CONTENT TEMPLATE

Table 1: NHMRC Evidence Statement for clinical question 1a: For women who are positive for hr-HPV types other than 16 or 18 and have pLSIL/dLSIL reflex liquid based cytology (intermediate risk), what is the safety and effectiveness of immediate colposcopy compared to colposcopy delayed by 12 months based on later HPV test results (assuming referral to colposcopy if any HPV positive at 12 months)?
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 possible or definite LSIL (pLSIL/dLSIL), and comparing these with current risk thresholds for immediate colposcopy and 12-month follow-up/later colposcopy.

<table>
<tr><td colspan="2">Primary PICO question 1a: For women who are positive for hr-HPV types other than 16 or 18 and have pLSIL/dLSIL reflex liquid based cytology (intermediate risk), what is the safety and effectiveness of immediate colposcopy compared to colposcopy delayed by 12 months based on later HPV test results (assuming referral to colposcopy if any HPV positive at 12 months)?

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

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 directly answered this question.

Systematic review addressing secondary PICO question
Six prospective cohort studies (level II evidence) met the inclusion criteria: Four “cross-sectional” studies (participants underwent immediate colposcopy) and 2 longitudinal studies.

None of the studies were specifically designed to answer the PICO question and as a result it was never clear as to whether women with hr-HPV other positive p/dLSIL cytology were similar to the benchmark groups in terms of important confounders such as smoking and thus all 6 studies were considered at high risk of bias.</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>
</table>

Both longitudinal studies reported CIN3+ risks for hr-HPV other positive dLSIL (LSIL Bethesda) cytology and for the benchmark for 12-month follow-up, all dLSIL cytology regardless of HPV status; one with active 2-year follow-up and exit colposcopy, and the other with passive 18-year follow-up. Two cross-sectional studies reported CIN3+ risks on immediate colposcopy for women with hr-HPV other positive pLSIL (ASC-US, Bethesda 2001) (1 study) or dLSIL cytology (2 studies) and the benchmarks for immediate colposcopy, p/dHSIL cytology or 16/18 hr-HPV positive, as well as the benchmark for 12-month follow-up, all dLSIL. **Grade not applicable:** The primary source of evidence was modelling therefore it is not possible to grade the evidence base.		
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)*		
Evidence from modelling **In relation to 12 month follow-up vs. immediate colposcopy in women with oncogenic HPV types (not 16/18) and a pLSIL/LSIL reflex cytology result:** • the 20 year risk of developing invasive cervical cancer in women with oncogenic HPV types (not 16/18) and a pLSIL/LSIL reflex cytology result who have 12 month follow-up surveillance, is lower than the risk in women with a screening cytology result of LSIL in the pre-renewal NCSP (i.e. the risk in this group is lower than the accepted benchmark risk for 12-month follow-up in Australia). Grade N**A** **Systematic review addressing secondary PICO question** The risk of CIN3+ for hr-HPV other-positive dLSIL cytology was lower than that for the 12-month follow-up benchmark, definite LSIL cytology regardless of HPV status at 2 years follow-up in cohorts aged ≥ 18 or 30 years and after 18 years follow-up in a cohort aged ≥ 16 years at baseline. The risk of CIN3+ on immediate colposcopy for hr-HPV other positive p/dLSIL cytology was consistently less than the risk for the immediate colposcopy benchmarks, p/d HSIL or hr-HPV 16/18, and similar to if not less than the 12-month follow-up benchmark in cohorts aged ≥25 or ≥21 years or ≥18 years. One study provided data showing that for subgroups aged ≥ 30 years the risk at immediate colposcopy for hr-HPV other positive dLSIL cytology was higher than the benchmark for 12-month follow-up. These findings from the systematic review are consistent with the modelling evidence. **Grade B**	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)*		

Evidence from modelling **In relation to 12 month follow-up vs. immediate colposcopy in women with oncogenic HPV types (not 16/18) and a pLSIL/LSIL reflex cytology result:** • the 20 year risk of developing invasive cervical cancer in women with oncogenic HPV types (not 16/18) and a pLSIL/LSIL reflex cytology result who have 12 month follow-up surveillance, is lower than the risk in women with a screening cytology result of LSIL in the pre-renewal NCSP (i.e. the risk in this group is lower than the accepted benchmark risk for 12-month follow-up in Australia). • colposcopy referral of this group substantially increases the number of colposcopies in the Renewed NCSP, with >650 colposcopies required to avert an additional case of cervical cancer compared to 12 month follow-up in this group **Systematic review addressing secondary PICO question** Within the renewed NCSP, the policy of 12 month follow-up for women with pLSIL/LSIL would apply only to the subgroup of women at intermediate risk based on HPV testing with partial genotyping, in contrast to the current program in which the policy applies to an undifferentiated group of women with either high or intermediate risk. Accordingly, modelled results suggest that the risk in women with oncogenic HPV types (not 16/18) and a pLSIL/LSIL reflex cytology result who have 12 month follow-up surveillance, is lower than the risk in women with a screening cytology result of LSIL in the pre-renewed NCSP (i.e. the risk in this group is lower than the accepted benchmark risk for 12-month follow-up in Australia). More than half of women with HPV infection are expected to clear the infection within 12 months. Those with persistent infection would be identified at the 12-month HPV repeat test and referred to colposcopy, regardless of cytology. A 12 month follow-up rather than immediate colposcopy will avoid many unnecessary colposcopies and associated harms (including biopsy, overtreatment, anxiety and financial costs) in women with HPV-related cervical abnormalities that would resolve spontaneously without medical intervention. **Grade B**	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*		
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. **Systematic review addressing secondary PICO question** All studies were in populations presenting for routine screening in either North America or the UK. The age of cohorts varied from ≥ 16 to ≥ 50 years. One study reported results specifically for women aged ≥ 25 years. Only one study (ATHENA) reported vaccination levels (< 5% vaccinated). As HPV vaccination was	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**

only introduced in 2006 and was targeted at women under the age of 27 years it is assumed that none of the women in the ALTS study (completed prior to the introduction of vaccination) and the majority of women in the other studies were unvaccinated. Overall Grade: **A** (based on modelling)		
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 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**	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).*

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		
Modelling	Not applicable	NHMRC levels of evidence do not currently encompass modelling studies
Systematic reviews	D	Level I to III studies/SRs with a high risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	B	Substantial
4. Generalisability	A	Evidence directly generalisable to target population

5. Applicability	A	Evidence directly applicable to Australian healthcare context

Evidence statement:

Systematic review

Data from two prospective cohort studies indicate that women with a cytology finding of definite LSIL who test negative for HPV 16/18 but positive for other oncogenic types are at lower risk for CIN3+ over 2 years (and for up to approximately 18 years) than women with a cytology finding of definite LSIL regardless of HPV status who are currently referred to 12-month follow-up.

Modelling analysis

In relation to 12 month follow-up vs. immediate colposcopy in women with oncogenic HPV types (not 16/18) and a pLSIL/LSIL reflex cytology result:

the 20 year risk of developing invasive cervical cancer in women with oncogenic HPV types (not 16/18) and a pLSIL/LSIL reflex cytology result who have 12 month follow-up surveillance, is lower than the risk in women with a screening cytology result of LSIL in the pre-renewal NCSP (i.e. the risk in this group is lower than the accepted benchmark risk for 12-month follow-up in Australia).

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

Women with a positive HPV test result (not 16/18), and a LBC report of negative or pLSIL/LSIL, should have repeat HPV testing in 12 months.

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.

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

CONSENSUS-BASED RECOMMENDATION

If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation 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 and by emerging data from the Compass trial. 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**