Recommendation 2

Where resources permit, 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 VIA and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

In resource-constrained settings, where screening with an HPV test is not feasible, the expert panel suggests a strategy of screen with VIA and treat with cryotherapy (or LEEP when not eligible) over a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

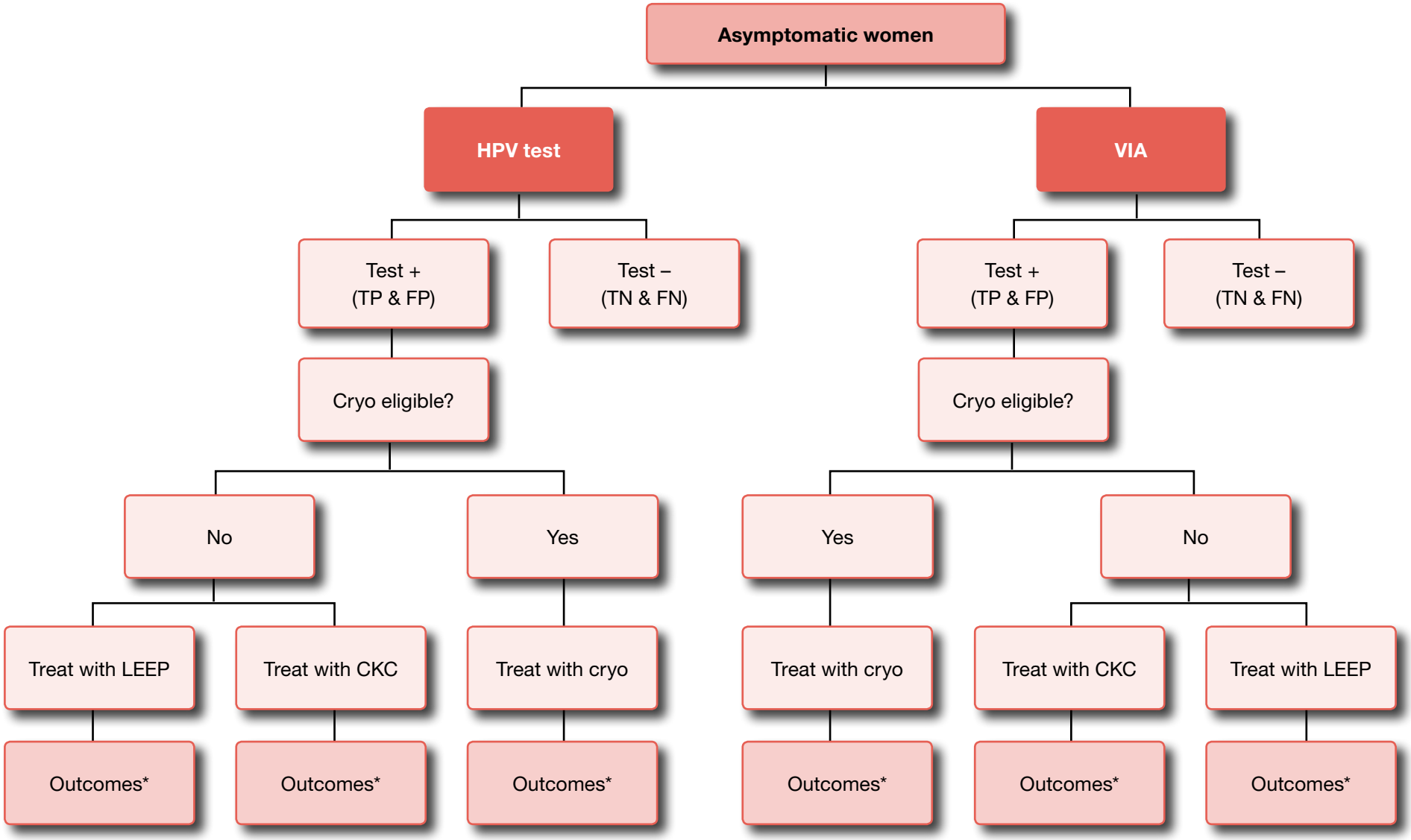
Remarks: The benefits of screen-and-treat with an HPV test or VIA, compared to no screening, outweighed the harms, but the reductions in cancer and related mortality were greater with an HPV test when compared to VIA. The availability of HPV testing is resource-dependent and, therefore, the expert panel suggests that an HPV test over VIA be provided where it is available, affordable, implementable, and sustainable over time. This recommendation applies to women regardless of HIV status.

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- to high-quality evidence for the diagnostic test accuracy data for all screen-and-treat strategies. 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 desirable effects of screen-and-treat strategies with cold knife conization may be greater than no screening, but may be similar to other screen-and-treat strategies with cryotherapy or LEEP. However, the risk of major and minor harms was greater when compared to those strategies.
Values and preferences *Are you confident about the assumed or identified relative values and are they similar across the target population?*	Yes ☒ / No ☐	A high value was placed on the complications (including risk of premature delivery) from treatment with cold knife conization after screening.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☒ / No ☐	Resources for cold knife conization are greater than for cryotherapy or LEEP.

Evidence for HPV test compared to VIA 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 VIA to screen for CIN2+

Diagnostic test accuracy

Pooled sensitivity HPV test	95% (95% CI: 84 to 98)	Pooled sensitivity VIA	69% (95% CI: 54 to 81)
Pooled specificity HPV test	84% (95% CI: 72 to 91)	Pooled specificity VIA	87% (95% CI: 79 to 92)

2.1 Diagnostic test accuracy (DTA) evidence profile

Outcome	No. of studies (No. of patients)	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	VIA	
True positives (patients with CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None[a]	None	None[b]	None	Undetected	⊕⊕⊕⊕ high	19 (17 to 20)	14 (11 to 16)	CRITICAL
TP absolute difference									5 more		
True negatives (patients without CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None[a]	None	Serious[b]	None[c]	Undetected	⊕⊕⊕⊖ moderate	823 (706 to 892)	853 (774 to 902)	CRITICAL
TP absolute difference									30 fewer		
False positives (patients incorrectly classified as having CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None[a]	None	Serious[b]	None[c]	Undetected	⊕⊕⊕⊖ moderate	157 (88 to 274)	127 (78 to 206)	CRITICAL
FP absolute difference									30 more		
False negatives (patients incorrectly classified as not having CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None[a]	None	None[b]	None	Undetected	⊕⊕⊕⊕ high	1 (0 to 3)	6 (4 to 9)	CRITICAL
FP absolute difference									5 fewer		

Footnotes:

[a] We used QUADAS to assess risk of bias. Many studies only performed one biopsy of an abnormal lesion. This was not downgraded and this was a borderline judgement.

[b] Estimates of HPV test and VIA sensitivity and specificity were variable despite similar cut-off values, and could not be explained by the quality of studies. For TP and FN this was a borderline judgement. We downgraded TN and FP and considered this in the context of other factors, in particular imprecision.

[c] Wide CI for TN and FP that may lead to different decisions depending on which of the confidence limits is assumed.

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

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	VIA +/– CKC	VIA +/– LEEP	VIA +/– cryo	No screen[10]
Mortality from cervical cancer[1]	20	30	30	81	88	88	250
Cervical cancer incidence[2]	28	43	43	112	124	124	350
CIN2+ recurrence[3]	1088	1677	1677	4328	4762	4762	13 400
Undetected CIN2+ (FN)	1000			6000			–
Major bleeding[4]	1511	397	60	1210	318	48	0
Premature delivery[5]	712	575	610	670	560	588	500
Infertility[6]	–	–	–	–	–	–	0
Major infections[7]	156	225	24	125	180	19	0
Minor infections[8]	1649	1061	1139	1321	850	913	0
Unnecessarily treated (FP)	157 000			127 000			–
Cancer found at first-time screening[9]	2454			3168			–

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%
- VIA: pooled sensitivity 69% (95% CI: 54 to 81), pooled specificity 87% (95% CI: 79 to 92)
- HPV test: pooled sensitivity 95% (95% CI: 84 to 98), pooled specificity 84% (95% CI: 72 to 91)
- 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	VIA +/– CKC	VIA +/– LEEP	VIA +/– 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]	1511	397	60	1210	318	48	0
Premature delivery[5]	712	575	610	670	560	588	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	156	225	24	125	180	19	0
Minor infections[8]	1649	1061	1139	1321	850	913	0

Footnotes:

[a] Events were calculated in a similar way to that used for 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. References to studies included in meta-analysis of diagnostic test accuracy

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.

De Vuyst H et al. Comparison of Pap smear, visual inspection with acetic acid, human papillomavirus DNA–PCR testing and cervicography. *International Journal of Gynecology & Obstetrics*, 2005, 89(2):120–126.

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.

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.