+Test of cure after high-grade squamous intra-epithelial lesion (HSIL) – Evidence Summary

PICO: For women who have been treated for histologically confirmed high-grade squamous intra-epithelial lesion (HSIL), what is the safety and effectiveness of HPV testing at 12 and 24 months and discharging if negative at both visits, compared to HPV and cytology co-testing at 12 and 24 months, or at 6 and 18 months, and discharging if double-negative at both visits?

Summary of findings

Only one study reported on risk of serious disease following tests performed at 12/24 months post treatment (5-year CIN3+ risk: 0.91% [HPV; Hybrid Capture 2] vs 0.68% [co-testing]; confidence intervals not available). ASCCP 2019 guidelines based on this study recommended post-treatment follow-up can be done using either HPV testing or co-testing and the follow-up timing/ regimen is equivalent (1-year repeat).

Two additional studies reported on findings based on HPV testing vs co-testing at multiple timepoints where the latest test was >12 months post-treatment (18 months or 24 months). Neither study found a significant difference in risk of serious disease between the two groups (the point estimate for risk was lower in those who were co-test negative, but confidence intervals overlapped). The 5-year CIN3+ risks were 0.4% (95%CI 0.0-2.5) [HPV; PCR testing] vs 0.0% (95%CI 0.0-2.9) [co-testing]; and 3.8% (95%CI 0.79-10.7) vs 0.0% (95%CI 0.0-6.6) in the studies where the later test was at 24 months and18 months, respectively.

Several other studies reported on the risk of serious disease in those who were HPV-negative vs co-test negative post-treatment, but all testing occurred at or within 12 months of treatment, and in some cases disease ascertainment appeared to be incomplete. These studies were considered less relevant, but nevertheless they generally found no significant difference in risk between the two groups over a range of follow-up periods (the point estimate for risk was lower in those who were co-test negative, but confidence intervals overlapped).

A systematic review of the diagnostic accuracy of HPV testing alone vs co-testing post-treatment found no significant difference in CIN2+ sensitivity between HPV testing (93%; 95% CI 88-96) and co-testing (96%; 95%CI 92-98), but specificity was lower for co-testing (70%; 95%CI 68-72 vs 77%; 95% CI 75-79 for HPV testing). The findings of three studies published since the systematic review were broadly consistent with its findings, but two of the three studies were based on fewer than 10 cases.

Detailed findings

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. Therefore, on the advice of the Working Party, evidence reviews were undertaken to address the following questions:

1. For women who have been treated for histologically confirmed HSIL and have had 2 consecutive negative annual HPV tests,
   (A) what are the **relative risks** of cervical, high-grade precancerous cervical lesions grade 3 or more (CIN3+), compared with women who have been treated for HSIL and have had 2 double consecutive negative annual HPV and cytology co-tests;
   (B) what is the **diagnostic accuracy** of HPV testing compared to co-testing?
2. For women who have been treated for histologically confirmed HSIL, what is the optimal time to initiate surveillance **(six months versus 12 months)**?

Evidence review for 2023 guidelines

Searches: EMBASE and Medline databases were searched on 29 March 2023 by combining terms for cervical intraepithelial neoplasia, CIN, recurrent, test of cure, surveillance, post-treatment, HPV, human papillomavirus, papillomavirus infections. The search was limited to English language articles published from 2015 onwards. Full details of the search strategy are included in the 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 HSIL.

Results

*Question 1A: For women who have been treated for histologically confirmed HSIL and have had 2 consecutive negative annual HPV tests, what are the **relative risks** of cervical, high-grade precancerous cervical lesions grade 3 or more (CIN3+), compared with women who have been treated for HSIL and have had 2 double consecutive negative annual HPV and cytology co-tests?*

One systematic review and seven observational studies (from 9 papers) that reported risk of CIN2+, CIN3+ or cancer were identified and these studies are summarized in **Table 1**. References from the 2015 guidelines were also assessed for relevant data and three references (Kitchener 2008, Kocken 2011 & Uijterwaal 2014) were found to report data relevant for this PICO and are also summarized in **Table 1**.

Table 1: ***Studies reporting risk of CIN3+ (or CIN2+) or cancer among women treated for HSIL***

Study	Country	Study design	Population	Findings	
				Clear resection margins	Clear or unclear resection margins
Risk* of subsequent *CIN3+ (or CIN2+) if at least 2 follow-up tests are negative					
Egemen 2020	USA	Retrospective Cohort	Women in the Kaiser Permanente of Northern California (KPNC)/National Cancer Institute Guidelines Cohort who underwent HPV (HC2) and cytology screening between 2003 to 2017 and were treated (LEEP/LLETZ) for CIN3 with results for at least one follow-up co-test N = 4695 Margin status: NR Follow-up: Initial follow-up with co-test at 6 months, post treatment. Colposcopy if HPV-positive or high-grade cytology. Otherwise annual co-test?		**Risk of CIN3+ at 5-year follow-up if:** *Two negative follow-up tests* Co-test negative on both tests: 0.68% (95%CI 0.14-1.22)* ^ HPV negative (HC2) on both tests: 0.91% (95%CI 0.38-1.44)* ^ *Three negative follow-up tests* Co-test negative on all 3 tests: 0.35% (95%CI -0.14-0.84)* ^ HPV negative (HC2) on all 3 tests: 0.44% (95%CI -0.01-0.88)* ^
Kocken 2011 & Uijterwaal 2014	Netherlands	Prospective Cohort	Women treated for CIN2 or CIN3 with LLETZ or cervical conisation between 1988 and 2004 with HPV (GP5+/6+ PCR) and cytology test results at 6 and 24 months post treatment N = 435 Margin status: Not reported Follow-up: Co-test at 12 months as well as 6 and 24 months post treatment and then 5 yearly cytology. Colposcopy if abnormal cytology or HPV test positive.		**Risk of CIN3+ at 5-year follow-up if:** *Two negative follow-up tests (6 and 24 months)* Co-test negative on both tests: 0.0% (95%CI 0.0-2.9) HPV negative (PCR) on both tests: 0.4% (95%CI 0.0-2.5) **Risk of CIN2+ at 5-year follow-up if:** *Two negative follow-up tests (6 and 24 months)* Co-test negative on both tests: 1.0% (95%CI 0.2-4.6) HPV negative (PCR) on both tests: 2.3% (95%CI 1.0-5.2)
Ruano 2015	Spain	Cohort (Retrospective and Prospective analysis)	Women treated for CIN2+ with LEEP in 2010 with HPV (8 high risk types or Cobas) and cytology test results post treatment N = 97 Clear margins: 66% Follow-up: HPV test, cytology, and colposcopy every 6 months. Follow-up range 19-30 months		**Risk of CIN2+ with median 2-year follow-up if:** *Negative follow-up tests at (at least) 6, 12 and 18 months?* Never positive on either HPV test or cytology**: 0% (0/54) 95%CI 0-6.6%; calculated Never HPV positive: 3.8% (3/79); 95%CI 0.79-10.7%; calculated
Polman 2017	Netherlands	Prospective Cohort (Post-hoc analysis)	Women treated for CIN2 or CIN3 with LLETZ between 2010 and 2012 with HPV (GP5+/6+ PCR) and cytology test results at 6 and 12 months post treatment		**Risk of CIN2+ with 1-year follow-up if:** *Negative follow-up tests at 6 and 12 months?*

Study	Country	Study design	Population	Findings	
				Clear resection margins	**Clear or unclear resection margins**
			N = 299 Margin status: NR Follow-up: Co-test at 6 and 12 months post treatment. At 12 months all women underwent colposcopy and biopsy (random biopsy if colposcopy normal)		Never positive on either HPV test or cytology**: 2.6% (4/155) Never HPV positive (PCR): 2.9% (6/204)
Risk of subsequent CIN3+ (or CIN2+) if initial follow-up test is negative					
Egemen 2020	USA	Retrospective Cohort	Women in the Kaiser Permanente of Northern California (KPNC)/National Cancer Institute Guidelines Cohort who underwent HPV (HC2) and cytology screening between 2003 to 2017 and were treated (LEEP/LLETZ) for CIN3 with results for at least one follow-up co-test N = 4695 Margin status: NR Follow-up: Initial follow-up with co-test at 6 months, post treatment. Colposcopy if HPV-positive or high-grade cytology. Otherwise annual follow-up co-test		**Risk of CIN3+ at 5-year follow-up if:** *First follow-up test negative* Co-test negative: 1.7%* HPV negative (HC2): 2.0%*
Clarke 2020	Systematic review of 10 studies (Brazil, Belgium, Italy, Netherlands, Spain, New Zealand, Thailand USA) published up to 2019	Systematic review	Women treated for CIN2 or CIN3 with cervical conization, LEEP or LLETZ with HPV (HC2 or PCR) and cytology test results at 6 months post treatment N = 1876 Margin status: NR Follow-up or confirmation of negative tests and/or colposcopy unclear.		**Risk of CIN2+ (follow-up period for risk ranged from 12 to >24 months) if:** *First follow-up test negative* Co-test negative: 0.68% (95%CI 0.2-2.0) HPV negative (PCR): 1.2% (95%CI 0.7-2.0) HPV negative (HC2): 1.4% (95%CI 0.9-2.1)
Garutti 2017	Italy	Prospective Cohort	Women treated for CIN2+ with LEEP between 2008 and 2013 with HPV (HC2) and cytology test results at 6 months post treatment. N = 310 Margin status: NR Follow-up: If HPV test, cytology and colposcopy negative at 6 months follow-up, cytology and colposcopy at 18 months		**Risk of CIN2+ with 5-year follow-up if:** First follow-up test negative Co-test negative: 0 (0/140) HPV negative (HC2): 0 (0/172)

Study	Country	Study design	Population	Findings	
				Clear resection margins	Clear or unclear resection margins
			If either HPV test, cytology or colposcopy positive at 6 months follow-up, cytology and colposcopy at 12, 18 and 24 months – maximum follow-up = 5 years.		
Gosvig 2015a & b	Denmark	Prospective Cohort	Women treated for CIN2+ with cervical conisation (mainly LEEP) between 2002 and 2005 with cytology and HPV (HC2) test results at 4-6 months post treatment. N = 588 Clear margins: 71.3% Follow-up: Co-test at 4-6 months post treatment Annual cytology testing for 5 years recommended. (HPV test results at 4-6 months post treatment were not used for referral to colposcopy, treatment, or management)	**Risk of CIN2+ with 2-year follow-up if:** *First follow-up test negative* Co-test negative: 0/316 HPV negative: 0/347	**Risk of CIN2+ at 3-year follow-up if:** *First follow-up test negative* Co-test negative: 0.5% (95% CI 0.0-1.2) HPV negative (HC2): 0.7% (95% CI 0.0-1.4) **Risk of CIN2+ at 5-year follow-up if:** *First follow-up test negative* Co-test negative: 0.8% (95% CI 0.0-1.6) HPV negative (HC2): 0.9% (95% CI 0.0-1.7) **Risk of CIN2+ at 8-year follow-up if:** *First follow-up test negative* Co-test negative: 2.9% (95% CI 1.1-4.7) HPV negative (HC2): 2.8% (95% CI 1.1-4.4) **Risk of CIN2+ at 10-year follow-up if:** *First follow-up test negative* Co-test negative: 6.1% (95% CI 0.0-12.1) HPV negative (HC2): 5.7% (95% CI 0.0-11.4)
Bruhn 2022 [Earlier study in one Danish hospital (Bruhn 2018) also identified, but excluded from this table as its findings would be contained within this larger study covering all Danish hospitals]	Denmark	Retrospective Cohort	Women who underwent cervical conization in 2013 identified in the national Danish Pathology Data Bank with cytology and HPV (HC2 in one region, or Cobas in 4 regions) test results post treatment N = 5174 83.5% HSIL (CIN2/CIN3/AIS) at treatment Follow-up: Dependent on margin status and co-test results at 6 months post treatment. If clear margins and cytology and HPV test both negative, return to regular screening every 3 or 5 years (interval depending on age). If HPV and cytology positive, or high-grade cytology, colposcopy Otherwise (ie HPV positive cytology negative or HPV negative cytology <HG) repeat co-test in 6 months.	**Likely incomplete verification (no routine follow-up of co-test negatives; FU of HPV-only if cytology ASC-H+), therefore described as detection rather than risk** **Detection of CIN3+ with 3-year follow-up if:** *First follow-up test negative and returned to screening, or with more than one follow-up test and all are negative* Never positive on either HPV test or cytology**: 0.20% (4/2008)	**Considering both clear and not clear margins** **Likely incomplete verification (for clear margins, no routine follow-up of co-test negatives; FU of HPV- only if cytology ASC-H+), therefore described as detection rather than risk** **Detection of CIN3+ with 3-year follow-up if:** *First follow-up test negative and returned to screening, or with more than one follow-up test and all are negative* Never positive on either HPV test or cytology**: 0.63% (22 / 3478) Never HPV positive: 0.89% (33 /3711) **Risk of CIN2+ with 3-year follow-up if:**

Study	Country	Study design	Population	Findings	
				Clear resection margins	Clear or unclear resection margins
				Never HPV positive: 0.24% (5/2110) **Detection of CIN2+ with 3-year follow-up if:** *First follow-up test negative and returned to screening, or with more than one follow-up test and all are negative* Never positive on either HPV test or cytology**: 0.45% (9/2008) Never HPV positive: 0.62% (13/2110)	*First follow-up test negative and returned to screening, or with more than one follow-up test and all are negative* Never positive on either HPV test or cytology**: 0.89% (31 /3478) Never HPV positive: 1.4% (52 / 3711)
Visioli 2023	Italy	Retrospective Cohort	Women treated for CIN2/CIN3 lesions with excisional treatments (laser conization, LLETZ + Laser, LEEP/cold-knife conization) performed between 2006 and 2014 N = 1063 Clear margins: 80% Follow-up: 2006-2010: HPV testing at 6 and 24 months Colposcopy if HPV positive Routine screening interval resumed if all tests negative. 2011 onwards: co-testing at 6, 24 and 48 months Colposcopy if at least one test positive Routine screening interval resumed if all tests negative	**Risk of CIN3+ with 5-year follow-up if:** First follow-up test negative HPV negative: 0.3% (95% CI 0.1–1.4) **Risk of CIN2+ with 5-year follow-up if:** First follow-up test negative HPV negative: 0.6% (95% CI 0.2–1.8)	**Risk of CIN3+ with 5-year follow-up if:** First follow-up test negative HPV negative: 0.5% (95% CI 0.1–1.4) Co-test negative: 0.0% (95% CI 0.0–0.01) **Risk of CIN2+ with 5-year follow-up if:** First follow-up test negative HPV negative: 0.9% (95% CI 0.4–2.0) Co-test negative: 0.8% (95% CI 0.3–2.7)
Kitchener 2008	UK	Prospective Cohort	Women treated for CIN primarily by LLETZ, with HPV (HC2) and cytology test results at 6 months post treatment N = 917 76.3% HSIL (CIN2/CIN3/AIS) at treatment Clear margins: 64% Follow-up: Co-test at 6 and 12 months and cytology at 24 months		**Risk of CIN2+ with 2-year follow-up if:** First follow-up test negative Co-test negative: 0.7% (5/744) HPV negative (HC2): 0.9% (7/783)

Study	Country	Study design	Population	Findings	
				Clear resection margins	Clear or unclear resection margins
			Colposcopy if abnormal cytology or HPV positive, otherwise according to local practice (some co-test negative underwent colposcopy?)		
Kocken 2011 & Uijterwaal 2014	Netherlands	Prospective Cohort	Women treated for CIN2 or CIN3 with LLETZ or cervical conisation between 1988 and 2004 with HPV (GP5+/6+ PCR) and cytology test results at 6 and 24 months post treatment N = 435 Margin status: Not reported Follow-up: Co-test at 12 months as well as 6 and 24 months post treatment, and then 5 yearly cytology. Colposcopy if abnormal cytology or HPV test positive.		**Risk of CIN3+ at 5-year follow-up if:** *First follow-up (6 months) test negative* Co-test negative: 1.1% (95%CI 0.3-3.4) HPV negative (PCR): 1.3% (95%CI 0.5-3.5) **Risk of CIN2+ at 5-year follow-up if:** *First follow-up (6 months) test negative* Co-test negative: 3.0% (95%CI 1.4-6.1) HPV negative (PCR): 4.4% (95%CI 2.5-7.5)

* proportional hazards model

^ confidence intervals obtained from https://lhncbc.nlm.nih.gov/LHC-research/LHC-projects/image-processing/cervixca.html accessed 19 Jun 2023

** positive cytology = ASC-US or greater

CI = confidence interval; CIN = cervical intraepithelial neoplasia; HC2 = Hybrid Capture 2; HPV = human papillomavirus; LEEP = loop electrosurgical excision procedure; LLETZ = large loop excision of transformation zone; NR = not reported

Question 1B: What is the diagnostic accuracy of HPV testing compared to co-testing?

One systematic review and three observational studies were identified that the diagnostic accuracy of HPV testing compared to co-testing and these studies are summarized in **Table 2**.

Table 2: ***Studies investigating the diagnostic accuracy of HPV testing compared to co-testing***

Study	Country	Study design	Population	Findings	
				HPV test	Co-test
SYSTEMATIC REVIEW					
Rossi 2021, (incorporating studies included in a systematic review by Kocken 2012)	Systematic review of 9 cross-sectional studies (Brazil, Belgium, Italy, Denmark,	Systematic review	Women treated for CIN2 or CIN3 with cervical conisation or LLETZ with HPV (HC2 or PCR) and cytology test results at 6 months post treatment N = 2100	HPV positive at 6 months **CIN2+:** Sensitivity = 93% (95% CI 88-96) Specificity = 77% (95% CI 75-79)	Co-test positive* at 6 months **CIN2+:** Sensitivity = 96% (95%CI 92-98) Specificity = 70% (95%CI 68-72)

	Spain, NZ, USA) published up to 2016 with variable follow-up		Margin status: NR Follow-up or confirmation of negative tests and/or colposcopy unclear		
OBSERVATIONAL STUDIES (PUBLISHED FROM 2015 ONWARDS)					
Polman 2017	Netherlands	Cross-sectional with 12 months follow-up	Women treated for CIN2 or CIN3 with LLETZ between 2010 and 2012 with HPV (GP5+/6+ PCR) and cytology test results at 6 and 12 months post treatment N = 299 Margin status: NR Follow-up: At 12 months all women underwent colposcopy and biopsy (random biopsy if colposcopy normal)	HPV positive at either 6 or 12 months **CIN2+:** Sensitivity = 85% (95% CI 73-96) Specificity = 76% (95% CI 71-81) **CIN3+:** Sensitivity = 100% (95% CI 81-100) Specificity = 72% (95% CI 67-77)	Co-test positive* at either 6 or 12 months **CIN2+:** Sensitivity = 90% (95% CI 80-99) Specificity = 58% (95% CI 52-64) **CIN3+:** Sensitivity = 100% (95% CI 81-100) Specificity = 55% (95% CI 49-61)
Bruhn 2018	Denmark	Cross-sectional with 3 years follow-up	Women who underwent cervical conisation in 2013 with cytology and HPV (Cobas) test results at 6 months post treatment N = 128 Clear margins: 71.3% Follow-up: Dependent on margin status and test results for 3 years follow-up. Recommended: If clear margins and cytology and HPV test both negative - return to regular screening every 3 or 5 years depending on age If HPV and cytology positive or high-grade cytology - colposcopy Otherwise repeat co-test in 6 months	HPV positive at 6 months **CIN2+:** Sensitivity = 83% (5/6) Specificity = 70% (85/122)	Co-test positive* at 6 months **CIN2+:** Sensitivity = 83% (5/6) Specificity = 69% (NR)
Khunamornpong 2015	Thailand	Cross-sectional 2 years follow-up	Women treated for CIN2 or CIN3+ with LEEP between 2010 and 2012 with HPV (HC2) and cytology test results at 6 months post treatment N = 82 Clear margins: 86.6% Follow-up: cytology at 12 and 18 months and co-test at 24 months, with colposcopy if either HPV test or cytology positive	HPV positive at 6 months **HSIL:** Sensitivity = 50% (1/2; calculated 95%CI 1.3-98.7%) Specificity = 94% (75/80; calculated 95%CI 86.0-97.9%)	Co-test positive* at 6 months **HSIL:** Sensitivity = 100% (2/2; calculated 95%CI 15.8-100.0%) Specificity = 83% (66/80; calculated 95%CI 72.4-90.1%)

* Cytology ≥ ASC-US

CI = confidence interval; CIN = cervical intraepithelial neoplasia; HC2 = Hybrid Capture 2; HPV = human papillomavirus; LEEP = loop electrosurgical excision procedure; LLETZ = large loop excision of transformation zone; NR = not reported

*Question 2: For women who have been treated for histologically confirmed HSIL, what is the optimal time to initiate screening (**six months versus 12 months**)?*

Two observational studies were identified that reported risk of CIN2+, CIN3+ or cancer at 6 months and 12 months and these studies are summarized in **Table 3**. References from the 2015 guidelines were also assessed for relevant data and one study (Kitchener 2008) reported data relevant for this PICO and is also summarized in **Table 3**.

Table 3: ***Studies reporting risk of CIN3+ (or CIN2+) or cancer among women treated for HSIL at 6 months and 12 months***

Study	Country	Study design	Population	Findings
OBSERVATIONAL STUDIES (PUBLISHED FROM 2015 ONWARDS)				
Mo 2015	China	Retrospective Cohort	Women treated for CIN2 or CIN3 with LEEP between 2011 and 2012 with HPV (HC2) and cytology test results at 3, 6 and 12 months post treatment N = 158 27.8% Carcinoma in situ on LEEP Clear margins: 74% Follow-up: Co-test at 3, 6, 12 and 18 months and then annual until 2 consecutive negative co-tests Colposcopy if positive on either test.	**CIN2+:** 25 CIN2+ identified at 18 months follow-up 2/25 CIN2+ detected by 6 months by co-testing 12/25 CIN2+ detected by 12 months by co-testing
Ruano 2015	Spain	Cohort (Retrospective and Prospective analysis)	Women treated for CIN2+ with LEEP in 2010 with HPV (8 high risk types or Cobas) and cytology test results post treatment N = 97 Clear margins: 66% Follow-up: HPV test, cytology and colposcopy every 6 months. Follow-up range 19-30 months	**CIN2+:** 15 CIN2+ identified with median 2-year follow-up 9/15 CIN2+ identified in first 6 months by co-testing or colposcopy
OBSERVATIONAL STUDIES REPORTING RELEVANT DATA FROM 2015 REVIEW				
Kitchener 2008	UK	Cohort	Women treated for CIN primarily by LLETZ, with HPV (HC2) and cytology test results at 6 months post treatment N = 917 76.3% HSIL (CIN2/CIN3/AIS) at treatment	At 6 months 3 CIN2, 5 CIN3 and 1 AIS detected by co-testing At 12 months 1 CIN2, 3 CIN3 detected by co-testing At 6 months 4 CIN2, 5 CIN3 and 1 AIS detected by co-testing or other means

			Clear margins: 64% Follow-up: Co-test 6 and 12 months post treatment and cytology at 24 months. Colposcopy if abnormal cytology or HPV positive, otherwise according to local practice (some co-test negative underwent colposcopy?)	At 12 months 3 CIN2, 3 CIN3 detected by co-testing or other means

Existing Guidelines

Current (2017) Australian guidelines

Consensus-based recommendation REC10.7: People treated for HSIL should have annual co-tests starting 12 months post-treatment until they have two consecutive negative co-tests, when they can return to routine 5-yearly screening.

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 (2023)	NHS England	Individuals who have been treated for CIN1, CIN2, or CIN3 should be invited 6 months after treatment for a test of cure repeat cervical sample. . The nature and timing of follow up depends on their screening result, that is: individuals with a sample that has been reported as hrHPV negative should be recalled in 3 years, whatever their age; where the 3 year test is negative, individuals can return to routine recall individuals with a sample that has been reported as positive for hrHPV should be referred to colposcopy; reflex cytology is performed as it helps to inform colposcopic examination individuals whose hrHPV result is unavailable should have repeat testing at 3 months individuals who reach the age of 65 must continue to be invited for follow up tests and or be referred for further investigations as necessary until they have completed all follow up protocols and satisfy the requirements for being ceased from the programme.	Not reported
Secondary prevention of cervical cancer (2022)	American Society of Clinical Oncology (2022 – unchanged from 2016 recommendation) (Shastri 2022)	After women receive treatment for precursor lesions, follow-up should consist of HPV DNA testing at 12 months. If 12-month results are positive, continue annual screening; if not, return to routine screening	Other guidelines and consensus

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)	In patients treated for histologic or cytologic HSIL, after the initial HPV-based test *(HPV or co-test)* at 6 months, annual HPV or cotesting is preferred until 3 consecutive negative tests have been obtained. After the initial intensive surveillance period, continued surveillance at 3-year intervals is recommended for at least 25 years after treatment of high-grade histology (histologic HSIL, CIN 2, CIN 3, or AIS) or high-grade cytology (HSIL or persistent ASC-H) even if this is beyond the age of 65 years. When patients with a history of treated high-grade histology or cytology reach the age of 65 years, if they have completed the initial 25-year surveillance period, continued surveillance at 3-year intervals is acceptable and may continue as long as the patient is in reasonably good health. Discontinuation of screening is recommended if a patient has a limited life expectancy.	Kaiser Permanente Northern California data
Genital tract cancers in females: Human papillomavirus related cancers (cervical, vaginal & vulvar) (2016)	British Columbia Medical Association	CIN 2+ treated (cone, LEEP, ablative therapy), · HPV negative, discharge from colposcopy – follow average risk screening guidelines • HPV positive, discharge from colposcopy - annual screening until there are 3 no significantly abnormal* Pap tests within 5 years, and then follow average risk guidelines. ** Significant abnormality is anything more severe than atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesion (LSIL).*	Consensus – no systematic review undertaken
Cervical cancer screening (2016)	Towards Optimized Practice (TOP Alberta doctors)	Suggest annual screening with Pap for life.	Consensus – no evidence of systematic review undertaken
Development of evidence-based guidelines for follow up of women treated for cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3) in Italian screening programmes (2021)	Italian Group on cervical screening (GISCi) (Rossi 2021)	In the follow up of women treated for CIN2 or CIN3 the panel recommends to use HPV test instead of Pap test alone. There is no clear advantage in using HPV test alone or adding cytology to HPV (co-testing) and both strategies can be used in the follow up of women treated for CIN2 or CIN3. There are no elements to suggest of not adding a colposcopy to the first follow up episode in women treated for CIN2 or CIN3. The panel recommend to call women for the first episode of follow up 6 months post treatment for CIN2 or CIN3, instead after 12 months. In the follow up of women treated for CIN2 or CIN3 the panel suggests to obtain two negative follow up episodes (instead of one) before referring the woman to routine screening. Both 6 or 12 month intervals between first and second follow up episodes may be used in women treated for CIN2 or CIN3 with negative results at the first episode.	Systematic review of diagnostic accuracy

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. Biomarkers (5-type HPVmRNA, HPV type-specific persistence) must not be used to follow up patients treated for CIN 2/3 lesions.	Unsure – systematic reviews undertaken but in German

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APPENDICES

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

1	Uterine Cervical Neoplasms.mp.
2	Cervical Intraepithelial Neoplasia.mp.
3	High grade squamous intraepithelial lesion.mp.
4	HSIL.mp.

5	CIN*.mp.
6	1 or 2 or 3 or 4 or 5
7	excision*.tw.
8	surg*.tw.
9	cone biops*.tw.
10	(cone adj3 biops*).tw.
11	coni?ation.tw.
12	(LEEP or LLETZ or SWETZ or NETZ).tw.
13	loop electro-excisional procedure.tw.
14	laser.tw.
15	Fischer cone.tw.
16	electro-surg*.tw.
17	recurrent.tw.
18	"test of cure".tw.
19	(post-treatment or posttreatment).tw.
20	surveillance.tw.
21	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 or 20
22	HPV.tw.
23	Human papillomavir*.tw.
24	Papillomavirus Infections/
25	(hybrid capture 2 or HC2 or HCII).tw.

26	cobas.tw.
27	22 or 23 or 24 or 25 or 26
28	6 and 21 and 27
29	limit 28 to english language
30	limit 29 to humans
31	limit 30 to yr="2015 - Current"
32	limit 31 to conference abstracts
33	limit 32 to medline
34	32 not 33
35	31 not 34
36	remove duplicates from 35