comparators and outcomes

<table>
<thead>
<tr>
<th>Question</th>
<th>POPULATION</th>
<th>INTERVENTION</th>
<th>COMPARATORS</th>
<th>MAIN OUTCOMES</th>
<th>PERSPECTIVE</th>
<th>BACKGROUND</th>
<th>CONFLICT OF INTEREST</th>
</tr>
</thead>
</table>
| Should HPV mRNA versus HPV DNA or VIA or cytology in a screen-and-treat strategy be used in women? | General population of women and women living with HIV                        | HPV mRNA detection            | Other tests (HPV DNA, VIA, cytology)              | • Cervical cancer  
• Mortality  
• High-grade cervical intraepithelial neoplasia or worse (CIN2+)  
• HPV infection  
• Preterm birth (early/late)  
• Pre-cancer treatments  
• Adverse events (direct consequences of pre-cancer treatments): major infections or bleeding, procedure-associated pain, cervical stenosis, infertility, spontaneous abortion (first trimester/second trimester), perinatal deaths, premature rupture of membrane, unnecessary interventions, increased viral shedding in women living with HIV  
• Costs (number of tests)  
• Equity  
• Acceptability  
• Feasibility (coverage of treatment, coverage of screening) | Population                                                                  | The following algorithms were considered when using HPV mRNA detection as the primary screening test:  
1. HPV mRNA as the primary screening test, followed by treatment  
2. HPV mRNA as the primary screening test, followed by VIA triage, followed by treatment  
3. HPV mRNA as the primary screening test, followed by colposcopy triage, followed by treatment  
4. HPV mRNA as the primary screening test, followed by cytology triage, followed by colposcopy and treatment | None                                                                         |
Assessment

Desirable effects
How substantial are the desirable anticipated effects?

**JUDGEMENT**

- Trivial
- Small
- Moderate
- Large
- Varies
- Don’t know

**RESEARCH EVIDENCE**

**GENERAL POPULATION Outcomes from longitudinal studies**


Long-term data suggest that women who test negative for HPV mRNA may have a higher subsequent incidence of CIN3+ than those who test negative for HPV DNA, especially over longer screening intervals (5+ years), but the data are sparse and the findings are inconsistent across studies (low-certainty evidence).


Review of the literature found relative sensitivity and specificity for CIN2+ are 0.97 (95% CI: 0.95–1.00) and 1.03 (95% CI: 1.02–1.05), and for CIN3+ are 0.98 (95% CI: 0.95–1.02) and 1.03 (95% CI: 1.01–1.06) (moderate-certainty evidence).

The GDG agreed that there are trivial differences between using HPV mRNA and HPV DNA as primary screening tests. The GDG agreed that there may be a risk of higher incidence of CIN3+ in the long term. The GDG agreed that the relative accuracy of HPV mRNA tests is similar or slightly lower than HPV DNA test. The GDG also agreed that there may be similar reductions in cervical cancer incidence and deaths when using HPV mRNA testing with or without triage compared with HPV DNA testing, but there may be fewer pre-cancer lesion treatments when using HPV mRNA testing.

The GDG agreed that the evidence from the general population would not apply to women living with HIV.

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### HPV RNA vs DNA tests in CC screening

**Relative accuracy to detect CIN2+**

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparator</th>
<th>Design</th>
<th>n</th>
<th>hHrHPV mRNA tests vs validated hHrHPV DNA</th>
<th>n</th>
<th>hHrHPV DNA, outcome CIN2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>JPHR 2019</td>
<td>HC2</td>
<td>I</td>
<td>1</td>
<td>0.98 (0.95, 1.00)</td>
<td>1</td>
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<tr>
<td>Meehan 2019</td>
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<tr>
<td>6:1 A:1 B:1</td>
<td>HC2</td>
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**Relative accuracy to detect CIN3+**

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Source: El-Naggar 2017 CIN3+.

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**ADDITIONAL CONSIDERATIONS**

The GDG agreed that the evidence from the general population would not apply to women living with HIV.

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Source: El-Naggar 2017 CIN3+.
## Desirable effects

### How substantial are the desirable anticipated effects?

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Detection rate over time</strong>&lt;br&gt;Systematic review of the evidence (low certainty: inconsistent across studies, and little data from the studies)</td>
<td>![Graph showing detection rate ratio (DDR) of CIN3+] (observed in 2nd round, among women who were APIMA- vs DNA- at baseline)</td>
<td>![Zorzi, 2019: separate screening cohorts, no matched DNA &amp; RNA testing](Source: Zorzi M, Del Mistro A, Giorgi Rossi P, Laurino L, Battagello J, Lorio M, et al. Risk of CIN2 or more severe lesions after negative HPV-mRNA E6/E7 overexpression assay and after negative HPV-DNA test: concurrent cohorts with a 5-year follow-up. <em>Int J Cancer</em>. 2020 Jun 1;146(11):3114–23. doi:10.1002/ijc.32695.)</td>
</tr>
</tbody>
</table>

**Modelling**<br>The model used data extracted from the cross-sectional studies in the systematic review on sensitivity and specificity, and was validated against the available longitudinal evidence.<br><br>HPV mRNA testing compared with HPV DNA testing at 5-year screening intervals:<br>- 8–12% higher relative cervical cancer incidence<br>- 6–8% higher cervical cancer mortality<br>- 27–33% fewer pre-cancer treatments<br>- lower costs (6–10% lower)<br><br**HPV mRNA detection vs VIA or cytology screening**<br>- greater reductions in cervical cancer incidence and mortality

See Summary Table below.
Desirable effects
How substantial are the desirable anticipated effects?

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<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-collected vs provider-collected samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relative accuracy (self/clin) for CIN2+</strong> (mRNA: APTIMA)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**APTIMA on self- vs clinician-toke samples**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CIN2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>study</td>
<td>setting</td>
</tr>
<tr>
<td>Nnave, 2013</td>
<td>screening</td>
</tr>
<tr>
<td>Demeuere, 2015</td>
<td>high-risk group</td>
</tr>
<tr>
<td>Cheminot, 2014</td>
<td>follow-up</td>
</tr>
<tr>
<td>Aschili, 2010</td>
<td>follow-up</td>
</tr>
<tr>
<td>Overall (2 x 32%, p &lt; 0.001)</td>
<td></td>
</tr>
</tbody>
</table>

WOMEN LIVING WITH HIV
No evidence was found for women living with HIV.

Table: Summary table of effects based on modelling

<table>
<thead>
<tr>
<th>Screening ages</th>
<th>Cervical cancer double* (%)</th>
<th>Cervical cancer single* (%)</th>
<th>NMT in event &amp; survival cancers (yrs)</th>
<th>Discounted lifetime cost ($AUD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No screening</td>
<td>1.00 (1.00)</td>
<td>1.00 (1.00)</td>
<td>1.00 (1.00)</td>
<td>1.00 (1.00)</td>
</tr>
<tr>
<td>Primary VIA stage 0</td>
<td>54.5 (55.5)</td>
<td>44.3 (45.3)</td>
<td>1.02 (1.02)</td>
<td>1.02 (1.02)</td>
</tr>
<tr>
<td>Primary VIA stage 1</td>
<td>72.1 (73.1)</td>
<td>57.5 (58.5)</td>
<td>1.04 (1.04)</td>
<td>1.04 (1.04)</td>
</tr>
<tr>
<td>Primary VIA stage 2</td>
<td>58.5 (59.5)</td>
<td>47.4 (48.4)</td>
<td>1.07 (1.07)</td>
<td>1.07 (1.07)</td>
</tr>
<tr>
<td>Primary VIA stage 3</td>
<td>80.4 (81.4)</td>
<td>63.2 (64.2)</td>
<td>1.10 (1.10)</td>
<td>1.10 (1.10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screening ages</th>
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</thead>
<tbody>
<tr>
<td>Self-collected</td>
<td>54.5 (55.5)</td>
<td>44.3 (45.3)</td>
<td>1.02 (1.02)</td>
<td>1.02 (1.02)</td>
</tr>
<tr>
<td>Provider-collected</td>
<td>72.1 (73.1)</td>
<td>57.5 (58.5)</td>
<td>1.04 (1.04)</td>
<td>1.04 (1.04)</td>
</tr>
<tr>
<td>Overall</td>
<td>80.4 (81.4)</td>
<td>63.2 (64.2)</td>
<td>1.10 (1.10)</td>
<td>1.10 (1.10)</td>
</tr>
</tbody>
</table>

*Outcomes represent total events over the lifetime of a cohort of 100,000 women.
### Undesirable effects

How substantial are the undesirable anticipated effects?

- Large
- Moderate
- Small
- Trivial
- Varies
- Don’t know

### Certainty of evidence

What is the overall certainty of the evidence of effects?

- Very low
- Low
- Moderate
- High
- No included studies

### Values

Is there important uncertainty about or variability in how much people value the main outcomes?

- Important uncertainty or variability
- Possibly important uncertainty or variability
- Probably no important uncertainty or variability
- No important uncertainty or variability

The outcomes previously identified in the 2013 first edition of the WHO screening and treatment guidelines, using methods from the *WHO handbook for guideline development*, were agreed on by the GDG as the outcomes of importance for these new PICO questions.

A systematic review of qualitative research was conducted and included 43 studies. There was, however, very little data reporting the value of the outcomes (data was primarily about the acceptability of the different tests and treatments – see below).

The GDG agreed that greater weight should be placed on reducing cervical cancers.

### Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

- Favours the comparison
- Probably favours the comparison
- Does not favour either the intervention or the comparison
- Probably favours the intervention
- Favours the intervention
- Varies
- Don’t know
### Resources required
How large are the resource requirements (costs)?

- Large costs
- Moderate costs
  - Negligible costs and savings
- Moderate savings
- Large savings
- Varies
- Don't know

The test prices are generally in the same range in high-income countries and both require large equipment.

### Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

- Very low
- Low
- Moderate
- High
- No included studies

### Cost-effectiveness
Does the cost-effectiveness of the intervention favour the intervention or the comparison?

- Favours the comparison
- Probably favours the comparison
- Does not favour either the intervention or the comparison
- Probably favours the intervention
- Favours the intervention
- Varies
- No included studies

The cost-effectiveness was modelled (see figure below).

The GDG agreed that the cost-effectiveness of algorithms using HPV mRNA primary screening was similar to algorithms using HPV DNA testing.
### JUDGEMENT

**Equity**

What would be the impact on health equity?

<table>
<thead>
<tr>
<th>Reduced</th>
<th>Probably reduced</th>
<th>Probably no impact</th>
<th>Probably increased</th>
<th>Increased</th>
<th>Varies</th>
<th>Don’t know</th>
</tr>
</thead>
</table>

No research evidence.

While there is no evidence yet, the GDG agreed that providing HPV mRNA testing would be similar to HPV DNA testing and therefore may lead to greater access to screening compared with VIA or cytology.

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### Acceptability

Is the intervention acceptable to key stakeholders?

<table>
<thead>
<tr>
<th>No</th>
<th>Probably no</th>
<th>Probably yes</th>
<th>Yes</th>
<th>Varies</th>
<th>Don’t know</th>
</tr>
</thead>
</table>

The evidence gathered for HPV DNA testing was used as the GDG agreed that it was similar to the evidence for HPV mRNA testing.

Below is a summary of the relevant evidence for HPV DNA testing:

**A survey of GDG members** was conducted to explore concerns about costs and integration of different algorithms:

- respondents were moderately to very concerned about the ability to finance ALL algorithms (cytology > HPV > VIA) for scale-up and sustainability
- more were very concerned about the ability to minimize costs to patients for HPV and cytology algorithms.
A survey of 561 women was conducted online via SurveyMonkey in 2020, and was completed anonymously. All women aged 15 years and older, regardless of their prior cervical cancer screening or treatment status, were eligible to participate.

The survey results indicated that:
- Most women (83%) in the general population stated that they would not face problems in attending a screening programme.
- There was clear and strong preference for immediate treatment following a diagnosis of a cervical intraepithelial lesion (78%) among all women.
- Follow-up visits after treatment for a cervical lesion were likely to cause difficulties to the respondents.
- There was aversion to the use of a speculum during screening.
- The community requests better counselling, patient education and more availability of choices of treatment and screening tests.

A systematic review of qualitative studies was conducted and included 43 studies. The results showed that the studies consistently demonstrate very high acceptability (70% or higher, several with 90%) across the studies for self-sampling, VIA, HPV DNA tests or a triage-based method. Studies also showed that women desired to decide whether to receive treatment, few said they would prefer to consult with their partner and few felt obligated to consult with their partner prior to treatment. Factors lowering acceptability included lack of reminders, payment for test, no tertiary education, no children, recent HIV diagnosis, poor awareness of cervical cancer, poor provider–patient relationships.

A systematic review of reviews of provider perspectives on VIA and HPV testing was conducted. The results indicated:

VIA
- Perceived limitations of VIA – low sensitivity and specificity, and subjectivity – leading to missed cases and unnecessary referral to colposcopy or treatment
- Perceived incompetency – standardized training needed
- Lack of criteria for VIA positive result

HPV
- Lack of understanding about HPV tests and meaning of positive result
- In low- and middle-income countries, perception that implementing HPV testing would increase uptake, lead to more treatment (if same day) and be more sensitive to detect pre-cancer lesions
- Self-sampling could reduce opportunities to see women for other care

**Feasibility**
Is the intervention feasible to implement?

- No
- Probably no

The evidence gathered for HPV DNA testing was used as the GDG agreed that it was similar to the evidence for HPV mRNA testing.
Below is a summary of the relevant evidence for HPV DNA testing:

A survey of GDG members was conducted to explore feasibility/implementation issues:

- > 70% of respondents were moderately to very concerned about generating demand for screening for all algorithms; ~80% was the highest for VIA
- more were very concerned about access to HPV or cytology screening (30–40%) compared with VIA
- more were moderately or very concerned about scale-up and sustainability of maintaining a trained workforce for VIA and cytology (~90%) vs HPV testing (~55%)
- over 50% of respondents were moderately or very concerned about the ability to meet infrastructural demands for HPV testing or cytology
- ability to maintain registry (aggregate or patient level) was moderately or very concerning in all algorithms (> 75%)
- variable concerns about integration with other programmes (by level of concern cytology > HPV > VIA)
<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>DESIRABLE EFFECTS</th>
<th>UNDESIRABLE EFFECTS</th>
<th>CERTAINTY OF EVIDENCE</th>
<th>VALUES</th>
<th>BALANCE OF EFFECTS</th>
<th>RESOURCES REQUIRED</th>
<th>CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES</th>
<th>COST EFFECTIVENESS</th>
<th>EQUITY</th>
<th>ACCEPTABILITY</th>
<th>FEASIBILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trivial</td>
<td>Small</td>
<td>Moderate</td>
<td>Large</td>
<td>Varies</td>
<td>Don't know</td>
<td>Varies</td>
<td>No included studies</td>
<td>Varies</td>
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<td>Important uncertainty or variability</td>
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<td>Negligible costs and savings</td>
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Conclusions

**Recommendation**

In the general population of women, HPV DNA is the recommended primary screening test, but HPV mRNA detection may also be used.

When providing HPV mRNA testing, WHO suggests:

- providing it with or without triage;
- using samples taken by the health-care provider; and
- 5-year screening intervals.

[Conditional recommendation, low-certainty evidence]

**Remarks:**

- HPV DNA is the recommended screening test. Choosing the alternative option of HPV mRNA testing implies having the capacity to provide follow-up screening at 5-year intervals.

**Note:** No recommendation was made for using HPV mRNA in women living with HIV because evidence on the outcomes of using HPV mRNA detection applicable to this population was not identified.

**Justification**

Despite the similar cross-sectional sensitivity and specificity of HPV mRNA testing compared with HPV DNA testing, a conditional recommendation was made for the use of HPV mRNA as a primary screening test because the longitudinal evidence on HPV mRNA test performance is uncertain. Modelling data suggest that there may be similar reductions in cervical cancer cases and deaths when using HPV mRNA testing with or without triage compared with HPV DNA testing with or without triage. In addition, there may be fewer treatments for pre-cancerous lesions when using HPV mRNA testing. However, the evidence from the mathematical model is uncertain, as the predicted reductions in cases and deaths when using HPV mRNA testing overlap with the uncertainty intervals for those with HPV DNA testing, and the model validation was performed against limited longitudinal data. Some longitudinal data with follow-up of more than five years and a model trial validation exercise (based on follow-up at 4–7 years) suggest that the incidence of CIN3+ may be higher in women who were negative for HPV mRNA compared with those who were negative for HPV DNA. There also do not appear to be other reasons related to feasibility or resources in favour of selecting HPV mRNA testing rather than HPV DNA testing.

The evidence available did not include women living with HIV, and data from the general population of women was not applicable to that population. Therefore, no recommendation was made for women living with HIV.