

## Glandular cytology normal colposcopy surveillance vs excision – Evidence Summary

### PICO

For women with a positive oncogenic HPV test result and a referral cytology of atypical endocervical cells of unknown significance or atypical glandular cells of unknown significance (AGUS) with a negative colposcopy what is the safety and effectiveness of surveillance when compared with treatment with excisional cone biopsy?

A systematic review was undertaken in 2023 and did not find any randomized controlled trials (RCTs) or pseudo-randomised trials that met the inclusion criteria for this PICO. Therefore, on the advice of the Working Party, evidence reviews were undertaken to address the following questions:

1. For women with a negative colposcopy what are the risks of cancer and precancerous high-grade lesions associated with a cytology predicting a glandular lesion:
  - with a positive oncogenic HPV test; or
  - in absence of HPV test.

### Summary of findings

Five retrospective observational studies were included, reporting the risk of CIN2+, CIN3+ or cancer in the sub-group of women with glandular abnormalities and a negative colposcopy. None of the studies reported HPV status. Four studies reported histology results, but none clearly explains the reasons why women underwent just biopsy or an excision procedure.

One study included 69 women with borderline glandular cytologic, from which 24 had normal colposcopy. They underwent LLETZ (n=5) or endometrial biopsy pipelle (n=19). In total, 3 cases of cancer or high-grade lesions were detected (12.5%), all by endometrial biopsy: 1 CIN2/CIN3, 1 CGIN and 1 CC. The other three studies analyse the histology results together, without differentiating between collection method (excision versus biopsy). One included 27 women with atypical glandular abnormality and normal colposcopy, that underwent excisional procedure (LLETZ or cone biopsy) or biopsy (cervical punch and endometrial biopsy), and detected a total of 4 cases of cancer or high-grade lesions (15%): 2 AIS and 2 CIN2/CIN3. Other included 19 women with borderline glandular cytology and normal colposcopy, from which 15 underwent biopsy (unspecified), with none confirmed abnormalities. The third study included 60 women with BNCs and normal colposcopy, who underwent either biopsy or cytology. In total, 7 high-grade lesions (CIN2+) were detected (12%): 6 detected through biopsy (unspecified) and 1 through cytology.

Finally, there was one study that reported only cytology results. Women with AGC and normal colposcopy underwent a 4 monthly follow-up visits, which included thorough pelvic examination, cervical smear, PCR and genotyping. After two follow-up visits, cytology was consistently negative in all 29 women.

## Detailed findings

### Evidence review for 2023 guidelines

**Searches:** EMBASE and Medline databases were searched on 5 May 2023 by combining search terms for glandular cytology with either terms for normal colposcopy or with terms for colposcopy and HPV. Searches were limited to articles published in English from 1st January 2005 onwards and full details of the search strategy are included in the Appendices.

### Results

Five observational studies that reported risk of CIN2+, CIN3+ or cancer were identified, and these studies are summarized in **Table 1**.

**Table 1: Studies reporting risk of CIN2+, CIN3+ or cancer among women with a cytology predicting a glandular lesion and a negative colposcopy**

Study	Country	Study design	Population	Findings
Chummun 2012	Ireland	Retrospective Cohort	<p>Women with a single diagnosis of <b>AGC</b> (endometrial or endocervical, not otherwise specified or favour neoplastic) in 2009 and underwent colposcopy (N = 156)</p> <p>Mean age = 41 years</p> <p>Satisfactory colposcopy = 80.1%</p> <p>Women with <b>normal colposcopy who underwent treatment or biopsy (Unclear as to reason for and method of biopsy) N=27</b></p> <p>Follow-up: NR</p> <p>HPV status: NR</p>	<p><b>Women with AGC and normal colposcopy</b></p> <p>AIS histology: 2/27 (7.4%) (unclear as to how biopsied)</p> <p>CIN2 or CIN3 histology: 2/27 (7.4%) (unclear as to how biopsied)</p>
Jadoon 2009	UK	Retrospective Cohort	<p>Women diagnosed initially or for the second time with <b>borderline glandular cytology</b> between 2001 and 2005 who underwent colposcopy (N = 56)</p> <p>Mean age = 38 years</p> <p>Satisfactory colposcopy = 98.2%</p> <p>Women with <b>normal colposcopy N = 19</b></p>	<p>Women <b>with borderline glandular cytology and normal colposcopy</b> who underwent <b>biopsy (unspecified)</b></p> <p>CIN2+ histology: 0/15</p> <p>CIN3+ histology: 0/15</p> <p>Women <b>with borderline glandular cytology and normal colposcopy</b> who had <b>24-month cytology follow-up</b></p>

Study	Country	Study design	Population	Findings
			<p>Follow-up: Women followed up with cytology at 6,12, and 24 months</p> <p>HPV status: NR</p>	Abnormal smears on follow-up cytology by 24 months: 0/18
Kodiathodi 2014	UK	Retrospective Cohort	<p>Women diagnosed with <b>borderline nuclear change in endocervical cells (BNCs)</b> (defined as the cytological changes thought to be of glandular in origin and are not sufficiently severe to be classed as dyskaryosis/glandular neoplasia) and referred for colposcopy between Jan 2006 to Dec 2011 (N = 167)</p> <p>Mean age = 43 years</p> <p>Satisfactory colposcopy = 93%</p> <p>Women with <b>normal colposcopy N = 60</b></p> <p>Follow-up: Women with satisfactory and negative colposcopy were followed up with cytology and coloscopy in 6 months. If normal, they were returned to routine recall.</p> <p>HPV status: NR</p>	<p>Women with <b>BNC and normal colposcopy</b> who underwent <b>biopsy (unspecified) or cytology</b></p> <p>High grade histology (CIN2+ or worse) in the first year of follow-up: 6/60</p> <p>High grade smear on cytology in the first year of follow-up: 1/60</p>
Patel 2010	UK	Retrospective Cohort	<p>Women diagnosed with <b>borderline glandular cytology</b> and referred for colposcopy between June 2006 and August 2008 (N = 69)</p> <p>Mean age = 39.6 years</p> <p>Satisfactory colposcopy = 89.8%</p> <p>Women with <b>normal colposcopy N = 24</b></p> <p>Follow-up: <b>NR</b></p> <p>HPV status: NR</p>	<p>Women aged &lt; 35 years with <b>borderline glandular cytology</b> and <b>normal or benign with visible squamocolumnar junction colposcopy</b> who underwent <b>large loop excision transformation zone?</b></p> <p>CIN 2 &amp; 3 = 0/5 CGIN = 0/5 Cervical Cancer = 0/5</p> <p>Women aged &gt; 35 years with <b>borderline glandular cytology*</b> and <b>normal or benign with visible squamocolumnar junction colposcopy</b> who underwent <b>endometrial biopsy with pipelle?</b></p> <p>CIN 2 &amp; 3 = 1/19 CGIN = 1/19 Cervical Cancer = 1/19</p>
Zaferino 2011	Brazil	Retrospective Cohort	<p>Women diagnosed with <b>AGC not otherwise specified and favor neoplastic</b> between March 2002 and March 2005 (N = 108)</p> <p>Mean age = 42.7 years</p> <p>Satisfactory colposcopy = NR</p> <p>Women with <b>negative colposcopy N=29</b></p>	<p>Women with <b>AGC and normal colposcopy</b> who had two follow-up cytology</p> <p>CIN 2 or worse = 0/29</p>

Study	Country	Study design	Population	Findings
			<p>Follow-up: Four monthly follow-up visits were scheduled for women with negative colposcopy with a thorough pelvic examination, including cervical smear, PCR and genotyping.</p> <p>HPV status = NR for women with normal colposcopy</p>	

AGC = atypical glandular cells (Bethesda 2001); AIS = adenocarcinoma in situ; CGIN = cervical glandular intraepithelial neoplasia; CIN = cervical intraepithelial neoplasia; CIN2 = CIN grade 2; CIN3 = CIN grade 3; NR = not reported; PCR = polymerase chain reaction; SCC = squamous cell carcinoma

### Existing Guidelines

#### Current (2017) Australian guidelines

*Consensus-based recommendation REC11.2:* 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.

#### Other existing potentially relevant guidelines published from 2015 onwards

Guideline	Organisation	Recommendation	Evidence base
Cervical screening: programme and colposcopy management - Colposcopic diagnosis, treatment and follow-up	NHS England	<p><b>Individuals referred with high grade dyskaryosis (moderate or severe)</b> on their test result are at significant risk of CIN 2 or 3, even if colposcopy was normal. Biopsy should be undertaken in <math>\geq 95\%</math> of individuals with high grade dyskaryosis (moderate or severe) on their test result. If there is no CIN or low grade CIN on the biopsy these cases should be discussed at the MDT. If no treatment is carried out, close surveillance with colposcopy and cervical samples every 6 months is advised. If at follow up there is persistent high grade cytology, or CIN2 or CIN3 is present on biopsy, excisional treatment is recommended (<math>\geq 90\%</math>).</p> <p><b>Individuals referred with low grade dyskaryosis or less</b> and who have an adequate and normal colposcopic examination are at low risk of developing cervical cancer. These individuals are returned to community-based 3 year recall.</p>	Not reported

Guideline	Organisation	Recommendation	Evidence base
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) (Perkins 2020) and endorsed by American College of Obstetricians and Gynecologists and affirmed by the American Cancer Society (Fontham 2020)	For patients with cytology showing AGC not otherwise specified or atypical endocervical cells not otherwise specified in whom histologic HSIL (CIN 2+) or AIS/cancer is not identified, cotesting at 1 and 2 years is recommended. If both cotests are negative, repeat cotesting at 3 years is recommended. If any test is abnormal, then colposcopy is recommended (BII). If CIN 2 or CIN 3 but no glandular lesion is identified histologically for patients with cytology atypical glandular, endocervical, or endometrial cells not otherwise specified, management should be according to the 2019 guidelines for the lesion diagnosed (Section I) (CII). For patients with atypical glandular or endocervical cells "favor neoplasia" or endocervical AIS cytology, if invasive disease is not identified during initial colposcopic workup, a diagnostic excisional procedure is recommended. The diagnostic excisional procedure used in this setting should provide an intact specimen with interpretable margins (BII). Endocervical sampling above the excisional bed is preferred (BII).	Kaiser Permanente Northern California data
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 (SICPCV)	For women with all subcategories of AGC and AIS, except atypical endometrial cells, colposcopy with endocervical sampling is recommended regardless of HPV testing results (Level of evidence: II - Strength of recommendation: A)	Consensus based on literature review – no evidence of systematic review undertaken
Diagnosis and Management of adenocarcinoma in situ (Teoh 2020)	Society of Gynecologic Oncology	Atypical glandular cells (AGC) and HPV-16 and -18 are associated with AIS and should be evaluated with colposcopy, endocervical sampling, and endometrial biopsy, as recommended by the ASCCP Risk-Based Management Consensus Guidelines ( <a href="http://www.asccp.org/consensus-guidelines">http://www.asccp.org/consensus-guidelines</a> ). Given the association of HPV-18 with AIS, endocervical sampling in the setting of a positive HPV-18 test result regardless of colposcopy findings is acceptable (CIII).	Consensus based on literature review – no evidence of systematic review undertaken

## References

American College of Obstetricians and Gynecologists. Updated cervical cancer screening guidelines 2021 <https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2021/04/updated-cervical-cancer-screening-guidelines> Accessed March 2023.

Chummun K, Fitzpatrick M, Lenehan P et al. Diagnostic and therapeutic dilemma associated with atypical glandular cells on liquid-based cervical cytology. *Cytopathology*. 2012;23:378-382.

Ciavattini A, Giannella L, Carpini GD, Tsioglou D, Sopracordevole F, Chiossi G, Di Giuseppe J, of Colposcopy IS. Adenocarcinoma in situ of the uterine cervix: Clinical practice guidelines from the Italian society of colposcopy and cervical pathology (SICPCV). *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2019 Sep 1;240:273-7.

Fontham ETH, Wolf AMD, Church TR, Etzioni R, Flowers CR, Herzig A, et al. Cervical cancer screening for individuals at average risk: 2020 Guideline update from the American Cancer Society. *CA Cancer J Clin* 2020; 70:321-346.

Jadoon BA, Kehoe S, Romain K et al. Analysis of outcome in women with borderline glandular change on cervical cytology. *European Journal of Obstetrics, Gynecology, & Reproductive Biology*. 2009;147:83-85.

Kodiathodi S, Chattopadhyay S, Baldwin A, Franks P. Management of borderline change in endocervical cells: a more dependable approach. *British journal of cancer*. 2014 Aug;111(5):851-7.

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.

Patel A, Thampy N, Hemming D, Naik R. A clinical review of borderline glandular cells reported on liquid-based cervical cytology. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2010 Aug;117(9):1051-9.

Perkins RB, Guido RS, Castle PE, Chelmow D, Einstein MH, Garcia F, et al. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis* 2020; 24:102-131.

Teoh D, Musa F, Salani R, Huh W, Jimenez E. Diagnosis and management of adenocarcinoma in situ: a society of gynecologic oncology evidence-based review and recommendations. *Obstetrics and gynecology*. 2020 Apr;135(4):869.

Zeferino LC, Rabelo-Santos SH, Villa LL, Sarian LO, Costa MC, do Amaral Westin MC, de Ângelo-Andrade LA, Derchain S. Value of HPV-DNA test in women with cytological diagnosis of atypical glandular cells (AGC). *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2011 Nov 1;159(1):160-4.

## APPENDICES

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

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 humans
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