HPV16/18 normal colposcopy

Evidence summary report

PICO: For women who have a HPV16/18 positive test, no referral cytology or negative, pLSIL or LSIL cytology and a normal colposcopy what is the safety and effectiveness of a random biopsy, endocervical brush/lavage, endocervical curettage or endometrial sampling at colposcopy in detecting CIN3+?

A systematic review was conducted in 2023 for the above PICO which did not find any RCTs or pseudo-RCTs assessing the ability of any of these procedures to detect CIN3+ lesions for women who have a HPV16/18 positive test, no referral cytology or negative, pLSIL or LSIL cytology and a normal colposcopy. Therefore, on the advice of the Working Party, evidence reviews were undertaken to try and address the following questions:

1. What is the sensitivity of additional procedures to detect cervical cancer, CIN3+ (primary) CIN2+ (secondary) for women with a HPV positive test (ideally 16/18 positive) and a normal colposcopy either with no referral cytology or a negative, pLSIL or LSIL referral cytology?

2. What are the detection rates for cervical cancer, CIN3+ (primary) CIN2+ (secondary) of additional procedures for women with a HPV positive (ideally 16/18 positive) test and a normal colposcopy, by referral cytology (negative, pLSIL or LSIL) where possible?

3. What is the risk of cervical cancer, CIN3+ (primary) and CIN2+ (secondary) for women with a HPV positive (ideally 16/18 positive) test and a normal colposcopy, ideally stratified by cytology?

Summary of Findings

No studies were found that reported the diagnostic accuracy of additional procedures to detect cervical cancer, CIN3+ or CIN2+.

Four studies reported the CIN2+ yield of biopsies (random or targeted to nonsuspicious lesions), with or without endocervical curettage (ECC), in women with HR-HPV positive (only one study reported the rate of HPV16/18), negative, LSIL or ASC-US cytology and normal colposcopy. In the most comparable study (25% with HPV16/18 and negative (NILM) cytology), women underwent a single random biopsy. The detection rate of CIN2+ in HPV16/18+, was 8.6% (19/220) [95% CI 5.6-13.1]; in HPV16+, 10.5% (16/152) - 8 CIN2, 7 CIN3, 1 >CIN3; and in HPV18+, 4.4% (3/68) - 2 CIN2, 1 CIN3]. In a pooled analysis of 17 population-based screening studies with unknown rate of HPV16/18, women underwent random 4-quadrant biopsies +/- ECC. The pooled rate of CIN2+ detected in those with negative cytology was 2.1% (27/1283) - 22 CIN2, 5 CIN3; and in those with ASC-US/LSIL was 8.0% (74/921) - 51 CIN2, 22 CIN3, 1 cancer. In a study reported in this analysis which met out

inclusion criteria and was age restricted to 35-45 years, women underwent a 4-quadrants random biopsy at the SCJ and ECC. The rate of CIN2+ detected in those with normal cytology was 1.7% (2/116) [95% CI 0.3-5.6]; in those with ASC-US was 2.8% (1/36) [95% CI 0.1-13]; and in those with LSIL was 12.5% (4/32) [95% CI 4.1-27.5]. Another study included women with HR-HPV, negative cytology (NILM, ASCUS or AGC) and normal colposcopy, but all participants had at least slight acetowhitening, leading to targeted biopsies. Most women (85%, n=125) had a transformation zone type 3 and underwent ECC. The rate of CIN2+ detected (either by biopsies or ECC, separated results not reported) was 2.7% (4/146).

pLSIL or LSIL cytology was reported in three studies. In one study, CIN2+ was detected on LLETZ and the risk was 22.7% (5/22).

The other two studies reported the risk over the follow-up period. In one study, the 3-year risk of CIN2+ was 6.3% (11/175) in women with borderline nuclear abnormalities (BNA) and 12.9% (12/93) in women with mild dyskaryosis. In the other study, with 2 years of follow-up, the risk of CIN3+ by baseline cytology, was: 3.9% (15/388) [95% CI 2.2-6.3] for normal cytology; 8.2% (37/451) [95% CI 5.8-11.1] for ASC-US; and 8.4% (42/500) [95% CI 6.1-11.2] for LSIL. The risk of CIN2+ was: 7.2% (28/388) [95% CI 4.8-10.3] for normal cytology; 13.7% (62/451) [95% CI 10.7-17.3] for ASC-US; and 17.8% (89/500) [95% CI 14.5-21.4] for LSIL.

Detailed Findings

Evidence review for 2023 guidelines

Searches: EMBASE and Medline databases were searched in May 2023 by combining terms for normal colposcopy and the interventions of interest or excisional procedures. The search was conducted from 2005 onwards and was limited to articles published in English. Full details of the search strategy are included in the Appendices.

Results:

Question 1: What is the sensitivity of additional procedures to detect cervical cancer, CIN3+ (primary) CIN2+ (secondary) for women with a HPV positive test (ideally 16/18 positive) and a normal colposcopy either with no referral cytology or a negative, pLSIL or LSIL referral cytology?

For women with a 16/18 HPV positive test and negative or low-grade cytology and a normal colposcopy no studies were found that reported the diagnostic accuracy of combining standard colposcopy with any of the interventions of interest.

Question 2: What are the detection rates for cervical cancer, CIN3+ (primary) CIN2+ (secondary) of additional procedures for women with a HPV positive (ideally 16/18 positive) test and a normal colposcopy, by referral cytology (negative, pLSIL or LSIL) where possible?

For women with a normal colposcopy with positive HPV best and negative or low-grade cytology on referral:

- three studies reported the CIN2+ yield of **random biopsies with or without performing an ECC** (Huh 2014, Song 2015, Hu 2017 – includes Song 2015 data)
- one study reported on the effects of obtaining **ECC for women with T3TZ and targeted biopsies** of nonsuspicious findings (Wittenborn 2023)
- no studies were identified that reported on other additional interventions of interest.

Results are presented in

Table 1.

Table 1. Results of studies reporting on the effect of performing random biopsies with or without ECC for women with a normal colposcopy who have a positive high-risk HPV test, and negative, pLSIL or LSIL cytology

Study	Study design	Population and Intervention	Results
Non-targeted (random) biopsies			
Huh 2014 (United States of America)	Cross-sectional *ATHENA (Addressing the Need for Advanced HPV Diagnostics) Trial* conducted across 61 sites.	**HPV (16/18/other) positive** women aged ≥25 years with **negative (NILM) cytology** who underwent colposcopy in 2008-2009 due to positive screening test (HPV or cytology). Subgroup of women **with negative colposcopy (satisfactory colposcopy but without visible cervical lesions)** underwent a single random biopsy at the SCJ. N = 880 HPV 16/18: 17.3%/7.7% No targeted biopsies obtained or ECC performed.	***CIN2+ yield*** *with single random biopsy* *Rate of CIN2+ detected on random biopsy only:* NILM cytology and HPV16+: 10.5% (16/152) - 8 CIN2, 7 CIN3, 1 >CIN3 NILM cytology and HPV18+: 4.4% (3/68) - 2 CIN2, 1 CIN3 NILM cytology and HPV16/18+: 8.6% (19/220) [95% CI 5.6-13.1] NILM cytology and HPV other+: 2.3% (15/660) [95% CI 1.4-3.7] - 9 CIN2, 6 CIN3
Non-targeted (random) biopsies +/- endocervical curettage (ECC)			
Song 2015 (China) *Reported in Hu 2017*	Cross-sectional *SPOCCS (Shanxi Province Cervical Cancer Screening Study) 1*	**HPV (16/18/other) positive** women aged 35-45 years with **normal, ASC-US or LSIL cytology** who underwent colposcopy in 1999. All women underwent colposcopy regardless of screening test result. Subgroup of women **with negative colposcopy (no lesions in any quadrant)** underwent a random biopsy in four quadrants at the SCJ. It was acceptable to take more than one biopsy per quadrant depending on the colposcopic impression. ECC was performed in all women. Normal cytology: N = 116 ASC-US cytology: N = 36 LSIL cytology: N = 32 % HPV 16/18: NR No targeted biopsies obtained.	***CIN2+ yield*** *with random biopsy and/or ECC* *Rate of CIN2+ detected on random biopsy and/or ECC:* Normal cytology and HPV16/18/other+: 1.7% (2/116) [95% CI 0.3-5.6] ASC-US cytology and HPV16/18/other+: 2.8% (1/36) [95% CI 0.1-13] LSIL cytology and HPV16/18/other+: 12.5% (4/32) [95% CI 4.1-27.5] *Rate of CIN2+ detected on random biopsy only or ECC only:* NR

Study	Study design	Population and Intervention	Results
Hu 2017 (China)	Cross-sectional Pooled analysis of 17 population-based screening studies*	**HR-HPV (not defined) positive** women aged 15-59 years with **negative, or ASC-US/LSIL cytology** who underwent colposcopy in 1999-2008 due to positive screening test (VIA, HPV, or cytology). Subgroup of women with **negative colposcopy (no lesion in any quadrant)** underwent random 4-quadrant punch biopsies (± ECC) at the SCJ. Negative cytology: N = 1283 ASC-US/LSIL cytology: N = 921 % HPV 16/18: NR No targeted biopsies obtained. Number of women who underwent ECC NR.	***CIN2+ yield** with random biopsy and/or ECC* *Rate of CIN2+ detected on random biopsy* and/or *ECC:* Negative cytology and HR-HPV+: 2.1% (27/1283) - 22 CIN2, 5 CIN3 ASC-US/LSIL cytology and HR-HPV+: 8% (74/921) - 51 CIN2, 22 CIN3, 1 cancer *Rate of CIN2+ detected on random biopsy only or ECC only:* NR
Targeted biopsy of non-suspicious findings +/- Endocervical curettage (ECC)			
Wittenborn 2023 (Germany)	Cross-sectional	**HPV (16/18/other) positive** women (age range NR) who underwent colposcopy in 2021 due to repeat HPV positive test at 12 months with **NILM**, **ASCUS or AGC cytology**. Subgroup of women **with normal colposcopy** (findings including e.g. metaplasia, viral warts, or polyps). All women had at least **slight acetowhitening** which was an indication for at least one targeted biopsy. Women with transformation zone type 3 underwent ECC (n = 125). N = 146 % HPV 16/18: NR No random biopsies obtained.	*Rate of CIN2+ detected by ECC or targeted biopsy of non-suspicious findings:* NILM, ASCUS or AGC cytology and HPV16/18/other+: 2.7% (4/146) ***CIN2+ yield** with ECC* *Rate of CIN2+ detected on ECC only:* NR

AGC = atypical glandular cells; ASCUS = atypical squamous cells of undetermined significance; CI = confidence interval; CIN = cervical intraepithelial neoplasia; ECC = endocervical curettage; HPV = human papilloma virus; HR-HPV = high risk human papilloma virus; N = number; NA = not applicable; NILM = negative for intraepithelial lesion or malignancy; NR = not reported; SCJ = squamocolumnar junction; VIA = visual inspection with acetic acid.

* Shanxi Province Cervical Cancer Screening Study (SPOCCS 1; SPOCCS 2; SPOCCS 3-Xiangyuan, -Beijing, -Henan, -Xinjiang, and -Shanghai); Screening Technologies to Advance Rapid Testing (START 2003, 2004, 2005, 2006, and 2007); IARC-Yangcheng; IARC-Shenzhen; Fast HPV trial; Prevalence Survey; Hybrid Capture 2 clinical trial.

To further examine the effects of the interventions of interest, evidence for women for whom HPV status is either unknown or not reported was included.

For women with a normal colposcopy with negative or low-grade cytology on referral and HPV status not reported or unknown:

- one study reported the additional CIN2+ yield obtained with **random biopsies alone and with ECC alone** (Song 2017)
- three studies reported on the effects of performing an **ECC with or without biopsies** (van der Marel 2015, Liu 2017, Goksedef 2013)

Results are presented in Table 2.

Table 2. Studies reporting on the effect of performing random biopsies alone or ECC alone, or ECC with or without biopsies for women with a normal colposcopy with negative, pLSIL or LSIL cytology and HPV status either unknown or not reported

Study	Study design	Population and Intervention	Results
Endocervical curettage and non-targeted (random) biopsies			
Song 2017 (China) *Reported in Hu 2017 and overlap with Song 2015*	Cross-sectional *SPOCCS (Shanxi Province Cervical Cancer Screening Study) 1 and 2*	Women aged 35-49 years with **LSIL cytology** who underwent colposcopy in 1999-2002 due to a positive screening test (VIA, HPV, or cytology). Subgroup of women **with negative colposcopy (no lesions in any quadrant)** underwent a random biopsy in four quadrants at the SCJ. It was acceptable to take more than one biopsy per quadrant depending on the colposcopic impression. ECC was performed in all women. N = NR HPV status NR. No targeted biopsies obtained.	***Additional CIN2+ yield*** *with random biopsy or with ECC* *Rate of CIN2+ detected on ECC only:* 0.6% in 35-39y (n/N NR) 0.8% in 40-44y (n/N NR) 1.1% in 45-49y (n/N NR) *Rate of CIN2+ detected on random biopsy only:* 8.1% in 35-39y (n/N NR) 8.3% in 40-44y (n/N NR) 6.3% in 45-49y (n/N NR) *% CIN2+ detected by random biopsy only or ECC only:* NR
van der Marel 2015 (Netherlands)	Cross-sectional *EVAH study*	Women aged ≥17 years with **LSIL or ASC-US cytology** who underwent colposcopy in 2010-2012 due to a positive screening test (cytology). Subgroup of women with ***less than low-grade*** **colposcopic impression** (aceto-whitening suggestive of metaplastic changes or no lesions) underwent up to four targeted biopsies or a single random biopsy of normal tissue if no lesions or <four targeted biopsies obtained. ECC was performed in all women. N = 41 HPV status NR.	**No CIN2+ detected by any method** amongst those with less than low-grade colposcopic impression, and low-grade cytology
Liu 2017 (United States of America)	Cross-sectional *Biopsy Study*	Women with **LSIL or ASCUS cytology** who underwent colposcopy in 2009-2012 due to positive screening test and who underwent ECC due to age ≥30 years. Subgroup of women with **normal colposcopy (no lesion identified on colposcopy)** underwent ECC ± random biopsy (a single random biopsy of normal-appearing cervical epithelium in any quadrant of the cervix was added if fewer than four lesion-directed biopsies were taken). N = 23 HPV status NR.	*Rate of CIN2+ detected by ECC:* 4.3% (1/23) [95% CI 0.8–21.0] ***Additional CIN2+ yield*** *with ECC* *Rate of CIN2+ detected on ECC only:* NR *% CIN2+ detected by ECC only:* NR
Goksedef 2013 (Turkey)	Cross-sectional	Women with **LSIL or ASCUS cytology** (age range NR) who underwent colposcopy in 2003-2011 who underwent ECC. Subgroup of women with satisfactory colposcopy and **normal colposcopic findings (not defined)** underwent ECC according to clinician's judgment ± biopsy (random biopsy NR; targeted biopsy performed in case of suspicious lesions). N = 238	*Rate of CIN2+ detected on ECC:* 1.7% (4/238) *% CIN2+ detected by ECC only:* NR

Study	Study design	Population and Intervention	Results
		HPV status NR. Subgroup of women with satisfactory colposcopy who underwent ECC without biopsy (indication for ECC NR): N = 59 HPV status NR.	***CIN2+ yield*** *with ECC* *Rate of CIN2+ detected on ECC only:* 1.7% (1/59)

ASCUS = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; ECC = endocervical curettage; HPV = human papilloma virus; LSIL = low-grade squamous intraepithelial lesions; N = number; NR = not reported; SCJ = squamocolumnar junction.

* When this study was conducted, HPV testing was not used routinely in Denmark but could be performed as a triage method in women ≥ 30 years old with ASCUS cytology.

Question 3: What is the risk of cervical cancer, CIN3+ (primary) and CIN2+ (secondary) for women with a HPV positive (ideally 16/18 positive) test and a normal colposcopy ideally by cytology?

For women with a normal colposcopy with negative or low-grade cytology on referral and a positive high-risk HPV test:

- Three studies reported on the risk of CIN2+ potentially missed on colposcopy based on either immediate cervical excision of the TZ or follow-up of up to 3 years (results presented in Table 3).

Table 3. Results of studies reporting on the risk of CIN2+ missed on colposcopy for women with a normal colposcopy who have a positive high-risk HPV test, and negative, pLSIL or LSIL cytology

Study	Study design	Population and Intervention	Results
Bassal 2018 (Israel)	Retrospective cohort	**HPV 16/18 positive** women with consecutive **LSIL or ASC-US** cytology results and normal findings on colposcopy and ECC in 2009-2013 who underwent LLETZ. N = 22 HPV 16/18: 100%	**CIN2+ detection rate** *On LLETZ* 22.7% (5/22)
Cruickshank 2014 (United Kingdom)	Retrospective cohort (single arm of RCT) *TOMBOLA trial (Trial of management of borderline and other low grade abnormal smears)*	Women aged 20-59 years with cytology of **mild dyskaryosis or borderline nuclear abnormalities** and initial normal colposcopy (normal transformation zone, type 1 or 2) who were followed-up for 36 months with or without exit colposcopy and LLETZ. N = 884 normal baseline colposcopy *792 (%) had HPV16/18 test at baseline of whom 10% were HPV16 positive and 7% were HPV18 positive. N = 530 normal exit colposcopy (at 36 months) Women with normal transformation zone (not defined) at initial colposcopy received no biopsy or treatment and were followed-up in general practice with cytology tests every 6 months.	*Colposcopy findings and/or histopathological results for women who attended an exit colposcopy after 36 months of follow-up of low-grade cervical cytology result and an adequate and normal colposcopy examination at study entry:* 529 with normal exit colposcopy had no histology. 1 woman with normal exit colposcopy had inadequate biopsy specimen. ***Risk of CIN2+*** *over 36 months of follow-up by baseline cytology and HPV status:* BNA, high-risk HPV+: 6.3% (11/175) Mild dyskaryosis, high-risk HPV+: 12.9% (12/93)
Wang 2005 (United States of America)	Retrospective cohort (single arm of RCT)	**HPV 16/18/other positive** women (age range NR) with **LSIL or ASC-US** cytology and initial normal cervigram (not defined) in 1996-1998 who were followed-up every 6 months (type of testing at FU not specified)	***Risk of CIN2+*** *over 24 months of follow-up by baseline cytology and HPV status:* Normal cytology, HPV+: 7.2% (28/388) [95% CI 4.8-10.3]

Study	Study design	Population and Intervention	Results
	ASCUS/LSIL Triage Study (ALTS)	with or without exit colposcopy at 24 months. Initial colposcopic impression not available for all women. Visual examination of cervix via cervicography (photograph taken after acetic acid application) used in lieu of baseline colposcopy. Normal cytology: N = 388 ASC-US cytology: N = 451 LSIL cytology: N = 500 % HPV 16/18: NR	ASC-US cytology, HPV+: 13.7% (62/451) [95% CI 10.7-17.3] LSIL cytology, HPV+: 17.8% (89/500) [95% CI 14.5-21.4] ***Risk of CIN3+*** *over 24 months of follow-up by baseline cytology and HPV status:* Normal cytology, HPV+: 3.9% (15/388) [95% CI 2.2-6.3] ASC-US cytology, HPV+: 8.2% (37/451) [95% CI 5.8-11.1] LSIL cytology, HPV+: 8.4% (42/500) [95% CI 6.1-11.2]

ASCUS = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; ECC = endocervical curettage; HPV = human papilloma virus; LLETZ = large-loop excision of the transformation zone; LSIL = low-grade squamous intraepithelial lesions; N = number; NR = not reported; SCJ = squamocolumnar junction.

Existing guidelines

Current (2017) Australian guidelines

Practice point REC7.8: Biopsy of low-grade lesions is encouraged but not always necessary

Women with a LBC prediction of pLSIL or LSIL and a colposcopic impression of low-grade disease or less may not always require a biopsy. However, biopsy is accepted practice for confirmation of the colposcopic impression and exclusion of high-grade disease, and should be encouraged, especially for less experienced colposcopists.

Consensus-based recommendation REC8.1: Normal colposcopy following LBC prediction of negative or pLSIL/LSIL

For women with a positive oncogenic HPV (any type) test result, a LBC report of negative or pLSIL/LSIL, and normal colposcopy, the HPV test should be repeated in 12 months:

- If HPV is not detected at 12 months, the woman should return to routine 5-yearly HPV screening.
- If the woman has a positive oncogenic HPV (not 16/18) test result at 12 months and a LBC report of negative or pLSIL/LSIL, the HPV test should be repeated in another 12 months.
- If the woman has a positive oncogenic HPV (any type) test at the 24 month HPV test, she should be referred directly for colposcopic assessment, which will be informed by the result of the reflex LBC.
- If the woman has a positive oncogenic HPV (not 16/18) test result at 12 months and a LBC prediction of pHSIL/HSIL or any glandular abnormality, she should be referred for colposcopic assessment at the earliest opportunity, ideally within 8 weeks.
- If the woman has a positive oncogenic HPV (16/18) test result at 12 months, she should be referred directly for colposcopic assessment at the earliest opportunity, ideally within 8 weeks, and the reflex LBC result will inform the colposcopy.

Consensus-based recommendation REC8.7: Downgrading of discordant results

For women who have a positive oncogenic HPV (any type) test result, normal colposcopy, and a subsequent LBC report of pLSIL/LSIL or less on cytopathology review, management should be according to the reviewed cytological report (i.e. repeat HPV test in 12 months).

Other existing potentially relevant consensus-based guidelines

Guideline	Organisation	Recommendation
Colposcopic diagnosis, treatment and follow-up, in Guidance: Cervical screening: programme and colposcopy management	NHS England	1.6 Colposcopically directed punch biopsy: hrHPV positive and negative cytology or low-grade cytological abnormality (low-grade dyskaryosis or less) and a low grade or negative colposcopic examination do not necessarily require colposcopic biopsy.
Cervical Cancer Screening with HPV Testing: Updates on the Recommendation (Carvalho 2022)	Brazilian Association for the Lower Genital Tract Pathology and Colposcopy (ABPTGIC)	6. What is the recommendation when an HPV test is positive, the cytology shows atypia, but the colposcopy is normal? (HPV+ CYTO+ COLPO negative: ?) There is no sufficient evidence to state a firm recommendation regarding discordant colposcopic impressions and other test results. Despite the lack of consensus, the cytology result can guide the management: if the cytology result shows ASCUS or LSIL, it is possible to repeat the HPV test in 12months; if the cytology shows ASC-H or HSIL+, it is possible to refer the patient to an excisional procedure, waiting or not for the results of an endocervical assessment. 10. What is the recommendation when the HPV genotyping test is positive for types 16 or 18, but the colposcopy is normal? (HPV16/18+, Colpo negative: ?) When the HPV test is positive for types 16 or 18 and the colposcopy is normal, the result of the cytology test should be confirmed to guide the subsequent approach. If the cytology result is negative (ASC-US or LSIL), follow-up in one year with an HPV test is recommended. If the cytology result shows HSILþ, excision should be considered. In case of a negative cytology result, follow-up should include new cytology and colposcopy examinations in six months and a new HPV test in one year.
Evidence-Based Consensus Recommendations for Colposcopy Practice for Cervical Cancer Prevention in the United States (Wentzensen 2017a) ASCCP Colposcopy Standards: Risk-Based Colposcopy Practice (Wentzensen 2017b)	American Society of Colposcopy and Cervical Pathology	2. Number and type of biopsies taken at colposcopy: Recommendation: Multiple biopsies targeting all areas with acetowhitening, metaplasia, or higher abnormalities are recommended. Usually, at least 2 and up to 4 targeted biopsies from distinct acetowhite lesions should be taken. 3. Biopsy practice in women with low risk of precancer: Recommendation: Nontargeted biopsies are not recommended for women referred to colposcopy at the lowest end of risk, i.e., those with less than high-grade squamous intraepithelial lesion cytology, no evidence for HPV16/18, and a completely normal colposcopic impression (i.e., no acetowhitening, metaplasia, or other visible abnormality). Endocervical sampling: Refer to Massad 2013
2012 Updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors (Massad 2013)	American Society of Colposcopy and Cervical Pathology	Management of Women with ASC-US: Endocervical sampling is preferred for women in whom no lesions are identified and for those with an inadequate colposcopy but is acceptable for women with an adequate colposcopy and a lesion identified in the transformation zone. Management of Women with LSIL or ASC-US: Endocervical curettage in pregnant women is unacceptable.
Diagnosis and Management of Adenocarcinoma in Situ: A Society of Gynecologic Oncology Evidence-Based Review and Recommendations (Teoh 2020)	Society of Gynecologic Oncology (United States of America)	Per Wentzensen 2017a and 2017b: Low risk: cytology less than HSIL and HPV16- and HPV18-negative: No biopsies if normal colposcopic finding; 2-4 targeted biopsies of acetowhite, metaplastic, or abnormal lesions if acetowhitening, metaplasia, other abnormality. Society of Gynecologic Oncology specific recommendation: Intermediate risk: cytology HSIL, ASC-H, or HPV16- or HPV18-positive: Nontarget biopsies can be considered†. For HPV18-positive: endocervical sampling‡ acceptable regardless of colposcopic findings. 2–4 targeted biopsies of acetowhite, metaplastic, or abnormal lesions if acetowhitening, metaplasia, other abnormality.

Guideline	Organisation	Recommendation
		† Insufficient evidence for or against nontarget biopsies in this population. ‡ Endocervical sampling can be done with a curette or a brush.
Colposcopic Management of Abnormal Cervical Cytology and Histology (Bentley 2012)	Executive Council Of The Society Of Canadian Colposcopists	Managing Women With ASCUS or LSIL on Referral for Colposcopy: 06. A colposcopically identified lesion should be biopsied. 07. If no lesion is identified, biopsies of the transformation zone should be considered.
Colposcopy standards: Guidelines for endocervical curettage at colposcopy (Massad 2023)	American Society of Colposcopy and Cervical Pathology	ECC is recommended for all patients undergoing colposcopy for a known positive test for HPV types 16 or 18. ECC is preferred for patients aged 40 years and older undergoing colposcopy. ECC is acceptable for all nonpregnant patients undergoing colposcopy

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APPENDICES

Appendix A: Medline, Embase database (via Ovid platform) search strategy

Database(s): **Embase Classic+Embase** 1947 to 2023 May 02**, Ovid MEDLINE(R) ALL** 1946 to May 02, 2023
Search Strategy:

#	Searches
1	(normal adj5 (colposcop$ or cervi$)).tw.
2	(negative adj5 colposcop$).tw.
3	((no lesion$ or without lesion$ or no abnormal$ or without abnormal$ or no aceto$ or without aceto$ or no metaplasia or without metaplasia or benign) adj5 colposcop$).tw.
4	(biops$ adj3 (random or non-targeted or non targeted or quadrant or non-directed or non directed or blind)).tw.
5	(endocervic$ adj4 (curett$ or brush$ or lavage$ or sampl$)).tw.
6	endometrial sampl$.tw.
7	(LEEP or LLETZ or cone or coniz$ or conis$ or excisional biops$ or diagnostic excision$ or excision$ procedure$).tw.
8	(loop adj2 excision$).tw.
9	1 or 2 or 3
10	4 or 5 or 6 or 7 or 8
11	9 and 10
12	limit 11 to english language
13	limit 12 to yr="2005 -Current"
14	limit 13 to conference abstracts [Limit not valid in Ovid MEDLINE(R); records were retained]
15	limit 14 to medline
16	14 not 15
17	13 not 16
18	remove duplicates from 17