Recommendation 3

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 cytology followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

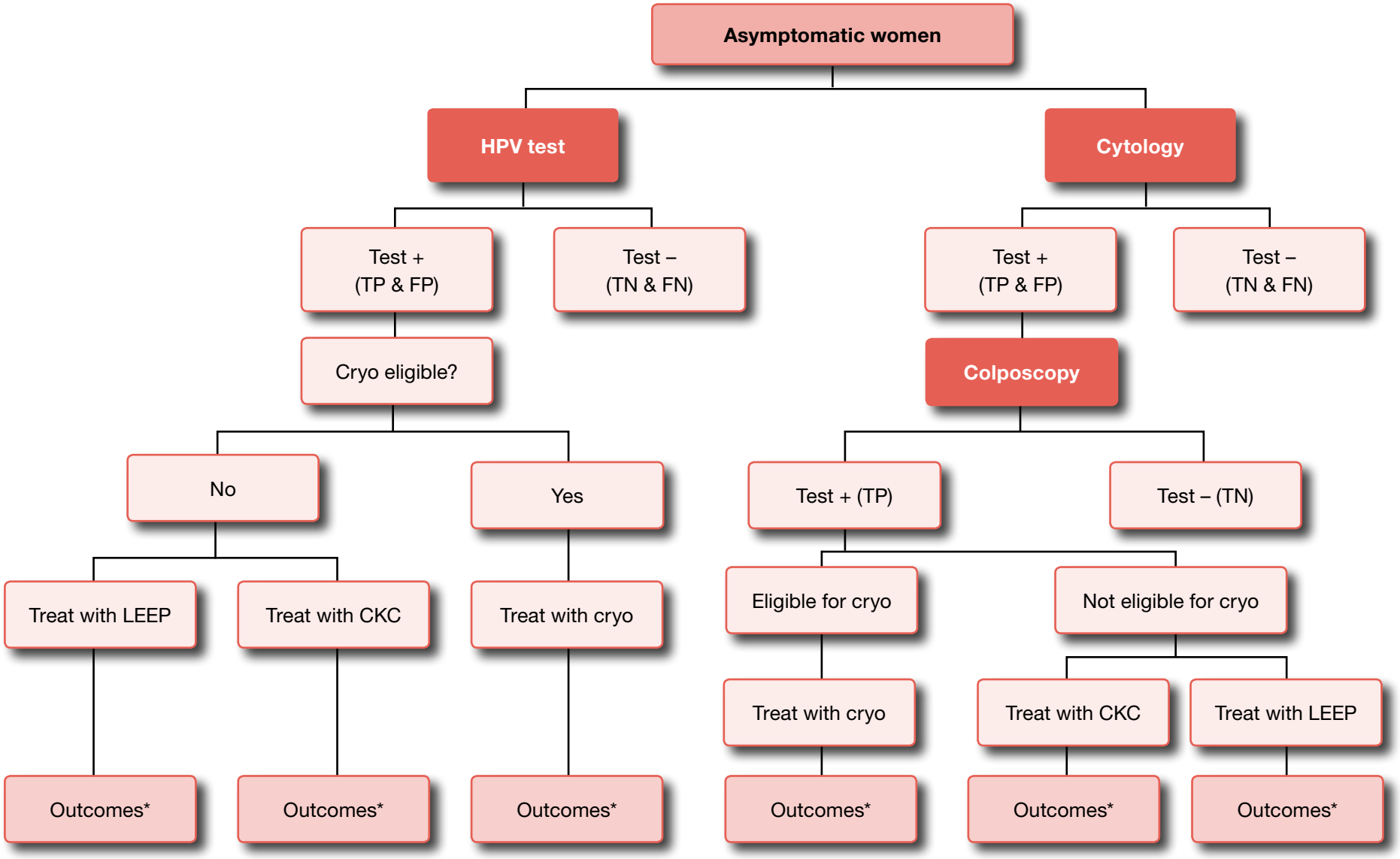
Remarks: The reductions in cancer and related mortality were slightly greater with an HPV test only compared to cytology followed by colposcopy. Although there may be overtreatment of populations with high HPV prevalence and consequently more harms, as well as fewer cancers seen at first-time screening with an HPV test, there are greater resources required in cytology programmes due to quality control, training, and waiting time. The addition of colposcopy also requires a second visit. However, in countries where an appropriate/high-quality screening strategy with cytology (referring women with ASCUS or greater results) followed by colposcopy already exists, either an HPV test or cytology followed by colposcopy could be used.

Evidence-to-recommendation table

Decision domain	Judgement	Summary of reason for judgement
Quality of evidence *Is there high- or moderate-quality evidence?*	Yes: ☐ No: ☒	There is low-quality evidence for the diagnostic test accuracy data for cytology followed by colposcopy compared 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.
Balance of benefits versus harms and burdens *Are you confident that the benefits outweigh the harms and burdens for the recommended strategy?*	Yes: ☐ No: ☒	The benefits of HPV test alone were greater than with cytology followed by colposcopy. However, there may be greater harms with HPV test alone (due to overtreatment with HPV test alone) and fewer cancers detected with HPV test.
Values and preferences *Are you confident about the assumed or identified relative values and are they similar across the target population?*	Yes: ☒ No: ☐	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.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes: ☒ No: ☐	There may be additional resources required in cytology programmes due to increased training of providers, quality control, and waiting time. Colposcopy following cytology also requires a second visit. However, in countries where an appropriate/high-quality screening strategy with cytology exists, resources would be required to change over to HPV test.

Evidence for HPV test compared to cytology followed by colposcopy to screen for CIN2+

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 cytology (ASCUS) followed by colposcopic impression to screen for CIN2+

Diagnostic test accuracy

Pooled sensitivity HPV test	94% (95% CI: 89 to 97)	Pooled sensitivity cytology (ASCUS)	70% (95% CI: 57 to 81)	Pooled sensitivity colposcopic impresssion	95% (95% CI: 86 to 98)
Pooled specificity HPV test	90% (95% CI: 86 to 93)	Pooled specificity cytology (ASCUS)	95% (95% CI: 92 to 97)	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 cytology (ASCUS) followed by colposcopic impression

Outcome	No. of studies (No. of patients)[a]	Study design	Factors that may decrease quality of evidence					DTA QoE	Effect per 1000 patients/year for pretest probability of 2%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		HPV test	Cytology followed by colposcopic impression	
True positives (patients with CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious [b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	19 (18 to 19)	13	CRITICAL
TP absolute difference									6 more		
True negatives (patients without CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious [b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	882 (843 to 911)	952	CRITICAL
TP absolute difference									70 fewer		
False positives (patients incorrectly classified as having CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious [b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	98 (69 to 137)	28	CRITICAL
FP absolute difference									70 more		
False negatives (patients incorrectly classified as not having CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious [b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	1 (1 to 2)	7	CRITICAL
FP absolute difference									6 fewer		

Footnotes:

[a] This is the number of studies that assessed data for HPV test and cytology.

[b] We used QUADAS to assess risk of bias. Half of the studies only performed one biopsy of an abnormal lesion and had unclear blinding of tests. Colposcopy studies had unclear blinding of index test results. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for cytology followed by colposcopy were calculated based on sensitivity and specificity of the two tests. Direct data were not available.

[d] Estimates of HPV test, cytology (ASCUS) and colposcopy sensitivity and specificity were variable despite similar cut-off values; inconsistency was not explained by quality of studies. This was downgraded one level in the context of other factors, in particular imprecision.

[e] Wide CI for sensitivity and specificity of cytology followed by colposcopy and therefore wide CI for TP, TN, FP, FN, 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 cytology (ASCUS) followed by colposcopic impression

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	Cyto→colp imp +/– CKC	Cyto→colp imp +/– LEEP	Cyto→colp imp +/– cryo	No screen[10]
Mortality from cervical cancer[1]	20	30	30	89	96	96	250
Cervical cancer incidence[2]	28	20	43	125	135	135	350
CIN2+ recurrence[3]	1088	1677	1677	4782	5194	5194	13 400
Undetected CIN2+ (FN)	1000			7000			–
Major bleeding[4]	1004	264	40	358	94	14	0
Premature delivery[5]	641	550	573	550	518	520	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	104	150	16	37	53	6	0
Minor infections[8]	1096	705	757	391	251	270	0
Unnecessarily treated (FP)	98 000			28 000			–
Cancer found at first-time screening[9]	2454			4794			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 2%
- HPV test: pooled sensitivity 94% (95% CI: 89 to 97), pooled specificity 90% (95% CI: 86 to 93)
- Cytology (ASCUS): pooled sensitivity 70% (95% CI: 57 to 81), pooled specificity 95% (95% CI: 92 to 97)
- Colposcopic impression: pooled sensitivity 95% (95% CI: 86 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.

[1] We assume no mortality from cervical cancer in TN and FP. To calculate the mortality from cervical cancer, we assumed 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).

[2] We assume no cervical cancer in TN or FP. To calculate cervical cancer incidence in women with persistent CIN2+, 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).

[3] We assume no CIN2+ in TN and FP. Our calculations in the model are based on 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see above for calculations). TP are treated and recurrence rates of CIN2+ are 5.3% in cryotherapy and LEEP, and 2.2% in CKC.

[4] 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.

[5] 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.

[6] We did not identify any data about the risk of infertility after treatment for CIN2+.

[7] 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.

[8] 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.

[9] 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 tests 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 conducted).

[10] '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.

2.3 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies by age

	HPV +/– CKC	HPV +/– LEEP	HPV +/– cryo	Cyto→colp imp +/– CKC	Cyto→colp imp +/–LEEP	Cyto→colp imp +/– cryo	No screen[10]
15–39 years[a]							
Mortality from cervical cancer	6	9	9	25	28	28	71
Cervical cancer incidence	8	12	12	36	39	39	100
CIN2+ recurrence	1109	1698	1698	4925	5337	5337	13 829
40–49 years[a]							
Mortality from cervical cancer	37	57	57	165	179	179	464
Cervical cancer incidence	52	79	79	231	250	250	650
CIN2+ recurrence	1062	1651	1651	4609	5022	5022	12 886
50–74 years[a]							
Mortality from cervical cancer	68	105	105	305	330	330	857
Cervical cancer incidence	96	146	146	427	462	462	1200
CIN2+ recurrence	1015	1604	1604	4293	4706	4706	11 943
Complications (same across all groups)							
Major bleeding[4]	1004	264	40	358	94	14	0
Premature delivery[5]	641	550	573	550	518	520	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	104	150	16	37	53	6	0
Minor infections[8]	1096	705	757	391	251	270	0

Footnotes:

[a] Events were calculated similar to Table 2.2. However, events for cervical cancer are based on incidence of cervical cancer in Eastern Africa of 100/1 000 000 cervical cancers per year in women age 15–39 years; 650 for age 40–49 years; and 1200 for age 50–74 years, provided by WHO (http://globocan.iarc.fr/, accessed 30 October 2012). It is assumed that the recurrence of CIN is constant across age groups but the incidence of cervical cancer and associated mortality increases, thus reducing the overall recurrence of CIN (a proportion of those with CIN will develop cancer or die). These data should be used primarily to make comparisons across screen-and-treat strategies, not within columns for different age groups.

[4,5,6,7,8,10] See footnotes for Table 2.2.

3. Evidence used for decision-making: HPV test compared to cytology (ASCUS) followed by colposcopic impression and biopsy when indicated to screen for CIN2+

Diagnostic test accuracy

Pooled sensitivity HPV test	94% (95% CI: 89 to 97)	Pooled sensitivity cytology (ASCUS)	70% (95% CI: 57 to 81)
Pooled specificity HPV test	90% (95% CI: 86 to 93)	Pooled specificity cytology (ASCUS)	95% (95% CI: 92 to 97)

(Reference standard: colposcopy with biopsy when indicated)

3.1 Diagnostic test accuracy (DTA) evidence profile: HPV test compared to cytology (ASCUS) followed by colposcopic impressed and biopsy when indicated

Outcome	No. of studies (No. of patients)[a]	Study design	Factors that may decrease quality of evidence					DTA QoE	Effect per 1000 patients/year for pretest probability of 2%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		HPV test	Cytology followed by colposcopy with biopsy	
True positives (patients with CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	19 (18 to 19)	14	CRITICAL
TP absolute difference									5 more		
True negatives (patients without CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	882 (843 to 911)	980	CRITICAL
TP absolute difference									98 fewer		
False positives (patients incorrectly classified as having CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	98 (69 to 137)	0	CRITICAL
FP absolute difference									98 more		
False negatives (patients incorrectly classified as not having CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	1 (1 to 2)	6	CRITICAL
FP absolute difference									5 fewer		

Footnotes:

[a] This is the number of studies that assessed data for HPV test and cytology.

[b] We used QUADAS to assess risk of bias. Half of studies only performed one biopsy of an abnormal lesion and had unclear blinding of tests. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for cytology followed by colposcopy +/– biopsy were calculated based on sensitivity and specificity of the two tests. Direct data were not available.

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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	Cyto→colp biopsy +/– CKC	Cyto→colp biopsy +/–LEEP	Cyto→colp biopsy +/– cryo	No screen[10]
Mortality from cervical cancer[1]	20	30	30	81	88	88	250
Cervical cancer incidence[2]	28	20	43	113	124	124	350
CIN2+ recurrence[3]	1088	1677	1677	4328	4762	4762	13 400
Undetected CIN2+ (FN)	1000			6000			–
Major bleeding[4]	1004	264	40	120	32	5	0
Premature delivery[5]	641	550	573	517	506	509	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	104	150	16	12	18	2	0
Minor infections[8]	1096	705	757	131	84	91	0
Unnecessarily treated (FP)	98 000			0			–
Cancer found at first-time screening[9]	2454			4794			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).

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- Cytology (ASCUS): Pooled sensitivity 70% (95% CI: 57 to 81), pooled specificity 95% (95% CI: 92 to 97)
- 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.

[1] We assume no mortality from cervical cancer in TN and FP. To calculate the mortality from cervical cancer, we assumed 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).

[2] We assume no cervical cancer in TN or FP. To calculate cervical cancer incidence in women with persistent CIN2+, 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).

[3] We assume no CIN2+ in TN and FP. Our calculations in the model are based on 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see above for calculations). TP are treated and recurrence rates of CIN2+ are 5.3% in cryotherapy and LEEP, and 2.2% in CKC.

[4] 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.

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[9] 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 tests 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 conducted).

[10] '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.

3.3 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies by age

	HPV +/– CKC	HPV +/– LEEP	HPV +/– cryo	Cyto→colp biopsy +/– CKC	Cyto→colp biopsy +/–LEEP	Cyto→colp biopsy +/– cryo	No screen[10]
15–39 years[a]							
Mortality from cervical cancer	6	9	9	23	25	25	71
Cervical cancer incidence	8	12	12	32	35	35	100
CIN2+ recurrence	1109	1698	1698	4457	4891	4891	13 829
40–49 years[a]							
Mortality from cervical cancer	37	57	57	150	164	164	464
Cervical cancer incidence	52	79	79	209	229	229	650
CIN2+ recurrence	1062	1651	1651	4174	4608	4608	12 886
50–74 years[a]							
Mortality from cervical cancer	68	105	105	276	303	303	857
Cervical cancer incidence	96	146	146	386	424	424	1200
CIN2+ recurrence	1015	1604	1604	3891	4325	4325	11 943
Complications (same across all groups)							
Major bleeding[4]	1004	264	40	120	32	5	0
Premature delivery[5]	641	550	573	517	506	509	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	104	150	16	12	18	2	0
Minor infections[8]	1096	705	757	131	84	91	0

Footnotes:

[a] Events were calculated similar to Table 3.2. However, events for cervical cancer are based on incidence of cervical cancer in Eastern Africa of 100/1 000 000 cervical cancers per year in women age 15–39 years; 650 for age 40–49 years; and 1200 for age 50–74 years, provided by WHO (http://globocan.iarc.fr/, accessed 30 October 2012). It is assumed that the recurrence of CIN is constant across age groups but the incidence of cervical cancer and associated mortality increases, thus reducing the overall recurrence of CIN (a proportion of those with CIN will develop cancer or die). These data should be used primarily to make comparisons across screen-and-treat strategies, not within columns for different age groups.

[4,5,6,7,8,10] See footnotes for Table 3.2.

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.

Bigras G, De Marval F. The probability for a Pap test to be abnormal is directly proportional to HPV viral load: Results from a Swiss study comparing HPV testing and liquid-based cytology to detect cervical cancer precursors in 13 842 women. *British Journal of Cancer*, 2005, 93(5):575–581.

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.

de Cremoux P et al. Efficiency of the hybrid capture 2 HPV DNA test in cervical cancer screening. A study by the French Society of Clinical Cytology. *American Journal of Clinical Pathology*, 2003, 120(4):492–499.

Depuydt CE et al. BD-ProExC as adjunct molecular marker for improved detection of CIN2+ after HPV primary screening. *Cancer Epidemiology Biomarkers and Prevention*, 2011, 20(4):628–637.

Hovland S et al. A comprehensive evaluation of the accuracy of cervical pre-cancer detection methods in a high-risk area in East Congo. *British Journal of Cancer*, 2010, 102(6):957–965.

Mahmud SM et al. Comparison of human papillomavirus testing and cytology for cervical cancer screening in a primary health care setting in the Democratic Republic of the Congo. *Gynecologic Oncology*, 2012, 124(2):286–291.

Monsonego J 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.

Pan Q et al. A thin-layer, liquid-based Pap test for mass screening in an area of China with a high incidence of cervical carcinoma: a cross-sectional, comparative study. *Acta Cytologica*, 2003, 47(1):45–50.

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.

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 Obstetricia 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.