HPV16/18 Type 3 transformation zone (Type 3 TZ)

Evidence summary report

PICO: For women who have a HPV16/18 positive test, no referral cytology or negative, pLSIL or LSIL cytology and a Type 3 TZ (unsatisfactory 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 additional CIN3+ lesions for women who have a HPV16/18 positive test, no referral cytology or negative, pLSIL or LSIL cytology and a Type 3 TZ. 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 Type 3 TZ (unsatisfactory colposcopy) either with no referral cytology or a negative, pLSIL or LSIL referral cytology?
2. What are the detection rates for additional cervical cancer, CIN3+ (primary) CIN2+ (secondary) of additional procedures for women with a HPV positive (ideally 16/18 positive) test and a Type 3 TZ (unsatisfactory colposcopy), by referral cytology (negative, pLSIL or LSIL) where possible?
3. What is the risk of histologically confirmed cervical cancer, CIN3+ (primary) and CIN2+ (secondary) for women with a HPV positive (ideally 16/18 positive) test and a Type 3 TZ (unsatisfactory colposcopy), ideally stratified by referral cytology?

Summary of Findings

There were no studies reporting sensitivity of additional procedures to detect cervical cancer in this context.

Four studies reported the rate of CIN2+ detected on endocervical curettage (ECC) as an additional procedure in women with a Type 3 TZ and HPV detected (one study: HPV16 only; 3 studies: any hrHPV type) and either no referral cytology (one study), negative cytology (two studies) or negative/pLSIL/AGC cytology (one study). In the most comparable study (HPV16 detected, negative cytology) ECC detected CIN2+ in 9.4% (3/32) participants. In the three studies where HPV detected was not restricted to HPV16/18, ECC detected CIN2+ in 5.3% (1/19); 11.5% (3/26) and 1.0% (2/209) participants. In this last study, all participants had slight aceto-whitening areas and targeted biopsies, and so the rate of CIN2+ detected by either biopsy or ECC was 4.8% (10/209).

Four studies reported on the risk of CIN2+ missed on colposcopy based on either immediate TZ excision (two studies) or excision during a period of follow-up but excluding findings from biopsies taken at the initial colposcopy (two studies), informing underlying risk of disease. In the most comparable study (HPV16/18 positive, pLSIL/LSIL cytology), CIN2+ was detected in 8.1% participants (3/37) during follow-up (median FU 29 months). In the next most comparable study (any HPV type detected [54% with HPV16/18]; cytology <ASC-H; Australian), CIN2+ was detected on excision in 6.7% (1/15) participants for whom HSIL was not suspected on cervical biopsy or colposcopy, and during follow-up in 1.6% (4/245; FU time not reported) of participants who were not scheduled for treatment as a result of their initial colposcopy. Based on worst histopathology from either cervical biopsy at colposcopy or at excisional treatment among 16/18+ with negative/ pLSIL/ LSIL cytology, the CIN2+ detection rate was 5.3% (14/266).. A study which included women aged >40 years, with persistent HPV (39% with HPV16/18) and normal cytology, who underwent excision (LEEP), detected CIN2+ in 14.2% (4/28) of participants. Across the cohort of participants who also underwent targeted

or random biopsies (n=24), all cases of CIN2+ (2/2) were missed by this method. In another study, restricted to those aged ≥45 years, 7.5% (6/80) of those with HPV detected (any type) and 2.3% (1/44) of those with any HPV detected and normal cytology had CIN2+ detected by LLETZ. Across the total study cohort (including some with abnormal cytology but no HPV detected/ reported), 54.5% (18/33) cases of CIN2+ were missed on previous biopsy (including 4-blind-biopsies when no lesion was apparent).

Detailed Findings

Evidence review for 2023 guidelines

Searches: EMBASE and Medline databases were searched in March 2023 by combining terms for type 3 transformation zone and the interventions of interest. 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 an HPV positive test (ideally 16/18 positive) and a Type 3 TZ (unsatisfactory 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 Type 3 TZ 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 additional cervical cancer, CIN3+ (primary) CIN2+ (secondary) of additional procedures for women with a HPV positive (ideally 16/18 positive) test and a Type 3 TZ (unsatisfactory colposcopy), by referral cytology (negative, pLSIL or LSIL) where possible?

For women with a Type 3 TZ with positive HPV test and negative or low-grade cytology on referral:

- four studies reported additional yield with **endocervical curettage (ECC)** (results presented in Table 1)
- no studies were identified that reported on other additional interventions of interest.

Table 1. Results of studies reporting on the effect of performing ECC for women with a Type 3 TZ who have a positive high-risk HPV test, and negative, pLSIL or LSIL cytology

Study	Study design	Population and Intervention	Results
Endocervical curettage (ECC)			
Ureyen 2018 (Turkey)	Cross-sectional	**HPV16 positive** women with **normal** cytology (age range NR) who underwent colposcopy in 2015-2016. Subgroup with Type 3 TZ (TZ not fully visible and has endocervical component) who underwent ECC and had no suspicious lesions on colposcopy **– no targeted biopsies**. N = 32 ECC undertaken if Type 3 TZ. No random biopsies obtained – cervical biopsies collected when suspicious lesions. 100% HPV 16 positive	***Additional CIN2+ yield*** *with ECC* *Rate of CIN2+ detected on ECC only:* 9.4% (3/32) *% CIN2+ detected by ECC only:* NA: The 32 women only underwent ECC?
Berger 2023 (Germany)	Cross-sectional	**HPV (16/18/other) positive** women aged ≥35 years with **negative cytology** who underwent colposcopy due to repeat HPV positive test at 12 months in 2021. Subgroup with Type 3 TZ (SCJ not visible) who underwent ECC and had no minor or major changes on colposcopy – **no targeted biopsies**. N = 19 ECC undertaken if Type 3 TZ. No random biopsies obtained – cervical biopsies collected when minor or major changes. % HPV 16/18: NR	***Additional CIN2+ yield*** *with ECC* *Rate of CIN2+ detected on ECC only:* 5.3% (1/19) – 1 CIN3 1 vaginal intraepithelial neoplasia (5.3%) *% CIN2+ detected by ECC only* NA: The 19 women only underwent ECC?
Goldstein 2020 (China)	Cross-sectional	**HPV (16/18/other) positive** women (self-collected sample – no cytology results) aged 35-65 years who underwent digital colposcopy in 2018 due to HPV positive test. Subgroup with Type 3 TZ (could not adequately visualise entire TZ) who underwent ECC – colposcopy impression NR – **unclear if any targeted biopsies obtained**. N = 26 ECC undertaken if TZ was not fully visible on digital colposcopy. Random biopsies not obtained – cervical biopsies collected if digital colposcopy positive for cervical abnormalities. % HPV 16/18: NR	***Additional CIN2+ yield*** *with ECC* *Rate of CIN2+ detected on ECC only:* 11.5% (3/26) - 3 CIN2 *% CIN2+ detected by ECC only* NR
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 **normal** cytology or **ASCUS or AGC cytology**. Subgroup with Type 3 TZ (not defined) who underwent ECC. All had at least slight acetowhitening which was an indication for targeted biopsy. N = 209 ECC undertaken if Type 3 TZ. No random biopsies obtained. % HPV 16/18: NR	*Rate of CIN2+ detected (targeted biopsy or ECC)* 4.8% (10/209) ***Additional CIN2+ yield*** *with ECC* *Rate of CIN2+ detected on ECC only:* 1.0% (2/209) *% CIN2+ detected by ECC only:* 20% (2/10) CIN2+

AGC = atypical glandular cells; ASCUS = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; ECC = endocervical curettage; HPV = human papilloma virus; N = number; NA = not applicable; NR = not reported; SCJ = squamocolumnar junction; TZ = transformation zone.

To examine the effects of interventions other than ECC, evidence for women for whom HPV status is either unknown or not reported was included, although this is expected to limit direct applicability for those with 16/18 detected.

For women with Type 3 TZ with negative or low-grade cytology on referral and HPV status not reported or unknown:

- one study reported on the effects of obtaining **random biopsies and performing an ECC** (results presented in Table 2)
- one study reported additional yield **with random biopsies** (results presented in Table 2).

Table 2. Studies reporting on the effect of performing ECC and random biopsies, or random biopsies alone for women with a Type 3 TZ 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			
van der Marel 2015 (Netherlands and Spain)	Cross-sectional sub analysis of *EVAH study*	Women aged ≥17 years with **LSIL or ASCUS cytology** who underwent colposcopy in 2010-2012. Subgroup with unsatisfactory colposcopy (SCJ partially or not visible) underwent ECC. Indications for targeted cervical biopsy unclear. N = 55 **HPV status NR**. Single random biopsy of normal tissue if no lesions or <4 targeted biopsies obtained. Further subgroup with *less than low-grade* colposcopic impression (aceto-whitening suggestive of metaplastic changes or no lesions) underwent targeted or non-targeted (random) biopsy. N = 36	**No CIN2+ detected by any method** amongst those with unsatisfactory colposcopy or less than low-grade colposcopic impression, and low-grade cytology
Non-targeted (random) biopsies			
Jespersen 2021 (Denmark)	Cross-sectional	Women aged ≥18 years with **ASCUS or LSIL cytology** who underwent colposcopy in 2017-2020. Of 91 HPV tested*, 89% HPV positive with 13% 16/18 positive. Subgroup with Type 3 TZ (SCJ not visible) **and normal colposcopy** (included women with transparent acetowhitening, discrete vessel changes, fine punctuations and/or mosaic changes) who underwent 4 (quadrant) blind/random biopsies. N = 47 HPV status NR No ECC performed.	***Additional CIN2+ yield*** *with random biopsy* 2.1% (1/47)

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; TZ = transformation zone.

* 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 histologically confirmed cervical cancer, CIN3+ (primary) and CIN2+ (secondary) for women with a HPV positive (ideally 16/18 positive) test and a Type 3 TZ (unsatisfactory colposcopy), ideally stratified by referral cytology?

For women with Type 3 TZ with negative or low-grade cytology on referral and a positive high-risk HPV test:

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

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

Study	Study design	Population and Intervention	Results
Chin 2021 (Australia)	Retrospective cohort-single arm	**HPV positive** (16/18/other) women aged 25-74 years who underwent colposcopy in 2018-2020. Women with Type 3 TZ (not defined): N = 560 HPV 16/18: 54% 55 women (9.8%) found to have CIN2+ on cervical biopsy at initial colposcopy or following cervical excisional procedure. Subgroup with no HSIL suspected on referral cervical screening tests, repeated cytology, cervical biopsy or colposcopy who underwent **cervical excision**: n = 15 Subgroup not scheduled for treatment and with follow-up records: n = 245 Length of follow-up NR	**CIN2+ detection rate** *On excision when HSIL not suspected on cervical biopsy or colposcopy* 1/15 (6.7%) *During follow-up of those not scheduled for treatment* 4 /245 (1.6%) *CIN2+ based on worst histopathology from either cervical biopsy at colposcopy or at excisional treatment among 16/18+ with negative/ pLSIL/ LSIL cytology*: 5.3% (14/266)
Aarnio 2019 (Sweden)	Retrospective cohort	Women aged >40 years with persistent **HPV positive** test (16/18/other) and **normal cytology** with Type 3 TZ (upper limit of TZ not visible) on colposcopy who **underwent LEEP** regardless of biopsy or colposcopic findings in 2013-2016. N = 28 HPV 16/18 at baseline: 39% 14 women were HPV negative at time of LEEP (time between baseline and LEEP HPV tests NR) Women with no abnormality on colposcopy underwent a random biopsy. ECC NR. Subgroups: Persistent HPV16 positive at time of LEEP = 3 Persistent HPV positive (16/18/other) at time of LEEP = 14	**CIN2+ detection rate** *On LEEP* 14.2% (4/28) – 3 CIN3, 1 CIN2 *On LEEP only (missed on biopsy; 4 patients did not undergo biopsy)* 8.3% (2/24) – 2 CIN3 (1 HPV16, 1 HPV other) 100% (2/2) CIN2+ detected by LLETZ missed on biopsy (including random biopsy if no colposcopic abnormality) *Subgroups* Persistent HPV16 positive at time of LEEP 33.3% (1/3) – 1 CIN3 Persistent HPV positive (16/18/other) at time of LEEP 28.6% (4/14) – 3 CIN3, 1 CIN2
Bogani 2019 (Italy)	Retrospective cohort	**HPV positive** (16/18/other) women with **LSIL or ASCUS cytology** and unsatisfactory colposcopy (lack of visualisation of entire SCJ) on initial colposcopy in 2005-2015 followed for a median of 29 months. N = 71 HPV 16/18: 52% ECC or random biopsy NR Colposcopy details NR. Women colposcopically evaluated 6 months later. Subgroups HPV 16/18 positive at initial colposcopy n = 37 HPV other high-risk positive at initial colposcopy n = 34	**Risk of developing CIN2+ on follow-up** 9.9% (7/71) - 0 cervical cancer *Subgroups* **HPV 16/18 positive at initial colposcopy** **8.1% (3/37)** HPV other positive at initial colposcopy 11.8% (4/34) Persistent HPV 33.3% (5/15)

Study	Study design	Population and Intervention	Results
		HPV persistence (repeat positive HPV test at 6-12 months) n = 15 HPV regressed (Initially HPV positive and HPV negative on subsequent test at 6-12 months) n = 48	HPV regressed 2.1% (1/48)
Gustafson 2022 (Denmark)	Cross-sectional	Women aged ≥45 years with **HPV positive** test (16/18/other) or **abnormal cytology** (≥ ASCUS) with Type 3 TZ (2011 International Federation of Cervical Pathology and Colposcopy) on colposcopy (14% colposcopic abnormalities including acetowhitening) who **underwent LLETZ** regardless of biopsy or colposcopic findings in 2019-2021. N = 102 % HPV 16/18: NR Women with no lesions on colposcopy underwent 4 *blind* biopsies. Indications for LLETZ – Type 3 TZ? Subgroups: HPV positive normal cytology n = 44 HPV positive cytology ≥ ASCUS n = 36	**CIN2+ detection rate** *On LLETZ* 32.4% (33/102) *On LLETZ only (missed on biopsy)* 17.6% (18/102) - 16 HPV positive with 19% (3/16) HPV16/18 positive 54.5% (18/33) CIN2+ detected by LLETZ missed on biopsy (including blind biopsies if no lesions apparent) *Subgroups* HPV positive normal cytology 2.3% (1/44) HPV positive cytology ≥ ASCUS 13.9% (5/36) HPV positive, any cytology: 7.5% (6/80)

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; Type 3 TZ = transformation zone.

Existing guidelines

Current (2017) Australian guidelines

Practice point REC8.11: Role of ECC in Type 3 TZ colposcopy following LBC prediction of pLSIL/LSIL

Despite a lack of evidence, endocervical curettage can be considered for women who have a positive oncogenic HPV test result (any type) with a LBC report of persistent pLSIL/LSIL and colposcopy reported as Type 3 TZ.† A negative ECC may provide additional reassurance for a conservative (observational) approach.

†Type 3 TZ indicates failure to visualise the upper limit of the TZ, or the entire TZ is within the endocervical canal. It corresponds to 'unsatisfactory' in previous terminology.

Practice point REC7.7: Biopsy visible lesion if suspicious for invasion when T3 TZ colposcopy

In some situations, when there is a visible high-grade lesion on the ectocervix but there is a T3 TZ (lesion extends into canal out of visual range), it may be reasonable to take a cervical biopsy of the visible lesion if there is any suspicion of superficially invasive or invasive carcinoma.

Other existing potentially relevant consensus-based guidelines

Guideline	Organisation	Recommendation
Colposcopy standards: Guidelines for endocervical curettage at colposcopy (Massad 2023)	American Society of Colposcopy and Cervical Pathology	ECC is recommended when the SCJ is not fully visualized at colposcopy. These recommendations notwithstanding, omitting ECC at the time of colposcopy is acceptable under the following circumstances: In nulliparous patients aged younger than 30 years with cytology reported as ASCUS or low-grade SIL, regardless of whether the SCJ is fully visualized.
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

Guideline	Organisation	Recommendation
		with an adequate colposcopy and a lesion identified in the transformation zone. Endocervical curettage in pregnant women is unacceptable
Prevention of cervical cancer - Part 2 on Triage, Treatment and Follow-up (Hillemanns 2019)	Association of Scientific Medical Societies in Germany (AWMF), German Cancer Society (DKG) and German Cancer Aid (DKH)	11.3. If the transformation zone is classified as Type 1 or Type 2 at diagnostic colposcopy, colposcopy-guided biopsies should be obtained from the highest-grade lesion(s); if the transformation zone is classified as Type 3, endocervical curettage should be carried out.

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APPENDICES

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

Database(s): **Embase Classic+Embase** 1947 to 2023 March 22**, Ovid MEDLINE(R) ALL** 1946 to March 22, 2023
Search Strategy:

#	Searches
1	(colposcop$ adj5 (satisfactory or unsatisfactory or adequacy or inadequacy or adequate or inadequate)).tw.
2	(Transformation zone adj5 (type 3 or T3)).tw.
3	(colposcop$ adj5 (transformation zone or T zone or TZ)).tw.
4	(TZ adj5 (type 3 or T3)).tw.
5	(colposcop$ adj5 squamocolumnar junction).tw.
6	(colposcop$ adj5 SCJ).tw.
7	1 or 2 or 3 or 4 or 5 or 6
8	Transformation zone.tw.
9	(t zone or TZ or type 3 or T3).tw.
10	squamocolumnar junction.tw.
11	SCJ.tw.
12	8 or 9 or 10 or 11
13	((random biops$ or non-targeted biops$ or non targeted biops$ or quadrant biops$) and (colposcop$ or cervi$)).tw.
14	(endocervic$ adj4 (curett$ or brush$ or lavage$ or sampl$)).tw.
15	endometrial sampl$.tw.
16	13 or 14 or 15
17	12 and 16
18	7 or 17
19	limit 18 to english language
20	limit 19 to yr="2005 -Current"
21	limit 20 to conference abstracts [Limit not valid in Ovid MEDLINE(R); records were retained]
22	limit 21 to medline
23	21 not 22
24	20 not 23
25	remove duplicates from 24