European Commission Initiative on Cervical Cancer (EC-CvC) – European Cervical Cancer Prevention Guidelines

QUESTION

Should (i) cervical cytology or (ii) co-testing vs. HPV detection test be used as the primary screening test for cervical screening in asymptomatic populations with cervix aged 30–50 years?	
POPULATION:	Asymptomatic populations with cervix aged 30–50 years
INTERVENTION:	(i) Cervical cytology, (ii) Co-testing with cervical cytology and HPV detection test
COMPARISON:	HPV detection test
OUTCOMES:	Death from cervical cancer, diagnosis of cervical cancer*, detection of cervical intraepithelial neoplasia grade 2 and above (CIN2+)* , recall for assessment (colposcopy/screening test at a shorter interval), quality of life, overdiagnosis, precancer treatments, major adverse events (direct consequence of precancer treatment), HPV infection, preterm birth (PTB). *First-round screening: refers to the initial round of testing in a population. High detection rates suggest the presence of previously undiagnosed disease. Second-round screening: reflects follow-up testing after an initial negative result. Lower detection rates in this round typically suggest effective earlier screening and a lower current risk in the population. Outcomes can be considered desirable or undesirable depending on the direction of the association. For example, if an intervention leads to fewer follow-up procedures, this may be seen as a desirable effect from an individual's perspective. Conversely, if it results in lower detection of disease, this may indicate reduced effectiveness, which would be considered undesirable. The overall net benefit of an intervention is determined by weighing these desirable and undesirable effects against each other. In this document, we use inclusive language (for example, individuals with cervix, populations with cervix) unless referencing an original study.
AUTHORS:	Working group (WG) - Broutet N (clinical and policy chair), Qaseem A (methodological chair) Arbyn M, Armaroli P, Arrospide A, Berkhof J*, Carcopino X, Carozzi FM, Cruickshank M, Dillner J*, Elfstrom M*, Gallwas J, Giorgi Rossi P*, Hillemanns P, Ivanus U*, Kyrgiou M, Nowakowski A*, Russel N*, Strömsholm EM*, Uusküla A, Veerus P, Wentzensen N. Topic specific group - Kellen E, Mark B. (* indicates the WG members who were also in the topic specific group for this question). Systematic review team - Alonso P, Canelo C, de la Torre L, Fernández KF, Gravholt D, Jimenez E, Mateos M, Nieto W, Pereira Nunes Pinto AC, Rigau D, Stallings E. Steering group - Basu P, Bhatla N, Dimitrova N, Garcia Escribano M, Janusch Roi A, Lauby-Secretan B, Lucas E, Mackie A, Morgano GP, Neamtiu L, Ramirez T, Taghavi K.
SETTING:	EUROPEAN UNION (EU)
PERSPECTIVE:	In this question, we focus on the general (unvaccinated) population, and a separate recommendation will address vaccinated cohorts or populations. Now that all EU countries have implemented vaccination programmes, the earliest beginning in 2008 and targeting birth cohorts in the 1990s, vaccinated cohorts are reaching screening age. As a result, the general population is becoming increasingly heterogeneous, with fully vaccinated, partially vaccinated and unvaccinated individuals. This shift in HPV vaccination status must be carefully considered when determining age to initiate screening as well as screening strategies, since the risk of cervical cancer in the younger age groups is decreasing. The impact of screening is recognised to be highly dependent on the coverage of the populations targeted with the vaccine.
BACKGROUND:	The primary objective of cervical screening is to reduce mortality and life years lost due to the disease. Cervical screening also aims to reduce the incidence of invasive disease by detecting and treating precancerous lesions (CIN2, CIN3, adenocarcinoma in situ (AIS)) before they progress to cancer.

	Data from time trends and case-control and cohort studies have generated observational evidence that organised cervical screening by cervical cytology can significantly reduce incidence of and mortality from cervical cancer. Earlier European Guidelines for Quality Assurance in Cervical Cancer Screening (first and second editions) recommended cytology-based screening, which remained the primary screening method for many years. However, several randomised controlled trials (RCTs) have demonstrated that the HPV detection test is a more effective screening method, leading to strong endorsement of HPV detection test as a primary screening test in international guidelines. The EC-CvC WG acknowledged the vast work done prior to this initiative to generate evidence in favour of HPV detection tests, and emphasised the importance of building upon existing recommendations and on research supporting them when necessary. One such instance is the 'strong' recommendation from WHO 's 2021 guideline to use the HPV detection test over cervical cytology for primary cervical screening. HPV detection tests were also recommended in the 2015 supplement to the second European guideline for cervical cancer screening. Subsequently, the European Council also issued a statement in support of the prior work and evaluations. It is recognised that many EU Member States have implemented broadly or piloted HPV-detection-based screening over the last 10 years. In the present evaluation to determine the benchmark age group and the primary recommendations of the EC-CvC, no screening is not considered as a suitable comparator. The HPV detection test, which has already been adopted as the gold standard, serves as the ideal comparator. This decision is based on a large body of evidence supporting HPV detection as the preferred screening method in the age group 30-50 years. The EC-CvC WG also acknowledges the existing knowledge base, guidelines and policies that strongly endorse screening in this population. Further details are available in the "Supporting Material – Background document".
CONFLICT OF INTERESTS:	Conflicts of interest (CoI) for all EC-CvC WG and topic-specific group members were assessed and managed by the International Agency for Research on Cancer (IARC) following an established procedure in line with the institutional rules. Participation of individual members in the development of the recommendations was restricted based on the CoI disclosure. For this particular question, no members were recused from voting.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cervical cancer is almost completely preventable but remains leading cause of cancer mortality among European women below the age of 45, with disparities both within and between European countries (1). Additionally, in the next 40 years, morbidity and mortality from cervical cancer is projected to increase in Europe (2). In 2020, the World Health Organization (WHO) launched a strategy to eliminate cervical cancer as a public health problem globally, with the goal of reducing the annual incidence to under 4 cases per 100,000 women by 2030 (3). However, the age-standardised incidence rate of cervical cancer in the EU was 11.7 per 100 000 females in 2022, with substantial variation between countries (from 5.2 to 32.6 per 100 000 females (4). Modelling studies suggest that cervical cancer elimination is possible by the end of the century, if countries can achieve 90% coverage with HPV vaccination programs, cervical screening for 70% of women by 35 and 45 years of age, and treatment for 90% of women who have cervical precancerous lesions or cervical cancer (2).	**The EC-CvC WG has prioritised the question, for inclusion in the European Cervical Cancer Prevention Guidelines:** *Should (i) cervical cytology or (ii) co-testing vs. HPV detection test be used as the primary screening test for cervical screening in asymptomatic populations with cervix aged 30–50 years?* Cytology, HPV detection test and co-test were prioritised as primary screening tests and considered in the comparative effectiveness analysis of cervical screening in individuals aged 30–50 years. HPV detection

<table>
<tr><td></td><td></td><td>test was accepted as the comparator for evaluating other screening tests, based on the justification outlined in the background section. In this context, cervical cytology and co-testing are considered the interventions, assessed against HPV detection test.

The recommended screening method will determine the screening benchmark (age 30-50 years). Starting and finishing age of screening will be explored in subsequent priority questions</td></tr>
<tr><td colspan="3">

Desirable Effects

How substantial are the desirable anticipated effects?

</td></tr>
<tr><td>JUDGEMENT</td><td>RESEARCH EVIDENCE</td><td>ADDITIONAL CONSIDERATIONS</td></tr>
<tr>
<td>Trivial: (ii) Co-testing with cervical cytology and HPV detection test

Small: (i) Cervical cytology

Moderate:

Large:

Varies:

Don't know:</td>
<td><u>i) Cervical cytology vs HPV detection tests</u>

Empirical evidence on cervical cytology vs HPV detection test

Empirical evidence was found relating to all the outcomes except the following:

· Death from cervical cancer: mortality

· Quality of life

· Overdiagnosis of CIN2, CIN3 and AIS

· Pre-cancer treatments

· Major adverse events (direct consequence of pre-cancer treatment)

· Preterm birth (PTB)

<table>
<tr><th rowspan="2">Outcomes</th><th rowspan="2">№ of participants (studies) Follow-up</th><th rowspan="2">Certainty of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr>
<tr><th>Risk with HPV detection test</th><th>Risk difference with cervical cytology</th></tr>
<tr><td>Diagnosis of cervical cancer: first-</td><td>638771</td><td>⊕⊕◯◯</td><td>RR 0.78</td><td colspan="2">Study population</td></tr>
</table>
</td>
<td><u>EC-CvC WG judgement:</u> cervical cytology vs HPV detection test – <i>lower rate of colposcopy referrals with cervical cytology was considered a small desirable effect.</i>

A lower referral rate to colposcopy with cervical cytology compared with HPV detection test was identified in 3 large RCTs and was considered the main desirable effect of primary cytology screening. The WG also reviewed findings from observational studies below to confirm consistency with RCTs.

<u>Supplementary evidence supporting EC-CvC WG judgement</u>

Four observational studies including 244,343 participants provide supporting evidence for the outcome of recall to colposcopy and/or new test (1, 3, 4, 6):

• Recall for colposcopy: risk ratio (RR) = 0.72 (95% CI: 0.36–1.47) – <i>four studies</i>
• Recall for new test: RR = 0.04 (95%</td>
</tr>
</table>

round screening	(3 RCTs)[1,2,3]	Low[a,b,c]	(0.45 to 1.33)	33 per 100.000	**7 fewer per 100.000** (18 fewer to 11 more)
Diagnosis of cervical cancer: second-round screening	200288 (1 RCT)[4]	⊕⊕⊕○ Moderate[a]	**RR 1.58** (1.08 to 2.32)	Study population	
				42 per 100.000	**24 more per 100.000** (3 more to 55 more)
Detection of Cervical Intraepithelial Neoplasia Grade 2 and above (CIN2+): first-round screening	393239 (5 RCTs)[1,2,3,5,6,d]	⊕⊕⊕⊕ High[e,f]	**RR 0.65** (0.57 to 0.74)	Study population	
				1071 per 100.000	**375 fewer per 100.000** (461 fewer to 278 fewer)
Detection of Cervical Intraepithelial Neoplasia Grade 2 and above (CIN2+): second-round screening	51509 (2 RCTs)[5,6]	⊕⊕⊕⊕ High	**RR 3.01** (1.95 to 4.64)	Study population	
				106 per 100.000	**213 more per 100.000** (100 more to 385 more)
Detection of Cervical Intraepithelial Neoplasia Grade 3 and above (CIN3+): first-round screening	691785 (5 RCTs)[1,2,3,5,6,g]	⊕⊕⊕⊕ High[e,h]	**RR 0.68** (0.54 to 0.86)	Study population	
				466 per 100.000	**149 fewer per 100.000** (214 fewer to 65 fewer)
Detection of Cervical Intraepithelial Neoplasia Grade 3 and above (CIN3+): second-round screening	51509 (2 RCTs)[5,6]	⊕⊕⊕⊕ High	**RR 3.91** (2.02 to 7.57)	Study population	
				43 per 100.000	**125 more per 100.000** (44 more to 283 more)

CI: 0.02–0.07) – *one study*

PTB outcome

The EC-CvC WG considered PTB as a priority outcome, but the evidence review did not identify studies that directly assessed the association between screening strategy and PTB. A meta-analysis summarising the association between precancer treatment and PTB was used to estimate the effect (6). The risk was estimated with modelling using the prevalence of different lesions, the treatment algorithm and the risk of PTB after treatment. The risk of PTB in individuals with confirmed CIN2+ was lower following cervical cytology, at 74.5 per 100 000 participants screened, compared with 100 per 100 000 following HPV detection testing. This is a lifetime risk and could not be stratified by age.

Modelling evidence from low- and middle-income countries (LMICs) –Policy1-Cervix model(7)

WHO used the Policy1-Cervix model to evaluate the impact of 7 primary screening scenarios across 78 LMICs, with 70% of coverage for the general population of women aged 30 to 50 years. It is noted that this evidence may have limited applicability to the EU. Since the comparison of tests and age groups applicable to this recommendation and data for this outcome were scarce, the EC-CvC WG took these results into consideration too.

Compared with HPV screening every 5 years (with HPV16/18 genotyping triage), cytology screening with HPV triage for atypical squamous cells of undetermined significance (ASC-US) every 3 years was associated with a

Recall for assessment: colposcopy	159645 (3 RCTs)[1,3,7]	⊕⊕⊕⊕ High[e,i]	**RR 0.58** (0.42 to 0.79)	Study population	
				4818 per 100.000	**2024 fewer per 100.000** (2795 fewer to 1012 fewer)
Recall for assessment: new test	156661 (1 RCT)[2]	⊕⊕⊕○ Moderate[a]	**RR 1.12** (1.06 to 1.17)	Study population	
				3522 per 100.000	**423 more per 100.000** (211 more to 599 more)
HPV infection	81843 (4 RCTs)[1,5,7,8]	⊕⊕○○ Low[j,k]	-	738 HPV infections per 100,000 participants.	

1. Elfström KM, Eklund C, Lamin H, Öhman D, Hortlund M, Elfgren K, et al. Organized primary human papillomavirus–based cervical screening: A randomized healthcare policy trial. PLoS Med. 2021;18(5):e100367
2. Leinonen MK, Nieminen P, Lönnberg S, Malila N, Hakama M, Pokhrel A, et al. Detection rates of precancerous and cancerous cervical lesions within one screening round of primary human papillomavirus DNA testing: prospective randomised trial in Finland. BMJ. 2012;345:e7789
3. Nygård M, Engesæter B, Castle PE, Berland JM, Eide ML, Iversen OE, Jonassen CM, Christiansen IK, Vintermyr OK, Tropé A. Randomized Implementation of a Primary Human Papillomavirus Testing-based Cervical Cancer Screening Protocol for Women 34 to 69 Years in Norway. Cancer Epidemiol Biomarkers Prev. 2022 Sep 2;31(9):1812-1822.
4. Wang J, Elfström KM, Dillner J. Human papillomavirus-based cervical screening and long-term cervical cancer risk: a randomised health-care policy trial in Sweden. Lancet Public Health. 2024 Nov;9(11):e886-e895. doi: 10.1016/S2468-2667(24)00218-4. PMID: 39486904.
5. Ogilvie GS, van Niekerk D, Krajden M, Smith LW, Cook D, Gondara L, Ceballos K, Quinlan D, Lee M, Martin RE, Gentile L, Peacock S, Stuart GCE, Franco EL, Coldman AJ. Effect of Screening With Primary Cervical HPV Testing vs Cytology Testing on High-grade Cervical Intraepithelial Neoplasia at 48 Months: The HPV FOCAL Randomized Clinical Trial. JAMA. 2018 Jul 3;320(1):43-52.
6. 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. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol. 2010 Mar;11(3):249-57
7. Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, Gillio-Tos A, Minucci D,

35% lower rate of PTB over a lifetime.

Naldoni C, Rizzolo R, Schincaglia P, Volante R, Zappa M, Zorzi M, Cuzick J, Segnan N; New Technologies for Cervical Cancer Screening Working Group. Results at recruitment from a randomized controlled trial comparing human papillomavirus testing alone with conventional cytology as the primary cervical cancer screening test. J Natl Cancer Inst. 2008 Apr 2;100(7):492-501.

8. Canfell K, Caruana M, Gebski V, Darlington-Brown J, Heley S, Brotherton J, Gertig D, Jennett CJ, Farnsworth A, Tan J, Wrede CD, Castle PE, Saville M. Cervical screening with primary HPV testing or cytology in a population of women in which those aged 33 years or younger had previously been offered HPV vaccination: Results of the Compass pilot randomised trial. PLoS Med. 2017 Sep 19;14(9):e1002388.

a. Downgraded one level as studies have a high risk of bias concerning the randomisations process. Allocation concealment and baseline group differences were noted, indicating potential imbalances at the outset that may introduce bias.
b. I2 = 67.26%; unexplained and important heterogeneity
c. Pending decision from panel and corresponding threshold
d. Canfell et al. 2017 has not been included in the CIN2+ analysis because no events ini the cytologyc group.
e. Low and high risk studies show similar effects, so did not downgrade for risk of bias
f. High statistical heterogeneity (I^2= 64%) was considered not important given the consistency of results across studies.
g. Canfell 2017 has not been included into the CIN 3+ analysis because no events on the Cytology group
h. High statistical heterogeneity (I^2= 78%) was considered not important given the consistency of results across studies.
i. High statistical heterogeneity (I^2= 97%) was considered not important given the consistency of results across studies.
j. In Elfström et al. 2021, allocation was not concealed and the analysis was not deemed inappropriate.
k. Age ranges for this outcome in Oglivie et al. 2018 and Canfell et al. 2017 (25––65 years) are lower than the PICO age range (30––50 years).

Modelling studies on cervical cytology vs HPV detection test

No modelling evidence was found relating to the following outcomes:

· Detection of Cervical Intraepithelial Neoplasia Grade 3 and above (CIN3+)
· Overdiagnosis of CIN2, CIN3 and AIS
· Pre-cancer treatments
· Major adverse events (direct consequence of pre-cancer treatment)
· HPV infection
· Preterm birth (PTB)

Outcomes	**№ of studies**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects[*] (95% CI)**	
				Risk with HPV detection test	**Risk difference with cervical cytology**
Death From cervical cancer: mortality	3 non-randomised studies[1,2,3]	⨁◯◯◯ Very low[a,b,c]	**RR 1.28** (0.94 to 2.62)[d]	Low	
				89 per 100.000[3,e]	**25 more per 100.000** (5 fewer to 144 more)
Diagnosis of cervical cancer: second-round screening	3 non-randomised studies[1,2,3]	⨁◯◯◯ Very low[a,b,c]	**RR 1.17** (0.96 to 2.62)[d]	Low	
				283 per 100.000[3,e]	**48 more per 100.000** (11 fewer to 458 more)
Detection of Cervical Intraepithelial Neoplasia Grade 2 and above (CIN2+)	3 non-randomised studies[1,2,3]	⨁◯◯◯ Very low[a,b,c]	**RR 1.00** (0.80 to 1.02)[d]	Low	
				5840 per 100.000[3,e]	**0 fewer per 100.000** (1168 fewer to 117 more)
Recall for assessment	1 non-randomised study[3]	⨁⨁◯◯ Low[a,b]	**RR 1.07**	Low	
				38.430 per 100.000[3,e]	**2690 more per 100.000**
Quality of life assessed with: Quality adjusted life years (QALYs)	2 non-randomised studies[1,3]	⨁◯◯◯ Very low[a,b,c]	**RR 1.00** (0.91 to 1.00)[d]	Low	
				14.007 per 100.000[3,e]	**0 fewer per 100.000** (1261 fewer to 0 fewer)

Life years gained	2 non-randomised studies[1,2]	⊕⊕◯◯ Low[a,b]	**RR 1** (1 to 1)[d]	Low	
				14.000 per 100.000[3,e]	**0 fewer per 100.000** (0 fewer to 0 fewer)

1. Lew JB, Simms K, Smith M, Lewis H, Neal H, Canfell K. Effectiveness Modelling and Economic Evaluation of Primary HPV Screening for Cervical Cancer Prevention in New Zealand. PLoS One. 2016 May 17;11(5):e0151619.
2. Kim JJ, Burger EA, Regan C, Sy S. Screening for Cervical Cancer in Primary Care: A Decision Analysis for the US Preventive Services Task Force. JAMA. 2018 Aug 21;320(7):706-714
3. Naber SK, de Kok IM, Matthijsse SM, van Ballegooijen M. The potential harms of primary human papillomavirus screening in over-screened women: a microsimulation study. Cancer Causes Control. 2016 Apr;27(4):569-81

a. Models had adequate credibility of model development including calibration, internal validation and cross-validation.
b. Downgraded 2 levels due to the risk of bias in the bodies of evidence that informed the input parameters. The model relies on estimates of each test's' accuracy, incidence/prevalence of premalignant lesions and transmission dynamics of HPV infection at different age groups, and assumptions about the rate of progression of adenomas.
c. Imprecision in the effects across models (structural uncertainty) is not fully explained by differences in diagnostic pathways or input parameters
d. The point estimate represents the median between models when there are 2 or more studies. Values in brackets represent the range of estimates across models.
e. Baseline risk was computed from the predicted events for primary HPV screening by a modelling study for the Netherlands.

ii) Co-testing vs HPV detection tests

Empirical evidence on co-testing vs HPV detection tests

The analysis comprises five studies, providing only narrative evidence for the outcomes of CIN2+ and CIN3+ detection. Please see additional considerations from the EC-CvC WG for further details.

No empirical evidence was found relating to the following:

· Death from cervical cancer: mortality
· Diagnosis of cervical cancer
· Recall for assessment: colposcopy/ new test

EC-CvC WG judgement: **co-testing vs HPV detection tests** –*the increase in CIN3+ detection with co-testing was considered a trivial desirable effect.*

The desirable effect of co-testing vs HPV detection is a trivial increase in the detection of CIN3+. Although the evidence review was limited by the design of the included studies – which did not include a study arm for HPV detection test alone* – the EC-CvC WG based its judgement on the best available data and

- Quality of life
- Overdiagnosis of CIN2, CIN3 and AIS
- Pre-cancer treatments
- Major adverse events (direct consequence of pre-cancer treatment)
- HPV infection
- Preterm birth (PTB)

Outcomes	**№ of participants (studies) Follow-up**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects* (95% CI)**	
				Risk with HPV detection test	**Risk difference with co-testing with cervical cytology and HPV detection test**
Detection of Cervical Intraepithelial Neoplasia Grade 2 and above (CIN2+)	197997 (5 non-randomised studies)[1,2,3,4,5]	⊕◯◯◯ Very low[a]	-	It is not possible to compute the effect size, because both tests were applied to the same group of participants. However, narratively synthesising the results from both arms of these trials: as seen in Elfström et al. 2014, at 13 years follow-up, the rates of CIN2+ in the intervention arm were similar between individuals who were negative on HPV detection test and cervical cytology (double negative) and only HPV negative (1.63%, 1.11% to 2.32%). The non-significant gain in lowered risk for CIN2+ of being double negative (cytology and HPV negative) implies that double testing is not likely to represent an improvement in effect, while it certainly would increase costs and lower specificity. Similar results were seen in the Kaiser Permanente cohort (Castle et al. 2018), and in the POBASCAM, FOCAL and ARTISTIC trials.	
Detection of Cervical Intraepithelial Neoplasia Grade 3 and above (CIN3+)	691785 (4 non-randomised studies)[1,3,4,5]	⊕◯◯◯ Very low[a]	-	It is not possible to compute the effect size, because both tests were applied to the same group of participants. However, narratively synthesising the results from both arms of these trials: as seen in Elfström et al. 2014, individuals with a double negative test result had similar rates of CIN3+ to HPV-negative individuals, reaching a cumulative incidence of 0.84% (0.48% to 1.47%) in the intervention arm at 13 years. The non-significant gain in lowered risk for CIN3+ of being double negative (cytology and HPV negative) implies that double testing is not likely to represent an improvement in effect, while it certainly would increase costs and lower specificity. Similar results were seen in the Kaiser Permanente cohort (Castle et al. 2018),	

noted that the studies included a large number of participants.

Cumulative incidence of CIN3+ over 13 years of follow-up by study arm and baseline test result (5) (see figure in research evidence section)

Elfström et al. 2014 reported that although sensitivity in co-testing was higher than with the HPV detection test alone, the specificity was lower throughout the 13-year follow-up. Furthermore, the absolute difference in cumulative incidence of CIN3+ between co-testing and HPV detection remained constant over time and was minimal. Similar findings were reported in the Kaiser Permanente cohort (8), as well as in the POBASCAM (9), FOCAL (10) and ARTISTIC (11) trials.

*The EC-CvC WG highlighted that, prior to the publicaiton of the 2015 EU guidelines recommending HPV-based screening, it was not feasible to conduct studies implementing HPV detection as a standalone intervention as it would have been unethical to offer HPV detection without concurrent cervical cytology. As a result, most available studies included a co-testing arm and a cervical cytology arm, rather than a direct comparison between co-testing and the HPV detection test alone. However, the EC-CvC WG considered that the downstream consequences of co-testing can be attributed more to HPV detection than to cervical cytology, and acknowledged the indirectness of the evidence. The key studies listed in this table were identified by the WG as sentinel evidence for evaluating co-testing versus HPV detection test.

				and in the POBASCAM and ARTISTIC trials.

1. Inturrisi F, Rozendaal L, Veldhuijzen NJ, Heideman DAM, Meijer CJLM, Berkhof J. Risk of cervical precancer among HPV-negative women in the Netherlands and its association with previous HPV and cytology results: A follow-up analysis of a randomized screening study. PLoS Med. 2022 Oct 28;19(10):e1004115
2. Gottschlich A, Gondara L, Smith LW, Cook D, Martin RE, Lee M, Peacock S, Proctor L, Stuart G, Krajden M, Franco EL, van Niekerk D, Ogilvie G. Human papillomavirus-based screening at extended intervals missed fewer cervical precancers than cytology in the HPV For Cervical Cancer (HPV FOCAL) trial. Int J Cancer. 2022 Sep 15;151(6):897-905.
3. Elfström KM, Smelov V, Johansson AL, Eklund C, Nauclér P, Arnheim-Dahlström L, Dillner J. Long term duration of protective effect for HPV negative women: follow-up of primary HPV screening randomised controlled trial. BMJ. 2014 Jan 16;348:g130
4. Gilham C, Sargent A, Kitchener HC, Peto J. HPV testing compared with routine cytology in cervical screening: long-term follow-up of ARTISTIC RCT. Health Technol Assess. 2019 Jun;23(28):1-44
5. Castle PE, Kinney WK, Xue X, Cheung LC, Gage JC, Zhao FH, Fetterman B, Poitras NE, Lorey TS, Wentzensen N, Katki HA, Schiffman M. Effect of Several Negative Rounds of Human Papillomavirus and Cytology Co-testing on Safety Against Cervical Cancer: An Observational Cohort Study. Ann Intern Med. 2018 Jan 2;168(1):20-29. doi: 10.7326/M17-1609. Epub 2017 Nov 28. PMID: 29181509.

a. Studies do not isolate the performance of HPV testing alone, but infer it from cotesting.

Cumulative incidence of CIN3+ over 13 years of follow-up by study arm and baseline test result (5)

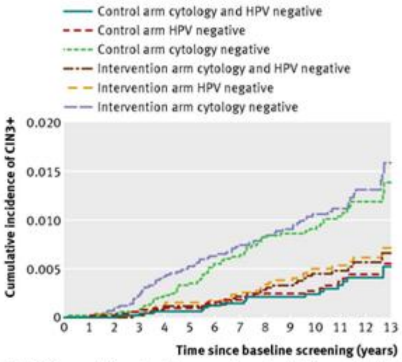


Fig 3 Cumulative incidence of cervical intraepithelial neoplasia grade 3 or worse (CIN3+) over 13 years of follow-up by study arm and baseline test result (test result groups not mutually exclusive). HPV=human papillomavirus

Modelling studies on co-testing vs HPV detection test

The analysis includes three studies, assessing five outcomes.

No modelling evidence was found relating to the following outcomes:

· Detection of Cervical Intraepithelial Neoplasia Grade 3 and above (CIN3+)

· Overdiagnosis of CIN2, CIN3 and AIS

· Pre-cancer treatments

· Major adverse events (direct consequence of pre-cancer treatment)

· HPV infection

· Preterm birth

Outcomes	№ of studies	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with HPV detection test	**Risk difference with co-testing with cervical cytology and HPV detection test**
Death from cervical cancer: mortality	2 non-randomised studies[1,2]	⊕⊕◯◯ Low[a,b]	**RR 1.00** (0.98 to 1.04)[c]	Low	
				89 per 100.000[3,d]	**0 fewer per 100.000** (2 fewer to 4 more)
Diagnosis of cervical cancer: second-round screening	2 non-randomised studies[1,2]	⊕⊕◯◯ Low[a,b]	**RR 1.00** (0.99 to 1.03)[c]	Low	
				283 per 100.000[3,d]	**0 fewer per 100.000** (3 fewer to 8 more)
Detection of Cervical Intraepithelial Neoplasia Grade 2 and above (CIN2+)	2 non-randomised studies[1,2]	⊕⊕◯◯ Low[a,b]	**RR 1.01** (1.01 to 1.02)[c]	Low	
				5840 per 100.000[3,d]	**58 more per 100.000** (58 more to 117 more)
Recall for assessment		⊕⊕◯◯	**RR 1.12**	Low	

	1 non-randomised study[2]	Low[a,b]		38.430 per 100.000[3,d]	**4612 more per 100.000**
Quality of life assessed with: Quality adjusted life years	1 non-randomised study[1]	⊕⊕◯◯ Low[a,b]	**RR 1** (1 to 1)[c]	Low	
				14.007 per 100.000[3,d]	**0 fewer per 100.000** (0 fewer to 0 fewer)
Life years gained	2 non-randomised studies[1,2]	⊕⊕◯◯ Low[a,b]	**RR 1** (1 to 1)[c]	Low	
				14.000 per 100.000[3,d]	**0 fewer per 100.000** (0 fewer to 0 fewer)

1. Lew JB, Simms K, Smith M, Lewis H, Neal H, Canfell K. Effectiveness Modelling and Economic Evaluation of Primary HPV Screening for Cervical Cancer Prevention in New Zealand. PLoS One. 2016 May 17;11(5):e0151619.
2. Kim JJ, Burger EA, Regan C, Sy S. Screening for Cervical Cancer in Primary Care: A Decision Analysis for the US Preventive Services Task Force. JAMA. 2018 Aug 21;320(7):706-714.
3. Naber SK, de Kok IM, Matthijsse SM, van Ballegooijen M. The potential harms of primary human papillomavirus screening in over-screened women: a microsimulation study. Cancer Causes Control. 2016 Apr;27(4):569-81

a. Models had adequate credibility of model development including calibration, internal validation and cross-validation.
b. Downgraded 2 levels due to the risk of bias in the bodies of evidence that informed the input parameters. The model relies on estimates of each test's accuracy, incidence/prevalence of premalignant lesions and transmission dynamic of HPV infection at different age groups, and assumptions about the rate of progression of adenomas.
c. Baseline risk was computed from the predicted events for primary HPV screening by a modelling study for the Netherlands.
d. The point estimate represents the median between models when there are 2 or more studies. Values in brackets represent the range of estimates across models.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

Trivial:

Small:

Moderate: (ii) Co-testing with cervical cytology and HPV detection test

Large: (i) Cervical cytology

Varies:

Don't know:

RESEARCH EVIDENCE

i) Cervical cytology vs HPV detection tests

Empirical evidence on cervical cytology vs HPV detection tests

Empirical evidence was found relating to all the outcomes except the following:

· Death from cervical cancer: mortality

· Quality of life

· Overdiagnosis of CIN2, CIN3 and AIS

· Pre-cancer treatments

· Major adverse events (direct consequence of pre-cancer treatment)

· Preterm birth (PTB)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with HPV detection test	Risk difference with cervical cytology
Diagnosis of cervical cancer: first-round screening	638771 (3 RCTs)[1,2,3]	⊕⊕◯◯ Low[a,b,c]	**RR 0.78** (0.45 to 1.33)	Study population	
				33 per 100,000	**7 fewer per 100,000** (18 fewer to 11 more)
Diagnosis of cervical cancer: second-round screening	200288 (1 RCT)[4]	⊕⊕⊕◯ Moderate[a]	**RR 1.58** (1.08 to 2.32)	Study population	
				42 per 100,000	**24 more per 100,000** (3 more to 55 more)

ADDITIONAL CONSIDERATIONS

EC-CvC WG judgement: cervical cytology vs HPV detection tests – *delayed detection of CIN2+ with cervical cytology was considered a large undesirable effect.*

The undesirable effect of cervical cytology vs HPV detection tests is the lower detection of CIN2+ in round 1 of screening (RR, 0.65; 95% CI, 0.57 to 0.74), followed by a higher detection of CIN2+ in round 2 of screening (RR, 3.01; 95% CI, 1.95 to 4.64). This suggests that screening with cervical cytology may delay the detection of CIN2+ compared with HPV detection tests.

The decision to judge this as a large effect is based on consistent evidence from RCTs and large observational studies demonstrating that the efficacy of screening with cervical cytology to prevent cervical cancer is lower than that of HPV detection test. Long-term follow-up data shows higher incidence and mortality from cervical cancer among individuals screened with cervical cytology compared with those screened with HPV detection tests. While the WG made their judgement on the highest quality of evidence (RCTs), additional studies (observational and modelling studies) were also considered to ensure consistency with trial findings.

Supplementary evidence supporting EC-CvC WG judgement

WHO used the Policy1-Cervix model to evaluate the impact of 7 primary screening scenarios across 78 LMICs, with 70% coverage for the general population of individuals aged 30 to 50 years (7).

Detection of Cervical Intraepithelial Neoplasia Grade 2 and above (CIN2+): first-round screening	393239 (5 RCTs)[1,2,3,5,6,d]	⊕⊕⊕⊕ High[e,f]	**RR 0.65** (0.57 to 0.74)	Study population 1,071 per 100,000	**375 fewer per 100,000** (461 fewer to 278 fewer)
Detection of Cervical Intraepithelial Neoplasia Grade 2 and above (CIN2+): second-round screening	51509 (2 RCTs)[5,6]	⊕⊕⊕⊕ High	**RR 3.01** (1.95 to 4.64)	Study population 106 per 100,000	**213 more per 100,000** (100 more to 385 more)
Detection of Cervical Intraepithelial Neoplasia Grade 3 and above (CIN3+): first-round screening	691785 (5 RCTs)[1,2,3,5,6,g]	⊕⊕⊕⊕ High[e,h]	**RR 0.68** (0.54 to 0.86)	Study population 466 per 100,000	**149 fewer per 100,000** (214 fewer to 65 fewer)
Detection of Cervical Intraepithelial Neoplasia Grade 3 and above (CIN3+): second-round screening	51509 (2 RCTs)[5,6]	⊕⊕⊕⊕ High	**RR 3.91** (2.02 to 7.57)	Study population 43 per 100,000	**125 more per 100,000** (44 more to 283 more)
Recall for assessment: colposcopy	159645 (3 RCTs)[1,3,7]	⊕⊕⊕⊕ High[e,i]	**RR 0.58** (0.42 to 0.79)	Study population 4,818 per 100,000	**2,024 fewer per 100,000** (2,795 fewer to 1,012 fewer)
HPV infection	81843 (4 RCTs)[1,5,7,8]	⊕⊕◯◯ Low[j,k]	-	738 HPV infections per 100,000 participants.	

1. Elfström KM, Eklund C, Lamin H, Öhman D, Hortlund M, Elfgren K, et al. Organized primary human

Compared with HPV detection tests every 5 years (with HPV16/18 genotyping triage), cervical cytology every 3 years (with HPV triage for ASC-US) was associated with 21% more cervical cancer cases, 23% more cervical cancer deaths, 35% fewer PTBs, 39% fewer precancer treatments and 0.03% fewer health-adjusted life years (HALYs) over a lifetime.

papillomavirus–based cervical screening: A randomized healthcare policy trial. PLoS Med. 2021;18(5):e1003679

2. Leinonen MK, Nieminen P, Lönnberg S, Malila N, Hakama M, Pokhrel A, et al. Detection rates of precancerous and cancerous cervical lesions within one screening round of primary human papillomavirus DNA testing: prospective randomised trial in Finland. BMJ. 2012;345:e7789.
3. Nygård M, Engesæter B, Castle PE, Berland JM, Eide ML, Iversen OE, Jonassen CM, Christiansen IK, Vintermyr OK, Tropé A. Randomized Implementation of a Primary Human Papillomavirus Testing-based Cervical Cancer Screening Protocol for Women 34 to 69 Years in Norway. Cancer Epidemiol Biomarkers Prev. 2022 Sep 2;31(9):1812-1822.
4. Wang J, Elfström KM, Dillner J. Human papillomavirus-based cervical screening and long-term cervical cancer risk: a randomised health-care policy trial in Sweden. Lancet Public Health. 2024 Nov;9(11):e886-e895. doi: 10.1016/S2468-2667(24)00218-4. PMID: 39486904.
5. Ogilvie GS, van Niekerk D, Krajden M, Smith LW, Cook D, Gondara L, Ceballos K, Quinlan D, Lee M, Martin RE, Gentile L, Peacock S, Stuart GCE, Franco EL, Coldman AJ. Effect of Screening With Primary Cervical HPV Testing vs Cytology Testing on High-grade Cervical Intraepithelial Neoplasia at 48 Months: The HPV FOCAL Randomized Clinical Trial. JAMA. 2018 Jul 3;320(1):43-52.
6. 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. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol. 2010 Mar;11(3):249-57
7. Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, Gillio-Tos A, Minucci D, Naldoni C, Rizzolo R, Schincaglia P, Volante R, Zappa M, Zorzi M, Cuzick J, Segnan N; New Technologies for Cervical Cancer Screening Working Group. Results at recruitment from a randomized controlled trial comparing human papillomavirus testing alone with conventional cytology as the primary cervical cancer screening test. J Natl Cancer Inst. 2008 Apr 2;100(7):492-501.
8. Canfell K, Caruana M, Gebski V, Darlington-Brown J, Heley S, Brotherton J, Gertig D, Jennett CJ, Farnsworth A, Tan J, Wrede CD, Castle PE, Saville M. Cervical screening with primary HPV testing or cytology in a population of women in which those aged 33 years or younger had previously been offered HPV vaccination: Results of the Compass pilot randomised trial. PLoS Med. 2017 Sep 19;14(9):e1002388.

a. Downgraded one level as studies have a high risk of bias concerning the randomisations process. Allocation concealment and baseline group differences were noted, indicating potential imbalances at the outset that may introduce bias.
b. I2 = 67.26%; unexplained and important heterogeneity
c. Pending decision from panel and corresponding threshold
d. Canfell et al. 2017 has not been included in the CIN2+ analysis because no events ini the cytologyc group.
e. Low and high risk studies show similar effects, so did not downgrade for risk of bias
f. High statistical heterogeneity (I^2= 64%) was considered not important given the consistency of results across studies.

g. Canfell 2017 has not been included into the CIN 3+ analysis because no events on the Cytology group

h. High statistical heterogeneity (I²= 78%) was considered not important given the consistency of results across studies.

i. High statistical heterogeneity (I²= 97%) was considered not important given the consistency of results across studies.

j. In Elfström et al. 2021, allocation was not concealed and the analysis was not deemed inappropriate.

k. Age ranges for this outcome in Oglivie et al. 2018 and Canfell et al. 2017 (25−−65 years) are lower than the PICO age range (30−−50 years).

Modelling studies on cervical cytology vs HPV detection tests

No modelling evidence was found relating to the following outcomes:

· Detection of Cervical Intraepithelial Neoplasia Grade 3 and above (CIN3+)

· Overdiagnosis of CIN2, CIN3 and AIS

· Pre-cancer treatments

· Major adverse events (direct consequence of pre-cancer treatment)

· HPV infection
· Preterm birth (PTB)

Outcomes	№ of studies	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with HPV detection test	Risk difference with cervical cytology
Death From cervical cancer: mortality	3 non-randomised studies[1,2,3]	⊕◯◯◯ Very low[a,b,c]	**RR 1.28** (0.94 to 2.62)[d]	Low	
				89 per 100.000[3,e]	**25 more per 100.000** (5 fewer to 144 more)
Diagnosis of cervical cancer: second-round screening	3 non-randomised studie)[1,2,3]	⊕◯◯◯ Very low[a,b,c]	**RR 1.17** (0.96 to 2.62)[d]	Low	
				283 per	**48 more per**

				100.000[3,e]	**100.000** (11 fewer to 458 more)
Detection of Cervical Intraepithelial Neoplasia Grade 2 and above (CIN2+)	3 non-randomised studies[1,2,3]	⊕◯◯◯ Very low[a,b,c]	**RR 1.00** (0.80 to 1.02)[d]	Low	
				5.840 per 100.000[3,e]	**0 fewer per 100.000** (1.168 fewer to 117 more)
Recall for assessment	1 non-randomised study[3]	⊕◯◯◯ Very low[a,b]	**RR 1.07** [d]	Low	
				38.430 per 100.000[3,e]	**2.690 more per 100.000**
Quality of life assessed with: Quality adjusted life years (QALYs)	2 non-randomised studies[1,3]	⊕◯◯◯ Very low[a,b,c]	**RR 1.00** (0.91 to 1.00)[d]	Low	
				14.007 per 100.000[3,e]	**0 fewer per 100.000** (1.261 fewer to 0 fewer)
Life years gained	2 non-randomised studies[1,2]	⊕◯◯◯ Very low[a,b]	**RR 1** (1 to 1)[d]	Low	
				14.000 per 100.000[3,e]	**0 fewer per 100.000** (0 fewer to 0 fewer)

1. Lew JB, Simms K, Smith M, Lewis H, Neal H, Canfell K. Effectiveness Modelling and Economic Evaluation of Primary HPV Screening for Cervical Cancer Prevention in New Zealand. PLoS One. 2016 May 17;11(5):e0151619.
2. Kim JJ, Burger EA, Regan C, Sy S. Screening for Cervical Cancer in Primary Care: A Decision Analysis for the US Preventive Services Task Force. JAMA. 2018 Aug 21;320(7):706-714.
3. Naber SK, de Kok IM, Matthijsse SM, van Ballegooijen M. The potential harms of primary human papillomavirus screening in over-screened women: a microsimulation study. Cancer Causes Control. 2016 Apr;27(4):569-81

a. Models had adequate credibility of model development including calibration, internal validation and cross-validation.

b. Downgraded 2 levels due to the risk of bias in the bodies of evidence that informed the input parameters. The model relies on estimates of each test's' accuracy, incidence/prevalence of premalignant lesions and transmission dynamics of HPV infection at different age groups, and assumptions about the rate of progression of adenomas.

c. Imprecision in the effects across models (structural uncertainty) is not fully explained by differences in diagnostic pathways or input parameters

d. The point estimate represents the median between models when there are 2 or more studies. Values in brackets represent the range of estimates across models.

e. Baseline risk was computed from the predicted events for primary HPV screening by a modelling study for the Netherlands.

1. Lew JB, Simms K, Smith M, Lewis H, Neal H, Canfell K. Effectiveness Modelling and Economic Evaluation of Primary HPV Screening for Cervical Cancer Prevention in New Zealand. PLoS One. 2016 May 17;11(5):e0151619.

2. Kim JJ, Burger EA, Regan C, Sy S. Screening for Cervical Cancer in Primary Care: A Decision Analysis for the US Preventive Services Task Force. JAMA. 2018 Aug 21;320(7):706-714.

3. Naber SK, de Kok IM, Matthijsse SM, van Ballegooijen M. The potential harms of primary human papillomavirus screening in over-screened women: a microsimulation study. Cancer Causes Control. 2016 Apr;27(4):569-81

(ii) Co-testing vs HPV detection

Empirical evidence on co-testing vs HPV detection tests

The same narrative review was discussed as in desirable effects. This review consists of key studies identified by the EC-CvC WG as sentinel evidence for evaluating co-testing versus the HPV detection test. The EC-CvC experts discussed the downstream consequences of the test accuracy of co-testing and acknowledge the indirectness of the evidence.

No empirical evidence was found relating to the following:·

- Death from cervical cancer: mortality
- Diagnosis of cervical cancer
- Recall for assessment: colposcopy/new test
- Quality of life
- Overdiagnosis of CIN2, CIN3 and AIS
- Pre-cancer treatments
- Major adverse events (direct consequence of pre-cancer treatment)
- HPV infection

EC-CvC WG judgement: co-testing vs HPV detection tests – *lower test specificity with co-testing, leading to more unnecessary colposcopies and treatments, was considered a moderate undesirable effect*.

The undesirable effect of co-testing vs HPV detection test is its lower specificity, which results in more unnecessary colposcopies and treatments, without meaningful improvement in the detection of CIN2+, compared with HPV detection alone. This has been summarised in the IARC Handbook on cervical screening (*IARC Handbooks* Vol. 18) (12).

Although the evidence available could not be quantified, the EC-CvC WG agreed that large studies (n = 197 997) found co-testing had a

- Preterm birth (PTB)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with HPV detection test	Risk difference with co-testing with cervical cytology and HPV detection test
Detection of Cervical Intraepithelial Neoplasia Grade 2 and above (CIN2+)	197997 (5 non-randomised studies)[1,2,3,4,5]	⊕◯◯◯ Very low[a]	-	It is not possible to compute the effect size, because both tests were applied to the same group of participants. However, narratively synthesising the results from both arms of these trials: as seen in Elfström et al. 2014, at 13 years follow-up, the rates of CIN2+ in the intervention arm were similar between individuals who were negative on HPV detection test and cervical cytology (double negative) and only HPV negative (1.63%, 1.11% to 2.32%). The non-significant gain in lowered risk for CIN2+ of being double negative (cytology and HPV negative) implies that double testing is not likely to represent an improvement in effect, while it certainly would increase costs and lower specificity. Similar results were seen in the Kaiser Permanente cohort (Castle et al. 2018), and in the POBASCAM, FOCAL and ARTISTIC trials.	
Detection of Cervical Intraepithelial Neoplasia Grade 3 and above (CIN3+)	691785 (4 non-randomised studies)[1,3,4,5]	⊕◯◯◯ Very low[a]	-	It is not possible to compute the effect size, because both tests were applied to the same group of participants. However, narratively synthesising the results from both arms of these trials: as seen in Elfström et al. 2014, individuals with a double negative test result had similar rates of CIN3+ to HPV-negative individuals, reaching a cumulative incidence of 0.84% (0.48% to 1.47%) in the intervention arm at 13 years. The non-significant gain in lowered risk for CIN3+ of being double negative (cytology and HPV negative) implies that double testing is not likely to represent an improvement in effect, while it certainly would increase costs and lower specificity. Similar results were seen in the Kaiser Permanente cohort (Castle et al. 2018), and in the POBASCAM and ARTISTIC trials.	

1. Inturrisi F, Rozendaal L, Veldhuijzen NJ, Heideman DAM, Meijer CJLM, Berkhof J. Risk of cervical precancer among HPV-negative women in the Netherlands and its association with previous HPV and cytology results: A follow-up analysis of a randomized screening study. PLoS Med. 2022 Oct

lower test specificity than HPV detection test. This translates to a lower positive predictive value (the number of test positives that have CIN2+ histology), which means that a higher number of unnecessary colposcopies and treatments are expected (which were priority outcomes for this question), without added benefit in CIN2+ detection and increased costs. The increased number of colposcopies associated with co-testing is also identified in the resource requirements section, through modelling studies. These undesirable effects in the absence of any benefit were judged moderate by the WG.

Supplementary evidence supporting EC-CvC WG judgement

One study used the National Breast and Cervical Cancer Early Detection Program of the Centers for Disease Control and Prevention, Atlanta, USA, and the Kaiser Permanente of Northern California cohort, USA, to quantify potential trade-offs with primary HPV detection compared with co-testing in 4 US populations with differing precancer or cancer prevalence. In all settings, co-testing required more laboratory tests and more colposcopies compared with primary HPV testing. The outcome measured was the number of additional colposcopies needed to find one additional CIN3 or cancer. The populations for this outcome included: no prior HPV test, and never or rarely screened. Therefore, this outcome and the subpopulations included differ from the PICO and are used as additional evidence. Overall, these data suggest that co-testing confers an unfavourable benefit-to-harm ratio over primary HPV testing (13).

28;19(10):e1004115.
2. Gottschlich A, Gondara L, Smith LW, Cook D, Martin RE, Lee M, Peacock S, Proctor L, Stuart G, Krajden M, Franco EL, van Niekerk D, Ogilvie G. Human papillomavirus-based screening at extended intervals missed fewer cervical precancers than cytology in the HPV For Cervical Cancer (HPV FOCAL) trial. Int J Cancer. 2022 Sep 15;151(6):897-905.
3. Elfström KM, Smelov V, Johansson AL, Eklund C, Nauclér P, Arnheim-Dahlström L, Dillner J. Long term duration of protective effect for HPV negative women: follow-up of primary HPV screening randomised controlled trial. BMJ. 2014 Jan 16;348:g130.
4. Gilham C, Sargent A, Kitchener HC, Peto J. HPV testing compared with routine cytology in cervical screening: long-term follow-up of ARTISTIC RCT. Health Technol Assess. 2019 Jun;23(28):1-44. doi: 10.3310/hta23280. PMID: 31219027; PMCID: PMC6600121.
5. Castle PE, Kinney WK, Xue X, Cheung LC, Gage JC, Zhao FH, Fetterman B, Poitras NE, Lorey TS, Wentzensen N, Katki HA, Schiffman M. Effect of Several Negative Rounds of Human Papillomavirus and Cytology Co-testing on Safety Against Cervical Cancer: An Observational Cohort Study. Ann Intern Med. 2018 Jan 2;168(1):20-29. doi: 10.7326/M17-1609. Epub 2017 Nov 28. PMID: 29181509.

a. Studies do not isolate the performance of HPV testing alone, but infer it from cotesting.

Modelling studies on co-testing vs HPV detection tests

No modelling evidence was found relating to the following outcomes:

· Overdiagnosis of CIN2, CIN3 and AIS

· Pre-cancer treatments

· Major adverse events (direct consequence of pre-cancer treatment)

· HPV infection

· Preterm birth (PTB)

Outcomes	№ of studies	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with HPV detection test	Risk difference with co-testing with cervical cytology and HPV detection test
Death from cervical cancer:		⊕◯◯◯	**RR 1.00**	Low	

mortality	2 non-randomised studies[1,2]	Very low[a,b]	(0.98 to 1.04)[c]	89 per 100.000[3,d]	**0 fewer per 100.000** (2 fewer to 4 more)
Diagnosis of cervical cancer: second-round screening	2 non-randomised studies)[1,2]	⊕◯◯◯ Very low[a,b]	**RR 1.00** (0.99 to 1.03)[c]	Low	
				283 per 100.000[3,d]	**0 fewer per 100.000** (3 fewer to 8 more)
Detection of Cervical Intraepithelial Neoplasia Grade 2 and above (CIN2+)	2 non-randomised studies[1,2]	⊕◯◯◯ Very low[a,b]	**RR 1.01** (1.01 to 1.02)[c]	Low	
				5840 per 100.000[3,d]	**58 more per 100.000** (58 more to 117 more)
Recall for assessment	1 non-randomised study[2]	⊕◯◯◯ Very low[a,b]	**RR 1.12**	Low	
				38.430 per 100.000[3,d]	**4612 more per 100.000**
Quality of life assessed with: Quality adjusted life years	1 non-randomised study[1]	⊕◯◯◯ Very low[a,b]	**RR 1** (1 to 1)[c]	Low	
				14.007 per 100.000[3,d]	**0 fewer per 100.000** (0 fewer to 0 fewer)
Life years gained	2 non-randomised studies[1,2]	⊕◯◯◯ Very low[a,b]	**RR 1** (1 to 1)[c]	Low	
				14.000 per 100.000[3,d]	**0 fewer per 100.000** (0 fewer to 0 fewer)

1. Lew JB, Simms K, Smith M, Lewis H, Neal H, Canfell K. Effectiveness Modelling and Economic Evaluation of Primary HPV Screening for Cervical Cancer Prevention in New Zealand. PLoS One. 2016 May 17;11(5):e0151619.
2. Kim JJ, Burger EA, Regan C, Sy S. Screening for Cervical Cancer in Primary Care: A Decision Analysis for the US Preventive Services Task Force. JAMA. 2018 Aug 21;320(7):706-714.
3. Naber SK, de Kok IM, Matthijsse SM, van Ballegooijen M. The potential harms of primary human papillomavirus screening in over-screened women: a microsimulation study. Cancer Causes Control. 2016 Apr;27(4):569-81

a. Models had adequate credibility of model development including calibration, internal validation and

	cross-validation. b. Downgraded 2 levels due to the risk of bias in the bodies of evidence that informed the input parameters. The model relies on estimates of each test's accuracy, incidence/prevalence of premalignant lesions and transmission dynamic of HPV infection at different age groups, and assumptions about the rate of progression of adenomas. c. Baseline risk was computed from the predicted events for primary HPV screening by a modelling study for the Netherlands. d. The point estimate represents the median between models when there are 2 or more studies. Values in brackets represent the range of estimates across models.	

Net balance

Net Balance

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Large net desirable: **Moderate net desirable:** **Small net desirable:** **Null net balance:** **Small net undesirable:** **Moderate net undesirable:** (i) Cervical cytology, (ii) Co-testing with cervical cytology and HPV detection test **Large net undesirable:**		**<u>EC-CvC WG judgement:</u> cervical cytology vs HPV detection tests** – *small desirable effects and large undesirable effects led to a judgement of net moderate undesirable balance.* **<u>EC-CvC WG judgement:</u> co-testing vs HPV detection tests** – *trivial desirable effects and moderate undesirable effects led to a judgement of net moderate undesirable balance.*

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Very low: **Low:** (ii) Co-testing with cervical cytology and HPV detection test **Moderate:** **High:** (i) Cervical cytology **No included studies:**		**EC-CvC WG judgement: cervical cytology vs HPV detection test** – *high certainty of evidence based on five large RCTs, supported by consistent findings from large observational studies.* **EC-CvC WG judgement: co-testing vs HPV detection tests** – *low certainty of evidence due to reliance on modelling and indirect comparisons from observational studies; available observational studies show trivial desirable effects and notable undesirable effects.* The EC-CvC WG noted that, prior to the 2015 EU guidelines endorsing HPV detection test, it was considered unethical to include an HPV-detection-only arm in trials. As a result, most available studies compare co-testing with cervical cytology rather than with HPV detection test alone. This indirectness, along with the lack of trial data that was synthesised, limits the certainty of the evidence. Although direct comparisons are unfeasible, large observational studies provide indirect evidence showing only trivial desirable effects of co-testing compared with HPV detection, alongside considerable undesirable effects – including reduced specificity, increased interventions and potential inequity.

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

Important uncertainty or variability:

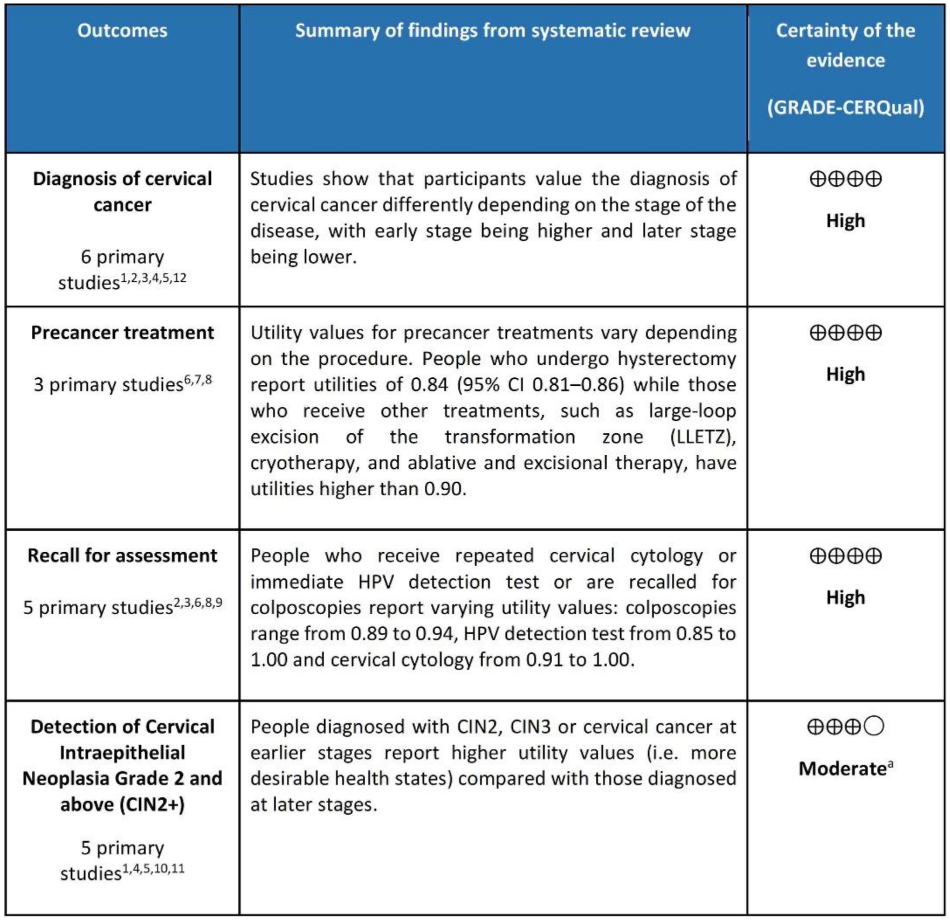
Possibly important uncertainty or variability:

Probably no important uncertainty or variability: (i) Cervical cytology, (ii) Co-testing with cervical cytology and HPV detection test

No important uncertainty or variability:

Search date: *21 June 2024*

Summary of findings from systematic review to evaluate patients' values and preferences regarding priority outcomes



Outcomes	Summary of findings from systematic review	Certainty of the evidence (GRADE-CERQual)
Diagnosis of cervical cancer 6 primary studies[1,2,3,4,5,12]	Studies show that participants value the diagnosis of cervical cancer differently depending on the stage of the disease, with early stage being higher and later stage being lower.	⊕⊕⊕⊕ **High**
Precancer treatment 3 primary studies[6,7,8]	Utility values for precancer treatments vary depending on the procedure. People who undergo hysterectomy report utilities of 0.84 (95% CI 0.81–0.86) while those who receive other treatments, such as large-loop excision of the transformation zone (LLETZ), cryotherapy, and ablative and excisional therapy, have utilities higher than 0.90.	⊕⊕⊕⊕ **High**
Recall for assessment 5 primary studies[2,3,6,8,9]	People who receive repeated cervical cytology or immediate HPV detection test or are recalled for colposcopies report varying utility values: colposcopies range from 0.89 to 0.94, HPV detection test from 0.85 to 1.00 and cervical cytology from 0.91 to 1.00.	⊕⊕⊕⊕ **High**
Detection of Cervical Intraepithelial Neoplasia Grade 2 and above (CIN2+) 5 primary studies[1,4,5,10,11]	People diagnosed with CIN2, CIN3 or cervical cancer at earlier stages report higher utility values (i.e. more desirable health states) compared with those diagnosed at later stages.	⊕⊕⊕◯ **Moderate**[a]

CI: Confidence interval; CIN: Cervical intraepithelial neoplasia.

Certainty of the evidence was assessed using the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative research) tool.

a We downgraded the certainty by one level due to serious concerns with risk of bias.

EC-CvC WG judgement: **cervical cytology and co-testing vs HPV detection tests** – *no important variability in how individuals value outcomes; both tests involve similar procedures and cancer prevention is valued equally regardless of the method.*

The EC-CvC WG notes that the values assessment provides evidence on the value people place on the outcomes themselves, which should be independent of the specific intervention used. For example, the prevention of one cancer is valued equally, regardless of whether it is prevented by HPV detection or cytology. It is noted that both procedures would most commonly be done following a speculum exam. The WG judged there is probably no important uncertainty or variability in how individuals value the outcomes.

References

1. Simonella L, Howard K, Canfell K. A survey of population-based utility scores for cervical cancer prevention. BMC Res Notes. 2014 Dec 11;7:899.

2. de Kok IMCM, Korfage IJ, van den Hout WB, Helmerhorst TJM, Habbema JDF, Essink-Bot ML, van Ballegooijen M. Quality of life assumptions determine which cervical cancer screening strategies are cost-effective. Int J Cancer. 2018 Jun 1;142(11):2383-2393.

3. Howard K, Salkeld G, McCaffery K, Irwig L. HPV triage testing or repeat Pap smear for the management of atypical squamous cells (ASCUS) on Pap smear: is there evidence of process utility? Health Econ. 2008 May;17(5):593-605.

4. Ock M, Park JY, Son WS, Lee HJ, Kim SH, Jo MW. Estimation of utility weights for human papilloma virus-related health states according to disease severity. Health Qual Life Outcomes. 2016 Nov 28;14(1):163.

5. Park J, Kim Y, Kim J, Kang S, Kim K, Kim JH, Moon HS, Lee EJ, Hur SY, Kim Y. Health-Related Quality of Life of Patients with Cervical Cancer According to the Duration of Treatment and Cancer Progression. Asian Pac J Cancer Prev. 2022 Jun 1;23(6):1945-1950.

6. Whynes DK, Sharp L, Cotton SC, Cruickshank M, Gray NM, Little J, Waugh N. Impact of alternative management policies on health-related quality of life in women with low-grade abnormal cervical cytology referred for colposcopy. Eur J Obstet Gynecol Reprod Biol. 2013 Jul;169(1):88-92.

7. Malnikow J, Kupperman M, Birch S, Chan BKS, Nuovo J. Management of the low-grade abnormal Pap smear: What are women's preferences?. The Journal of family practice. 2002 Oct;51(10):849.

8. Sawaya GF, Sanstead E, Alarid-Escudero F, Smith-McCune K, Gregorich SE, Silverberg MJ, Leyden W, Huchko MJ, Kuppermann M, Kulasingam S. Estimated quality of life and economic outcomes associated with 12 cervical cancer screening strategies: a cost-effectiveness analysis. JAMA internal medicine. 2019 Jul 1;179(7):867-78.

9. Korfage IJ, Essink-Bot ML, Westenberg SM, Helmerhorst T, Habbema JD, van Ballegooijen M. How distressing is referral to colposcopy in cervical cancer screening?: a prospective quality of life study. Gynecologic oncology. 2014 Jan 1;132(1):142-8.

10. Murasawa H, Konno R, Okubo I, Arakawa I. Evaluation of health-related quality of life for hypothesized medical states associated with cervical cancer. Asian Pacific Journal of Cancer Prevention. 2014;15(22):9679-85.

11. Zhao M, Zhang M, He L, Zuo C, Ding S, Golden AR, Cai L. Health-Related Quality of Life with Cervical Cancer and Precancer: A Cross-Sectional Study in Yunnan Province, China. Clin. Exp. Obstet. Gynecol. 2023, 50(8), 161.

12. Ju X, Canfell K, Howard K, Garvey G, Hedges J, Smith M, et al. Population-based utility scores for HPV infection and cervical squamous cell carcinoma among Australian Indigenous women. PLoS One.

	2021;16(7):e0254575.	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Favors the comparison: (i) Cervical cytology, (ii) Co-testing with cervical cytology and HPV detection test **Probably favors the comparison:** **Does not favor either the intervention or the comparison:** **Probably favors the intervention:** **Favors the intervention:** **Varies:** **Don't know:**		**EC-CvC WG judgement: cervical cytology vs HPV detection test** – *evidence favours HPV detection test; small desirable effects and moderate-large undesirable effects with no important variability in how individuals value outcomes.* **EC-CvC WG judgement: co-testing vs HPV detection tests** – *evidence favours HPV detection test; small desirable effects and moderate undesirable effects with no important variability in how individuals value outcomes.*

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

Large costs: (ii) Co-testing with cervical cytology and HPV detection test

Moderate costs:

Negligible costs and savings:

Moderate savings:

Large savings:

Varies: (i) Cervical cytology

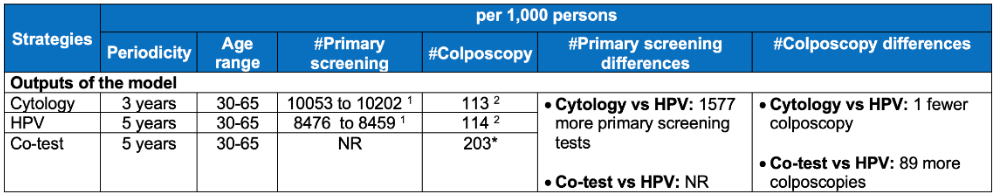
Don't know:

Date of the search: *January 2024*

The resources and costs were extracted from the modelling, and cost-effectiveness studies were included.

To support generalisability, the EC-CvC WG considered practical, context-independent measures, such as the number of referrals for triage, colposcopy or treatment per additional case detected, as far as possible. However, the studies reported only the number of primary screening tests and the number of colposcopy referrals after the primary screening.

Resources



Strategies	per 1,000 persons					
	Periodicity	Age range	#Primary screening	#Colposcopy	#Primary screening differences	#Colposcopy differences
Outputs of the model						
Cytology	3 years	30-65	10053 to 10202 [1]	113 [2]	• **Cytology vs HPV:** 1577 more primary screening tests • **Co-test vs HPV:** NR	• **Cytology vs HPV:** 1 fewer colposcopy • **Co-test vs HPV:** 89 more colposcopies
HPV	5 years	30-65	8476 to 8459 [1]	114 [2]		
Co-test	5 years	30-65	NR	203*		

NR: not reported

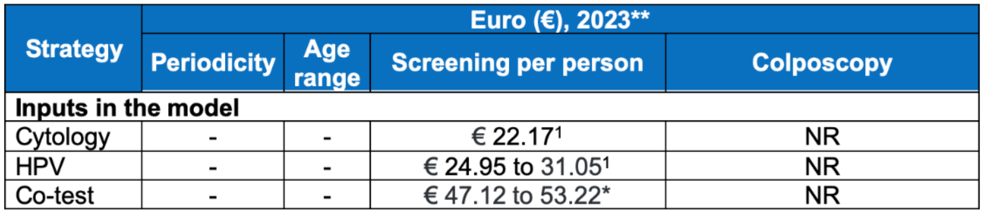
* Estimated using the values of cervical cytology + HPV detection test reported in Naber et al. 2016.

References

1. Kim JJ, Burger EA, Regan C, Sy S. Screening for Cervical Cancer in Primary Care: A Decision Analysis for the US Preventive Services Task Force. JAMA. 2018 Aug 21;320(7):706-714.

2. Naber SK, de Kok IM, Matthijsse SM, van Ballegooijen M. The potential harms of primary human papillomavirus screening in over-screened women: a microsimulation study. Cancer Causes Control. 2016 Apr;27(4):569-81.

Costs



Strategy	Euro (€), 2023**			
	Periodicity	Age range	Screening per person	Colposcopy
Inputs in the model				
Cytology	-	-	€ 22.17[1]	NR
HPV	-	-	€ 24.95 to 31.05[1]	NR
Co-test	-	-	€ 47.12 to 53.22*	NR

-: Not applicable

NR: not reported

*Estimated using the values of cervical ytology + HPV reported in Lew et al. 2016.

EC-CvC WG judgement: cervical cytology vs HPV detection test – *The EC-CvC WG agreed that the resources required for HPV detection tests are variable and context-dependent, and therefore judged the costs associated with cytology compared to HPV detection test as varies.*

The EC-CvC WG agreed that the model input on HPV detection tests may be outdated and not reflecting the real costs. The WG highlighted the changing cost of HPV detection tests over time, noting that prices have decreased in Europe in recent years, largely due to healthcare cost-control measures. They emphasised the role of centralisation of procurement to reduce unit costs. While the costs of cervical cytology are well established, the resource requirements for HPV detection testing remain less well defined. As a result, the WG concluded that the resources required for HPV detection are context-dependent and variable.

EC-CvC WG judgement: co-testing vs HPV detection test – *resources required are likely higher with co-testing due to added cytology processing and increased follow-up procedures*.

The EC-CvC WG concluded that the resource requirements for co-testing, compared with HPV detection alone, are likely to be large due to the additional resources needed to perform and process cervical cytology, as well as the additional colposcopies and treatments that would be indicated when co-testing is used compared with HPV.

Supplementary evidence supporting EC-CvC WG judgement

One study (14) performed a systematic review between 2014 and December 2021

**The costs were adjusted for inflation using GDP 2023 values reported by the International Monetary Fund (IMF) and converting the currency using the euro foreign exchange reference rates of the European Central Bank.

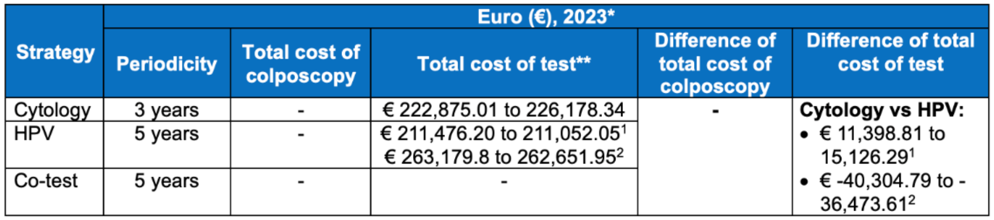
a. The cost of the HPV varied based on the acquisition volume, with lower costs for high volumes and higher costs for low volumes.

b. The cost for cytology and HPV screening includes the test, laboratory fees, and other related expenses (not reported).

<u>References</u>

1. Lew JB, Simms K, Smith M, Lewis H, Neal H, Canfell K. Effectiveness Modelling and Economic Evaluation of Primary HPV Screening for Cervical Cancer Prevention in New Zealand. PLoS One. 2016 May 17;11(5):e0151619.

Total costs



Strategy	Euro (€), 2023*				
	Periodicity	Total cost of colposcopy	Total cost of test**	Difference of total cost of colposcopy	Difference of total cost of test
Cytology	3 years	-	€ 222,875.01 to 226,178.34	-	**Cytology vs HPV:** • € 11,398.81 to 15,126.29[1] • € -40,304.79 to -36,473.61[2]
HPV	5 years	-	€ 211,476.20 to 211,052.05[1] € 263,179.8 to 262,651.95[2]		
Co-test	5 years	-	-		

-: Not possible to estimate.

*The costs were adjusted for inflation using GDP 2023 values reported by the International Monetary Fund (IMF) and converted into euros using the euro foreign exchange reference rates of the European Central Bank.

**The total costs were estimated by multiplying the number of tests by the cost per test.

1 Refers to the total cost when the HPV test is taken in high volume (€24.95). 2 Refers to the total cost when the HPV test is taken in low volume (€31.05).

<u>References</u>

1. Kim JJ, Burger EA, Regan C, Sy S. Screening for Cervical Cancer in Primary Care: A Decision Analysis for the US Preventive Services Task Force. JAMA. 2018 Aug 21;320(7):706-714.
2. Naber SK, de Kok IM, Matthijsse SM, van Ballegooijen M. The potential harms of primary human papillomavirus screening in over-screened women: a microsimulation study. Cancer Causes Control. 2016 Apr;27(4):569-81.

on European online platforms for the public procurement of HPV detection tests in Italy. It identified that the median unit price per HPV detection test was €10.75, ranging from €4.30 to €204.80. Additionally, the cost was volume dependent, with the unit price not exceeding €5 for 6 contracts with a volume of at least 100 000 tests.

One cost-effectiveness study conducted by WHO (7) in LMICs reported updated 2019 prices, with a mean of $15.09 for primary screening (including laboratory fees, transportation, etc.) and $8.15 for the test alone. Adjusted for 2023 using the GDP value of LMICs in Europe, these costs are equivalence to $19.99 and $10.80, respectively.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Very low: (i) Cervical cytology **Low:** **Moderate:** (ii) Co-testing with cervical cytology and HPV detection test **High:** **No included studies:**		**EC-CvC WG judgement: cervical cytology vs HPV detection test** – *very low certainty of evidence on resource requirements.* While the costs of cervical cytology are well established, the resource requirements for HPV detection testing remain less well defined. **EC-CvC WG judgement: co-testing vs HPV detection tests** – *moderate certainty of increased resource requirements due to added cytology and more unnecessary colposcopies and treatments.* The EC-CvC WG agreed that the certainty of evidence on increased resource requirements with co-testing, compared with HPV detection, is moderate. Large observational studies consistently report higher resource demands due to the added cytology component and increased rates of unnecessary colposcopies and treatments relative to HPV testing alone. The modelling studies with low certainty were not considered for this judgement.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

Favors the comparison: (ii) Co-testing with cervical cytology and HPV detection test

Probably favors the comparison: (i) Cervical cytology

Does not favor either the intervention or the comparison:

Probably favors the intervention:

Favors the intervention:

Varies:

No included studies:

***Date of the search:** January 2024*

We identified three cost-effectiveness studies; however, considered that the HPV input costs (based on data from 2007 and 2009) of these studies were not transferable. In the analysis, we included only one cost-effectiveness study.

(i) Cervical cytology vs HPV detection tests

Outcomes	№ of studies	Certainty of the evidence (GRADE)	ICER	Incremental cost per person	Incremental effect per person
ICER per QALY	1 cost-effectiveness study[1,a]	⊕◯◯◯ Very low[b,c,d]	Dominated (Median Euro -8,751.18, Range EuroRanghe	Range	
				Euro 8.14 to Euro 21.49 in the simulated population (e)*	-0.0016 to -0.0020 in the simulated population*

1. Jie-Bin Lew, Kate Simms,Megan Smith,Hazel Lewis,Harold Neal,Karen Canfell. Effectiveness Modelling and Economic Evaluation of Primary HPV Screening for Cervical Cancer Prevention in New Zealand.PLOS One. 2016 May 17;11(5):e0151619

a. Microsimulation model
b. Downgraded one level due to the risk of bias of the bodies of evidence that informed the input parameters. The model relies on estimates of the accuracy of each test, incidence/prevalence of cervical cancer at different age groups, and assumptions about the rate of progression and regression.
c. The model evaluated two strategies for the comparison between HPV vs. Pap. One strategy implemented follow-up with Co-test in 12 months for the intermediate risk group, while the other used colposcopy. The follow-up with Co-test reported a higher ICER.
d. The model did not evaluate the age range of 35-50; instead, it assessed the comparison in a population aged 30 to 69, which included additional rounds of screening. The study assumed that all women were screened with Pap between the ages of 20 to 29, which could affect the baseline risk for the comparison.
e. Adjusted for inflation using GDP 2023 values reported by the International Monetary Fund (IMF) and converted from New Zealand dollars to euros using the conversion rate reported by the European Central Bank on August 9, 2024.

*The study did not report the number of women simulated; consequently, the estimation of the costs and effects per person was not possible

(ii) Co-testing vs HPV detection tests

EC-CvC WG judgement: cervical cytology vs HPV detection test – *cost-effectiveness probably favours HPV detection test.*

While HPV detection is generally more cost-effective than cervical cytology – in part due to higher test-sensitivity and the possibility of extended screening intervals – the EC-CvC WG concluded that cost-effectiveness varies based on country-specific factors. These include differences in test procurement, programme delivery and existing screening infrastructure. Therefore, the WG judged that the evidence probably favours HPV detection, while recognising the need for adaptation in individual settings.

EC-CvC WG judgement: co-testing vs HPV detection tests – *cost-effectiveness favours HPV detection test.*

The EC-CvC WG agreed that co-testing is associated with higher costs due to the added cytology component and increased follow-up procedures (unnecessary colposcopies and treatments), with only trivial additional clinical benefit. Modelling studies show co-testing is more expensive and less effective than HPV detection so the WG judged that the evidence favours the comparison (HPV detection).

The WG highlights that there is no agreed-upon cost-effectiveness threshold specific to European countries, limiting the direct applicability of existing studies. Many cost-effectiveness analyses are over a decade old and may not reflect current pricing, implementation models or healthcare system priorities. Therefore, results should be interpreted with caution.

Supplementary evidence supporting EC-CvC WG judgement

Outcomes	№ of studies	Certainty of the evidence (GRADE)	ICER		
				Incremental cost per person	Incremental effects per person
ICER per QALY	1 cost-effectiveness study[1,a]	⨁⨁◯◯ Low[b,c,d]	Dominated (Median € -30,870.61 from € -30,979.16 to € -30,762.07) (e)	Range	
				€ 55.63 to € 56.03 in the simulated population (e)*	-0.0018 in the simulated population *

1. Lew JB, Simms K, Smith M, Lewis H, Neal H, Canfell K. Effectiveness Modelling and Economic Evaluation of Primary HPV Screening for Cervical Cancer Prevention in New Zealand. PLoS One. 2016 May 17;11(5):e0151619

a. Microsimulation model
b. The model evaluated the comparison in a population aged 30 to 69. The study assumed that all women were screened with Pap between 20 to 29 years old in both arms.
c. The model evaluated two strategies for the comparison between Co-test vs. Pap. One strategy implemented follow-up with Co-test in 12 months for the intermediate risk group, and the other used colposcopy for the intermediate risk group. However, the estimations were similar.
d. Downgraded one level due to the risk of bias of the bodies of evidence that informed the input parameters. The model rely on estimates of the accuracy of each test, incidence/prevalence of cervical cancer at different age groups, and assumptions about the rate of progression and regression.
e. Adjusted for inflation using GDP 2023 values reported by the International Monetary Fund (IMF) and converted from New Zealand dollars to euros using the exchange rate reported by the European Central Bank on August 9, 2024.

*The study did not report the number of women simulated; consequently, the estimation of the costs and effects per person was not possible

In addition to the systematic review, the EC-CvC WG considered evidence from 2 cost-effectiveness studies (15, 16) for the comparison of cytology vs HPV; however, the WG considered that the input costs for HPV detection (based on data from 2007 and 2009) were not transferable. The studies reported ICER per QALY ranging from €9,305 to €26,081 for the Netherlands context in 2007 and 2009, concluding that the implementation of HPV detection is cost-effective in both cases based on their specific thresholds.

The EC-CvC WG also discussed other cost-effectiveness studies based on LMICs. One of these was conducted by WHO as part of the cervical screening guidelines (7). This study simulated the effects and costs over a lifetime using the Policy1-Cervix model, incorporating inputs from 78 LMICs. The study compared different screening strategies, including HPV detection and cervical cytology, in an unvaccinated population. When compared with no screening, the study found that screening with HPV detection test without triage (screening every 5 years for ages 30–50 years) was consistently on the cost-effectiveness frontier; screening with HPV detection tests and any triaging strategy (screening every 5 years for age 30–50 years) was generally near the cost-effectiveness frontier; however, primary cytology screening strategies (screening every 3 years for age 30–50 years) were furthest from the cost-effectiveness frontier.

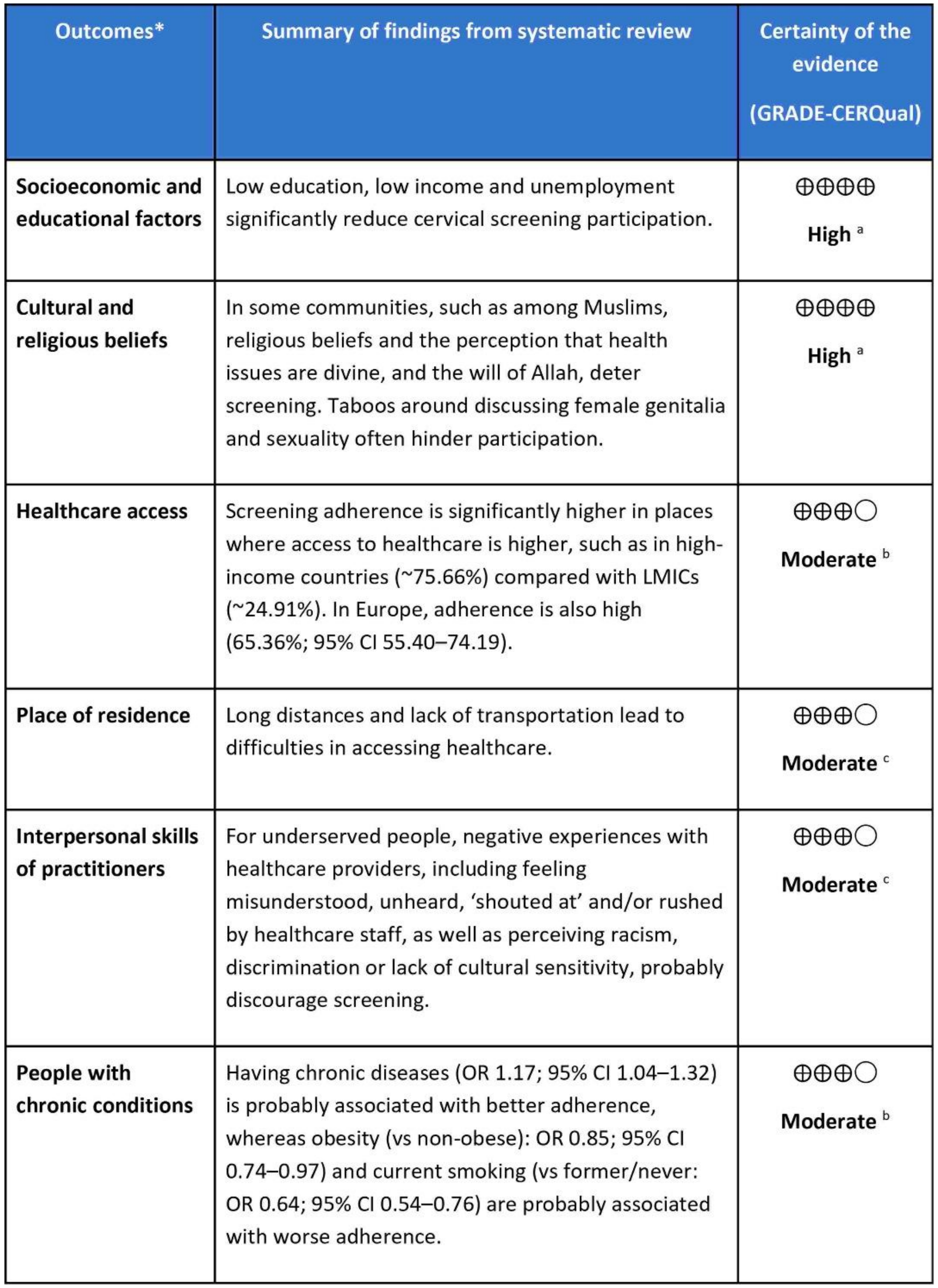
Additionally, when the strategies were compared against each other, HPV detection with cytology triage dominated cervical cytology with HPV triage, being less costly ($61 vs $80, US$ 2019) and providing greater

		benefits (65.7009 HALY vs 65.6859 HALY)(7). The evidence on cost-effectiveness considered reflects the dominance of the HPV strategy over cytology or co-testing, as the simulation showed that HPV has lower costs and higher effectiveness over a lifetime horizon.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Reduced: **Probably reduced:** (ii) Co-testing with cervical cytology and HPV detection test **Probably no impact:** (i) Cervical cytology **Probably increased:** **Increased:** **Varies:** **Don't know:**	No direct evidence was identified in systematic reviews or primary studies in relation to equity-related factors of cervical cytology or co-testing vs HPV detection test. The evidence tells us that socioeconomic and educational disadvantages, cultural discrimination, religious beliefs and difficulties in accessing healthcare probably decrease screening rates, particularly among low-income and migrant groups. Negative experiences with healthcare providers and specific challenges faced by some populations, such as transgender men, probably further hinder participation. However, interventions such as providing translated materials, ensuring female practitioners and offering free screenings can enhance participation and address some of these equity-related barriers. **Summary of findings from systematic review to evaluate equity in cervical screening participation**	**EC-CvC WG judgement: cervical cytology vs HPV detection tests** – *cervical cytology probably has no impact on equity compared with HPV detection*. The EC-CvC WG concluded that the impact on equity is probably minimal when comparing cervical cytology with HPV detection. While HPV detection may offer improvements in programme efficiency and sensitivity, both tests are already in use in many settings, and the differences in equity impact are unlikely to be substantial. The WG agreed that HPV detection test in allowing for self-collected sampling has potential to improve equity in access to screening. The WG considered that HPV detection using self-collected sampling, though not directly addressed in the comparison, could be a relevant factor influencing equity, particularly in under-screened populations.



Outcomes*	Summary of findings from systematic review	Certainty of the evidence (GRADE-CERQual)
Socioeconomic and educational factors	Low education, low income and unemployment significantly reduce cervical screening participation.	⊕⊕⊕⊕ **High** [a]
Cultural and religious beliefs	In some communities, such as among Muslims, religious beliefs and the perception that health issues are divine, and the will of Allah, deter screening. Taboos around discussing female genitalia and sexuality often hinder participation.	⊕⊕⊕⊕ **High** [a]
Healthcare access	Screening adherence is significantly higher in places where access to healthcare is higher, such as in high-income countries (~75.66%) compared with LMICs (~24.91%). In Europe, adherence is also high (65.36%; 95% CI 55.40–74.19).	⊕⊕⊕◯ **Moderate** [b]
Place of residence	Long distances and lack of transportation lead to difficulties in accessing healthcare.	⊕⊕⊕◯ **Moderate** [c]
Interpersonal skills of practitioners	For underserved people, negative experiences with healthcare providers, including feeling misunderstood, unheard, 'shouted at' and/or rushed by healthcare staff, as well as perceiving racism, discrimination or lack of cultural sensitivity, probably discourage screening.	⊕⊕⊕◯ **Moderate** [c]
People with chronic conditions	Having chronic diseases (OR 1.17; 95% CI 1.04–1.32) is probably associated with better adherence, whereas obesity (vs non-obese): OR 0.85; 95% CI 0.74–0.97) and current smoking (vs former/never: OR 0.64; 95% CI 0.54–0.76) are probably associated with worse adherence.	⊕⊕⊕◯ **Moderate** [b]

OR: Odds ratio.

Supplementary evidence supporting EC-CvC WG judgement

Self-collected sampling for HPV detection

While some studies suggest that self-collected HPV detection tests may be less uncomfortable or embarrassing than clinician-collected tests and could increase overall population coverage – particularly among groups with lower participation rates, such as immigrants and transgender men – no evidence was found assessing whether self-collected sampling will reduce existing inequalities (17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28)

EC-CvC WG judgement: co-testing vs HPV detection tests –*co-testing probably reduces equity compared with HPV detection*.

The EC-CvC WG judged that co-testing probably reduces equity, due to the greater complexity, higher cost and increased number of procedures associated with its implementation. These factors may exacerbate disparities, particularly in under-resourced settings, where access to cytology and follow-up services is already limited.

Certainty of the evidence was assessed using the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative research) tool.

* Based on 19 systematic reviews (804 primary studies).

a Although indirect evidence is provided by studies on cervical screening in general, no inconsistency was reported across results from studies on different tests and age ranges.

b We downgraded the certainty by one level due to serious imprecision.

c We downgraded the confidence by one level due to serious concerns with adequacy

References

1. Afsah YR, Kaneko N. Barriers to cervical cancer screening faced by immigrant Muslim women: a systematic scoping review. BMC Public Health. 2023 Nov 30;23(1):2375.
2. Chan DNS, So WKW. A Systematic Review of the Factors Influencing Ethnic Minority Women's Cervical Cancer Screening Behavior: From Intrapersonal to Policy Level. Cancer Nurs. 2017 Nov/Dec;40(6):E1-E30.
3. Chan DNS, Law BMH, So WKW, Fan N. Factors associated with cervical cancer screening utilisation by people with physical disabilities: A systematic review. Health Policy. 2022 Oct;126(10):1039-1050.
4. Chorley AJ, Marlow LA, Forster AS, Haddrell JB, Waller J. Experiences of cervical screening and barriers to participation in the context of an organised programme: a systematic review and thematic synthesis. Psychooncology. 2017 Feb;26(2):161-172.
5. Connolly D, Hughes X, Berner A. Barriers and facilitators to cervical cancer screening among transgender men and non-binary people with a cervix: A systematic narrative review. Prev Med. 2020 Jun;135:106071.
6. Crawford J, Ahmad F, Beaton D, Bierman AS. Cancer screening behaviours among South Asian immigrants in the UK, US and Canada: a scoping study. Health Soc Care Community. 2016 Mar;24(2):123-53.
7. Cudjoe J, Nkimbeng M, Turkson-Ocran RA, Commodore-Mensah Y, Han HR. Understanding the Pap Testing Behaviors of African Immigrant Women in Developed Countries: A Systematic Review. J Immigr Minor Health. 2021 Aug;23(4):840-856.
8. Dhillon N, Oliffe JL, Kelly MT, Krist J. Bridging Barriers to Cervical Cancer Screening in Transgender Men: A Scoping Review. Am J Mens Health. 2020 May-Jun;14(3):1557988320925691.
9. Gao X, Zhang W, Sun J, Adeloye D, Jin H, Rudan I, Song P, Jin M. Lifetime prevalence and adherence rate of cervical cancer screening among women living with HIV: a systematic review and meta-analysis. J Int AIDS Soc. 2023 May;26(5):e26090.
10. Giorgi Rossi P, Baldacchini F, Ronco G. The Possible Effects on Socio-Economic Inequalities of Introducing HPV Testing as Primary Test in Cervical Cancer Screening Programs. Front Oncol. 2014 Feb 10;4:20.
11. Greenley R, Bell S, Rigby S, Legood R, Kirkby V, McKee M; CBIG-SCREEN Consortium. Factors influencing the participation of groups identified as underserved in cervical cancer screening in

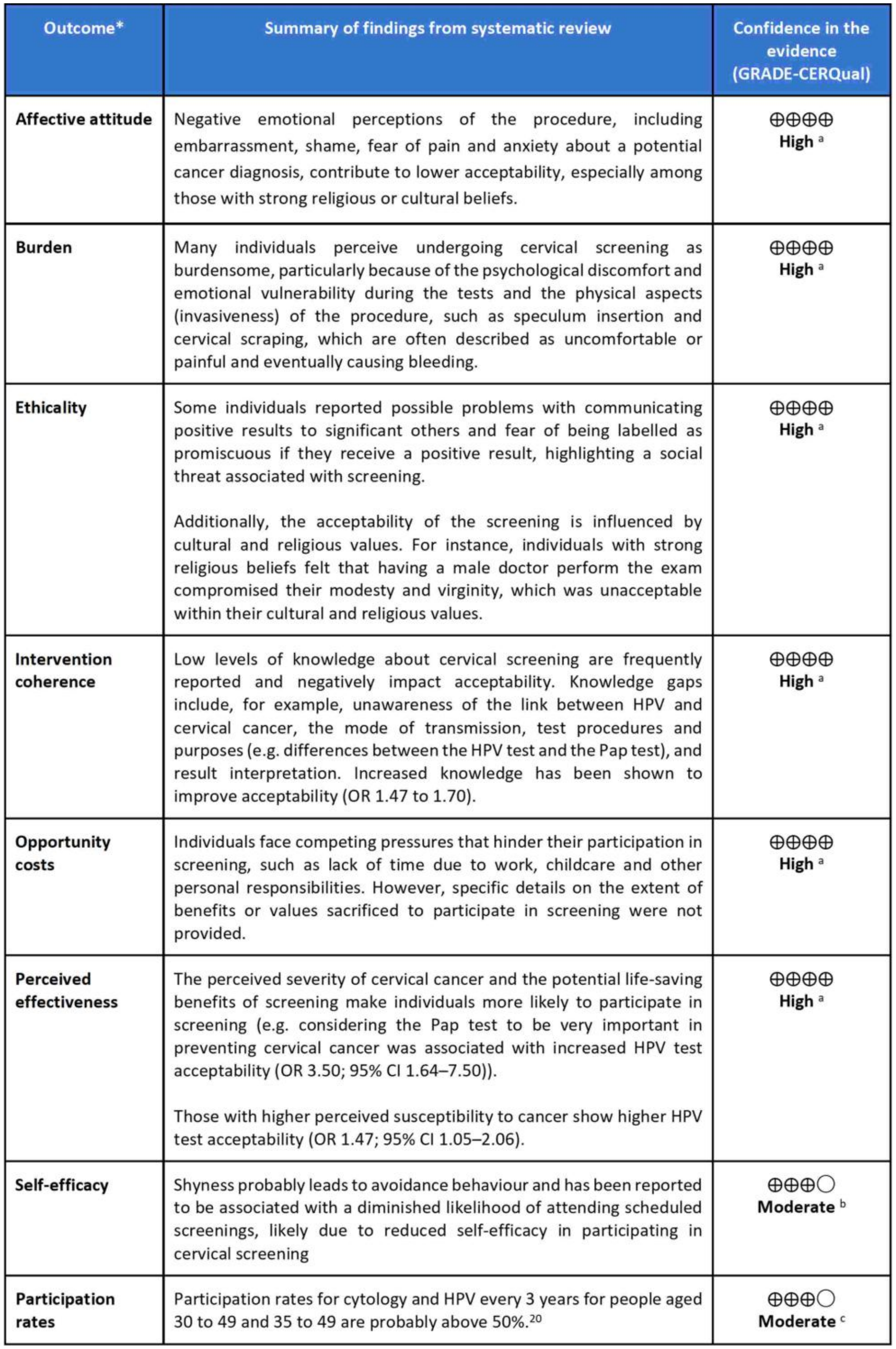
	Europe: a scoping review of the literature. Front Public Health. 2023 May 25;11:1144674. 12. Hendry M, Pasterfield D, Lewis R, Clements A, Damery S, Neal RD, Adke R, Weller D, Campbell C, Patnick J, Sasieni P, Hurt C, Wilson S, Wilkinson C. Are women ready for the new cervical screening protocol in England? A systematic review and qualitative synthesis of views about human papillomavirus testing. Br J Cancer. 2012 Jul 10;107(2):243-54. 13. Kirubarajan A, Leung S, Li X, Yau M, Sobel M. Barriers and facilitators for cervical cancer screening among adolescents and young people: a systematic review. BMC Womens Health. 2021 Mar 23;21(1):122. 14. Marques P, Nunes M, Antunes MDL, Heleno B, Dias S. Factors associated with cervical cancer screening participation among migrant women in Europe: a scoping review. Int J Equity Health. 2020 Sep 11;19(1):160. 15. Murfin J, Irvine F, Meechan-Rogers R, Swift A. Education, income and occupation and their influence on the uptake of cervical cancer prevention strategies: A systematic review. J Clin Nurs. 2020 Feb;29(3-4):393-415. 16. Vallone F, Lemmo D, Martino ML, Donizzetti AR, Freda MF, Palumbo F, Lorenzo E, D'Argenzio A, Caso D. Factors promoting breast, cervical and colorectal cancer screenings participation: A systematic review. Psychooncology. 2022 Sep;31(9):1435-1447. 17. Walji LT, Murchie P, Lip G, Speirs V, Iversen L. Exploring the influence of rural residence on uptake of organized cancer screening - A systematic review of international literature. Cancer Epidemiol. 2021 Oct;74:101995. 18. Wearn A, Shepherd L. Determinants of routine cervical screening participation in underserved women: a qualitative systematic review. Psychol Health. 2024 Jan-Feb;39(2):145-170. 19. Zhang W, Gao K, Fowkes FJI, Adeloye D, Rudan I, Song P, Jin M, Chen K. Associated factors and global adherence of cervical cancer screening in 2019: a systematic analysis and modelling study. Global Health. 2022 Dec 9;18(1):101.	

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
No: **Probably no:** **Probably yes:** **Yes:** (i) Cervical cytology **Varies:** (ii) Co-testing with cervical cytology	No direct evidence was identified from systematic reviews comparing the acceptability of HPV detection vs cervical cytology or co-testing. Most available data reflect general acceptability of cervical screening rather than head-to-head comparisons of screening tests used in different age groups. The evidence tells us that the acceptability of cervical screening is significantly influenced by emotional, cultural and practical barriers, including embarrassment, fear of pain, anxiety about test results, stigma and competing responsibilities, which reduce participation rates. While increased awareness and perceived severity of cervical cancer can improve participation, knowledge gaps about the screening process and its benefits further hinder acceptability.	**EC-CvC WG judgement:** **cervical cytology vs HPV detection tests** – *cervical cytology is an acceptable test strategy due to its longstanding use and familiarity among providers and individuals recieving screening.* The EC-CvC WG noted that although HPV detection is increasingly used, its acceptability may vary depending on how the test is delivered (e.g. self-collected vs

and HPV detection test **Don't know:**	**Summary of findings from systematic review to evaluate acceptability of cervical screening**	clinician-collected sampling). This judgement is based on indirect evidence, longstanding programmatic experience and additional considerations such as preferences for self-collected sampling. The current review addresses general screening acceptability rather than making a direct comparison between cervical cytology/co-testing and HPV detection. The WG experts highlighted that since both clinician-collected samples would require the same procedure, individuals' experiences would likely be similar. Although HPV self-sampling will also be the topic of a future review, the WG requested that be taken into consideration. The WG also considered that HPV detection test using self-collected sampling, though not directly addressed in the comparison, could be a relevant factor influencing acceptability, particularly in under-screened populations. **Supplementary evidence supporting EC-CvC WG judgement** Self-collected sampling for HPV detection Some studies comparing self-collected with clinician-collected HPV detection test suggest that many individuals prefer self-collection for cervical screening due to convenience, speed, privacy and reduced discomfort or embarrassment associated with pelvic exams. These studies suggest that self-collected sampling may increase screening participation, particularly among under-screened individuals. However, some individuals find the instructions for self-collected sampling confusing and are concerned about its accuracy, especially those who have more confidence in a



Outcome*	Summary of findings from systematic review	Confidence in the evidence (GRADE-CERQual)
Affective attitude	Negative emotional perceptions of the procedure, including embarrassment, shame, fear of pain and anxiety about a potential cancer diagnosis, contribute to lower acceptability, especially among those with strong religious or cultural beliefs.	⊕⊕⊕⊕ **High** [a]
Burden	Many individuals perceive undergoing cervical screening as burdensome, particularly because of the psychological discomfort and emotional vulnerability during the tests and the physical aspects (invasiveness) of the procedure, such as speculum insertion and cervical scraping, which are often described as uncomfortable or painful and eventually causing bleeding.	⊕⊕⊕⊕ **High** [a]
Ethicality	Some individuals reported possible problems with communicating positive results to significant others and fear of being labelled as promiscuous if they receive a positive result, highlighting a social threat associated with screening. Additionally, the acceptability of the screening is influenced by cultural and religious values. For instance, individuals with strong religious beliefs felt that having a male doctor perform the exam compromised their modesty and virginity, which was unacceptable within their cultural and religious values.	⊕⊕⊕⊕ **High** [a]
Intervention coherence	Low levels of knowledge about cervical screening are frequently reported and negatively impact acceptability. Knowledge gaps include, for example, unawareness of the link between HPV and cervical cancer, the mode of transmission, test procedures and purposes (e.g. differences between the HPV test and the Pap test), and result interpretation. Increased knowledge has been shown to improve acceptability (OR 1.47 to 1.70).	⊕⊕⊕⊕ **High** [a]
Opportunity costs	Individuals face competing pressures that hinder their participation in screening, such as lack of time due to work, childcare and other personal responsibilities. However, specific details on the extent of benefits or values sacrificed to participate in screening were not provided.	⊕⊕⊕⊕ **High** [a]
Perceived effectiveness	The perceived severity of cervical cancer and the potential life-saving benefits of screening make individuals more likely to participate in screening (e.g. considering the Pap test to be very important in preventing cervical cancer was associated with increased HPV test acceptability (OR 3.50; 95% CI 1.64–7.50)). Those with higher perceived susceptibility to cancer show higher HPV test acceptability (OR 1.47; 95% CI 1.05–2.06).	⊕⊕⊕⊕ **High** [a]
Self-efficacy	Shyness probably leads to avoidance behaviour and has been reported to be associated with a diminished likelihood of attending scheduled screenings, likely due to reduced self-efficacy in participating in cervical screening	⊕⊕⊕◯ **Moderate** [b]
Participation rates	Participation rates for cytology and HPV every 3 years for people aged 30 to 49 and 35 to 49 are probably above 50%.[20]	⊕⊕⊕◯ **Moderate** [c]

OR: Odds ratio.

clinician's' expertise (17, 18, 19, 20, 21, 22, 23, 24, 29, 25, 26, 27, 28).

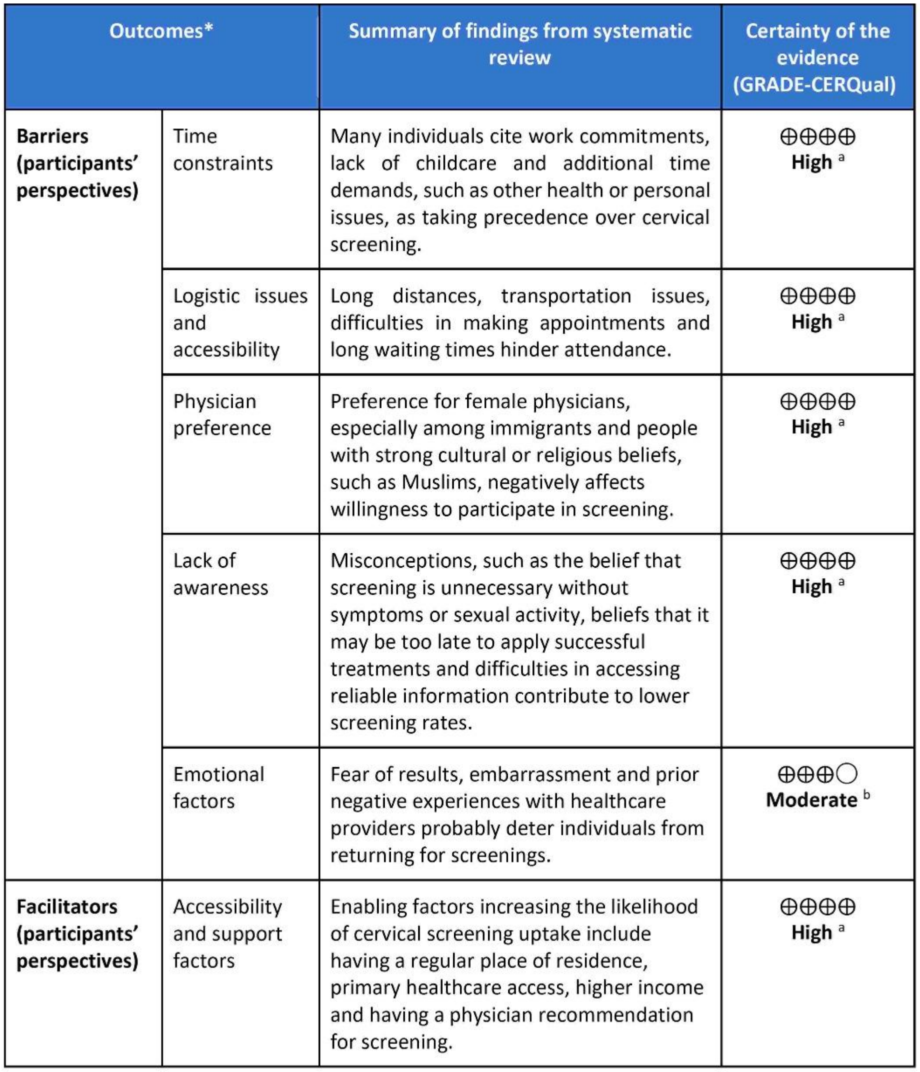
<u>EC-CvC WG judgement:</u> co-testing vs HPV detection tests – *acceptability of co-testing was judged to vary, depending on national practice and how added procedures are perceived by individuals and providers.*

Co-testing is a more complex procedure, involving the evaluation of two tests, and lacks strong evidence comparing its acceptability with HPV detection alone. The EC-CvC WG reported that adherence to screening was high in programmes offering both co-testing and cytology, but individuals' preferences specific to co-testing are not well documented.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
No: **Probably no:** **Probably yes:** **Yes:** (i) Cervical cytology **Varies:** (ii) Co-testing with cervical cytology and HPV detection test **Don't know:**	No direct evidence was identified in systematic reviews or primary studies related to the feasibility of cytology test or co-test versus HPV test. The available literature focused broadly on the feasibility of cervical screening programmes. The evidence tells us that cervical screening feasibility is significantly affected by a combination of practical, participant-related and systemic barriers. Key obstacles include competing life priorities, accessibility issues, emotional and awareness-related barriers, and preferences for female healthcare providers. Enabling factors, such as affordability, access to health services and physician recommendations, play a role in facilitating screening uptake. **Summary of findings from systematic review to evaluate feasibility of cervical screening participation**	**EC-CvC WG judgement: cervical cytology vs HPV detection tests** – *cervical cytology was judged feasible to implement due to its longstanding integration in screening programmes across Europe.* The EC-CvC WG noted that the more relevant question is the feasibility of HPV detection tests, concluding that, while initial investment in new infrastructure and training is needed, HPV detection tests are being increasingly adopted and integrated into national programmes in the EU. **Supplementary evidence supporting EC-CvC WG judgement** Self-collected sampling for HPV detection Self-collected sampling could facilitate implementation of screening by overcoming known barriers from participants’’ perspectives, such as difficulties accessing healthcare centres, time constraints and emotional factors such as embarrassment and discomfort. However, no studies have been found that compare implementation or sustainability of these tests in organised screening programmes (17, 18, 19, 20, 21, 22, 23, 24, 29, 25, 26, 27, 28) . **EC-CvC WG judgement: co-testing vs HPV detection tests** – *feasibility of implementing co-testing varies depending on existing infrastructure, resource availability and programme capacity.* The EC-CvC WG concluded that, while co-testing is technically feasible where both



Outcomes*		Summary of findings from systematic review	Certainty of the evidence (GRADE-CERQual)
Barriers (participants' perspectives)	Time constraints	Many individuals cite work commitments, lack of childcare and additional time demands, such as other health or personal issues, as taking precedence over cervical screening.	⊕⊕⊕⊕ **High** [a]
	Logistic issues and accessibility	Long distances, transportation issues, difficulties in making appointments and long waiting times hinder attendance.	⊕⊕⊕⊕ **High** [a]
	Physician preference	Preference for female physicians, especially among immigrants and people with strong cultural or religious beliefs, such as Muslims, negatively affects willingness to participate in screening.	⊕⊕⊕⊕ **High** [a]
	Lack of awareness	Misconceptions, such as the belief that screening is unnecessary without symptoms or sexual activity, beliefs that it may be too late to apply successful treatments and difficulties in accessing reliable information contribute to lower screening rates.	⊕⊕⊕⊕ **High** [a]
	Emotional factors	Fear of results, embarrassment and prior negative experiences with healthcare providers probably deter individuals from returning for screenings.	⊕⊕⊕◯ **Moderate** [b]
Facilitators (participants' perspectives)	Accessibility and support factors	Enabling factors increasing the likelihood of cervical screening uptake include having a regular place of residence, primary healthcare access, higher income and having a physician recommendation for screening.	⊕⊕⊕⊕ **High** [a]

Certainty of the evidence was assessed using the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative research) tool.

* Based on 13 systematic reviews (514 primary studies).
a Although indirect evidence is provided by studies on cervical screening in general, no inconsistency was reported across results from studies on different tests and age ranges.
b We downgraded the confidence by one level due to serious concerns with adequacy

References

cervical cytology and HPV detection infrastructure already exists, it adds logistical complexity, costs and resource demands, particularly in settings with limited capacity. No direct evidence was found comparing the feasibility of implementing or sustaining co-testing versus HPV detection alone.

	1. Afsah YR, Kaneko N. Barriers to cervical cancer screening faced by immigrant Muslim women: a systematic scoping review. BMC Public Health. 2023 Nov 30;23(1):2375. doi: 10.1186/s12889-023-17309-9. 2. Bongaerts TH, Büchner FL, Middelkoop BJ, Guicherit OR, Numans ME. Determinants of (non-)attendance at the Dutch cancer screening programmes: A systematic review. J Med Screen. 2020 Sep;27(3):121-129. 3. Chorley AJ, Marlow LA, Forster AS, Haddrell JB, Waller J. Experiences of cervical screening and barriers to participation in the context of an organised programme: a systematic review and thematic synthesis. Psychooncology. 2017 Feb;26(2):161-172. 4. Crawford J, Ahmad F, Beaton D, Bierman AS. Cancer screening behaviours among South Asian immigrants in the UK, US and Canada: a scoping study. Health Soc Care Community. 2016 Mar;24(2):123-53. 5. Cudjoe J, Nkimbeng M, Turkson-Ocran RA, Commodore-Mensah Y, Han HR. Understanding the Pap Testing Behaviors of African Immigrant Women in Developed Countries: A Systematic Review. J Immigr Minor Health. 2021 Aug;23(4):840-856. 6. Giorgi Rossi P, Baldacchini F, Ronco G. The Possible Effects on Socio-Economic Inequalities of Introducing HPV Testing as Primary Test in Cervical Cancer Screening Programs. Front Oncol. 2014 Feb 10;4:20. 7. Hendry M, Pasterfield D, Lewis R, Clements A, Damery S, Neal RD, Adke R, Weller D, Campbell C, Patnick J, Sasieni P, Hurt C, Wilson S, Wilkinson C. Are women ready for the new cervical screening protocol in England? A systematic review and qualitative synthesis of views about human papillomavirus testing. Br J Cancer. 2012 Jul 10;107(2):243-54. 8. Kirubarajan A, Leung S, Li X, Yau M, Sobel M. Barriers and facilitators for cervical cancer screening among adolescents and young people: a systematic review. BMC Womens Health. 2021 Mar 23;21(1):122. 9. Marques P, Nunes M, Antunes MDL, Heleno B, Dias S. Factors associated with cervical cancer screening participation among migrant women in Europe: a scoping review. Int J Equity Health. 2020 Sep 11;19(1):160. 10. Stuart G, D'Lima D. Perceived barriers and facilitators to attendance for cervical cancer screening in EU member states: a systematic review and synthesis using the Theoretical Domains Framework. Psychol Health. 2022 Mar;37(3):279-330. 11. Tatar O, Thompson E, Naz A, Perez S, Shapiro GK, Wade K, Zimet G, Gilca V, Janda M, Kahn J, Daley E, Rosberger Z. Factors associated with human papillomavirus (HPV) test acceptability in primary screening for cervical cancer: A mixed methods research synthesis. Prev Med. 2018 Nov;116:40-50. 12. Vallone F, Lemmo D, Martino ML, Donizzetti AR, Freda MF, Palumbo F, Lorenzo E, D'Argenzio A, Caso D. Factors promoting breast, cervical and colorectal cancer screenings participation: A systematic review. Psychooncology. 2022 Sep;31(9):1435-1447. 13. Wearn A, Shepherd L. Determinants of routine cervical screening participation in underserved women: a qualitative systematic review. Psychol Health. 2024 Jan-Feb;39(2):145-170.	

SUMMARY OF JUDGEMENTS

	(I) CERVICAL CYTOLOGY	(II) CO-TESTING WITH CERVICAL CYTOLOGY AND HPV DETECTION TEST
PROBLEM	**Yes**	
DESIRABLE EFFECTS	Small	Trivial
UNDESIRABLE EFFECTS	Large	Moderate
NET BALANCE	Moderate net undesirable	Moderate net undesirable
CERTAINTY OF EVIDENCE	High	Low
VALUES	Probably no important uncertainty or variability	Probably no important uncertainty or variability
BALANCE OF EFFECTS	Favors the comparison	Favors the comparison
RESOURCES REQUIRED	Varies	Large costs
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Moderate
COST EFFECTIVENESS	Probably favors the comparison	Favors the comparison
EQUITY	Probably no impact	Probably reduced
ACCEPTABILITY	Yes	Varies
FEASIBILITY	Yes	Varies

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
(i) Cervical cytology	●	○	○	○	○
(ii) Co-testing with cervical cytology and HPV detection test	●	○	○	○	○

CONCLUSIONS

Recommendation(s)

The EC-CvC WG recommends using HPV detection tests for primary screening in asymptomatic populations with cervix aged 30–50 years in the context of an organised population-based screening programme (strong recommendation, high-certainty of the evidence).

The EC-CvC WG recommends <u>not using</u> cervical cytology for primary screening in asymptomatic populations with cervix aged 30–50 years in the context of an organised population-based screening programme (strong recommendation, high-certainty of the evidence).

The EC-CvC WG recommends <u>not using</u> co-testing (combination of cervical cytology and HPV detection tests) for primary screening in asymptomatic populations with cervix aged 30–50 years in the context of an organised population-based screening programme (strong recommendation, low-certainty of the evidence).

Remark: The EC-CvC WG also recommends not initiating any new programmes based on cytology or co-testing. Existing cytology and co-testing programmes should transition to HPV-based screening.

Although it is outside the scope of the guideline, this recommendation may also be considered for programmes that are not organised and not population-based.

Justification

The overall justification for recommending HPV detection testing over cervical cytology and co-testing is grounded in the better clinical performance of HPV detection, particularly its high sensitivity for detecting high-grade lesions, which results in earlier diagnosis and treatment of precancer. HPV detection tests are considered more effective in preventing cervical cancer than cytology alone, with negligible differences when compared with co-testing. While cytology results in fewer referrals to colposcopy, this small benefit is outweighed by its lower detection rates and potential for delayed treatment. HPV detection offers higher effectiveness, cost-effectiveness and growing feasibility and acceptability in Europe. In contrast, co-testing provides only trivial additional benefit over HPV detection while increasing resource use and causing more unnecessary follow-up procedures (tests, colposcopies and treatments). Equity was a key consideration for the EC-CvC WG, who highlighted the potential for HPV detection tests (with the possibility for self-sampling) to improve access and reduce disparities. For the recommendation (i) comparing cytology with HPV detection, there was high certainty of evidence to support the recommendation. For the recommendation (ii) comparing co-testing with HPV detection tests, the certainty of evidence was low. However, evidence showed low certainty about trivial desirable effects alongside moderate/high undesirable effects, with net undesirable effects, and large costs associated with co-testing making the intervention not cost-effective. Furthermore, the EC-CvC WG considered that co-testing may reduce equity compared with HPV detection alone due to the need to combine it with cervical cytology, which may be less accessible to all individuals.

Subgroup considerations

This recommendation applies to general populations with cervix at average risk. Specific guidance for both higher-risk (immunocompromised) and lower-risk (vaccinated) populations will be detailed in later recommendations.

Implementation considerations

The EC-CvC WG agrees that ensuring equity is crucial to the implementation of this recommendation in screening programmes. Additionally, there is a need to expand the definition of equity to include all unscreened individuals with a cervix, not just those belonging to vulnerable or at-risk groups. A future section will explore programmatic questions about invitation strategies, focusing on how different methods can enhance coverage and equity.

The EC-CvC WG highlights that, in the implementation of this recommendation, quality assurance in HPV laboratories needs consideration to ensure the reliability of test results. The Quality Assurance Scheme being developed as part of EC-CvC will address many of the issues related to monitoring the implementation of this recommendation.

Monitoring and evaluation

The EC-CvC WG highlights the importance of closely monitoring the downstream impact of HPV-based screening programmes – including triage, colposcopy referrals and treatments – especially as they transition from cytology-based screening. The Quality Assurance Scheme, currently being developed under EC-CvC, will play a central role in supporting countries to monitor the implementation of this recommendation, ensuring that changes are evidence-based and do not lead to unintended consequences – for example, emergence of new inequalities in access or outcomes. The EC-CvC WG stresses that successful implementation depends not only on test performance but also on maintaining robust and adaptable monitoring systems that reflect the new realities of HPV-based screening programmes.

Research priorities

The EC-CvC WG considered research on ensuring equitable access to cervical screening in this age group a research priority.

REFERENCES SUMMARY

1. Arbyn, M., Raifu, A. O., Weiderpass, E., Bray, F., Anttila, A.. Trends of cervical cancer mortality in the member states of the European Union.Eur J Cancer; Oct 2009.

2. Simms, K. T., Steinberg, J., Caruana, M., Smith, M. A., Lew, J. B., Soerjomataram, I., Castle, P. E., Bray, F., Canfell, K.. Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020-99: a modelling study.Lancet Oncol; Mar 2019.

3. World Health Organisation, . Global strategy to accelerate the elimination of cervical cancer as a public health problem and its associated goals and targets for the period 2020 – 2030.United Nations General Assembly 2,; 2020.

4. ECIS , . ECIS - European Cancer Information System.2024.

5. Elfström, K. M., Smelov, V., Johansson, A. L., Eklund, C., Nauclér, P., Arnheim-Dahlström, L., Dillner, J.. Long term duration of protective effect for HPV negative women: follow-up of primary HPV screening randomised controlled trial.Bmj; Jan 16 2014.

6. 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.. 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.Lancet Oncol; Aug 2022.

7. Simms, Kate,T., Keane, Adam, Nguyen, Diep,Thi,Ngoc, Caruana, Michael, Hall, Michaela,T., Lui, Gigi, Gauvreau, Cindy, Demke, Owen, Arbyn, Marc, Basu, Partha, Wentzensen, Nicolas, Lauby-Secretan, Beatrice, Ilbawi, Andre, Hutubessy, Raymond, Almonte, Maribel, De Sanjosé, Silvia,, Kelly, Helen, Dalal, Shona, Eckert, Linda,O., Santesso, Nancy, Broutet, Nathalie, Canfell, Karen. Benefits, harms and cost-effectiveness of cervical screening, triage and treatment strategies for women in the general population.Nature Medicine; 2023.

8. 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.. Effect of Several Negative Rounds of Human Papillomavirus and Cytology Co-testing on Safety Against Cervical Cancer: An Observational Cohort Study.Ann Intern Med; Jan 2 2018.

9. Inturrisi, F., Rozendaal, L., Veldhuijzen, N. J., Heideman, D. A. M., Meijer, Cjlm, Berkhof, J.. Risk of cervical precancer among HPV-negative women in the Netherlands and its association with previous HPV and cytology results: A follow-up analysis of a randomized screening study.PLoS Med; Oct 2022.

10. Gottschlich, A., Gondara, L., Smith, L. W., Cook, D., Martin, R. E., Lee, M., Peacock, S., Proctor, L., Stuart, G., Krajden, M., Franco, E. L., van Niekerk, D., Ogilvie, G.. Human papillomavirus-based screening at extended intervals missed fewer cervical precancers than cytology in the HPV For Cervical Cancer (HPV FOCAL) trial.Int J Cancer; Sep 15 2022.

11. Gilham, C., Sargent, A., Kitchener, H. C., Peto, J.. HPV testing compared with routine cytology in cervical screening: long-term follow-up of ARTISTIC RCT.Health Technol Assess; Jun 2019.

12. International Agency for Research on Cancer (IARC), . Cervical cancer screening.IARC Handbooks of Cancer Prevention; 2022.

13. Das, S., Wentzensen, N., Sawaya, G. F., Egemen, D., Locke, A., Kinney, W., Lorey, T., Cheung, L. C.. Primary human papillomavirus testing vs cotesting: clinical outcomes in populations with different disease prevalence.J Natl Cancer Inst; Sep 1 2024.

14. Inturrisi F, , Berkhof J., . Pricing of HPV tests in Italian tender-based settings.J Med Econ; 2022.

15. Inge M C M de Kok, Joost van Rosmalen,Joakim Dillner,Marc Arbyn,Peter Sasieni,Thomas Iftner,Marjolein van Ballegooijen. Primary screening for human papillomavirus compared with cytology screening for cervical cancer in European settings: cost effectiveness analysis based on a Dutch microsimulation model.BMJ; 2012.

16. Johannes Berkhof, Veerle M. Coupe,Johannes A. Bogaards,Folkert J. van Kemenade,Theo J. Helmerhorst,Peter J. Snijders and Chris J. Meijer. The health and economic effects of HPV DNA screening in the Netherlands.International Journal of Cancer; 2010.

17. Braz, Natalia, Lorenzi, Noely, Sorpreso, Isabel, Aguiar, Lana, Baracat, Edmund, Soares, José. The acceptability of vaginal smear self-collection for screening for cervical cancer: A systematic review.Clinics; 2017.

18. Caleia, AI, Pires, C, Pereira, JF, Pinto-Ribeiro, F, Longatto-Filho, A. Self-Sampling as a Plausible Alternative to Screen Cervical Cancer Precursor Lesions in a Population with Low Adherence to Screening: A Systematic Review.BMC Public Health; 2020.

19. Camara , H, Zhang, Y, Lafferty, L, Vallely, AJ, Guy, R, Kelly-Hanku, A. Self-collection for HPV-based cervical screening: a qualitative evidence meta-synthesis.BMC Public Health; 2021.

20. Di Gennaro, G, Licata, F, Trovato, A, Bianco, A. Does self-sampling for human papilloma virus testing have the potential to increase cervical cancer screening? An updated meta-analysis of observational studies and randomized clinical trials.Front Public Health; 2022.

21. Huynh, J, Howard, M, Lytwyn, A. Self-collection for vaginal human papillomavirus testing: systematic review of studies asking women their perceptions.J Low Genit Tract Dis; 2010.

22. Morgan , K, Azzani, M, Khaing, SL, Wong, YL, Su, TT. Acceptability of Women Self-Sampling versus Clinician-Collected Samples for HPV DNA Testing: A Systematic Review.J Low Genit Tract Dis; 2019.

23. Nelson, EJ, Maynar , BR, Loux, T, Fatla, J, Gordon, R, Arnold, LD. The acceptability of self-sampled screening for HPV DNA: a systematic review and meta-analysis.Sex Transm Infect; 2017.

24. Nishimura, H, Yeh, PT, Oguntade, H, Kennedy, CE, Narasimhan, M. HPV self-sampling for cervical cancer screening: a systematic review of values and preferences.BMJ Glob Health; 2021.

25. Rosato, I, Dalla Zuanna, T, Tricarico, V, Barbiellini Amidei, C, Canova, C. Adherence to Cervical Cancer Screening Programs in Migrant Populations: A Systematic Review and Meta-Analysis.Int J Environ Res Public Health; 2023.

26. Stewart, DE, Gagliardi, A, Johnston, M, Howlett, R, Barata, P, Lewis, N, Oliver, T, Mai, V, HPV Self-collection Guidelines Panel, . Self-collected samples for testing of oncogenic human papillomavirus: a systematic review.J Obstet Gynaecol Can; 2007.

27. Tatar, O, Wade, K, McBride, E, Thompson, E, Head, KJ, Perez, S, Shapiro, GK, Waller, J, Zimet, G, Rosberger, Z. Are Health Care Professionals Prepared to Implement Human Papillomavirus Testing? A Review of Psychosocial Determinants of Human Papillomavirus Test Acceptability in Primary Cervical Cancer Screening.J Womens Health (Larchmt); 2020.

28. Verdoodt, F, Jentschke, M, Hillemanns, P, Racey, CS, Snijders, PJ, Arbyn, M. Reaching women who do not participate in the regular cervical cancer screening programme by offering self-sampling kits: a systematic review and meta-analysis of randomised trials.Eur J Cancer; 2015.

29. Racey, CS, Withrow, DR, Gesink, D. Self-collected HPV testing improves participation in cervical cancer screening: a systematic review and meta-analysis.Can J Public Health; 2013.