Section 9: Management of glandular abnormalities

Diagnosis

Cervical adenocarcinoma is usually associated with human papillomavirus (HPV) infection. An estimated 78% of adenocarcinomas are associated with HPV 16 or 18 infection.[1] Cervical cytology has been shown to be less sensitive for the detection of glandular lesions than for the detection of squamous intraepithelial lesions and squamous cell carcinoma, due to sampling and interpretation issues.[2] Primary HPV screening has been found to be more effective than cytology screening for the detection and prevention of cervical adenocarcinoma.[3]

Aotearoa New Zealand uses The Bethesda Reporting System (2014) (NZ modified) (See appendix 1).

Participants with atypical glandular cell (AGC) cytology are managed as high risk and should be referred to colposcopy,[4-6] except where atypical endometrial cells are reported referral to gynaecology should occur.

A meta-analysis examining outcomes of participants with AGC cytology reported 20% of participants with CIN2+ / AIS+ and 4% with cervical cancer.[5] Participants over the age of 50 with AGC cytology (any type) and HPV not detected have an elevated risk of endometrial cancer and warrant additional investigation [5 6]

Colposcopy has a low sensitivity for detecting glandular abnormalities, and participants with endocervical glandular abnormalities on cytology are at risk of AIS or adenocarcinoma even when colposcopy is normal.[7 8] Because of the high incidence of neoplasia and poor sensitivity of testing methods, diagnostic excisional procedures may be required.

Cytological glandular abnormalities can be associated with polyps, metaplasia and adenocarcinomas of the endometrium, ovary, fallopian tube and other sites, which are not detected through HPV cervical screening, as these abnormalities are not HPV related.[4] The detection and management of these conditions is outside the scope of this guideline.

Imaging

Participants who are referred with atypical glandular cells may not always have a colposcopically detectable lower genital tract abnormality. In this situation, a pelvic ultrasound of the upper genital tract could be performed. Imaging may detect gross disease of the upper genital tract, as abnormalities in these sites may be the cause of the screen-detected abnormal glandular cells. Further investigation, such as endometrial sampling to exclude an endometrial origin for atypical glandular cells, may be required.

Stratified mucin producing intraepithelial lesion (SMILE)

SMILE is a histological entity usually associated with CIN and abnormal glandular cells, but can occur in the absence of these. SMILE is not reliably identified by cytology and is usually diagnoses by histologic biopsy. Individuals with SMILE should be managed according to the guidance for AIS.

RECOMMENDATIONS – MANAGEMENT FOR PARTICIPANTS WITH ATYPICAL GLANDULAR CELLS (AGC) ADENOCARCINOMA IN SITU (AIS)	
R9.01 AGC cytology	**Evidence-based recommendation** Participants who have a cytology report of atypical glandular cells should be referred to colposcopy, except for those with atypical endometrial cells (and no other reason for referral to colposcopy) who should be referred to specialist gynaecology services.
R9.02 AGC cytology and HPV not detected	**Consensus-based recommendation** Participants who have a test result of HPV not detected and atypical glandular cells cytology (any type) should have an endometrial abnormality excluded. A repeat HPV test is recommended at the time of colposcopy.
R9.03 Management of AGC cytology with normal colposcopic findings	**Consensus-based recommendation** Participants who have a test result of HPV detected (any type) with atypical glandular cell cytology and normal colposcopic findings should have a multidisciplinary team review.
R9.04 Cytology confirmed at cytological review	**Consensus-based recommendation** If atypical glandular cells or AIS are confirmed on cytology review, type 3 excision and dilation and curettage (D&C) are recommended.

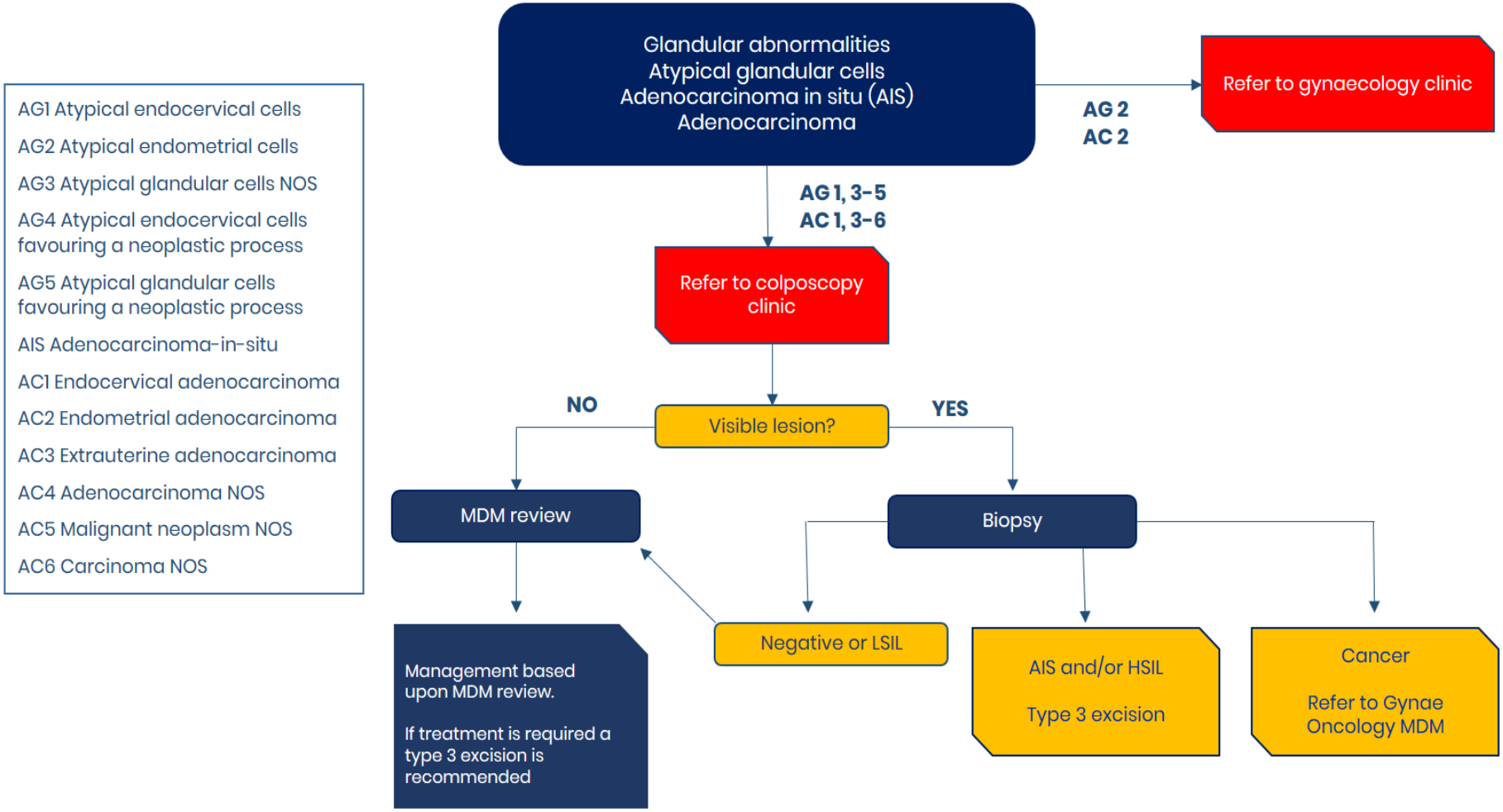
RECOMMENDATIONS – MANAGEMENT FOR PARTICIPANTS WITH ATYPICAL GLANDULAR CELLS (AGC) ADENOCARCINOMA IN SITU (AIS)	
R9.05 Cytology not confirmed at cytological review	**Consensus-based recommendation** Participants where atypical glandular cell cytology was not confirmed at cytology review should be managed in accordance with recommendations from a multidisciplinary review.
R9.06 Upper genital tract imaging	**Practice point** Upper genital tract imaging may be performed in cases where no lower genital tract abnormality is detected after a referral with an AGC cytology result.
R9.07 If AIS is confirmed on diagnostic biopsy	**Evidence-based recommendation** If AIS is confirmed on diagnostic biopsy a type 3 excision should be performed. Hysterectomy should not be undertaken without prior cone biopsy to exclude invasive carcinoma.

Adenocarcinoma

RECOMMENDATION – ADENOCARCINOMA	
R9.08 Referral to colposcopist for participants with a cytology result of invasive adenocarcinoma	**Consensus-based recommendation** Participants with invasive adenocarcinoma cytology should be urgently referred to a colposcopist to assess and confirm the diagnosis, except where the cancer type is endometrial adenocarcinoma (with no other reason requiring referral to colposcopy), where urgent referral should be to specialist gynaecology services.
R9.09 Management of adenocarcinoma	**Evidenced-based recommendation** Participants with histologically confirmed adenocarcinoma should be referred to a gynaecological oncologist and be reviewed at a Gynaecology Oncology MDM.
R9.10 Support for participants diagnosed with adenocarcinoma	**Practice Point** Receiving a cervical cancer diagnosis can be very distressing for participants. Ask all participants/whānau whether they require assistance or support. Refer to your local gynaecological cancer Clinical Nurse Specialist to provide support and advice.

RECOMMENDATION – ADENOCARCINOMA	
	Consider transport, cultural support and where appropriate offer referral to Support to Screening Services.

Figure 1: Management of participants with atypical and abnormal glandular abnormalities



References

1. International Collaboration of Epidemiological Studies of Cervical Cancer. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. Int J Cancer 2007 Feb 15;120(4):885-91 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17131323.
2. Wilbur DC, Chhieng DC, Guidos B, Mody DR. Epithelial abnormalities: glandular. In: Nayar R, Wilbur DC (Eds).The Bethesda system for reporting cervical cytology. Definitions, criteria and exploratory notes. 3rd ed.Springer; 2015.
3. Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet 2014 Feb 8;383(9916):524-32 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24192252.
4. Aitken, CA, Jansen, EEL, Siebers, AG et al., Risk of Gynecologic Cancer after Atypical Glandular CellsFound on Cervical Cytology: A Population-Based Cohort Study. Cancer Epidemiol Biomarkers Prev 2021;30:743–50 doi: 10.1158/1055-9965.EPI-20-1384
5. Verdoodt, F, Jiang, Mark Williams, M, Schnatz, P. & Arbyn, M. High-risk HPV testing in the management of atypical glandular cells: A systematic review and meta-analysis Int. J. Cancer: 2016 138, 303–310
6. Pradhan, D, Zaibo, L, Ocque, R, Patadji, S, Chenquan, Z. Clinical Significance of Atypical Glandular Cells in Pap Tests: An Analysis of More Than 3000 Cases at a Large Academic Women's Center. Cancer Cytopathology 2016 DOI: 10.1002/cncy.21724, wileyonlinelibrary.com
7. Ullal, A. Roberts, M. Bulmer, J.N. Mathers, M.E. Wadehra, V. The role of cervical cytology and colposcopy in detecting cervical glandular neoplasia. Cytopathology 2009, 20, 359–366.
8. Sharpless KE, Schnatz F, Mandavilli S, Greene JF, Sorosky JI. Dysplasia associated with atypical glandular cells on cervical cytology. Obstet Gynecol 2005;105:494–500.

Follow-up of atypical glandular cytology with no histological confirmation

Where participants have had a previous AGC cytology with no histological confirmation of a glandular abnormality, they should be reviewed at an MDM and they should complete a Test of Cure co-test before returning to regular interval screening.

Treatment of glandular lesions

Both cytological and colposcopic assessment of glandular abnormalities is difficult, including the distinction between in-situ and invasive disease. A participant presenting with a glandular abnormality on cytology has a 3.6% (95% CI 1.1-7.5%) risk of having invasive adenocarcinoma.[1] A type 3 excision should be undertaken when treating glandular abnormalities, studies have demonstrated that LLETZ and cold knife cone biopsy achieve comparable outcomes when treating AIS [2-4] If LLETZ biopsy is being utilised as the treatment method this **should be performed as a single pass excision**. If this is not achievable a cold knife cone biopsy is recommended [2 3 5]

Participants with a proven glandular abnormality who wish to remain fertile should be treated with local excision. Evidence indicates that in participants less than 35 years of age a more conservative type 2 excision (10-15mm) can be offered initially if the participant is counselled about the possibility of repeat therapy and the associated risks. [2 5]

RECOMMENDATIONS – TREATMENT OF AGC AND AIS	
R9.11 Specimen for histological assessment of glandular abnormalities	**Practice point** When diagnostic excision is performed while investigating glandular abnormalities, the method chosen should ensure that a single, intact specimen with interpretable margins is obtained for histological assessment.
R9.12 A type 3 excisional biopsy should be performed	**Practice point** A type 3 excision should be performed by the method the colposcopist feels most comfortable with to ensure adequate treatment. The depth and extent of the excisional treatment should be tailored to the participant's age and fertility requirements.

References

1. Verdoodt, F, Jiang, Mark Williams, M, Schnatz, P. & Arbyn, M. High-risk HPV testing in the management of atypical glandular cells: A systematic review and meta-analysis Int. J. Cancer: 2016 138, 303–310
2. Tan, JHJ, Malloy, MJ, Thangamani1, R, Gertig, D, Drennan, KT Management and long-term outcomes of women with adenocarcinoma *in situ* of the cervix: A retrospective study Aust N Z J Obstet Gynaecol 2020; 60: 123–129 DOI: 10.1111/ajo.13047
3. Jiang, Y, Chen, C, & Li, L Loop Electrosurgical Excision for Cervical Adenocarcinoma In Situ (ACIS): A Systematic Review and Meta-Analysis PLoS ONE 12(1): e0170587. doi:10.1371/journal.pone.0170587
4. Cohen PA, Leung, Y, Anderson, L, van der Griend, R, Chivers, P. et al., Excisional treatment comparison for in situ Endocervical adenocarcinoma (EXCISE): A phase 2 pilot randomized controlled trial to compare histopathological margin status, specimen size and fragmentation after loop electrosurgical excision procedure and cold knife cone biopsy. Gynecologic Oncology 159 (2020) 623–629 https://doi.org/10.1016/j.ygyno.2020.09.053
5. Teoh, D, Musa, F, Salani, R, Huh, & Jimenez, E, Diagnosis and Management of Adenocarcinoma in Situ A Society of Gynecologic Oncology Evidence-Based Review and Recommendations Obstet Gynecol 2020;135:869–78 DOI: 10.1097/AOG.0000000000003761

Follow-up after excisional treatment for AIS

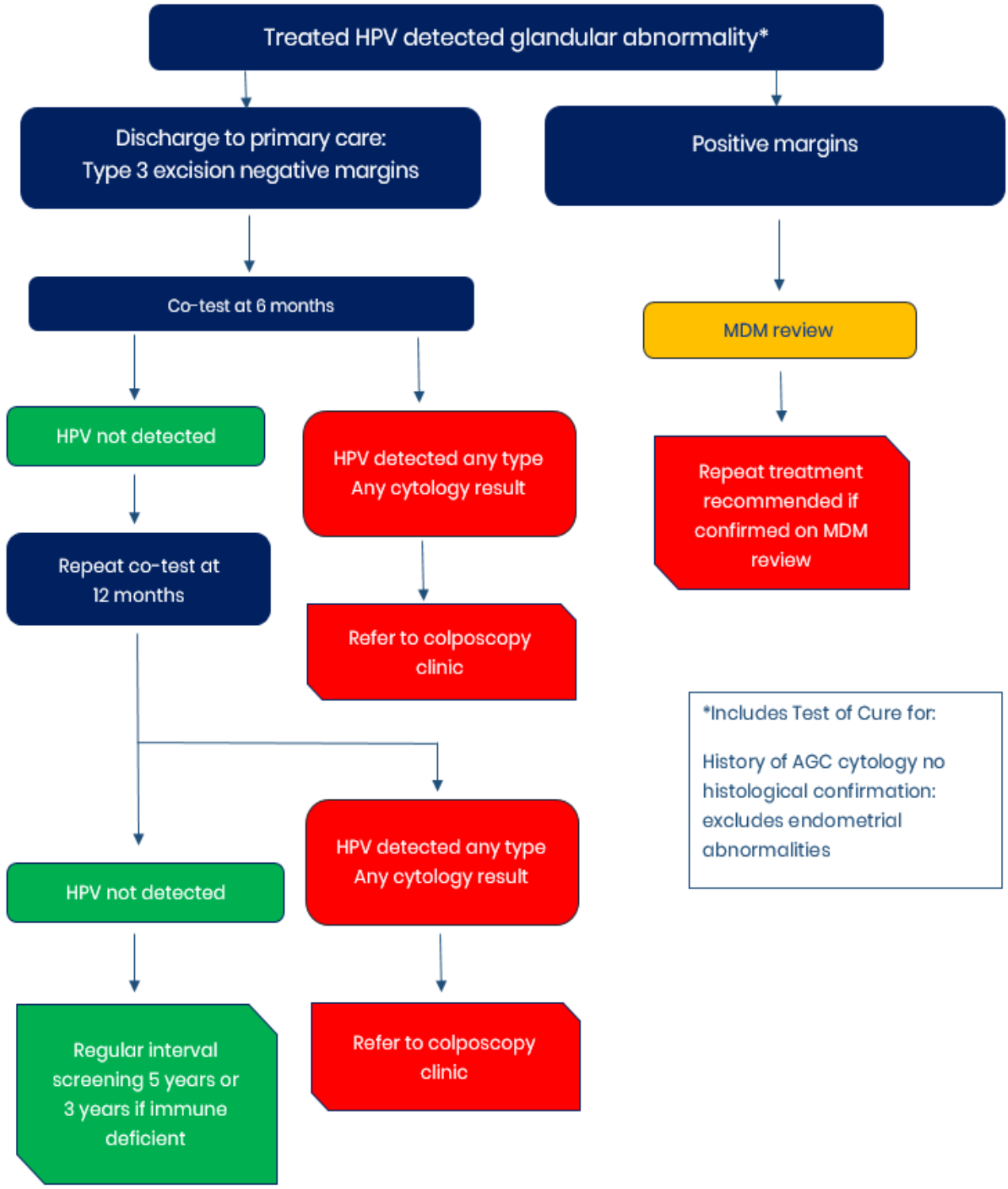
An Australian study reported that participants with adenocarcinoma in situ with a positive margin were more likely to have residual or recurrent disease (28.7%) compared with negative excisional margins (4.3%). Residual adenocarcinoma in situ was twice as common if adenocarcinoma in situ was present at endocervical (29.6%) and stromal (23.1%) margins compared with an ectocervical margin (13.6%). [1] Participants with positive excisional margins should be reviewed at a multidisciplinary review meeting and a repeat excision should be performed. [1-3]

A new recommendation when participants are treated for histologically confirmed HPV detected AIS and the final histology confirms clear margins, follow-up can occur in primary care. A positive HPV test has been shown to be the most significant independent predictor of residual disease. [4] [5] **A co-test** should be performed at 6 and 18 months for **Test of Cure**. Once the Test of Cure co-test has

been completed successfully, the participant may return to regular interval screening.

If a participant has HPV detected (any type) during the Test of Cure period, they should be referred for colposcopic assessment. If the participant has completed Test of Cure co-test and returned to regular interval screening, any further abnormalities should be managed as a new screening event and follow the management guidelines in this document. Participants who have had a hysterectomy can cease screening.

Figure 2: Management of Test of Cure co-test following a HPV detected glandular abnormality



If the HPV test result prior to treatment was not detected or the HPV status prior to treatment is unknown, the participant should have co-testing annually. If surveillance tests have been undertaken for 25 years or more since the time of treatment and all tests are negative, participants can be returned to the regular screening interval. They can exit screening at age 70 years or older if they have already had a negative co-test when aged 70 years or older.

If any abnormal result is obtained on follow-up co-testing, the person should be referred for colposcopic assessment. The exception would be where there is a HPV not detected and ASC-US or LSIL cytology, the co-test should be repeated in 12 months. If the co-test in 12 months is HPV not detected and ASC-US or LSIL cytology participants should be referred for colposcopic assessment.

Participants who have had a hysterectomy can cease screening.

RECOMMENDATIONS – FOLLOW-UP AFTER EXCISIONAL TREATMENT FOR AIS	
R9.13 Follow-up of completely excised histologically confirmed HPV positive AIS	**Consensus-based recommendation** Participants with histologically confirmed HPV positive AIS who have undergone complete excision with adequate margins should have their first follow-up in primary care with a Test of Cure co-test six months after treatment. If HPV is not detected and the cytology is negative, a follow-up Test of Cure co-test should be repeated 12 months later. After two consecutive negative co-tests 12 months apart the participant can return to regular interval screening. If a participant has HPV detected (any type) or any abnormal cytology during the Test of Cure period, they should be referred for colposcopic assessment.
R9.14 Repeat excision for incompletely excised AIS	**Evidenced-based recommendation** If AIS is incompletely excised at the endocervical or deep stromal margins (not the ectocervical margins), or if the margins cannot be assessed, further excision to obtain adequate margins should be performed.
R9.14 Role of hysterectomy in AIS	**Consensus-based recommendation** Where participants have been treated for AIS by local excision with clear margins, there is no evidence to support completion hysterectomy. In this situation, hysterectomy is not recommended.

RECOMMENDATIONS – FOLLOW-UP AFTER EXCISIONAL TREATMENT FOR AIS	
R9.15 Follow-up of completely excised HPV negative or HPV status unknown AIS	**Consensus-based recommendation** Those with completely excised AIS who were HPV not detected or have unknown HPV status prior to treatment, should have annual co-testing. If surveillance tests have been undertaken for 25 years or more since the time of treatment and all tests are negative, participants can be returned to the regular screening interval. They can exit screening at age 70 years or older if they have already had a negative co-test when aged 70 years or older. Participants who have had a hysterectomy can cease screening. If a participant has a HPV detected (any type) they should be referred to colposcopy. If a participant has a HPV not detected and ASC-US or LSIL cytology the co-test should be repeated in 12 months. If the subsequent co-test is HPV not detected and ASC-US or LSIL cytology referral to colposcopy is indicated.
R9.16 Supporting participants/ whānau to attend Test of Cure follow-up	**Practice point** Ask all participants / whānau whether they require assistance or support to attend their follow-up Test of Cure co-test. Consider transport, cultural support and where appropriate offer referral to Support to Screening Services.

References

1. Tan, JHJ, Malloy, MJ, Thangamani1, R, Gertig, D, Drennan, KT Management and long-term outcomes of women with adenocarcinoma in situ of the cervix: A retrospective study Aust N Z J Obstet Gynaecol 2020; 60: 123–129 DOI: 10.1111/ajo.13047
2. Salani, R, Puri, I & Robert E. Bristow, RE. Adenocarcinoma in situ of the uterine cervix: a metaanalysis of 1278 patients evaluating the predictive value of conization margin status. J Obstet Gynecol 2009;200:182.e1-182.e5.A doi: 10.1016/j.ajog.2008.09.012
3. Teoh, D, Musa, F, Salani, R, Huh, & Jimenez, E, Diagnosis and Management Of Adenocarcinoma in Situ A Society of Gynecologic Oncology Evidence-Based Review and Recommendations Obstet Gynecol 2020;135:869–78 DOI:

10.1097/AOG.0000000000003761

4. Costa, S, Venturoli, S, Negri, G, Sideri, M, Preti, M et al., Factors predicting the outcome of conservatively treated adenocarcinoma in situ of the uterine cervix: An analysis of 166 cases,. Gynaecologic Oncology 2012; 124: 490-495. DOI doi:10.1016/j.ygyno.2011.11.039
5. Belkic, K, Andersson, S, Alder, S, Mints, M, Megyessi, D. Predictors of treatment failure for adenocarcinoma in situ of the uterine cervix: Up to 14 years of recorded follow-up.