

## Recommendation 5

The expert panel suggests a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with an HPV test followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊕⊕⊕ evidence)

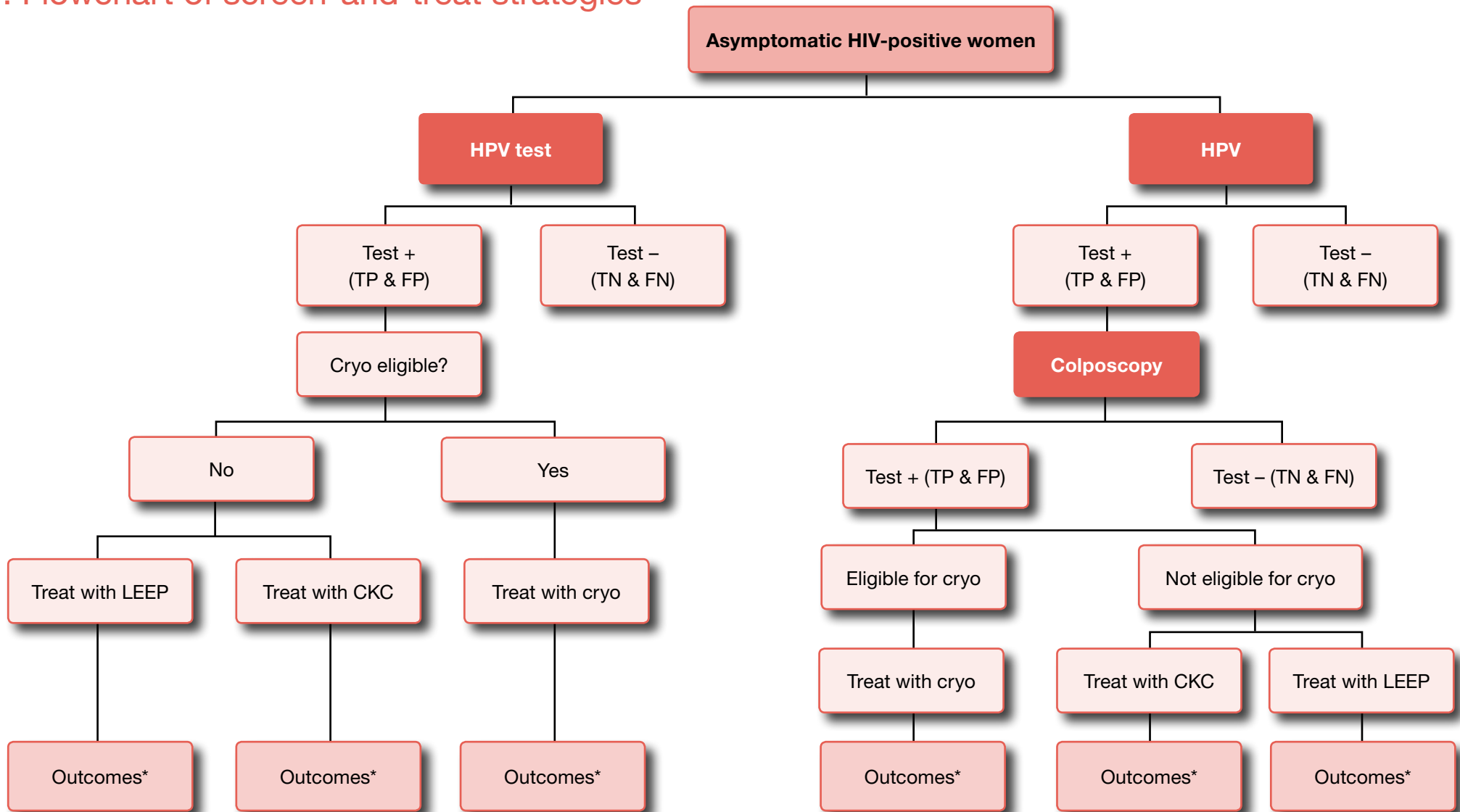
**Remarks:** The reductions in cancer and related mortality with either strategy outweigh the harms and costs of no screening, and were similar between the two strategies. Although overtreatment and, consequently, harms are reduced with the addition of colposcopy (with or without biopsy), there are more resource implications with colposcopy due to increased training of providers, quality control, waiting time, and the potential for more women to be lost to follow-up. The addition of colposcopy to an HPV test would also require a second visit. In countries without an existing screening strategy, an HPV test followed by colposcopy is not recommended. This recommendation applies to women regardless of HIV status.

### Evidence-to-recommendation table

Decision domain	Judgement	Summary of reason for judgement				
<b>Quality of evidence</b> <i>Is there high- or moderate-quality evidence?</i>	<table border="1"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input checked="" type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input checked="" type="checkbox"/>	There is low-quality evidence for the diagnostic test accuracy of HPV test followed by colposcopy and we did not have a direct comparison of this triage test to HPV test alone. There is low- to very-low-quality evidence for the effects of treatment and the natural progression of CIN from observational studies often with inconsistent results across studies. The link between test accuracy data and treatment effects is very uncertain.
Yes	No					
<input type="checkbox"/>	<input checked="" type="checkbox"/>					
<b>Balance of benefits versus harms and burdens</b> <i>Are you confident that the benefits outweigh the harms and burdens for the recommended strategy?</i>	<table border="1"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input checked="" type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The benefits of HPV test followed by colposcopy and HPV test alone may be similar. However, there were greater harms with HPV test alone (due to overtreatment with HPV test alone). There may also be slightly fewer cancers detected with HPV test followed by colposcopy.
Yes	No					
<input type="checkbox"/>	<input checked="" type="checkbox"/>					
<b>Values and preferences</b> <i>Are you confident about the assumed or identified relative values and are they similar across the target population?</i>	<table border="1"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	Yes	No	<input checked="" type="checkbox"/>	<input type="checkbox"/>	High value was placed on a screen-and-treat strategy versus no screening, since qualitative studies have shown that once women decide to be screened they find the screening tests and immediate treatment acceptable. High value was placed on the resources required and lower value on the harms.
Yes	No					
<input checked="" type="checkbox"/>	<input type="checkbox"/>					
<b>Resource implications</b> <i>Is the cost small relative to the net benefits for the recommended strategy?</i>	<table border="1"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	Yes	No	<input checked="" type="checkbox"/>	<input type="checkbox"/>	There may be additional resources required with the addition of colposcopy (with or without biopsy), there are more resource implications with colposcopy due to increased training of providers, quality control, waiting time, and potential for more women lost to follow-up. The addition of colposcopy to HPV test would also require a second visit.
Yes	No					
<input checked="" type="checkbox"/>	<input type="checkbox"/>					

# Evidence for an HPV test compared to an HPV test followed by colposcopy to screen for CIN2+ in women of HIV-positive status

## 1. Flowchart of screen-and-treat strategies



\* Outcomes are: mortality from cervical cancer, rate of cervical cancer detection, rate of CIN2+ detection, major bleeding, premature delivery, infertility, STI detection, major infections, and minor infections.

## 2. Evidence used for decision-making: HPV test compared to HPV test followed by colposcopic impression

### Diagnostic test accuracy

Pooled sensitivity HPV test	93% (95% CI: 87 to 96)	Pooled sensitivity colposcopic impression	95% (95% CI: 86 to 98)
Pooled specificity HPV test	88% (95% CI: 82 to 91)	Pooled specificity colposcopic impression	42% (95% CI: 26 to 61)

(Reference standard: colposcopy with biopsy when indicated)

### 2.1 Diagnostic test accuracy (DTA) evidence profile: HPV test compared to HPV test followed by colposcopic impression

Outcome	No. of studies (No. of patients) <sup>a</sup>	Study design	Factors that may decrease quality of evidence					DTA QoE	Effect per 1000 patients/year for pretest probability of 10%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		HPV test	HPV test followed by colposcopic impression	
True positives (patients with CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious <sup>b</sup>	None <sup>e</sup>	Serious <sup>d</sup>	None <sup>e</sup>	Undetected	⊕⊕⊕⊕ low	93 (87 to 96)	88	CRITICAL
<b>TP absolute difference</b>									5 more		
True negatives (patients without CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious <sup>b</sup>	None <sup>e</sup>	Serious <sup>d</sup>	None <sup>e</sup>	Undetected	⊕⊕⊕⊕ low	792 (738 to 819)	837	CRITICAL
<b>TN absolute difference</b>									55 fewer		
False positives (patients incorrectly classified as having CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious <sup>b</sup>	None <sup>e</sup>	Serious <sup>d</sup>	None <sup>e</sup>	Undetected	⊕⊕⊕⊕ low	108 (81 to 162)	63	CRITICAL
<b>FP absolute difference</b>									55 more		
False negatives (patients incorrectly classified as not having CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious <sup>b</sup>	None <sup>e</sup>	Serious <sup>d</sup>	None <sup>e</sup>	Undetected	⊕⊕⊕⊕ low	7 (4 to 13)	12	CRITICAL
<b>FN absolute difference</b>									5 fewer		

**Footnotes:**

- <sup>a</sup> This is the number of studies that assessed data for HPV test.
- <sup>b</sup> We used QUADAS to assess risk of bias. Many studies only performed one biopsy of an abnormal lesion. Colposcopy studies had unclear blinding of index test results. This was downgraded one level in the context of other factors, in particular indirectness.
- <sup>c</sup> Data for HPV test followed by colposcopy were calculated based on sensitivity and specificity of the two tests. Direct data were not available. Diagnostic test accuracy data were based on women of unknown HIV status; the data were not considered indirect and so the quality of evidence was not downgraded.
- <sup>d</sup> Estimates of HPV test and VIA sensitivity and specificity were variable despite similar cut-off values; inconsistency could not be explained by quality of studies. This was downgraded. This judgement was considered in the context of other factors, in particular imprecision.
- <sup>e</sup> Few participants contributed to colposcopy data. Therefore there were wide confidence intervals for colposcopy specificity, which may lead to different decisions depending on which confidence limits are assumed.

## 2.2 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies: HPV test compared to HPV test followed by colposcopy

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)						
	HPV +/- CKC	HPV +/- LEEP	HPV +/- cryo	HPV→colp imp +/- CKC	HPV→colp imp +/-LEEP	HPV→colp imp +/- cryo	No screen <sup>10</sup>
<b>Mortality from cervical cancer<sup>1</sup></b>	402	541	541	599	731	731	4350
<b>Cervical cancer incidence<sup>2</sup></b>	563	758	758	839	1024	1024	6075
<b>CIN2+ recurrence<sup>3</sup></b>	7617	10 500	10 500	11 215	13 954	13 954	79 575
<b>Undetected CIN2+ (FN)</b>	7000			12 000			–
<b>Major bleeding<sup>4</sup></b>	1726	454	68	1296	341	51	0
<b>Premature delivery<sup>5</sup></b>	742	585	626	682	564	594	500
<b>Infertility<sup>6</sup></b>	–	–	–	–	–	–	–
<b>Major infections<sup>7</sup></b>	179	257	27	134	193	20	0
<b>Minor infections<sup>8</sup></b>	1883	1211	1301	1414	910	977	0
<b>Unnecessarily treated (FP)</b>	108 000			63 000			–
<b>Cancer found at first-time screening<sup>9</sup></b>	2454			3545			0

**Footnotes:**

*The colours in the table:* In each GRADE evidence table, colour-coding is used to highlight the ‘desirability’ of the effects for that outcome relative to other outcomes. The continuum runs from dark gray (desirable) through light gray and light pink to dark pink (least desirable).

*The numbers in the table are based on*

- CIN2+ pretest probability 10% in women of HIV-positive status (Denny et al., 2008; De Vuyst et al., 2012; Joshi et al., 2012; Zhang et al., 2012)
- HPV test: pooled sensitivity 93% (95% CI: 87 to 96), pooled specificity 88% (95% CI: 82 to 91)
- Colposcopic impression: pooled sensitivity 95% (95% CI: 82 to 98), pooled specificity 42% (95% CI: 26 to 61)
- The overall QoE for each of these outcomes is very low ⊕⊕⊕⊕. Our lack of confidence in these effect estimates stems mainly from very-low-quality evidence for treatment effects and natural progression/history data.

- <sup>1</sup> We assume no mortality from cervical cancer in TN and FP. To calculate the mortality from cervical cancer in women of HIV-positive status, we assumed the same risk of mortality in women of unknown HIV status: 250 deaths per 350 women with cervical cancer. These numbers are based on Eastern Africa age-standardized rates of cervical cancer and mortality provided by WHO (<http://globocan.iarc.fr/>, accessed 30 October 2012).
- <sup>2</sup> We assume no cervical cancer in TN or FP. The calculations for cervical cancer incidence in women of HIV-positive status with persistent CIN2+ are based on a 2.7 standardized Risk Ratio of cancer when compared to women with unknown HIV status (De Vuyst et al., 2008). For women of unknown status, we assumed 350 cervical cancers per 14 000 women who have persistent CIN2+ (i.e. FN). This incidence is based on Eastern Africa age-standardized rate of cervical cancer of 350 cervical cancers per 1 000 000 women, of whom 2% have CIN2+ (20 000 women with CIN2+, and a subsequent 30% regression for a total of 14 000 with persistent CIN2+). These data are available from WHO (<http://globocan.iarc.fr/>, accessed 30 October 2012).
- <sup>3</sup> We assume no CIN2+ in TN and FP. Our calculations in the model are based on 90% natural persistence of CIN2+ with no treatment (10% regression) in FN. TP are treated and recurrence rates of CIN2+ are 5.3% in cryotherapy and LEEP, and 2.2% in CKC.
- <sup>4</sup> We assumed major bleed would be 0 in TN and FN as they were not treated. We assumed 0.000339 of the population treated with cryotherapy, 0.002257 with LEEP, and 0.001705 with CKC, based on pooled proportions in observational studies with no independent controls, will have major bleeding.
- <sup>5</sup> We assumed 5% population risk of premature delivery in 1% of women who become pregnant. Based on pooled meta-analysis of controlled observational studies, 0.001125 of the population treated with cryotherapy, 0.000925 with LEEP, and 0.001705 of the population treated with CKC will have premature delivery.
- <sup>6</sup> We did not identify any data about the risk of infertility after treatment for CIN2+.
- <sup>7</sup> We assumed major infection would be 0 in TN and FN as they were not treated. Based on pooled proportions from studies with no independent control, 0.000135 of the population treated with cryotherapy, 0.001279 with LEEP, and 0.000888 with CKC will have major infection.
- <sup>8</sup> We assumed minor infection would be 0 in TN and FN as they were not treated. Based on pooled proportions from studies with no independent control, 0.006473 of the population treated with cryotherapy, 0.006027 with LEEP, and 0.009368 with CKC will have minor infection.
- <sup>9</sup> Cancers detected at first-time screening calculated from Sankaranarayanan et al. (2005). Numbers for single screening tests were calculated as ‘screen-detected’ cancers in women who participated in the screening programme; and numbers for test with colposcopy were calculated as ‘screen-detected’ plus ‘clinically detected’ cancers. For a sequence of tests (e.g. HPV test followed by VIA), the greater number of cancers detected between tests was used. No cancers would be found in the ‘no screen’ group. This is not the annual incidence of cervical cancer (which is shown in a row above). It represents the cumulative rate of cancer development before screening started (i.e. the prevalence of cancer at the time when screening is first conducted).
- <sup>10</sup> ‘No screen’ numbers were calculated using the same assumptions above for FN, with the exception of premature delivery which was baseline risk in the population.

### 3. Evidence used for decision-making: HPV test compared to HPV test followed by colposcopy with biopsy when indicated

#### Diagnostic test accuracy

Pooled sensitivity HPV test	93% (95% CI: 87 to 96)
Pooled specificity HPV test	88% (95% CI: 82 to 91)

(Reference standard: colposcopy with biopsy when indicated)

#### 3.1 Diagnostic test accuracy (DTA) evidence profile: HPV test compared to HPV test followed by colposcopic impression

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True positives (patients with CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious <sup>b</sup>	None <sup>e</sup>	Serious <sup>d</sup>	None <sup>e</sup>	Undetected	⊕⊕⊕⊕ low	93 (87 to 96)	93	CRITICAL
<b>TP absolute difference</b>									0		
True negatives (patients without CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious <sup>b</sup>	None <sup>e</sup>	Serious <sup>d</sup>	None <sup>e</sup>	Undetected	⊕⊕⊕⊕ low	792 (738 to 819)	900	CRITICAL
<b>TN absolute difference</b>									108 fewer		
False positives (patients incorrectly classified as having CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious <sup>b</sup>	None <sup>e</sup>	Serious <sup>d</sup>	None <sup>e</sup>	Undetected	⊕⊕⊕⊕ low	108 (81 to 162)	0	CRITICAL
<b>FP absolute difference</b>									108 more		
False negatives (patients incorrectly classified as not having CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious <sup>b</sup>	None <sup>e</sup>	Serious <sup>d</sup>	None <sup>e</sup>	Undetected	⊕⊕⊕⊕ low	7 (4 to 13)	7	CRITICAL
<b>FN absolute difference</b>									0		

**Footnotes:**

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- <sup>c</sup> Data for HPV test followed by colposcopy +/- biopsy were calculated based on sensitivity and specificity of the two tests. Direct data were not available. Diagnostic test accuracy data were based on women of unknown HIV status; the data were not considered indirect and so the quality of evidence was not downgraded.
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### 3.2 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies: HPV test compared to HPV test followed by colposcopy with biopsy when indicated

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<b>Undetected CIN2+ (FN)</b>	7000			7000			–
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<b>Premature delivery<sup>5</sup></b>	742	585	626	612	540	558	500
<b>Infertility<sup>6</sup></b>	–	–	–	–	–	–	–
<b>Major infections<sup>7</sup></b>	179	257	27	83	119	13	0
<b>Minor infections<sup>8</sup></b>	1883	1211	1301	871	561	602	0
<b>Unnecessarily treated (FP)</b>	108 000			0			–
<b>Cancer found at first-time screening<sup>9</sup></b>	2454			3545			–

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  - <sup>10</sup> ‘No screen’ numbers were calculated using the same assumptions above for FN, with the exception of premature delivery which was baseline risk in the population.

## 4. References

### 4.1 References to studies included in meta-analysis of diagnostic test accuracy

- Agorastos T et al. Human papillomavirus testing for primary screening in women at low risk of developing cervical cancer. The Greek experience. *Gynecologic Oncology*, 2005, 96(3):714–720.
- Belinson J et al. Shanxi Province Cervical Cancer Screening Study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia. *Gynecologic Oncology*, 2001, 83(2):439–444.
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- Blumenthal PD et al. Adjunctive testing for cervical cancer in low resource settings with visual inspection, HPV, and the Pap smear. *International Journal of Gynecology & Obstetrics*, 2001, 72(1):47–53.
- Cardenas-Turanzas M et al. The performance of human papillomavirus high-risk DNA testing in the screening and diagnostic settings. *Cancer Epidemiology Biomarkers and Prevention*, 2008, 17(10):2865–2871.
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- Monsonogo J, Hudgens MG, Zerat L, Zerat JC, Syrjanen K, Halfon P et al. Evaluation of oncogenic human papillomavirus RNA and DNA tests with liquid-based cytology in primary cervical cancer screening: the FASE study. *International Journal of Cancer*, 2011, 129(3):691–701.

Petry KU et al. Inclusion of HPV testing in routine cervical cancer screening for women above 29 years in Germany: results for 8466 patients. *British Journal of Cancer*, 2003, 88(10):1570–1577.

Qiao YL et al. A new HPV–DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. *Lancet Oncology*, 2008, 9(10):929–936.

Shastri SS et al. Concurrent evaluation of visual, cytological and HPV testing as screening methods for the early detection of cervical neoplasia in Mumbai, India. *Bulletin of the World Health Organization*, 2005, 83(3):186–194.

Sodhani P et al. Test characteristics of various screening modalities for cervical cancer: a feasibility study to develop an alternative strategy for resource-limited settings. *Cytopathology*, 2006, 17(6):348–352

#### 4.2 References to studies included for diagnostic test accuracy of colposcopic impression

Belinson J et al. Shanxi Province Cervical Cancer Screening Study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia. *Gynecologic Oncology*, 2001, 83(2):439–444.

Cantor SB et al. Accuracy of colposcopy in the diagnostic setting compared with the screening setting. *Obstetrics & Gynecology*, 2008, 111(1):7–14.

Cremer ML et al. Digital assessment of the reproductive tract versus colposcopy for directing biopsies in women with abnormal Pap smears. *Journal of Lower Genital Tract Disease*, 2010, 14(1):5–10.

Cristoforoni PM et al. Computerized colposcopy: results of a pilot study and analysis of its clinical relevance. *Obstetrics & Gynecology*, 1995, 85(6):1011–1016.

Durdi GS et al. Correlation of colposcopy using Reid colposcopic index with histopathology – a prospective study. *Journal of the Turkish German Gynecology Association*, 2009, 10(4):205–207.

Ferris DG, Miller MD. Colposcopic accuracy in a residency training program: defining competency and proficiency. *Journal of Family Practice*, 1993, 36(5):515–520.

Homesley HD, Jobson VW, Reish RL. Use of colposcopically directed, four-quadrant cervical biopsy by the colposcopy trainee. *Journal of Reproductive Medicine*, 1984, 29(5):311–316.

Jones DE et al. Evaluation of the atypical Pap smear. *American Journal of Obstetrics & Gynecology*, 1987, 157(3):544–549.

Kierkegaard O et al. Diagnostic accuracy of cytology and colposcopy in cervical squamous intraepithelial lesions. *Acta Obstetrica et Gynecologica Scandinavica*, 1994, 73(8):648–651.

Mousavi AS et al. A prospective study to evaluate the correlation between Reid colposcopic index impression and biopsy histology. *Journal of Lower Genital Tract Disease*, 2007, 11(3):147–150.

Patil K et al. Comparison of diagnostic efficacy of visual inspection of cervix with acetic acid and Pap smear for prevention of cervical cancer: Is VIA superseding Pap smear? *Journal of SAFOG*, 2011, 3(3):131–134.

#### 4.3 Additional references

Denny L et al. Human papillomavirus infection and cervical disease in human immunodeficiency virus-1-infected women. *Obstetrics & Gynecology*, 2008, 111(6):1380–1387.

De Vuyst H et al. HIV, human papillomavirus, and cervical neoplasia and cancer in the era of highly active antiretroviral therapy. *European Journal of Cancer Prevention*, 2008, 17(6):545–554.

De Vuyst H et al. Prevalence and determinants of human papillomavirus infection and cervical lesions in HIV-positive women in Kenya. *British Journal of Cancer*, 2012, 107(9):1624–1630.

Joshi S et al. Screening of cervical neoplasia in HIV-infected women in India. *AIDS*, 2013, 27(4):607–615.

Sankaranarayanan R et al.; Osmanabad District Cervical Screening Study Group. A cluster randomized controlled trial of visual, cytology and human papillomavirus screening for cancer of the cervix in rural India. *International Journal of Cancer*, 2005, 116(4):617–623.

Zhang HY et al. HPV prevalence and cervical intraepithelial neoplasia among HIV-infected women in Yunnan Province, China: a pilot study. *Asian Pacific Journal of Cancer Prevention*, 2012, 13(1):91–96.