Glandular cytology and normal colposcopy – additional interventions Evidence summary report

PICO: For women with atypical endocervical cells of unknown significance cytology or atypical glandular cells of undetermined significance (AGUS) cytology, and a negative colposcopy, ideally with an oncogenic HPV-positive test, what is the sensitivity of endocervical sampling or biomarker tests for histologically-confirmed adenocarcinoma in situ (AIS)+ lesions?

A systematic review was conducted in 2023 for the above PICO which did not find any RCTs or pseudo-RCTs comparing different tissue sampling methods or biomarker tests for women with either of these cytologies and a negative colposcopy finding. Therefore, on the advice of the Working Party, an evidence review was undertaken to address this question.

Evidence review for 2023 guidelines update

Searches: Three different searches were conducted, from 2005 onwards and were limited to articles published in English. EMBASE and Medline databases were searched in May 2023 by combining terms for:

- normal colposcopy, biomarker tests and glandular cytology,
- normal colposcopy, lower grade glandular cytology and HPV,
- normal colposcopy and random biopsy, endocervical sampling or excisional biopsy.

Full details of the search strategies are included in the Appendices.

Results: No studies were identified that had relevant outcome data for women with atypical endocervical cells of unknown significance or AGUS and a normal colposcopic finding, who had been investigated using random sampling, endocervical/endometrial sampling or biomarker test methods. Ten studies were identified as potentially having unpublished relevant data and an email outlining the data required was sent to the lead author of each study. Two authors provided usable data, hence data for 3 studies was available for this report. These studies are summarized in Table 1.

Table 1: ***Studies investigating the effectiveness of additional interventions or tests to detect AIS+ or CIN2+ lesions for women with a negative colposcopy and lower grade glandular cytology***

Study	Study design	Population and intervention	Results
Jordao 2020 (Brazil) *Personal communication*	Retrospective cohort	Women aged 48.2 years (mean) who underwent colposcopy and endocervical cytological testing between Jan 2012 and Apr 2017 and had a Pap smear reported as ASC-H, HSIL or AGC without colposcopic abnormal findings and with the SCJ not fully visible. N = 78	For women with baseline cytology of AGC and normal colposcopy who underwent endocervical sampling, n = 25 No CIN2+ or AIS detected as a result of endocervical sampling results (none underwent excisional biopsy)

Study	Study design	Population and intervention	Results
		No HPV test results Follow-up = semiannual cytological and colposcopic follow-up for 2 years. Women with baseline cytology of AGC and normal colposcopy who underwent endocervical sampling n = 25	No CIN2+ or AIS detected on 2-year follow-up: 92.0% normal histology (23/25) 4.0% endocervical polyp (1/25) 4.0% endometrial polyp (1/25)
Pretorius 2019 (China) *Personal communication*	Cross-sectional (SPOCCS I trial)	Women who underwent colposcopy with cervical biopsies of each quadrant and ECC between 1999 and 2001 and had cytology ≥LSIL or HPV-positive atypical squamous cells of uncertain significance (ASC-US) N = 264 HPV status unclear Follow-up not applicable. At colposcopy, the cervix was divided visually into 4 quadrants and targeted biopsy of all colposcopically-defined lesions including metaplasia which was coded as normal, was performed by quadrant. Cervical quadrants with colposcopic impressions defined as normal had a "random" biopsy taken at the SCJ. **AGC cytology + normal colposcopy** N = 13	For women with baseline cytology of AGC and normal colposcopy who underwent cervical biopsy and ECC, n = 13 No CIN2+ detected on random biopsy or ECC
	Cross-sectional (SHENCCAST trial)	Women who underwent colposcopy with cervical biopsies of each quadrant and ECC between 2009 and 2010 N = 631 Follow-up not applicable. At colposcopy, the cervix was divided visually into 4 quadrants and targeted biopsy of all colposcopically-defined lesions (including metaplasia?), was performed by quadrant. Cervical quadrants with colposcopic impressions defined as normal had a "random" biopsy taken at the SCJ. **AGC cytology + normal colposcopy** N = 7 1/7 HPV (HPV16) positive	For women with baseline cytology of AGC and normal colposcopy who underwent cervical biopsy and ECC, n = 7 No CIN2+ detected on random biopsy or ECC
Pretorius 2015 (USA) *Personal communication*	Cross-sectional? (Kaiser Permanente Southern California-Fontana cohort)	Women who underwent colposcopy with cervical biopsies and ECC between 1996 and 2013 based on cytology and HPV testing N = 18,537 Median age = 32 years Follow-up not applicable? Indications for cone, LEEP or hysterectomy not reported. Women with a normal colposcopy underwent biopsy – not described – assume included random biopsies **AGC cytology + normal colposcopy** N = 96 Inadequate colposcopy: 33/96 HPV positive: 26/96	*For women with baseline cytology of AGC and normal colposcopy who underwent cervical biopsy and ECC, n = 96* CIN 2+: 30.2% (29/96) CIN 2+ detected by • biopsy (primarily random?) or ECC - 72% CIN2+ (21/29) • ECC only – 14% CIN2+(4/29) • LEEP, cone, hysterectomy or other only – 28% CIN2+ (8/29 – 2 AIS, 5 endometrial cancers and 1 carcinosarcoma uterus) *For women with baseline cytology of AGC, **HPV positive** and normal **adequate** colposcopy who underwent cervical biopsy and ECC* n = 15

Study	Study design	Population and intervention	Results
			CIN 2+: 40.0% (6/15) CIN 2+ detected by • biopsy (primarily random?) or ECC - 100% CIN2+ (6/6) • ECC only – 17% CIN2+ (1/6) • LEEP, cone, hysterectomy or other only – 0% *For women with baseline cytology of AGC, **HPV positive** and normal **inadequate** colposcopy who underwent cervical biopsy and ECC* n = 11 CIN 2+: 63.3% (7/11) CIN 2+ detected by • biopsy (primarily random?) or ECC - 71% CIN2+ (5/7) • ECC only – 14% CIN2+ (1/7) • LEEP, cone or hysterectomy only – 29% CIN2+ (2/7 – 2 AIS)

Abbreviations: AGC = atypical glandular cells; ASC-H = atypical squamous cells, possible high-grade lesion; CGIN = cervical glandular intraepithelial neoplasia; CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LEEP = loop electrosurgical excision procedure; LLETZ = large loop excision of transformation zone; LSIL = low-grade squamous lesion; other = cervicitis/inflammatory; SCJ = squamocolumnar junction

Existing guidelines

Current (2017) Australian guidelines

***Consensus-based recommendation* REC11.2: Follow-up after normal colposcopy and LBC prediction of atypical glandular/endocervical cells**

Women who have a positive oncogenic HPV test result (any type) with a LBC prediction of atypical glandular/endocervical cells of undetermined significance and normal colposcopy can be offered repeat co-testing (HPV and LBC) at 6–12 months:

If the follow-up co-test is negative, co-testing should be repeated annually until the woman has two consecutive negative co-tests, after which she can return to 5- yearly screening.

If there is either a positive oncogenic HPV (any type) test result or an abnormal LBC (any report other than negative), the woman should be referred for colposcopic assessment, and diagnostic excision of the TZ should be considered.

***Practice point* REC11.3: Exclusion of upper genital tract disease before diagnostic excision**

For women who have a positive oncogenic HPV test result (any type) and who have atypical glandular/endocervical cells of undetermined significance on cytology, investigation of the upper genital tract (endometrium, fallopian tube or ovary) using endometrial sampling and/or pelvic ultrasound should be considered, before diagnostic excision of the TZ is performed or the woman is advised to return for colposcopy and further tests in 6–12 months, in these groups of women:

women aged over 45 years

women aged over 35 years with a BMI greater than 30

women diagnosed with polycystic ovarian syndrome

women with abnormal vaginal bleeding.

Other existing potentially relevant consensus-based guidelines published from 2015 onwards

Guideline	Organisation	Recommendation
Cervical Screening: programme and colposcopy management – Colposcopic diagnosis, treatment and follow-up (2023)	NHS England	**The role of colposcopically directed or punch biopsy in the management of ?glandular neoplasia and borderline changes in endocervical cells samples** Punch biopsy in the management of ?glandular neoplasia and borderline changes in endocervical cell samples is not appropriate. Investigate and diagnose CGIN/stratified mucin producing intraepithelial lesion of the cervix (SMILE) through colposcopy and histopathological assessment of an excisional biopsy (including the endocervical canal) in order to distinguish between CGIN and invasive adenocarcinoma. **Endometrial biopsy** Endometrial sampling is indicated in individuals referred to colposcopy with ?glandular neoplasia or not otherwise specified (NOS). **Endocervical curettage in the assessment of ?glandular neoplasia of endocervical type** There is no clear role for endocervical curettage in the assessment of ?glandular neoplasia of endocervical type therefore the programme does not recommend this.
Diagnosis and Management of Adenocarcinoma in Situ (Teoh 2020)	Society of Gynecologic Oncology Endorsed by the American Society for Colposcopy and Cervical Pathology (ASCCP) (Perkins 2020), endorsed by American College of Obstetricians and Gynecologists and affirmed by American Cancer Society (Fontham 2020)	For pre-colposcopy test result of AGC, AIS and normal colposcopic finding, the recommendations are: Endocervical sampling‡ Endometrial sampling if 35 y of age or older, risk factors, or atypical endometrial cells specified on cytology Nontarget biopsies can be considered§
2019 ASCCP Risk-based management **consensus** guidelines for abnormal cervical cancer screening tests and cancer precursors (Perkins 2020)	American Society for Colposcopy and Cervical Pathology (ASCCP) and endorsed or affirmed by Society of Gynecologic Oncology (Teoh 2020) American College of Obstetricians and Gynecologists and the American Cancer Society (Fontham 2020)	For nonpregnant patients of all ages with all sub-categories of AGC and AIS, except when atypical endometrial cells are specified, colposcopy is recommended regardless of HPV test result; endocervical sampling is recommended at initial colposcopy except in pregnancy. Accordingly, triage by reflex HPV testing is not recommended, and triage by repeat cytology is unacceptable. Endometrial sampling is recommended in conjunction with colposcopy and endocervical sampling in nonpregnant patients 35 years or older with all categories of AGC and AIS. Endometrial sampling is also recommended for nonpregnant patients younger than 35 years at increased risk of endometrial neoplasia based on clinical indications (e.g., abnormal uterine bleeding, conditions suggesting chronic anovulation, or obesity). For patients with atypical endometrial cells specified, initial evaluation limited to endometrial and endocervical sampling is preferred, with colposcopy acceptable at the time of initial evaluation. If colposcopy was deferred and no endometrial pathology is identified, additional evaluation with colposcopy is then recommended.
Adenocarcinoma in situ of the uterine cervix: Clinical practice guidelines from the Italian society of colposcopy and cervical pathology (SICPCV) (Ciavattini 2019)	Italian society of colposcopy and cervical pathology	No actual recommendations made rather state: "All women with abnormal cervical cytology due to glandular lesions should undergo colposcopy with endocervical sampling; triage by reflex HPV testing is not recommended".

‡ Endocervical sampling can be done with a curette or a brush.

§ ASCCP Risk-Based Management Guidelines: http://www.asccp.org/consensus-guidelines

References

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NHS Cervical screening programme and colposcopy management 2023 https://www.gov.uk/government/publications/cervical-screening-programme-and-colposcopy-management/3-colposcopic-diagnosis-treatment-and-follow-up Accessed March 2023

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Pretorius RG, Belinson JL, Burchette RJ, Wu R, Qiao Y-L. Key determinants of the value of random cervical biopsy at colposcopy. J Low Genit Tract Dis 2019; 23: 241-247.

Pretorius RG, Belinson JL, Peterson P, Burchette RJ. Which colposcopies should include endocervical curettage? J Low Genit Tract Dis 2015; 19: 278-281.

Teoh D, Musa F, Salani R, Huh W, Jimenez E. Diagnosis and Management of Adenocarcinoma in Situ. Obstet Gynecol 2020; 135: 869-878.

Appendices

Medline, Embase database (via Ovid platform) search strategies

Search #1:

Database(s): **Embase Classic+Embase** 1947 to 2023 May 01, **Ovid MEDLINE(R) ALL** 1946 to May 01, 2023

#	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 no metaplasia or benign) adj5 colposcop$).tw
4	(biomarker$ or methylat* or p16 or p-16 or ki-67 or ki67 or dual stain$ or dual-stain$).tw
5	1 or 2 or 3
6	4 and 5
7	((glandular or endocervical) adj5 (cytology or cell$ or smear$)).tw
8	(AGUS or AG-US or AGC).tw
9	7 or 8
10	6 and 9
11	limit 10 to English language

#	Searches
12	limit 11 to yr=”2005 -Current”
13	limit 12 to conference abstracts
14	limit 13 to medline
15	13 not 14
16	12 not 15
17	remove duplicates from 16

Search #2:

Databases: Embase Classic+Embase 1947 to 2023 May 05, **Ovid MEDLINE(R) ALL** 1946 to May 05, 2023

#	Searches
1	(normal adj5 (colposcop$ or cervi$)).mp.
2	(negative adj5 colposcop$).mp.
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$).mp.
4	1 or 2 or 3
5	(AGUS or AGC or gland* or endocervi*).tw.
6	4 and 5
7	colposcop*.tw.
8	(AGUS or AGC or gland* or endocervi*).tw.
9	HPV.tw.
10	Human papillomavir*.tw.
11	hr$HPV.tw.
12	9 or 10 or 11
13	7 and 8 and 12
14	6 or 13
15	limit 14 to english language
16	limit 15 to human
17	limit 16 to human
18	limit 17 to yr="2005 -Current"

19	limit 18 to conference abstracts [Limit not valid in Ovid MEDLINE(R); records were retained]
20	limit 19 to medline
21	19 not 20
22	18 not 21
23	remove duplicates from 22

Search #3:

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

#	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