CONTENT TEMPLATE

Table 1: NHMRC Evidence Statement for clinical question 1b:

For women who are positive for hr-HPV types other than 16 or 18 and have negative or pLSIL/dLSIL reflex liquid based cytology (intermediate risk), what is the safety and effectiveness of repeating HPV testing in 12 and 24 months compared to repeating HPV test at 12 months only before returning to 5 yearly screening?
No studies found that directly answered this question. Modelling was used to directly address this question

A secondary PICO question was designed focussing on benchmarking ie examining the risk of high grade lesions in women who are positive for hr-HPV types other than 16 or 18 with normal cytology, and comparing this with current risk thresholds for 12-month follow-up/later colposcopy.

<table>
<tr><td colspan="2">Primary PICO question 1b: For women who are positive for hr-HPV types other than 16 or 18 and have negative or pLSIL/dLSIL reflex liquid based cytology (intermediate risk), what is the safety and effectiveness of repeating HPV testing in 12 and 24 months compared to repeating HPV test at 12 months only before returning to 5 yearly screening?

Secondary PICO 1b: For women undergoing routine cervical screening what is the risk of subsequent CIN3+ for women who are positive for HPV oncogenic types other than 16 and 18 and have negative cytology compared with women who have pLSIL/dLSIL regardless of HPV status or who have pLSIL/dLSIL and are positive for HPV oncogenic types other that 16 and 18?</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:

Modelling evidence
A comprehensive extensively validated Australian model of cervical disease, screening and vaccination was used to compare different screening management options to assess the implications for lifetime health outcomes and 20 year invasive cancer risk.

Grade: Not applicable as NHMRC levels of evidence do not currently encompass modelling studies

Systematic review addressing primary PICO question
No studies were found that met the inclusion criteria for this question.
Systematic review addressing secondary PICO question
No studies were found that met the inclusion criteria for this question</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

N/A the primary source of evidence was modelling therefore it is not possible to grade the evidence base</td></tr>
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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)*		
Modelling evidence addressing primary PICO question **In relation to 12 and 24 month follow-up vs. 12 month follow-up only in women with oncogenic HPV types (not 16/18) and a pLSIL/LSIL reflex cytology result:** • performing both 12 and 24 month follow-up results in <1% difference in cervical cancer incidence and mortality and <1% difference in colposcopies, compared with12 month follow-up. Grade: N**A**	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 unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Modelling evidence addressing primary PICO question **In relation to 12 and 24 month follow-up vs. 12 month follow-up only in women with oncogenic HPV types (not 16/18) and a pLSIL/LSIL reflex cytology result:** • performing both 12 and 24 month follow-up results in <1% difference in cervical cancer incidence and mortality and <1% difference in colposcopies, compared with 12 month follow-up. **Grade C**	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
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*		
Modelling evidence addressing primary PICO question A comprehensive extensively validated Australian model of cervical disease, screening and vaccination was used to compare different screening management options to assess the implications for lifetime health outcomes and 20 year invasive cancer risk. Model predictions correspond closely with Australian data when assessed against a large number of NCSP outputs. This model was previously used to support the decision to move to the renewed program. G**rade A**	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 hr-HPV types for women aged 25-69 years for the National Cervical Screening Program. A comprehensive extensively validated Australian model of cervical disease, screening and vaccination was used to compare different screening management options to assess the implications for lifetime	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian**

health outcomes and 20 year invasive cancer risk. Model predictions correspond closely with Australian data when assessed against a large number of NCSP outputs. This model was previously used to support the decision to move to the renewed program. The model directly simulates the Australian health care context in terms of health services and delivery of care and reflects cultural factors involved in determining the screening behaviours in the NCSP. **Grade A**		**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).*

- performing both 12 and 24 month follow-up in this group would be very cost-ineffective, with an incremental cost-effectiveness ratio of >$300,000/LYS, compared to 12 month follow-up only in this group.
- performing both 12 and 24 month follow-up of only older women in this group is more still cost-ineffective, with an incremental cost-effectiveness ratio of >$65,000/LYS if 12 and 24 month follow-up is used in women aged over 55 years, compared to performing 12 month follow-up only at all ages.

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	N/A	NHMRC levels of evidence do not currently encompass modelling studies
2. Consistency	N/A	Not applicable only evidence from a single model
3. Clinical impact	C	Substantial
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to Australian healthcare context

Evidence statement:

Modelling evidence

In relation to 12 and 24 month follow-up vs. 12 month follow-up only in women with oncogenic HPV types (not 16/18) and a pLSIL/LSIL reflex cytology result:
performing both 12 and 24 month follow-up results in <1% difference in cervical cancer incidence and mortality and <1% difference in colposcopies, compared with12 month follow-up

Indicate any dissenting opinions

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION** C

Recommendation for this PICO is in **bold**

If the repeat^ HPV test at 12 months is positive for any HPV type, reflex LBC should be performed and the woman should be referred for colposcopic assessment.

If the repeat^ HPV test at 12 months is negative, the woman should be advised to return to routine 5-yearly screening.

^12 months after testing positive to HPV (not 16/18) with pLSIL/LSIL reflex cytology

PRACTICE POINT (CONSENSUS-BASED RECOMMENDATION)
If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation (practice point) can be given.

N/A

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 uncertainty about participation in the Renewed NCSP over the 5-yearly interval and compliance with the follow-up recommendations for HPV-positive women. There is also uncertainty about the timing of impact of HPV vaccination on the numbers of women referred to colposcopy, and about the transitional aspects of the program and impact on colposcopy volumes. These issues will be informed by modelled analysis (see Modelling reports, safety monitoring of the Renewed NCSP, and by emerging data from the Compass trials. Women who test positive for HPV 16/18 on a self-collected sample will need further investigation. It is unclear at present whether these women would prefer to visit their usual primary care health professional to have a cervical sample for liquid-based cytology taken by someone they know and trust, or be referred directly to specialist colposcopist and have the sample taken at that time. A stepwise protocol involving primary care would involve an extra examination, but might be perceived as less threatening. Several options might be offered, one of which should be further assessment by a female primary care practitioner or specialist.

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? While all screening programs will fail to detect some cases, the implementation of this recommendation does not present any significant concerns about the potential for missed cancers. Rates of cervical cancer are low in Australia, compared with international rates. The renewed program based on HPV testing is estimated to further reduce cervical cancer incidence and cervical cancer death by over 20% compared with present levels	**YES**
Are there any resource implications associated with implementing this recommendation? Colposcopic assessment and management will be more challenging in the renewed National Cervical Screening Program because there will be a higher proportion of HPV-positive women with minimal or no cytological changes.	**YES**
Will the implementation of this recommendation require changes in the way care is currently organised? There will be some changes made to the IT systems underpinning the State and Territory cervical screening registries, however overall it is not anticipated that the implementation of these new recommendations will impact the way care is currently organised. The HPV test is collected in the same manner as the current care (Pap test) therefore it is not anticipated that there will be any significant impact to the way care is organised.	**NO**

Are the guideline development group aware of any barriers to the implementation of this recommendation? Health professionals may be reluctant to delay colposcopy in HPV-positive women, despite this being their current practice with low-grade cytology. Education of GPs and other primary care health professionals who provide cervical screening services, emphasising the safety of this approach, will be essential to implementation of this recommendation. Some women may be reluctant to accept a 12-month delay in colposcopy, especially if they are aware of their HPV-positive status. Education of women and careful explanation by their healthcare providers will be of paramount importance.	**YES**