Section 8: Management of histologically confirmed high grade squamous abnormalities

Diagnosis

Based on Lower Anogenital Squamous Terminology (LAST), the histology of high grade squamous lesions is reported as HSIL (CIN2) or HSIL (CIN3).[1] Histological diagnosis of HSIL (CIN2 and/or CIN3) is necessary before undertaking treatment, except when a diagnostic excision is required. Treatment undertaken at the time of initial colposcopic assessment is known as "see and treat" and is only recommended in certain circumstances.

RECOMMENDATION – DIAGNOSIS PRIOR TO TREATMENT	
R8.01 Histological diagnosis before treatment	**Consensus-based recommendation** For participants who have a visible lesion at colposcopy, histological confirmation of a high grade lesion is recommended before undertaking definitive treatment.

Treatment of HSIL

HSIL is the expression of persistent HPV infection that has the potential to progress to invasive carcinoma. [2] Based on studies on the natural history of HPV infections and cervical abnormalities, an estimated 30-70% of untreated CIN2 and about 15% of untreated CIN3 will regress with time alone. [2-4] About 5% of CIN2 and 14-31% of CIN3 are estimated to progress to invasive cancer without treatment. [2-7]

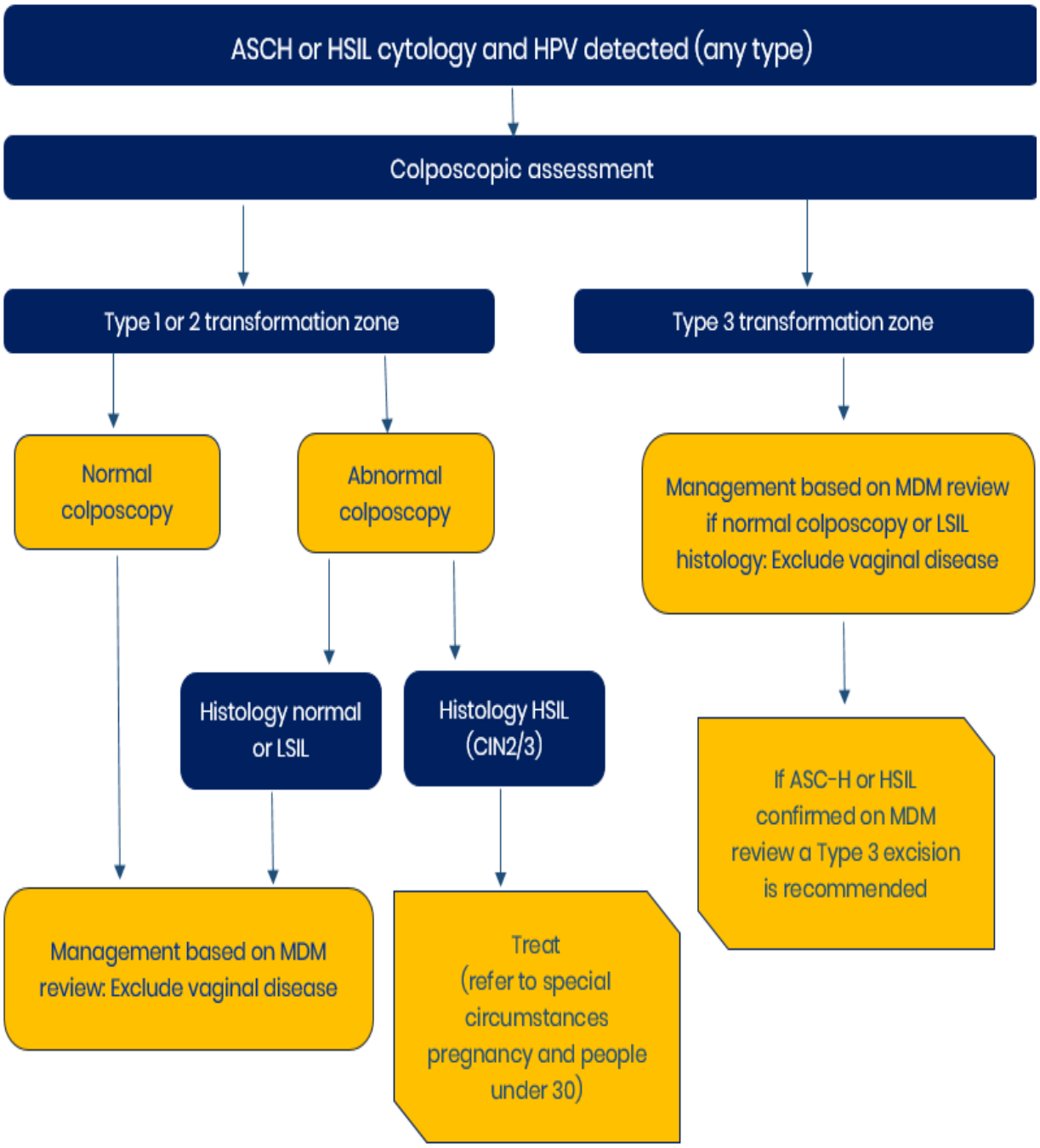
The timeframe during which invasion develops after CIN2 or CIN3 is usually many years, allowing time for detection, follow-up and treatment before invasion develops.

Although not all participants with HSIL will develop cervical cancer, the practice of treating all cases of HSIL (CIN2 and CIN3) is an effective way of reducing a participant's risk of subsequent cervical cancer. [2] Some participants with HSIL may be treated unnecessarily; however, it is not possible to identify these participants in advance and the benefits of treatment outweigh the harms. HSIL (CIN2) is more likely to regress in participants aged under 30 years, so a more conservative approach is warranted. [8]

To treat HSIL (CIN2 and/ CIN3) adequately, the entire lesion and TZ must be excised or destroyed. In Aotearoa New Zealand, usual practice is to remove lesions by excisional treatment. Ablative treatment is an option, but excisional treatment methods are preferred. Ablation should only be performed by colposcopists who are skilled in the practice.

RECOMMENDATION – TREATMENT OF HSIL	
R8.02 Treatment for HSIL	**Evidence-based recommendation** Participants with a histological diagnosis of HSIL should be treated to reduce the risk of developing invasive cervical carcinoma.
R8.03 Hysterectomy	**Consensus-based recommendation** Hysterectomy is not generally indicated for the management of HSIL alone. If performed for concurrent clinical indications, the following conditions must be met: • colposcopic assessment is satisfactory • a targeted biopsy has confirmed the diagnosis • there is no evidence of an invasive cancer on cytology, colposcopic assessment or biopsy • there is no evidence of a glandular lesion on cytology colposcopic assessment or biopsy • the entire lesion can be visualised. • exclude vaginal disease
R8.04 Supporting participants when being treated for high grade abnormalities	**Practice point** Some participants can find the treatment process stressful, and it can cause anxiety. Ask all participants/whānau whether they require assistance or support to attend their treatment appointment. Consider transport, cultural support and where appropriate offer referral to Support to Screening Services.

Figure 1 – Management of participants with ASC-H or HSIL cytology and HPV detected (any type)



Invasive carcinoma

RECOMMENDATION – INVASIVE CARCINOMA	
R8.05 Referral of participants with invasive disease	**Consensus-based recommendation** A participant with a histologically confirmed diagnosis of invasive or superficially invasive squamous cell carcinoma should be referred to a gynaecological cancer centre for multidisciplinary team review.
R8.06 Support for participants diagnosed with cervical cancer	**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. Consider transport, cultural support and where appropriate offer referral to Support to Screening Services.

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Active Surveillance of CIN2

Treatment of the cervix increases the risk of preterm birth and mid-trimester loss for women who go on to conceive after treatment. [1-3] The option to manage histologically confirmed CIN2 with active surveillance provides the opportunity to avoid over treatment for participants under the age of 30.

In Aotearoa New Zealand the PRINcess trial reported 53% of CIN2 lesions regressed within 24 months in participants under the age of 25 and there have been similar reports internationally. [4-6] There is evidence to support active surveillance of participants under the age of 30 with a histologically confirmed CIN2. [7-9] A meta-analysis examining active surveillance in participants under the age of 30 has reported a 60% regression at 24 months and 70% at 36 months. [8] The progression rate to CIN3 at 24 months was 11% [8] Persistent HPV 16 is an important factor in the persistence and progression of CIN2 abnormalities when being managed conservatively. [4-8] CIN2 lesions associated with HPV 16 had a 31% decreased chance of regression in participants aged under 25 years. [4]

It is important to discuss the benefits and risks with participants to guide shared decision making when deciding between active surveillance and treatment. If there is concern the participant may not return for follow up, treatment is indicated. Six monthly follow up is recommended over 24-month period. Participants should be

advised at any point during their follow up they can opt for treatment if they change their mind regarding active surveillance. Smoking cessation should be discussed if the participant smokes tobacco.

All cases must be discussed at MDM to review the biopsy and to ratify a decision for conservative management. It is important when active surveillance is chosen that MDM review occurs whenever the histology is reported as CIN2 during the follow up period. This ensures confirmation of histologic CIN2 as there is the potential for both downgrading to LSIL or upgrading to CIN3. [10 11]

During active surveillance biopsies should be taken of any abnormal colposcopic changes. If the colposcopic findings are normal biopsies are not indicated. If there is discordance between cytology, colposcopy and histology during the follow up period multidisciplinary review is recommended. Outcomes should be subject to regular local audit.

Participants can be discharged to primary care following regression of the CIN2 abnormality and should complete a Test of Cure HPV test which consists of two consecutive HPV not detected tests 12 months apart before returning to the regular screening interval of five years (or three years if immune deficient). Refer to Test of Cure HPV test guidelines following treatment of high grade abnormalities in Section 8.

RECOMMENDATIONS – ACTIVE SURVEILLANCE OF CIN2	
R8.07 Criteria for active surveillance of CIN2	**Evidence-based recommendation** Participants under the age of 30 can be offered active surveillance of CIN2 if: • There is a Type 1 or 2 TZ and a CIN3 or invasive lesion is excluded • CIN2 has been diagnosed on histology and reviewed at MDM to exclude an under or overcall • Participants agree to regular 6 monthly follow up colposcopy examinations including repeat cervical cytology, and repeat biopsy of any lesions present • Participants understand the time period for resolution of CIN2 can be at least 24 months • Treatment should be offered if the CIN2 has not resolved within 24 months.
R8.08 Supporting participant's choices of active surveillance of CIN2	**Practice Point** It is important to discuss the benefits and risks of active surveillance of CIN2 with participants to guide shared decision making when opting for surveillance or treatment.

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Repeat treatment of HSIL

Participants who have incomplete excision of HSIL (CIN2/3) with positive endocervical or stromal margins do not necessarily require immediate repeat excision. The rate of residual or recurrent HSIL from a post treatment analysis varied from 4-18%, with an average of 8% within 2 years. [1] Studies have shown HPV testing detects residual disease earlier and with higher sensitivity when compared to cytology or histological margin status [1-5] A meta-analysis reported HPV positivity had a higher sensitivity than margin status in predicting residual disease (91% vs 56%) and equivalent specificity (84%). [2] Therefore, participants should be offered Test of Cure HPV surveillance to avoid over treatment, with the exception of participants over the age of 50.

Evidence suggests participants over the age of 50 who have positive endocervical or stromal margins have an increased risk of residual disease. Following MDM review, repeat excision should be considered [6 7]

RECOMMENDATION – REPEAT TREATMENT	
R8.09 Repeat excision not necessarily required for incomplete excision of high grade lesions	**Evidence-based recommendation** Participants who have incomplete excision of HSIL (CIN2/3) with positive endocervical or stromal margins do not necessarily require immediate repeat excision and could be offered Test of Cure HPV test Exceptions are: • participants aged 50 years or over • participants who may not engage with recommended follow-up
R8.10 Recurrent disease after ablation	**Practice point** If high grade disease recurs after previous ablation, treatment should be by excision.

Superficially invasive squamous cell cancer (SISCCA)

Participants diagnosed as FIGO Stage IA1[8] squamous carcinoma after local excision do not require further excision if all of the following criteria are satisfied:[8-11]

- The margins are clear of CIN and invasive disease
- There is no evidence of lymphovascular space invasion, a histopathologist with specialised expertise in gynaecological pathology has reviewed the case and it has been discussed at a gynaecological oncology multidisciplinary meeting.

If the invasive lesion is excised but CIN extends only to the deep lateral and/or endocervical excision margin/s, then a repeat excision should be performed to confirm complete excision of the CIN and to exclude further invasive disease.

RECOMMENDATION – SUPERFICIALLY INVASIVE SQUAMOUS CELL CANCER	
R8.11 Role of repeat excision in superficially invasive squamous cell cancer (previously called 'micro-invasive')	**Practice point** In the presence of a superficially invasive squamous carcinoma, if HSIL (CIN2/3) extends to any excision margin, a repeat excision (usually a type 3 excision) is recommended. Management should be discussed at a gynaecological oncology multidisciplinary meeting.

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Test of Cure HPV test after treatment for HSIL

Participants who have been treated for a high grade squamous lesion continue to be at a higher risk of recurrence of HSIL and invasive cervical cancer for 10-25 years. [1] [2] This greater risk highlights the importance of continuing surveillance after treatment to detect residual or recurrent disease. Therefore, it is of importance to engage participants in the Test of Cure HPV test follow up pathway following

treatment.

Colposcopy is not routinely recommended after the treatment of a high grade abnormality. A Test of Cure HPV test can occur with the primary care provider. HPV testing is more sensitive in detecting residual disease than colposcopy or excision margin status, supporting a follow up approach which can occur in primary care. [3-5] There may be exceptions where the colposcopist has clinical concern which warrants closer follow up or further treatment.

Research and systematic reviews have reported HPV testing alone has similar negative predictive value as co-testing (HPV and cytology) with a slight increase in sensitivity with the co-test. [6-10] Data from the US has compared CIN3 risk based on follow up test methods and demonstrated a low risk of CIN3 following negative HPV tests as outlined in Table 1. [9] A meta-analysis has reported the overall risk of residual or recurrent high grade disease is 6.6% (95% CI 4.9–8.4) following treatment suggesting for many participants a single treatment is effective. [3]

Table 1: Risk of CIN3 following treatment of CIN3 [4]

Biopsy Result Before Treatment	**Current HPV Result**	**CIN3+ Immediate risk (%)**	**CIN3+ 1 year risk (%)**	**CIN3+ 5 year risk (%)**
CIN3	HPV-negative x2	0.05	0.62	0.91
CIN3	Co test-negative x2	0.00	0.28	0.68

A new recommendation is people completing Test of Cure following treatment for high grade squamous abnormalities can have a Test of Cure HPV test at 6 months and 18 months after treatment. Following two consecutive HPV not detected tests 12 months apart participants can return to regular interval screening. The Test of Cure HPV test can be a vaginal swab or cervical sample.

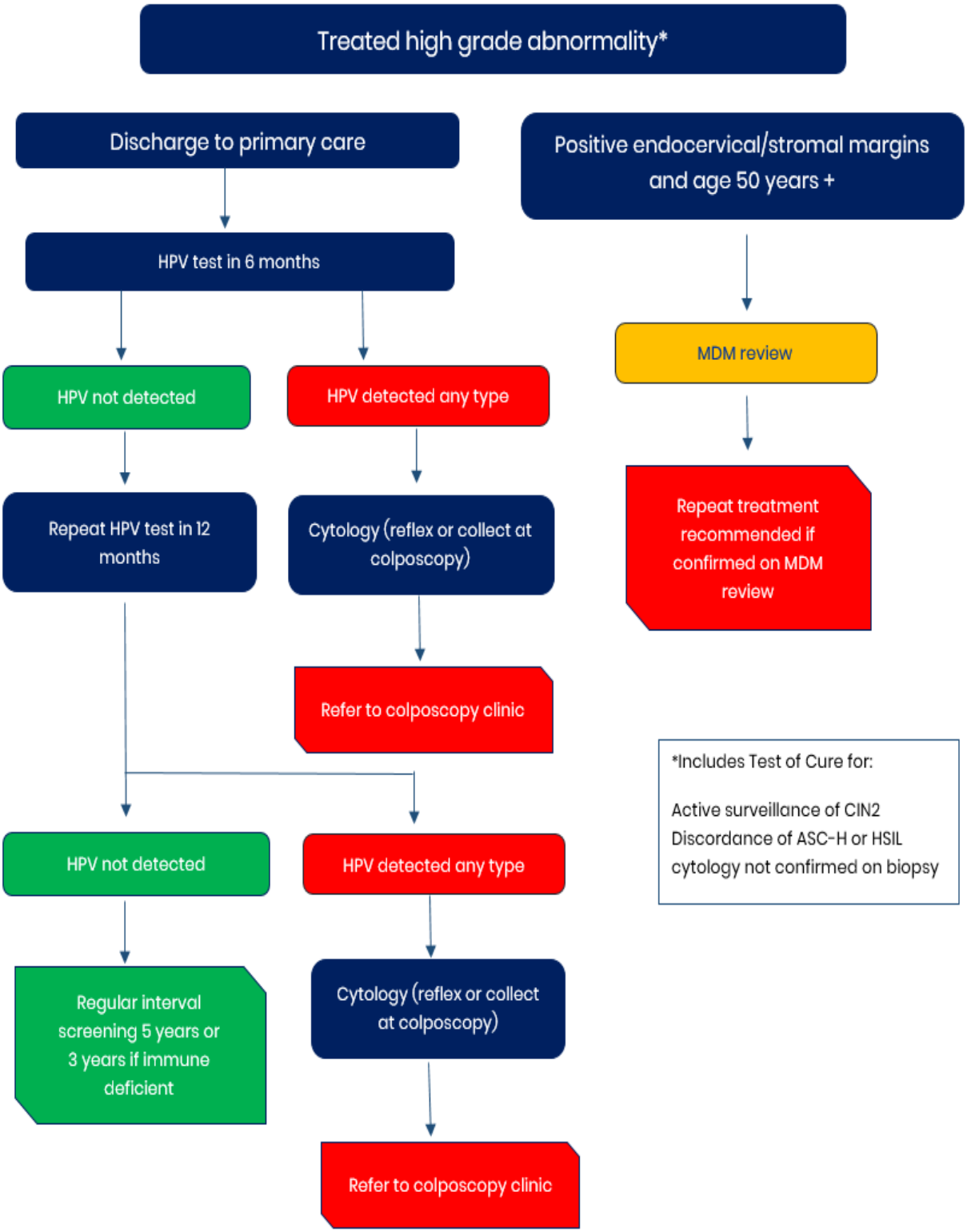
Providing the choice of self-testing as a Test of Cure HPV test has shown to be acceptable by participants. [11] In addition, the change to Test of Cure HPV test provides the opportunity to improve Test of Cure follow up among participants who have been treated.

The Test of Cure HPV test guidelines are also recommended for use with

participants who have had ASC-H or HSIL cytology discordance or following regression of CIN2 when participants have undergone active surveillance, to ensure participants can return safely to regular interval screening.

RECOMMENDATIONS – TEST OF CURE HPV TEST AFTER TREATMENT FOR HSIL	
R8.12 Test of Cure HPV test after treatment for HSIL (CIN2/3) See Figure 3	**Evidence-based recommendation** Participants who have been treated for HSIL (CIN2/3) should have a Test of Cure HPV test at six and 18 months' post treatment with their primary care screen taker. When the participant has tested negative for both tests on two consecutive occasions at least 12 months apart, they can return to regular interval screening.
R8.13 Abnormal Test of Cure results: HPV detected any type	**Evidence-based recommendation** If HPV (any type) is detected test during the Test of Cure period, irrespective of the cytology the participant should be referred to colposcopy. If HPV is detected on a vaginal swab a cervical cytology will be performed at colposcopy.
R8.14 Previous abnormal Test of Cure results: HPV not detected and ASC-US / LSIL cytology	**Consensus -based recommendation** During the transition from Test of Cure co-test to Test of Cure HPV test participants who have has a Test of Cure reported as HPV not detected and ASC-US or LSIL cytology should have an HPV test when next due and if the HPV is not detected they can return to regular interval screening.
R8.15 Abnormal HPV results following completed Test of Cure HPV test pathway	**Consensus-based recommendation** Once a participant has completed the Test of Cure HPV test pathway with two consecutive HPV not detected test results at least 12 months apart any subsequent HPV detected tests should be managed as per the primary screening pathway.
R8.16 Symptomatic participants – persistent abnormal vaginal bleeding following treatment	**Practice point** Participants with persistent abnormal vaginal bleeding following treatment should have a co-test and be investigated as clinically appropriate.
R8.17 Supporting participants to attend Test of Cure HPV test follow up	**Practice point** Ask all participants/whānau whether they require assistance or support to attend their follow up Test of Cure HPV test. Consider transport, cultural support and where appropriate offer referral to Support to Screening Services.

Figure 3: Management of Test of Cure HPV test following a high grade squamous abnormality



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Test of Cure Co-test after treatment for an HPV not detected high grade squamous abnormality

Whilst uncommon, HPV not detected high grade squamous abnormalities can occur and have been documented in the literature. There a number of factors which can contribute to a participant having a HPV not detected test result and a high grade squamous abnormality. These include false negative results, low viral load of high risk HPV, inadequate sampling, technical issues, reduced L1 gene expression in high-grade lesions, histological overcalls and low risk HPV infections. [1-4]

Low risk HPV types are not included in the HPV testing used in primary HPV screening as the harms associated with screening and colposcopy outweighs the benefits. [1-3] Low risk HPV types rarely if ever cause cervical cancer and high grade squamous abnormalities that not due to HPV of any type are very rare. [2 4 5]

A number of studies have reported high risk HPV may be detected on previously reported cases with HPV not detected high grade squamous abnormalities with further testing. [1-3] If a participant is referred with a co-test with HPV not detected and a high grade cytology, **it is recommended** a repeat HPV test is taken at the time of colposcopy. [3]

Participants with an HPV not detected result within the three years of their high grade squamous abnormality being diagnosed (and no previous HPV detected ever) are considered in the NCSP as having an HPV not detected high grade squamous abnormality.

A new recommendation is people completing Test of Cure following treatment for HPV not detected high grade squamous abnormality should have a Test of Cure co-test at 6 months and 18 months after treatment. It is thought participants with HPV not detected HSIL are at lower risk of recurrence following treatment when compared to participants with high risk HPV. [6] Following two consecutive negative Test of Cure co-tests 12 months apart participants can return to regular interval screening in the primary HPV screening programme.

Please refer to section nine for management for Test of Cure after treatment for Glandular abnormalities.

RECOMMENDATIONS – TEST OF CURE CO-TEST AFTER TREATMENT FOR HPV NOT DETECTED HSIL	
R8.18 Participants referred to colposcopy with a co-test reported as HPV not detected and high grade cytology	**Consensus-based recommendation** Participants who are referred to colposcopy with a HPV not detected and high grade cytology should have a repeat HPV test at the time of colposcopy.
R8.19 Test of Cure co-test test after treatment for HPV not detected HSIL (CIN2/3)	**Consensus-based recommendation** Participants who have been treated for a HPV not detected HSIL (CIN2/3) should have a Test of Cure co-test at six and 18 months' post treatment with their primary care screen taker. When the participant has tested negative for both tests on two consecutive occasions at least 12 months apart, they can return to regular interval screening.
R8.20 Positive Test of Cure result following treatment for HPV not detected HSIL (CIN2/3)	**Consensus -based recommendation** Participants with HPV not detected and LSIL following treatment should have a repeat co-test in 12 months. If the repeat co-test reports HPV not detected and LSIL the participant should be referred to colposcopy. Participants with Test of Cure co-test result of HPV not detected and high grade cytology should be referred for colposcopy. Participants with a Test of Cure co-test with HPV detected any type (irrespective of cytology result) should be referred to colposcopy.
R8.21 Abnormal HPV results following completed Test of Cure co-test pathway	**Consensus-based recommendation** Once a participant has completed the Test of Cure co-test pathway with two consecutive negative results at least 12

	months apart any subsequent HPV detected tests should be managed as per the primary screening pathway.

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