CONTENT TEMPLATE

Table 1: NHMRC Evidence Statement for clinical question 2a: For HPV positive women who are not in treatment follow-up and who have negative or LSIL cytology and who have undergone colposcopy and the colposcopy was negative, what is the safety and effectiveness of testing with repeat HPV test at 12 months when compared with repeat cytology and HPV testing in 12 months?

An indirect approach was planned in the event that no relevant randomised or pseudo-randomised controlled trials were identified, with a secondary PICO question focussing on the follow-up of women with a negative or possible or definite LSIL referral cytology who had a negative colposcopy.

<table>
<tr><td colspan="2">Primary PICO question 2a: For HPV positive women who are not in treatment follow-up and who have negative or LSIL cytology and who have undergone colposcopy and the colposcopy was negative, what is the safety and effectiveness of testing with repeat HPV test at 12 months when compared with repeat cytology and HPV testing in 12 months?

Secondary PICO question 2a: For HPV positive women who are not in treatment follow-up and who have negative or LSIL cytology on referral and who had colposcopy and the colposcopy was negative what are the predictors of subsequent detection of high-grade disease?</td><td>Report body of evidence tables</td></tr>
<tr><td colspan="3">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="4">Primary PICO question:
No studies were found that directly answered this question.

Secondary PICO question:
No studies were found that reported longitudinal risks associated with follow-up cytology or HPV status. Two prospective cohort studies (level II evidence) and two retrospective cohort studies (level III-2) reported risks of subsequent high grade lesions associated with baseline HPV status and/or cytology. Follow-up ranged from 1- 3 years. Two studies examined the risks of CIN3+ disease associated with different baseline cytology results, and one study examined the risks of CIN3+ disease associated with baseline HPV positive ASC-US and LSIL (regardless of HPV status) (Lukic 2011). Three studies examined the risks of CIN2+ disease associated with different baseline cytology results; one study examined the risks of CIN2+ associated with different baseline HPV status (Cruickshank 2014) and two studies examined risks associated with different combinations of baseline cytology and HPV status. Two studies (Kelly 2012; Cruickshank 2014) reported the risks associated with baseline cytology results in women who were HPV positive.

Three of the four studies were conducted in the UK and included women with a cytology classified as borderline dyskaryosis (prior to 2009); and thus when the differences in cytology reporting systems are considered the group considered potentially included women that would have been classified as pHSIL as well as classified as pLSIL.

Furthermore, the populations in the retrospective studies may not be representative of all women with</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or
II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
</table>

HPV positive borderline or mild dyskaryosis, or all women with borderline or mild dyskaryosis. One study only included women with a HPV result determined with a higher cut-off for the HPV test (Kelly 2012) and the other study only included women whose cytology at colposcopy was negative or borderline. All 4 studies were considered at high risk of bias; none of the studies were specifically designed to answer the PICO question, and as a result it was not clear as to whether women with different baseline cytology results or HPV status were similar in terms of important confounders such as smoking. Furthermore important study design aspects such as the potential blinded reading of subsequent colposcopies and histopathology (with respect to the baseline test status) was not described. **Grade: D**		
2. Consistency *(if only one study was available, rank this component as 'not applicable') See body of evidence tables in report – results and p value (95% CI)*		
HPV status was predictive of high grade disease regardless of referral cytology (1 large prospective cohort study – Cruickshank 2014). The evidence is not consistent as to whether baseline cytology predicts high grade disease independently of HPV status. Comparing borderline dyskaryosis (which may include some pHSIL cytology) with mild dyskaryosis cytology; • When **HPV status was not considered**, borderline dyskaryosis consistently carried a lower risk of high grade disease than mild dyskaryosis cytology over 2.5 – 3 years (1 prospective study – Cruickshank 2014 and 1 retrospective cohort study – Smith 2006). • When **only HPV positive women** were considered a prospective cohort study reported that borderline dyskaryosis carried a lower risk of high grade disease; in this study women with borderline dyskaryosis who were HPV negative had the lowest risk and HPV-positive women with mild dyskaryosis had the highest risk. However a retrospective study reported borderline dyskaryosis carried a lower risk of high grade disease. These differences may be due to differences in referral processes for the number of borderline cytology results prompting referral to colposcopy (3 required for colposcopy vs single required for colposcopy), and/or differences in the underlying risks between populations. A small prospective cohort study reported the risk of high grade disease was lower for women with HPV-positive ASC-US (pLSIL) than that for women with LSIL (dLSIL) regardless of HPV status. **Grade: C**	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**
3. Clinical impact *See body of evidence tables in report - relevance of evidence (Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The clinical question considered two different protocols or testing at 12 months (testing with repeat HPV test at 12 months vs. testing with repeat cytology and HPV testing in 12 months). Testing with a single test simplifies the downstream clinical management recommendations. This evidence was considered insufficient to underpin an evidence-based recommendation. In general terms, detection of HPV, especially for persistent HPV 16/18, has been shown to be associated with an increased risk of high grade disease, and the HPV test is more sensitive than cytology for detection of CIN2+ and CIN3+. There is no evidence to suggest that this does not apply to women with a normal	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**

(negative) colposcopy, and the consensus was therefore to recommend follow-up with HPV testing alone for women who are HPV positive and have a normal or LSIL cytology and a normal colposcopy. **Grade: C**		
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
No studies examined outcomes in women testing HPV-positive, who had negative cytology and negative colposcopy. No studies assessed the longitudinal outcomes (risks) associated with differing follow-up HPV and or cytology results. The identified relevant studies for the secondary question used differing cytology classification systems and/or subsequent management protocols and therefore although indirect comparisons can be made across studies, the findings cannot be assumed to be directly applicable to women in the renewed NCSP. **Grade: C**	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
MSAC has approved the introduction of HPV-based screening with partial genotyping to distinguish HPV types 16 and 18 from other oncogenic HPV types for women aged 25-69 years for the National Cervical Screening Program. The identified studies for the secondary question did not use the AMBS cytology classification system and therefore although they are somewhat applicable to the Australian healthcare context, some caveats must be borne in mind when interpreting the results **Grade: C**	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*

This evidence was considered insufficient to underpin an evidence-based recommendation. However, in general terms, detection of HPV, especially for persistent HPV 16/18, has been shown to be associated with an increased risk of high grade disease, and the HPV test is more sensitive than cytology for detection of CIN2+ and CIN3+. There is no evidence to suggest that this does not apply to women with a normal (negative) colposcopy, and the consensus was therefore to recommend follow-up with HPV testing alone for women who are HPV positive and have a normal or LSIL cytology and a normal colposcopy.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level I to III studies/SRs with a high risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	C	Moderate
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

Evidence statement:

No studies assessed the longitudinal outcomes (risks) associated with differing follow-up HPV and or cytology results. Overall this body of evidence suggests that positive HPV status is a strong predictor of high-grade disease being present or developing within a few years, irrespective of referral cytology, but it does not provide direct evidence on the performance of HPV testing alone vs co-testing (HPV and cytology) in this group of women. Therefore, this evidence was considered insufficient to underpin an evidence-based recommendation.

However, detection of HPV, especially for persistent HPV 16/18, has been shown to be associated with an increased risk of high grade disease, and the HPV test is more sensitive than cytology for detection of CIN2+ and CIN3+. There is no evidence to suggest that this does not apply to women with a normal (negative) colposcopy, and the consensus was to recommend follow-up with HPV testing alone for women who are HPV positive and have a normal or LSIL cytology and a normal colposcopy.

RECOMMENDATION	GRADE OF RECOMMENDATION Not applicable
Unable to make an evidence-based recommendation as insufficient evidence of the safety and effectiveness of the follow-up options for HPV-positive women with a negative colposcopy	
CONSENSUS-BASED RECOMMENDATION *The consensus was to recommend follow-up with HPV testing alone for women who are HPV positive and have a normal or LSIL cytology and a normal colposcopy.*	
Normal colposcopy following LBC prediction of LSIL For women with a positive HPV test result (any type), a LBC report of negative or pLSIL/LSIL, and normal colposcopy, the HPV test should be repeated 12 months later: • Women who have a negative HPV test result at 12 months should be returned to routine 5-yearly HPV screening. • For women who have a positive HPV test result (not 16/18) at 12 months and a LBC report of negative or pLSIL/LSIL, the HPV test should be repeated in another 12 months. • Women who have a positive HPV test result (16/18) at 12 months should be referred directly for repeated colposcopic assessment, with reflex LBC to inform colposcopy. • Women who have a positive HPV test result (not 16/18) at 12 months and a LBC report of pHSIL/HSIL should be referred directly for repeated colposcopic assessment.	
PRACTICE POINTS	

Table 2: Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
There is currently insufficient high-level evidence to guide the management of discrepancies between cytological findings and colposcopic impression in women who have positive HPV test results, or who have low-grade cytological abnormalities and Type 3 TZ (unsatisfactory) colposcopy. These consensus-based recommendations and practice points are considered conservative and offer a safe approach, but this may require review as future research results become available.

Table 3: Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care? It is not anticipated that there will be a significant change to clinical practice apart from the addition of HPV testing to the recommended surveillance.	**NO**
Are there any resource implications associated with implementing this recommendation? n/a	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised? It is not anticipated that there will be a significant change to clinical practice apart from the addition of HPV testing to the recommended surveillance.	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? n/a	**NO**