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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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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Contents

Evidence-to-decision table

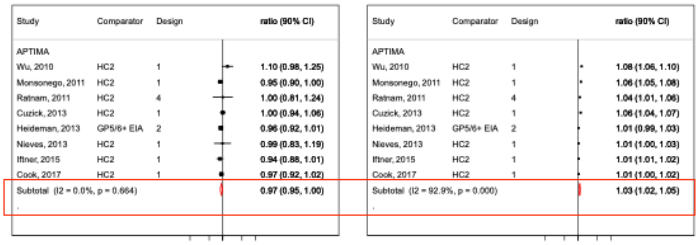
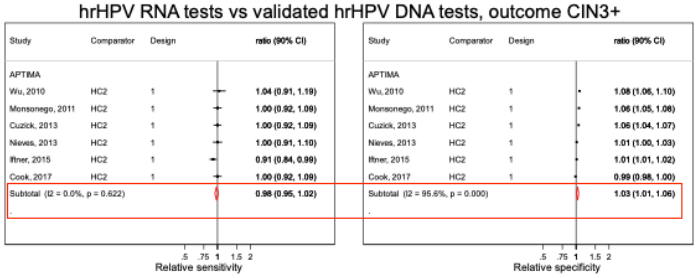
Population, intervention, comparators and outcomes

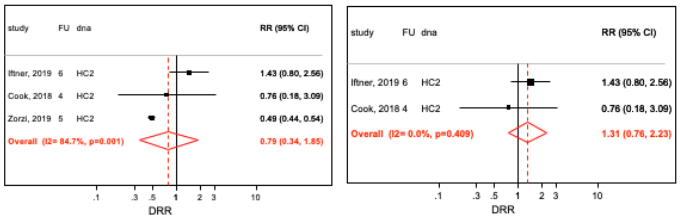
Should HPV mRNA versus HPV DNA or VIA or cytology in a screen-and-treat strategy be used in women? **Should HPV mRNA versus HPV DNA in a screen, triage and treat strategy be used in women?** **Should women be followed up at 5 or 10 years after a negative or positive HPV mRNA result?**	
POPULATION	General population of women and women living with HIV
INTERVENTION	HPV mRNA detection
COMPARATORS	Other tests (HPV DNA, VIA, cytology)
MAIN OUTCOMES	•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)
PERSPECTIVE	Population
BACKGROUND	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
CONFLICT OF INTERESTS	None

Assessment

Desirable effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**GENERAL POPULATION** **Outcomes from longitudinal studies** A systematic review conducted for the *IARC handbook* (Vol. 18) found few studies measuring the longitudinal performance and performance over repeat rounds of screening with HPV mRNA tests (*Source:* International Agency for Research on Cancer. IARC handbooks of cancer prevention: cervical cancer screening, Vol. 18. Lyon, France: IARC Press; 2021 (in press; https://handbooks.iarc.fr/publications/index.php). 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). **Test accuracy of HPV mRNA vs HPV DNA detection for CIN2+ and CIN3+** (*Source:* Arbyn et al. 2020 List of human papillomavirus assays suitable for primary cervical cancer screening. *Clin Microbiol Infect*. 2021;27(8):1083-95. doi:10.1016/j.cmi.2021.04.031.) 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). HPV RNA vs DNA tests in CC screening relative accuracy to detect CIN2+ hrHPV mRNA tests vs validated hrHPV DNA, outcome CIN2+  HPV RNA vs DNA tests in CC screening relative accuracy to detect CIN3+ hrHPV RNA tests vs validated hrHPV DNA tests, outcome CIN3+  Relative sensitivity Relative specificity	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.

Desirable effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
	Detection rate over time Systematic review of the evidence (low certainty: inconsistent across studies, and little data from the studies) **Detection rate ratio [DRR] of CIN3+ (observed in 2nd round, among women who were APIMA- vs DNA- at baseline)**  Zorzi, 2019: separate screening cohorts, no matched DNA & 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. *Int J Cancer*. 2020 Jun 1;146(11):3114–23. doi:10.1002/ijc.32695.) **Modelling** 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. HPV mRNA testing compared with HPV DNA testing at 5-year screening intervals: - 8–12% higher relative cervical cancer incidence - 6–8% higher cervical cancer mortality - 27–33% fewer pre-cancer treatments - lower costs (6–10% lower) **HPV mRNA detection vs VIA or cytology screening** - greater reductions in cervical cancer incidence and mortality See Summary Table below.	

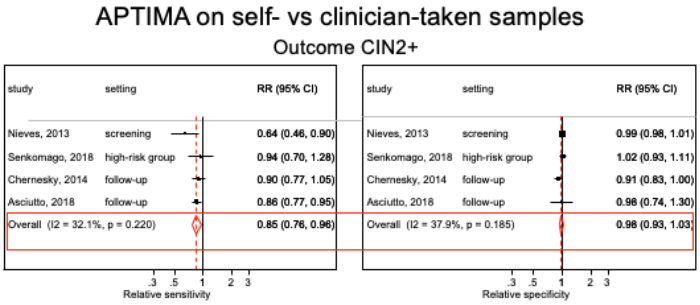
Desirable effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
	Self-collected vs provider-collected samples Relative accuracy (self/clin) for CIN2+ (mRNA: APTIMA)  **WOMEN LIVING WITH HIV** No evidence was found for women living with HIV.	

Table: Summary table of effects based on modelling

Summary table

	Screening ages	Cervical cancer deaths* (% reduction)	Pre-cancer treatments*	NNT to avert a cervical cancer death	Discounted lifetime cost* (2019 $US)
No Screening	-	1,456 (-)	0	-	$3
Primary VIA (high sens)	3yrly, 30-50 yrs (7X)	645 (56%)	147,341	182	$53
	5yrly, 30-50 yrs (5X)	721 (50%)	120,421	164	$41
Primary VIA	3yrly, 30-50 yrs (7X)	769 (47%)	137,176	199	$51
	5yrly, 30-50 yrs (5X)	877 (40%)	111,906	193	$39
Primary HPV	5yrly, 30-50 yrs (5X)	524 (64%)	50,214	54	$52
	10yrly, 30-50 yrs (3X)	664 (54%)	40,086	51	$35
	10yrly, 35-45 yrs (2X)	826 (43%)	18,527	29	$21
Cytology, HPV triage for ASC-US	3yrly, 30-50 yrs (7X)	700 (52%)	21,037	28	$81
	5yrly, 30-50 yrs (5X)	753 (48%)	18,633	26	$59
HPV, 16/18 triage	5yrly, 30-50 yrs (5X)	539 (63%)	34,388	37	$51
	10yrly, 30-50 yrs (3X)	682 (53%)	27,888	36	$34
	10yrly, 35-45 yrs (2X)	842 (42%)	13,119	21	$21
HPV, VIA triage	5yrly, 30-50 yrs (5X)	579 (60%)	30,174	34	$51
	10yrly, 30-50 yrs (3X)	733 (50%)	24,237	34	$35
	10yrly, 35-45 yrs (2X)	889 (39%)	11,620	20	$21
HPV, colp triage	5yrly, 30-50 yrs (5X)	562 (61%)	33,268	37	$57
	10yrly, 30-50 yrs (3X)	709 (51%)	26,631	36	$39
	10yrly, 35-45 yrs (2X)	862 (41%)	12,393	21	$23
HPV, cytology triage	5yrly, 30-50 yrs (5X)	581 (60%)	22,358	26	$61
	10yrly, 30-50 yrs (3X)	727 (50%)	18,068	25	$42
	10yrly, 35-45 yrs (2X)	879 (40%)	8,691	15	$25

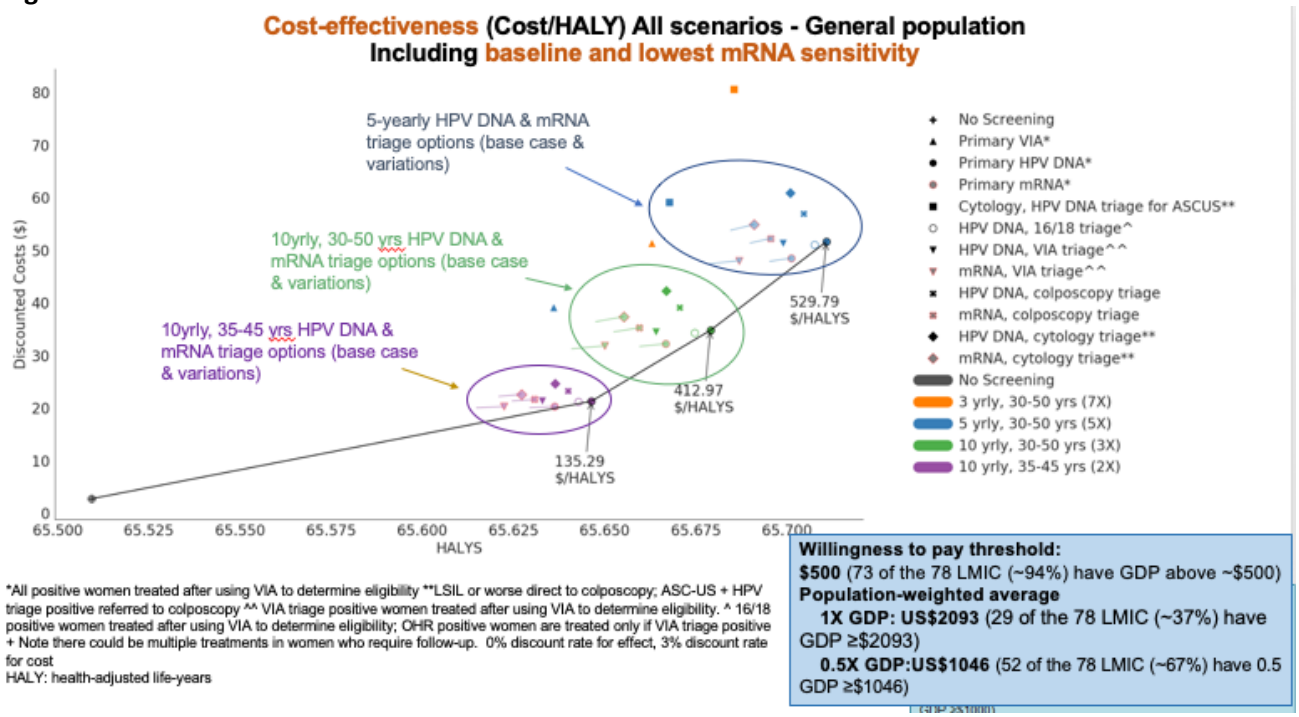
mRNA equivalent strategies	Screening ages	Cervical cancer deaths* (% reduction)	Pre-cancer treatments*	NNT to avert a cervical cancer death	Discounted lifetime cost* (2019 $US)
No Screening	-	1,456 (-)	0	-	$3
Primary HPV mRNA	5yrly, 30-50 yrs (5X)	583 (60%)	36,451	42	$48
	10yrly, 30-50 yrs (3X)	732 (50%)	29,055	40	$32
	10yrly, 35-45 yrs (2X)	885 (39%)	13,498	24	$20
HPVmRNA, VIA triage	5yrly, 30-50 yrs (5X)	654 (55%)	20,173	25	$48
	10yrly, 30-50 yrs (3X)	811 (44%)	16,152	25	$32
	10yrly, 35-45 yrs (2X)	951 (35%)	7,795	15	$20
HPVmRNA, colp triage	5yrly, 30-50 yrs (5X)	620 (57%)	24,223	29	$52
	10yrly, 30-50 yrs (3X)	772 (47%)	19,329	28	$35
	10yrly, 35-45 yrs (2X)	915 (37%)	9,037	17	$22
HPVmRNA, cyto triage	5yrly, 30-50 yrs (5X)	643 (56%)	15,980	20	$55
	10yrly, 30-50 yrs (3X)	793 (46%)	12,893	19	$37
	10yrly, 35-45 yrs (2X)	933 (36%)	6,214	12	$23

*Outcomes represent total events over the lifetime of a cohort of 100,000 women

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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.

Figure: Cost-effectiveness model



*All positive women treated after using VIA to determine eligibility **LSIL or worse direct to colposcopy; ASC-US + HPV triage positive referred to colposcopy ^^ VIA triage positive women treated after using VIA to determine eligibility. ^ 16/18 positive women treated after using VIA to determine eligibility; OHR positive women are treated only if VIA triage positive + Note there could be multiple treatments in women who require follow-up. 0% discount rate for effect, 3% discount rate for cost
HALY: health-adjusted life-years

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Equity What would be the impact on health equity?		
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	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.
Acceptability Is the intervention acceptable to key stakeholders?		
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	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.	

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	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.	

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Probably yes ○ Yes ○ Varies ○ Don't know	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)	

Summary of judgements

	JUDGEMENT						
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	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	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	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
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

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.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