Test of cure after adenocarcinoma in situ (AIS) – evidence summary

PICO: For women who have been treated for adenocarcinoma in situ (AIS) with complete excision and with clear histological margins, what is the safety and effectiveness of HPV and cytology annual co-testing up to 2 years, 5 years, 10 years or 15 years and discharging if double-negative on the last two tests compared to indefinite annual co-testing?

Summary of findings

Four studies were identified, none of which could directly address the question, as the follow-up periods were relatively short (longest timeframe: 40 months). Risk did not appear to meaningfully differ between those who were HPV negative vs co-test negative, but numbers were very small. American Society of Gynecologic Oncology and ASCCP recommendations for post-treatment surveillance of those with fertility-sparing management for AIS allow for co-testing surveillance to be extended to 3-yearly for patients who have consistently negative co-testing results in the first 5 years of surveillance.

Detailed findings

A systematic review was conducted in 2023 for the above PICO. No RCTs or pseudo-RCTs comparing different annual co-testing intervals for women treated for AIS were found. Therefore, on the advice of the Working Party, an evidence review was undertaken to address this question.

Evidence review for 2023 guidelines update

Searches: EMBASE and Medline databases were searched in March 2023 by combining terms for cervical intraepithelial neoplasia, adenocarcinoma in situ, conization, LEEP, laser, treatment and post-treatment. The search was conducted from 2015 onwards and was limited to articles published in English. Full details of search strategy included in Appendices. To cover the pre 2015 literature we also considered studies included in an evidence summary in the previous guidelines which addressed a different question regarding the management of women who have been treated for AIS.

Results: 4 studies were identified that reported the risk of AIS, CIN2, CIN3 or worse following conservative treatment for AIS for women with clear histological resection margins. These studies are summarized in Table 1.

Table 1: ***Studies investigating the safety and effectiveness of cytology and HPV co-testing in women who have been treated for adenocarcinoma in situ***

Study	Country	Study design	Population	Findings
Bai 2018	China	Retrospective cohort – single arm	44 women (mean age 36.1 years; range 28-55 years) who underwent LEEP between February 2006 and December 2016 and diagnosed with AIS (Pap test, punch biopsy, LEEP). The women were consecutive patients seen at Beijing Chao-Yang Hospital, China. There is no comparator group. Follow up was with cytology, high-risk HPV (Hybrid Capture II) test and colposcopy every 3-6 months. 33/44 margins clear 4/44 had multifocal lesions 38/44 had coexisting squamous lesions (≥ CIN1) 6/11 with positive/not evaluable margins underwent subsequent hysterectomy 3/11 with positive/not evaluable margins underwent subsequent cold knife conisation or second LEEP with clear margins Population followed up N = 38 **Subgroup with negative margins on initial LEEP** N = 33	**Risk of AIS or worse** on follow-up (mean 36.9 months) ***Negative margins*** *on initial LEEP or second conization* Of 33 women with free margins at baseline none (0/33) were diagnosed subsequently with AIS or worse on follow-up Results were not stratified by HPV vs co-testing results, or over how many rounds of repeat testing, but inferred risk is 0% in all groups, as there were no cases of AIS or worse during follow-up.
Upadhyay Baskota 2021	USA	Retrospective cohort – single arm	207 women (median age 36 years; range 22-65 years) who underwent LEEP/cone biopsy as primary treatment between June 2009 and July 2018 and diagnosed with AIS. The women were patients at Magee-Women's Hospital of the University of Pittsburgh Medical Center, USA. There is no comparator group. Follow up was for a median of 3.3 years (range 15 days – 9 years) using data on clinicopathological features, high-risk HPV test (HPV (Cervista DNA/Aptima mRNA)) and cytology 95/207 underwent hysterectomy 57/207 underwent a second LEEP/cone biopsy Only some with reported HPV and/or cytology follow-up results 74/207 had high-risk HPV follow-up 79/207 had cytology follow-up Interval between follow-up visits and reasons for hysterectomy and second LEEP/cone not reported HPV and cytology testing appear to have occurred at only one timepoint, rather than at 2 or more timepoints (results for HPV and cytology tests were reported as a single outcome) – unclear what timepoint the testing occurred at **Subgroup with negative margins** N = 107 (not lost to follow-up) 58/107 underwent hysterectomy 41/107 underwent a second LEEP/cone biopsy	- **Risk of AIS or invasive adenocarcinoma** on follow-up (median 3.3 years) ***Negative margins*** *on initial LEEP/cone biopsy* Of 107 women with free margins at baseline 9.3% (10/107) were diagnosed subsequently with AIS or invasive adenocarcinoma on follow-up 8 on hysterectomy and 2 on second LEEP/cone biopsy Of 45 women with free margins at baseline and **HPV negative** on follow-up, none were diagnosed subsequently with AIS or invasive adenocarcinoma on follow-up (risk = 0%; calculated 95%CI: 0-7.9%) Findings for co-test negative women were not available (but since they comprise a subset of the HPV-negative group, there must also have been zero cases; risk=0%; unknown denominator). Of 11 women with free margins at baseline and HPV positive on follow-up 9% (1/11) were diagnosed subsequently with AIS or invasive adenocarcinoma on follow-up -

Study	Country	Study design	Population	Findings
			Interval from LEEP/cone biopsy diagnosis to follow-up procedures was 15 days to 7 years 56/107 had high-risk HPV follow-up 45/56 HPV negative on follow-up	
Kitchener et al 2008	UK	Prospective cohort – single arm	917 women (median age 31.5 years; range 15-72 years) treated for CIN or CGIN (90% LLETZ, laser cone, cold knife cone). Treatment period nor reported. Start and finish dates for the study not stated. The women were patients at St Mary's Hospital, Manchester; Royal Free Hospital, London; and Aberdeen Royal Infirmary, Aberdeen. Follow up at 6 and 12 months, using cytology and HPV (Hybrid Capture II) testing, and at 24 months, using cytology alone with colposcopy at 6 and 12 months if either the cytology was abnormal or the HPV test was positive. A biopsy was performed if the colposcopy was abnormal. Subgroup with CGIN at baseline N = 9 Margin status NR	**Risk of AIS or invasive cancer** on follow-up (mean follow-up not stated) 1 of the 9 women with CGIN at baseline diagnosed with grade III adenocarcinoma at 23 months - negative resection margins with normal cytology and HPV negative tests at 6 and 12 months follow-up "One woman who was cytology negative/HPV negative at baseline was found to have a stage III adenocarcinoma. This woman originally had CGIN with clear margins. Subsequent review confirmed an absence of invasive disease in the original biopsy. One possibility is that she had microinvasive adenocarcinoma higher in the cervical canal undetected by the follow-up tests" Risk could not be ascertained for HPV vs co-testing, as test results and recurrence were not reported separately for the subgroup of 9 women with CGIN at baseline.
Costa 2007	Italy	Cohort – single arm	42 consecutive women (mean age 40.5y; range 27–63 years) diagnosed with AIS on conization (cold knife, LEEP or laser) between 2001 and 2004, and followed up for a mean of 40 months (range 3-84 months) using colposcopy, cytology, endocervical curettage and HPV (Hybrid Capture II) testing repeated at 6-month intervals. 4/42 had coexistent SCC on initial cone biopsy **Subgroup with negative margins** N = 21 5/21 underwent hysterectomy during follow-up	**Risk of CIN3, CGIN, AIS or invasive cancer** on follow-up (mean 40 months) ***Negative margins*** *on conization* Of 21 women with free margins at baseline 19% (4/21) were diagnosed subsequently with CIN3, CGIN, AIS or invasive cancer on follow-up – 4 AIS or cancer Risk could not be ascertained for HPV vs co-testing, as test results and recurrence were not reported separately for the group with negative margins. No CIN3, CGIN, AIS or cancer diagnosed at 24-month, 30-month, or 36-month follow-up visits. *For comparison with findings where margin status is not reported:* ***Positive or negative margins*** *on conization (n = 42)* Sensitivity (specificity) [NPV] by visit given for HPV vs co-testing Visit 1: 90.0% (58.3%) [87.5%] vs 90.0% (50.0%) [88.9%] Visit 2: 83.3% (58.8%) [90.9%] vs 100%.(52.6%) [100.0%]

Abbreviations: LEEP = loop electrosurgical excision procedure; LLETZ = large loop excision of transformation zone; CIN = cervical intraepithelial neoplasia; AIS = adenocarcinoma in situ; HPV = human papillomavirus; CGIN = cervical glandular intraepithelial neoplasia; NR = not reported; SCC = squamous cell carcinoma

Recent Australian AIS statistics

Numbers of AIS and percentage of AIS in each age group in 2019, 2020 and 2021 as reported by AIHW – AIHW NCSP Monitoring Reports 2020-2022.

Age group	**2019**		**2020**		**2021**	
(years)	N	% in age group	N	% in age group	N	*% in age group [25-74]*
<25	3	0.8%	3	0.8%	nr	
25–29	31	7.8%	26	7.2%	21	*5.8%*
30–34	111	27.8%	90	25.0%	69	*19.2%*
35–39	86	21.6%	100	27.8%	108	*30.1%*
40–44	72	18.0%	60	16.7%	73	*20.3%*
45–49	38	9.5%	37	10.3%	43	*12.0%*
50–54	20	5.0%	27	7.5%	21	*5.8%*
55–59	15	3.8%	8	2.2%	12	*3.3%*
60–64	11	2.8%	9	2.5%	7	*1.9%*
65–69	10	2.5%	0	0.0%	5	*1.4%*
70–74	1	0.3%	0	0.0%	0	*0.0%*
75+	1	0.3%	0	0.0%	nr	
25-74	**395**		**357**		**359**	
All ages	399		360		nr	

nr = not reported

Existing guidelines

Current (2017) Australian guidelines

Consensus-based recommendation REC11.13: Follow-up of completely excised AIS

Women with histologically-confirmed AIS who have undergone complete excision with clear margins should have annual co-testing indefinitely.†

If any abnormal result is obtained on follow-up co-testing, the woman should be referred for colposcopic assessment.

†Until sufficient data become available to support cessation of testing.

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	Individuals who undergo excision for CGIN are at risk of recurrence. If the CGIN has been completely excised at the time of first excision or subsequent re-excision, a test of cure (TOC) sample should be taken 6 months after treatment. If negative for hrHPV a second TOC sample is taken 12 months later (18 months after treatment or the subsequent re-excision). If this is also negative for hrHPV the individual can be recalled for screening in 3 years. These samples can be performed in the community. If at 6 or 18 months after treatment the test is positive for hrHPV the individual should be referred to colposcopy. A reflex cytology sample is processed to help inform colposcopy. If an individual fails TOC at 6 months only because of a positive hrHPV test, cytology is negative or inadequate and no abnormality is detected at colposcopic examination, they should have a second TOC sample 12 months later. If this sample is hrHPV negative, the individual can be discharged to recall in 3 years. Further recall will depend on the result of this test and the age of individual. If a positive hrHPV test with abnormal cytology is reported in either of the 6- or 18-month TOC samples, the individual must be referred to colposcopy for management. If no colposcopic abnormality is present and re-excision is not appropriate, the individual should revert to 10 years of follow up with annual hrHPV testing.
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)	i) For patients who undergo fertility-sparing management, surveillance with Pap plus HPV co-testing and endocervical sampling is recommended every 6 months for the first 3 years, then annually for at least 2 years or until hysterectomy is performed. ii) For patients who have consistently negative co-testing results in the first 5 years of surveillance, extending surveillance to every 3 years indefinitely is acceptable.
2019 ASCCP Risk-based management **consensus** guidelines for abnormal cervical cancer screening tests and cancer precursors	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 who have undergone hysterectomy for AIS, follow up includes HPV-based testing annually for 3 years and then at 3-year intervals for at least 25 years. For women have undergone an excisional procedure with negative margins and negative ECC and are undergoing fertility sparing management, co-testing with endocervical sampling and HPV testing every 6 months is recommended for 3 years. They can then move to annual surveillance for 2 years or until hysterectomy is performed. If there are any abnormal test results within this period, the patient should be managed per guidelines. If hysterectomy is not performed but all testing has been negative for 5 years, it is reasonable to space out surveillance to every 3 years. Limited data supports that HPV results are more predictive of recurrence than cytology, so if HPV testing continues to be negative, hysterectomy can be avoided. If HPV results in surveillance are positive, the patient should proceed to hysterectomy once childbearing is complete.
Adenocarcinoma in situ of the uterine cervix: Clinical	Italian society of colposcopy and cervical pathology	No actual recommendations made rather state *There are no definitive data about the optimal surveillance for women undergoing conization for AIS: long-term follow-up is required especially for women undergoing conservative treatment. It is*

Guideline	Organisation	Recommendation
practice guidelines from the Italian society of colposcopy and cervical pathology (SICPCV) (Ciavattini 2019)		*reasonable to recommend colposcopic evaluation with cytological and high-risk human papillomavirus (HPV) testing every 6 months for the first 2 years, and then every 12 months for the following 3 years. Then, the cytological follow-up should be continued every 12 months indefinitely. Brushing of the cervical canal or ECC should be performed on each clinical evaluation. Post-conization HPV positivity is a valid predictor of disease relapse and progression especially if the specific AIS histotype and the pre-treatment HPV status are also taken into consideration.*
Cervical cancer screening (2016)	Towards Optimized Practice (TOP Alberta doctors)	Suggest annual screening with Pap for life [in the context of a cytology-only program].
Prevention of cervical carcinoma Part 2	The Oncology Guidelines Program of the Association of Scientific Medical Societies in Germany (AWMF), the German Cancer Society (DKG) and German Cancer Aid (DKH). (Hillemanns 2019)	Follow-up after treatment for CIN/ACIS must consist of examinations combining HPV testing and cytology. Differential colposcopy should be performed if the findings at follow-up are abnormal (at least 1 of the test results is positive). Follow-up examinations combining HPV testing and cytology should be performed at 6, 12 and 24 months after completing treatment. The patient must continue to participate in regular screening, even if the findings at follow-up are unremarkable.

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

Bai H, Liu J, Wang Q, Feng Y, Lou T, Wang S, et al. Oncological and reproductive outcomes of adenocarcinoma in situ of the cervix managed with the loop electrosurgical excision procedure. BMC Cancer 2018; 18: 461.

Ciavattini A, Giannella L, Delli Carpini G, Tsiroglou D, Sopracordevole F, Chiossi G, et al. Adenocarcinoma in situ of the uterine cervix: Clinical practice guidelines from the Italian society of colposcopy and cervical pathology (SICPCV). Eur J Obstet Gynecol Reprod Biol 2019; 240:273-277.

Costa S, Negri G, Sideri M, Santini D, Martinelli G, Venturoli S, et al. Human papillomavirus (HPV) test and PAP smear as predictors of outcome in conservatively treated adenocarcinoma in situ (AIS) of the uterine cervix. Gynecol Oncol 2007; 106(1): 170-176.

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.

Hillemanns P, Friese K, Dannecker C, Klug S, et al. Prevention of Cervical Cancer – Guideline of the DGGG and the DKG (S3 Level, AWMF Register Number 015/027OL, December 2017) – Part 2 on Triage, Treatment and Follow-up. Geburtsh Frauenheilk. 2019;79:160–176

Kitchener HC, Walker PG, Nelson L, Hadwin R, Patnick J, Anthony GB, et al. HPV testing as an adjunct to cytology in the follow up of women treated for cervical intraepithelial neoplasia. BJOG 2008; 115: 1001-1007.

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

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. Obstet Gynecol 2020; 135: 869-878.

Towards Optimized Practice (TOP Alberta doctors). Cervical cancer screening 2016 https://actt.albertadoctors.org/media/w3vpspf2/cervical-cancer-screening-cpg.pdf Accessed March 2023.

Upadhyay Baskota S, Wang T, Zhao C. Follow-up findings in postconservative treatment surveillance for women with cervical adenocarcinoma in situ. J Low Genit Tract Dis 2021; 25: 38-42.

Appendices

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

Database(s): **Embase Classic+Embase** 1947 to 2023 March 24**, Ovid MEDLINE(R) ALL** 1946 to March 24, 2023
Search Strategy:

#	Searches
1	(CIN 2+ or CIN 3+).tw.
2	CIN2+.tw.
3	CIN3+.tw.
4	(adenocarcinoma in situ* adj5 (endocervi* or cervi*)).tw.
5	(AIS* adj5 (endocervi* or cervi*)).tw.
6	excision*.tw.
7	surg*.tw.
8	(cone adj3 biops*).tw.
9	coni?ation.tw.
10	(LEEP or LLETZ or SWETZ or NETZ).tw.

11	loop electro-excisional procedure.tw.
12	laser.tw.
13	Fischer cone.tw.
14	electro-surg*.tw.
15	recurren*.tw.
16	(test adj2 cure).tw.
17	(treat* adj5 surveillance).tw.
18	(treat* adj5 follow*).tw.
19	(post-treatment or posttreatment).tw.
20	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	1 or 2 or 3 or 4 or 5
22	20 and 21
23	limit 22 to english language
24	limit 23 to humans
25	limit 24 to yr="2015 -Current"
26	limit 25 to conference abstracts [Limit not valid in Ovid MEDLINE(R); records were retained]
27	limit 26 to medline
28	26 not 27
29	25 not 28
30	remove duplicates from 29