

***National Cervical
Screening Program
Renewal:
Executive summary***

REPORT

November 2013

MSAC application no. 1276

Assessment report

© Commonwealth of Australia [Year]

ISBN (Online) <number>

ISSN (Online) 1443-7139

Internet sites

© Commonwealth of Australia 2008

This work is copyright. You may download, display, print and reproduce this material in unaltered form only (retaining this notice) for your personal, non-commercial use or use within your organisation. Apart from any use as permitted under the Copyright Act 1968, all other rights are reserved. Requests and enquiries concerning reproduction and rights should be addressed to Commonwealth Copyright Administration, Attorney General's Department, Robert Garran Offices, National Circuit, Barton ACT 2600 or posted at <http://www.ag.gov.au/cca>

Electronic copies of the report can be obtained from the Medical Service Advisory Committee's Internet site at <http://www.msac.gov.au/>

Printed copies of the report can be obtained from:

The Secretary
Medical Services Advisory Committee
Department of Health and Ageing
Mail Drop 106
GPO Box 9848
Canberra ACT 2601

Enquiries about the content of the report should be directed to the above address.

The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

Publication approval number: <number>

Template Version updated Nov 08

Contents

Table of Contents

Contents i

Table of Contents.....	i
List of Tables.....	iii
List of Figures	vi
Assessment of National Cervical Screening Program Renewal.....	1
Purpose of Application.....	1
Proposal for public funding.....	2
Current arrangements for public reimbursement	3
Previous reviews	5
Prerequisites to implementation of any funding advice.....	6
Consumer Impact Statement	7
Evaluation methods.....	8
Clinical need	8
Comparator.....	10
Scientific basis of comparison: Systematic review	10
Scientific basis of comparison: Modelled evaluation.....	11
Approach to addressing primary and secondary questions.....	11
Overview of model platform.....	12
Approach to evaluation	14
Costs.....	15
Consideration of the effect of HPV vaccination.....	16
Screening test characteristics	17
Outcomes	19
Uncertainty and sensitivity analysis	21
Results of the evaluation	23
Comparative safety from the evidence review	23
Comparative effectiveness from the evidence review	24
Primary question 1: Cytology-based cervical screening.....	24
Primary question 2: Liquid-based cytology (LBC) cervical screening	25
Primary question 3: HPV testing	29
Effectiveness modelling and economic evaluation in the Australian setting.....	35
Primary Questions.....	35
Sensitivity analysis	54
Self-collected HPV tests.....	57
Discussion 103	
Comparative safety from the evidence review	103
Comparative effectiveness from the systematic review	103
Effectiveness modelling and economic evaluation.....	104
Overview	104

Key uncertainties.....	106
Overall conclusion	107
Comparative safety.....	107
Comparative clinical effectiveness	107
Cytology-based screening.....	107
LBC-based screening.....	107
HPV-based screening	108
Effectiveness modelling and economic evaluation in the Australian setting.....	109
Other relevant factors	110
Program related factors.....	110
References	111

List of Tables

Table E 1	Current MBS Item descriptors for cervical cytology	3
Table E 2	Explanatory note to MBS item numbers 2497 - 2509 and 2598 – 2616 for taking a cervical smear from a person who is unscreened or significantly under-screened.....	4
Table E 3	Previous MSAC reviews of cervical screening technologies.....	5
Table E 4	Research Questions.....	9
Table E 5	Direct test costs for screening (excluding related practitioner and PEI costs)	59
Table E 6	Summary of test characteristics modelled for conventional cytology, manually-read LBC, image-read LBC and HPV testing for different clinical applications for base case scenarios and sensitivity analysis, compared with observed data	60
Table E 7	Summary of health outcomes and budget impact for all potential screening scenarios compared to current practice - unvaccinated population	67
Table E 8	Summary of health outcomes and budget impact for all potential screening scenarios compared to current practice - cohort offered vaccination at age 12 years	67
Table E 9	Summary of health outcomes for selected strategies and probabilistic sensitivity analysis (PSA) findings- unvaccinated population	68
Table E 10	Summary of health outcomes for selected strategies and probabilistic sensitivity analysis (PSA) findings - cohort offered vaccination at age 12 years 69	
Table E 11	Summary of health and cost outcomes in selected candidate strategies – results of the probabilistic sensitivity analyses in unvaccinated cohort.....	70
Table E 12	Summary of health and cost outcomes in selected candidate strategies – results of the probabilistic sensitivity analyses in cohort offered vaccination at age 12 years	71
Table E 13	Summary of the effect of changing the screening end-age from 64 to 69 years on health and cost outcomes.....	72
Table E 14	Summary of health outcomes and budget impact for all screening scenarios when the screening end-age is changed to 69 years compared to current practice – unvaccinated population	73
Table E 15	Summary of health outcomes and budget impact for all screening scenarios when the screening end-age is changed to 69 years compared to current practice – cohort offered vaccination at age 12 years.....	74
Table E 16	Health outcomes of primary HPV testing strategies compared to selected candidate strategies from both manually-read and image-read LBC.....	75
Table E 17	Summary of health resources utilisation for all potential screening scenarios compared to current practice – unvaccinated cohort	78
Table E 18	Summary of health resources utilisation for all potential screening scenarios compared to current practice – cohort offered vaccination at age 12 years.....	79

Table E 19	Summary of health resources utilisation and the effect on mortality from the selected candidate strategies compared to current practice.....	80
Table E 20	Age-specific total number of treatments from the selected candidate strategies compared to current practice – unvaccinated cohort.....	81
Table E 21	Age-specific total number of treatments from the selected candidate strategies compared to current practice – cohort offered vaccination at age 12 years	82
Table E 22	Summary of treatment breakdown for high grade abnormalities (CIN 2 or CIN 3) - unvaccinated cohort	84
Table E 23	Summary of treatment breakdown for high grade abnormalities (CIN 2 or CIN 3) - cohort offered vaccination at age 12 years.....	85
Table E 24	Summary of the effect of screening initiation (fast vs slow uptake) on health and cost outcomes.....	86
Table E 25	Summary of the effect of screening program (call-and-recall program vs reminder-based program) on health and cost outcomes.....	87
Table E 26	Summary of the effect of poor compliance with 5-yearly call-and-recall (high proportion of early re-screening, CR2) compared with the equivalent strategy under assumptions of better compliance with 5-yearly screening (low proportion of early re-screening, most women re-attending on time (CR1)) for primary HPV testing strategies	88
Table E 27	Summary of the effect of HPV triage testing for women with low-grade cytology on health and cost outcomes – comparison among strategies incorporating HPV triage testing with different follow-up options (Option A, B) for women testing HPV positive and not incorporating HPV triage (no triage)	89
Table E 28	Summary of the effect of HPV exit testing for women 65+ years of age on health and cost outcomes.....	91
Table E 29	Changes in predicted health outcomes when no cytology is taken at colposcopy for women referred with 16/18 positive directly to colposcopy when compared to the baseline strategy where women always have a cytology available for management at colposcopy – unvaccinated cohort.....	92
Table E 30	Changes in predicted health outcomes when no cytology is taken at colposcopy for women referred with 16/18 positive directly to colposcopy when compared to the baseline strategy where women always have a cytology available for management at colposcopy – cohort offered vaccination at age 12.....	92
Table E 31	Health and cost outcomes in strategies where women never return for more cervical screening after being completely discharged after a normal HPV exit test (compared to the equivalent strategy where some women continue to return after an exit test at rates as observed under current practice) and assuming screening ends at 69 instead of 64 years for both sets of scenarios – unvaccinated cohort	93
Table E 32	Health and cost outcomes in strategies where women never return for more cervical screening after being completely discharged after a normal HPV exit test (compared to the equivalent strategy where some women	

	continue to return after an exit test at rates as observed under current practice) and assuming screening ends at 69 instead of 64 years for both sets of scenarios – cohort offered vaccination at age 12.....	95
Table E 33	Health and cost outcomes in strategies where women never return for cervical screening after being discharged after a normal HPV exit test and assuming screening ends at 69 instead of 64 years – unvaccinated cohort	97
Table E 34	Health and cost outcomes in strategies where women never return for cervical screening after being discharged after a normal HPV exit test and assuming screening ends at 69 instead of 64 years – cohort offered vaccination at age 12.....	98
Table E 35	Health and cost outcomes in primary HPV screening strategies if the routine screening interval is lengthened out to 6 years compared to the equivalent screening strategy under 5 yearly screening intervals – unvaccinated cohort.....	99
Table E 36	Health and cost outcomes in primary HPV screening strategies if the routine screening interval is lengthened out to 6 years compared to the equivalent screening strategy under 5 yearly screening intervals – cohort offered vaccination at age 12.....	100
Table E 37	Health and cost outcomes in primary HPV screening strategies if the routine screening interval is lengthened out to 6 years compared to current practice – unvaccinated cohort	101
Table E 38	Health and cost outcomes in primary HPV screening strategies if the routine screening interval is lengthened out to 6 years compared to current practice – cohort offered vaccination at age 12.....	102

List of Figures

Figure E 1	Simplified algorithm for the current cervical screening program	8
Figure E 2	Hybrid model of HPV transmission and vaccination; natural history of CIN and invasive cervical cancer; and cervical screening, diagnosis and treatment.....	59
Figure E 3	Cost-effectiveness plane showing current practice and potential screening scenarios with life-years as an outcome – unvaccinated cohort.....	63
Figure E 4	Cost-effectiveness plane showing current practice and potential screening scenarios with life-years as an outcome – cohort offered vaccination at age 12 years	63
Figure E 5	Cost-effectiveness plane showing current practice and primary HPV strategies with life-years as an outcome - unvaccinated cohort.....	64
Figure E 6	Cost-effectiveness plane showing current practice and primary HPV strategies with life-years as an outcome - cohort offered vaccination at age 12 years	64
Figure E 7	Predicted cancer incidence per 100,000 women for current practice and selected candidate strategies (base case results) – unvaccinated population	65
Figure E 8	Predicted cancer incidence per 100,000 women for current practice and selected candidate strategies (base case results) – cohort offered vaccination at age 12 years.....	65
Figure E 9	Predicted cancer mortality per 100,000 women for current practice and selected candidate strategies (base case results) – unvaccinated population	66
Figure E 10	Predicted cancer mortality per 100,000 women for current practice and selected candidate strategies (base case results) – cohort offered vaccination at age 12 years.....	66
Figure E 11	Predicted age-specific cancer incidence per 100,000 women for current practice and selected candidate strategies (recommended screening end age 69 years) – unvaccinated cohort.....	76
Figure E 12	Predicted age-specific cancer mortality per 100,000 women for current practice and selected candidate strategies (recommended screening end age 69 years) – unvaccinated cohort.....	76
Figure E 13	Predicted age-specific cancer incidence per 100,000 women for current practice and selected candidate strategies (recommended screening end age 69 years) – cohort offered vaccination at age 12 years	77
Figure E 14	Predicted age-specific cancer mortality per 100,000 women for current practice and selected candidate strategies (recommended screening end age 69 years) – cohort offered vaccination at age 12 years.....	77
Figure E 15	The relative trade-off between the percent increase in the mortality and the percent increase in colposcopies compared to current practice for all of the strategies considered (unvaccinated cohorts and cohorts offered vaccination are shown together on this graph).....	83

Assessment of National Cervical Screening Program Renewal

In 2011, the former Australian Population Health Development Principal Committee of the Australian Health Ministers' Advisory Council endorsed the plan to renew the National Cervical Screening Program. The Renewal of the National Cervical Screening Program (NCSP) commenced late 2011 and is planned for completion by mid-2014.

The Renewal aims to ensure the continuing success of the NCSP and that all Australian women, HPV vaccinated and unvaccinated, have access to a cervical screening program based on current evidence and best practice. The Renewal process will ensure the renewed program remains safe and continues to improve health outcomes of Australian women.

The objectives of the Renewal are to:

1. Assess the evidence for screening tests and pathways, the screening interval, age range and commencement for both vaccinated and non-vaccinated women;
2. Determine a cost-effective screening pathway and program model;
3. Investigate options for improved national data collection systems and registry functions to enable policy, planning, service delivery and quality management; and
4. Assess the feasibility and acceptability of the renewed program for women.

The first two objectives outlined above are being undertaken through the Medical Services Advisory Committee (MSAC) review process.

Purpose of Application

An application requesting review of the MBS listing of cervical cytology for screening asymptomatic women was received from the Standing Committee for Screening by the Department of Health in January 2012.

In Australia there are two programs designed to prevent cervical cancer; the National HPV Vaccination Program (NHVP) and the National Cervical Screening Program.

Australia was one of the first countries to introduce a national HPV vaccination program (NHVP). The HPV vaccines used protect against high-risk HPV types 16 and 18, which are detected in 70–80% of cervical cancers in Australia. The NHVP commenced in April 2007 with the provision of free HPV vaccinations through school-based programs, to females aged between 12 and 13 years, plus catch-up programs for women up to 26 years of age. From 2013, this program is being extended to males aged 12–13 years, plus a catch-up program for males aged 14 and 15 in 2013 and 2014.

An organised screening program was introduced in Australia in 1991 and is now called the National Cervical Screening Program (NCSP). The NCSP recommends routine screening with the Papanicolaou smear, or 'Pap test', every two years for women between the ages of 18 to 20 years (or one or two years after first having sexual intercourse) and 69 who have no symptoms or history suggestive of cervical pathology.

Since the introduction of the NCSP, the incidence and mortality of cervical cancer has significantly reduced (incidence from 17.2 per 100,000 women in 1991 in the target age group to 9.3 in 2008; mortality from 4.0 per 100,000 women in 1991 to 1.9 in 2007 (AIHW 2012)).

By international standards the current NCSP policy is regarded as intensive and as a consequence there have been recommendations from a number of national committees to review cervical screening policy (NHMRC, 2005). A Decision Analytic Protocol (DAP) was ratified by the Protocol Advisory Sub Committee in September 2012, following a period of public consultation (MSAC 2013). The DAP proposed three primary questions examining the safety, effectiveness and cost-effectiveness of:

1. Conventional cytology, using the International Agency for Research on Cancer (IARC) recommendations for age range and interval,
2. Liquid based cytology (LBC) (using the IARC recommendations for age range and interval for cytology)
3. Human Papillomavirus (HPV) testing as the primary screening test in women aged 25 to 65 years every 5 years.

All are to be compared with the protocol used in the current Australian cervical screening program.

The screening tool currently used by NCSP is the cytology from the Papanicolaou smear, or 'Pap test'. During a Pap test, cells are collected from the transformation zone of the cervix—the area of the cervix where the squamous cells from the outer opening of the cervix and glandular cells from the endocervical canal meet. This is the site where most cervical abnormalities and cancers develop. These cells are then transferred onto a slide for conventional cytology, and sent to a pathology laboratory for assessment. The cells collected are then examined under a microscope to look for abnormalities (AIHW 2013).

Liquid based cytology is a method of preparing cervical samples for examination in the laboratory. The sample is collected in a similar way to conventional cytology, however, the head of the spatula, broom or brush containing the cells is broken or rinsed into a vial containing preservative liquid. The sample is then sent to the laboratory for processing to remove obscuring material such as mucous, pus or blood before being placed on a slide.

There are currently two LBC systems available in Australia. These two systems use different technical methods for processing the cells before placement on a slide. One uses a cell filtration system (ThinPrep® Pap system, Hologic [Australia] Pty Ltd) and the other a cell enrichment system (SurePath™ LBC system, Beckton Dickinson Pty Ltd). Automated image analysis can also be used with LBC, which allows the cytotechnologist to be directed to an area on the slide that is most likely to contain abnormal cells. Automated image analysis aims to reduce the time required to read a slide and reduce detection error.

HPV tests detect the genetic material of high-risk oncogenic types of HPV associated with cervical cancer. There are different methods available for HPV testing; the two most common are polymerase chain reaction (PCR) and hybrid capture which utilises RNA probes to hybridise to the viral DNA. One of the available tests is the Hybrid Capture 2 (HC2) test (Qiagen Inc.) which identifies 13 high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) and 5 low-risk HPV types. A positive result indicates infection with one or more subtypes but cannot be used to identify the subtype. A number of alternative clinically-orientated systems provide partial genotyping for 16/18 (i.e. outputs that distinguish between these higher risk types and other oncogenic types).

Proposal for public funding

A proposed MBS item descriptor has not been developed. MSAC will need to consider whether to make item descriptors technology specific or to keep them generic.

Having regard to the substantial change that could be made to a very large and complex screening program and to the intention to address issues of implementation, quality frameworks and communication with consumers and health practitioners (Phase 2 of the renewal), consideration should also be given to the timing of any new listing. Phase 2 is not due to be complete until the end of 2014.

A team from the NHMRC Clinical Trials Centre and the Cancer Modelling Group, Lowy Cancer Research Centre, Prince of Wales Clinical School, at the University of New South Wales (UNSW), was engaged to conduct a systematic review of the literature and an economic evaluation of the NCSP for screening asymptomatic women.

A number of different screening pathways were reviewed and modelled.

Current arrangements for public reimbursement

Conventional cervical cytology (or Pap test) is primarily provided through general practice and other primary healthcare settings with rebates available from the Medicare Benefits Schedule (MBS). The current MBS item descriptor for conventional cervical cytology (for screening purposes) is outlined in Table E 1 below.

Table E 1 **Current MBS Item descriptors for cervical cytology**

<p>Item number 73053</p> <p>Cytology of a smear from cervix where the smear is prepared by direct application of the specimen to a slide, excluding the use of liquid based slide preparation techniques, and the stained smear is microscopically examined by or on behalf of a pathologist - each examination</p> <p>(a) for the detection of precancerous or cancerous changes in women with no symptoms, signs or recent history suggestive of cervical neoplasia, or</p> <p>(b) if a further specimen is taken due to an unsatisfactory smear taken for the purposes of paragraph (a); or</p> <p>(c) if there is inadequate information provided to use item 73055;</p> <p>Fee: \$19.60 Benefit: 75% = \$14.70 85% = \$16.70</p> <p>(See para <u>P16.11</u> of explanatory notes to this Category)</p>
<p>Explanatory notes P16.11 Cervical and Vaginal Cytology - (Items 73053 to 73057)</p> <p>Item 73053 applies to the cytological examination of cervical smears collected from women with no symptoms, signs or recent history suggestive of cervical neoplasia as part of routine, biennial examination for the detection of pre-cancerous or cancerous changes. This item also applies to smears repeated due to an unsatisfactory routine smear, or if there is inadequate information provided to use item 73055.</p> <p>Cytological examinations carried out under item 73053 should be in accordance with the agreed National Policy on Screening for the Prevention of Cervical Cancer. This policy provides for:</p> <p>(i) an examination interval of two years for women who have no symptoms or history suggestive of abnormal cervical cytology, commencing between the ages of 18 to 20 years, or one to two years after first sexual intercourse, whichever is later; and</p> <p>(ii) cessation of cervical smears at 70 years for women who have had two normal results within the last five years. Women over 70 who have never been examined, or who request a cervical smear, should be examined.</p> <p>This policy has been endorsed by the Royal Australian College of General Practitioners, the Royal Australian College of Obstetricians and Gynaecologists, The Royal College of Pathologists of Australasia, the Australian Cancer Society and the National Health and Medical Research Council.</p> <p>The <i>Health Insurance Act 1973</i> excludes payment of Medicare benefits for health screening services except where Ministerial directions have been issued to enable benefits to be paid, such as the Papanicolaou test. As there is now an established policy which has the support of the relevant professional bodies, routine screening in accordance with the policy will be regarded as good medical practice.</p> <p>The screening policy will not be used as a basis for determining eligibility for benefits. However, the policy will be used as a guide for reviewing practitioner profiles.</p> <p>Item 73055 applies to cervical cytological examinations where the smear has been collected for the purpose of management, follow up or investigation of a previous abnormal cytology report, or collected from women with symptoms, signs or recent history suggestive of abnormal cervical cytology.</p> <p>Items 73057 applies to all vaginal cytological examinations, whether for a routine examination or for the follow up or management of a previously detected abnormal smear.</p>

For cervical smears, treating practitioners are asked to clearly identify on the request form to the pathologist, by item number, if the smear has been taken as a routine examination or for the management of a previously detected abnormality.

The Practice Incentives Program (PIP) Cervical Screening Incentive aims to encourage general practitioners and/or non-specialist medical practitioners to screen under-screened women for cervical cancer (Australian Government, Department of Human Services, 2012). To be eligible for the Cervical Screening Incentive practices must be registered with the PIP, the practitioner must then use one of the specific cervical screening MBS item numbers when performing a cervical smear on an under-screened women in the target age range. These item numbers indicate that the requirements have been met and will then trigger a payment to the practices, the explanatory note to these items is shown in Table E 2.

Table E 2 Explanatory note to MBS item numbers 2497 - 2509 and 2598 – 2616 for taking a cervical smear from a person who is unscreened or significantly under-screened

A43	Taking a Cervical Smear from a Person who is Unscrened or Significantly Under-screned - (Items 2497 - 2509 and 2598 - 2616)
<p>The item numbers 2497, 2501, 2503, 2504, 2506, 2507, 2509, 2598, 2600, 2603, 2606, 2610, 2613 and 2616 should be used in place of the usual attendance item where as part of a consultation, a cervical smear is taken from a person between the ages of 20 and 69 years inclusive who has not had a cervical smear in the last four years.</p> <p>The items apply only to a person between the ages of 20 and 69 years inclusive who has a cervix, has had intercourse and has not had a cervical smear in the last four years.</p> <p>When providing this service, the doctor must satisfy themselves that the person has not had a cervical smear in the last four years by:</p> <p>(a) asking the person if they can remember having a cervical screen in the last four years; and</p> <p>(b) checking their own practice's medical records.</p> <p>If significant uncertainty still remains, the doctor may also contact the state cervical screening register.</p> <p>A person from the following groups are more likely than the general population to be unscreened or significantly underscreened - low socioeconomic status, culturally and linguistically diverse backgrounds, Indigenous communities, rural and remote areas and older people.</p> <p>Vault smears are not eligible for items 2497 - 2509 and 2598 - 2616.</p> <p>In addition to attracting a Medicare rebate, the use of these items will initiate a Cervical Screening SIP through the PIP.</p> <p>A PIP Cervical Screening SIP is available for taking a cervical screen from a person who has not been screened in the last for four years. The SIP will be paid to the medical practitioner who provided the service if the service was provided in a general practice participating in the PIP Cervical Screening Incentive. A further PIP Cervical Screening Incentive payment is paid to practices which reach target levels of cervical screening for their patients aged 20-69 years inclusive. More detailed information on the PIP Cervical Screening Incentive is available from the Medicare Australia PIP enquiry line on 1800 222 032 or from the Department of Human Services website.</p> <p>Related Items: 2497, 2501, 2503, 2504, 2506, 2507, 2509, 2598, 2600, 2603, 2606, 2610, 2613, 2616</p>	

Liquid Based Cytology (LBC) by any method is not listed on the MBS. It is, in fact, explicitly excluded from the MBS (see MBS descriptors, above). However, LBC, is currently provided by all private pathology laboratories for a fee additional to the MBS fee for conventional Pap smears, and is collected using the split-sample technique in conjunction with conventional Pap smears. The additional fee is paid by the patient (typically around \$30 or more).

The exception to this is in Queensland (namely Far North Queensland) where cell filtration LBC (ThinPrep®) is offered as an adjunctive test to conventional Pap smears in women meeting specific

criteria (Queensland Cervical Screening Program 2008); this program is funded by the Queensland State Government

The NHMRC Guidelines recommend HPV testing for women who have undergone treatment for high grade cervical abnormalities to monitor the effectiveness of treatment (termed ‘test of cure’). An MBS item is available for this purpose. HPV testing for any other purpose is not currently recommended by the NCSP and a Medicare rebate is not available.

Previous reviews

Previous MSAC reviews of technologies for screening for cervical cancer are listed in Table E 3.

Table E 3 Previous MSAC reviews of cervical screening technologies

No	Application title	Outcome
Reference 12a (2002)	Liquid based Cytology for Cervical Screening	MSAC advised that there was insufficient evidence to support public funding of liquid based cytology for cervical screening at the time of the assessment.
Reference 12b (2002)	Human Papillomavirus Testing in Women with Cytological Prediction of Low-grade Abnormality	MSAC advice was that there was currently insufficient evidence to support public funding at the time for the use of the HPV test for triaging of women with equivocal cervical screening results.
Reference 12c (2003)	Computer-assisted Image Analysis for Cervical Screening	MSAC advised that there was insufficient evidence to support public funding of computer-assisted image analysis for cervical screening at this time.
Reference 12d (2003)	Human Papillomavirus Testing for Cervical Cancer	MSAC advised that there was insufficient evidence to support public funding of HPV testing as a stand-alone screening test or as an adjunct to cervical cytology screening.
Application 1122 (2009)	Automation-Assisted and Liquid-Based Cytology for Cervical Cancer Screening	MSAC’s advice was, with respect to LBC, that in comparison to conventional cytology, LBC is safe, is at least as effective, but is not cost effective at the price requested and advised that LBC should not be supported for public funding. With respect to automated (computerised) testing of LBC, that in comparison to conventional cytology, automated LBC testing is safe, is at least as effective, but is not cost effective at the price requested. MSAC advised that automated testing of LBC specimens should not be supported for public funding.
Ref 39 (2009)	Human Papillomavirus Triage Test for Women with Possible or Definite Low-Grade Squamous Intraepithelial Lesions	MSAC’s advice was that HPV triage testing in cervical cancer was not cost effective in the Australian setting at the current price of HPV testing and did not support public funding.
Application 1157 (2013)	Cell enrichment liquid based cytology (LBC) in routine screening for the prevention of cervical cancer	After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of cell enrichment liquid based cytology (BD SurePath™) for cervical cancer screening, MSAC does not support public funding.

The current assessment, unlike previous MSAC reviews that assessed a single technology, assesses multiple screening pathways including different technologies, age ranges and intervals and both vaccinated and unvaccinated cohorts.

Prerequisites to implementation of any funding advice

LBC tests with manual or automated slide reading are *in vitro* diagnostic tests that are not of human origin and are therefore exempt from the regulatory requirements of the Therapeutic Goods Act 1989.

A number of HPV tests are currently being used in Australia, but there is only one entry in the Australian Register of Therapeutic Goods (ARTG). This is the cobas® 4800 Human Papillomavirus (HPV) Test, sponsored by Roche Diagnostics Australia Pty Limited. Other HPV tests currently used in Australia without ARTG listing (i.e. under TGA transitional arrangements), include: Hybrid Capture II test (Digene) and Cervista (Hologic). All in-vitro diagnostic medical devices (IVDs) supplied prior to 1 July 2010 are provided with a four year transition period (i.e. until 30 June 2014) to be brought into the regulatory framework. It would be expected that all products assessed and used as part of the NCSP would comply with the new regulatory framework.

[NOTE: an Errata was issued on 15 May 2014 and a statement was made on 13 June 2014 regarding the paragraph above and are available from <http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/ncsp-renewal#Medical-Services-Advisory-Committee-recommendations>]

The potential use of any particular HPV test as a primary test in the screening program would require that the test had been clinically validated prior to use, against a reference standard of histologically confirmed high grade intra-epithelial lesions. Tests which are highly sensitive at the expense of specificity, can be expected to increase positivity rates without commensurate reductions in cervical cancer and therefore move the program away from the optimal balance between benefits and harms and to increase the overall cost of the program. There is presently no framework to ensure that only clinically validated tests are used in the current indication for test of cure.

An international group has proposed guidelines stating that any new high-risk HPV test should reach a minimum relative sensitivity of at least 0.90 and a relative specificity of at least 0.98, using HC2 as a comparator test and CIN2+ as the threshold for disease. Moreover the new test should be highly reproducible (agreement >87%, minimum 500 samples) (Meijer *et al.* 2009).

The Australian Institute of Health and Welfare (AIHW) publishes regular monitoring reports on the National Cervical Screening Program. To support quality and consistency in national reporting, the AIHW has developed a set of program performance indicators for use by all states and territories. In view of the implementation of the NHVP, these indicators should include analysis by HPV vaccination status in the near future as vaccinated cohorts of young women are already entering the NCSP. Analysis of these indicators by vaccination status requires data linkage between the National HPV Vaccination Register (NHVPR) and the cervical screening registers. There are presently considerable legal and operational barriers preventing this linkage and to date the linkage for this purpose has not been possible.

Australian laboratories performing cervical cytology are required to use standardised reporting terminology, developed with the relevant Australian medical professional associations. A set of performance measures has also been introduced, against which laboratories are assessed as part of the formal accreditation process. These measures operate on an underlying assumption that the prevalence of high grade abnormalities is stable with time. This has largely held true over the last decade. However, it is anticipated that prevalence of high grade abnormalities will fall in vaccinated cohorts and early effects have already been reported. Most of the laboratory performance measures (particularly detection rates and PPVs for high grade abnormalities) require review in the near future whatever screening pathway is to be used.

Program reporting and monitoring has been strengthened by the establishment of cervical screening registers that operate in all states and territories. The registers have a key role in quality assurance by providing back-up reminders to women for routine screening and follow-up of abnormal Pap tests. They also provide clinical information and performance data to medical practitioners and pathology laboratories. Any of the proposed screening pathways would require substantial change to the structure and operation of the registers. These issues are to be addressed in Phase 2 of the Renewal. MSAC should be aware that in addition to resource requirements, considerable time may be needed to make the necessary changes.

Consumer Impact Statement

Objective four of the Renewal is to assess the feasibility and acceptability of the renewed program for women; this is a Phase 2 activity and is beyond the scope of the MSAC assessment. However, the DAP and the evidence review were both released for public consultation. A list of individuals and organisations that provided feedback to the evidence review public consultation is provided in Appendix K of the review of evidence.

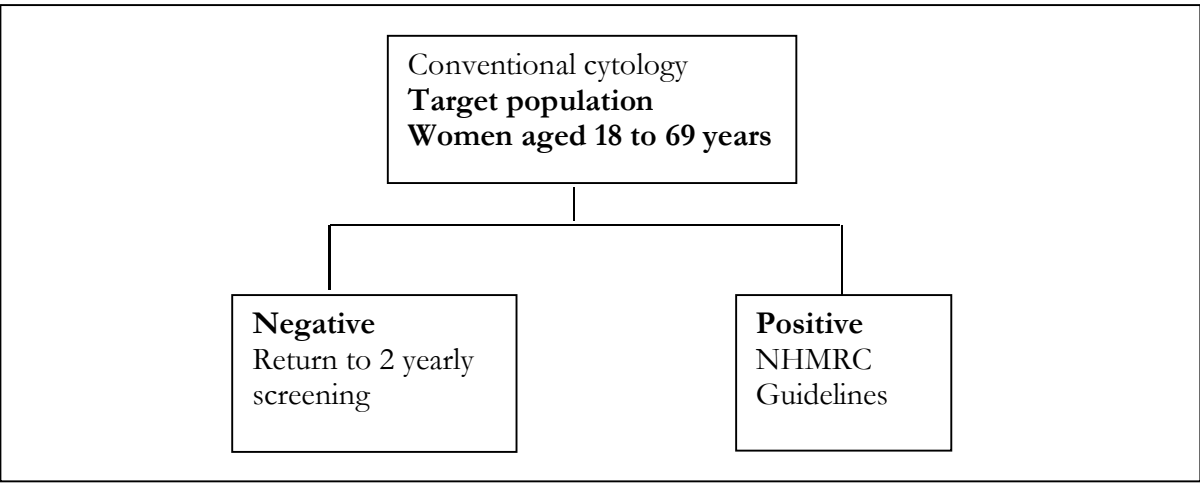
Evaluation methods

Clinical need

The proposed interventions are being considered in place of the current program (shown in Figure E1), that is, as a direct substitute. The science of cancer is one of the most rapidly changing areas in health and, while the success of the NCSP cannot be disputed, the environment in which the program operates has changed. Since the introduction of the NCSP in 1991, there is a greater depth of knowledge and understanding about the natural progression of cervical abnormalities and the development of cervical cancer.

Evidence about the screening age range and interval has also changed over time, and new tests for the early detection of pre-cancerous cervical changes have been developed. Furthermore, young Australian females and males are now provided with the opportunity to be vaccinated against HPV which will prevent high-risk HPV infections that may lead to the majority of, but not all, cervical cancer.

Figure E 1 Simplified algorithm for the current cervical screening program



The research questions are presented in Table E4. Intervention management algorithms are presented in the economic model.

Table E 4 Research Questions

		Comparator Current program	Scenario 1	Scenario 2	Scenario 3
Primary question	Primary screening test	Conventional cytology	Conventional cytology	LBC (cell filtration and cell enrichment separately)	HPV testing (including information on genotyping separately)
	Age range	Women aged 18–69 years	Women aged 25–64 years (IARC recommendations)		
	Interval	2 years	3 years (aged 25–49) and 5 years (aged 50–65) (IARC recommendations)		No less than 5 years (a range of intervals should be considered)
Secondary questions	Triage options**	<u>pLSIL/LSIL result</u> N/A (as per NHMRC Guidelines)	<u>pLSIL/LSIL result</u> N/A (as per NHMRC Guidelines)	<u>pLSIL/LSIL result</u> +/- reflex HPV testing	<u>HPV positive result</u> 1) +/- LBC co-testing 2) +/- LBC reflex testing
	Additional technology	N/A	N/A	+/- Automated image analysis	
	Exit strategy	Must have two normal cytology tests within the last 5 years	HPV test at age 64 years		
	Self-collection	N/A	N/A		YES
	Invitation and recall system	N/A (overdue reminders only)	YES		

** In this assessment triage tests include additional tests undertaken in the laboratory, using the original sample, which will assist in making a final recommendation on the index test, based on the combined results. This does not involve tests for the follow-up of an abnormal result.

Comparator

The comparator for any alternative cervical screening pathway (primary questions) is the current pathway promoted by the NCSP. All women between the ages of 18 (or one to two years after first having sexual intercourse, whichever is later) and 69 years of age should be screened every 2 years using conventional cytology.

The Renewal Steering Committee (following finalisation of the DAP), advised that the comparator for secondary questions are the screening strategies considered in the relevant primary question. However, because some of those questions originally designated as ‘secondary’ in the DAP involve changes to the primary screening modality, for the purposes of economic evaluation a large range of strategies were evaluated which incorporated all relevant variants generated by these primary and secondary questions when considered in combination.

Scientific basis of comparison: Systematic review

The assessment of the effectiveness of primary question 1, changing the age range and interval for cervical screening using conventional cytology to the IARC recommendations, is based on the following evidence:

- Three systematic reviews (Vesco *et al.* 2011, Peirson *et al.* 2012, Saslow *et al.* 2012)
- Five primary observational studies (level III-2, level III -3 and level IV) (Dinkelspiel *et al.* 2012, Lonnberg *et al.* 2012, Patel *et al.* 2012, Sasieni *et al.* 2012, Lonnberg *et al.* 2013)
- One Australian decision model (Creighton *et al.* 2010)
- Australian epidemiological data

The assessment of the effectiveness of primary question 2, LBC, is based on the following evidence:

- One previous MSAC review (MSAC 2009, Application 1122)
- Two systematic reviews (Vesco *et al.* 2011, Peirson *et al.* 2012)
- Three primary studies; two randomised trials (Level II) (Ronco *et al.* 2006, Siebers *et al.* 2009) and one pseudo-randomised trial (Level III-1) (Klug *et al.* 2013)

The assessment of the effectiveness of primary question 3, HPV primary screening (alone or in combination with LBC), is based on the following evidence:

- Three systematic reviews (Vesco *et al.* 2011, Arbyn *et al.* 2012, Peirson *et al.* 2012)
- Eight RCTs (Naucler *et al.* 2007, Kitchener *et al.* 2009, Sankaranarayanan *et al.* 2009, Ronco *et al.* 2010, Leinonen *et al.* 2012, Ogilvie *et al.* 2012, Rijkaart *et al.* 2012)

The evidence used to inform secondary questions is not listed here.

As no studies provided adequate evidence of impact on incidence or mortality rates of invasive cervical cancer in unvaccinated populations, and no studies were conducted in vaccinated populations, a modelled analysis of cervical cancer screening, diagnosis and treatment was conducted to explore the potential long-term benefits and harms of these technologies in the Australian setting.

Scientific basis of comparison: Modelled evaluation

This section summarises the methods of a modelled evaluation of the cost-effectiveness of a number of new strategies for cervical screening in the Australian National Cervical Screening Program (NCSP). The current NCSP recommendations for cervical screening are that sexually active women aged 18-20 to 69 years should be screened every 2 years using conventional cytology. The broad scenarios for the NCSP Renewal evaluation were specified in MSAC's Final Decision Analytic Protocol (DAP) for this assessment, but detailed scenario descriptions and clinical pathways were not specified in that document. Therefore, the clinical pathways for this evaluation and the data sources for the modelling assumptions were developed by the evaluation team at The Lowy Cancer Research Centre, University of NSW with the overarching guidance of the Renewal Steering Committee (RSC). With respect to the model of current practice, the clinical pathways for screening, diagnostic evaluation, treatment of cervical abnormalities, and post-treatment follow-up are as specified in the 2006 NHMRC Guidelines for Management of Abnormal Cervical Cytology. However, RSC input was used to guide specifications for some aspects of the current clinical pathways which are not given in detail in the 2006 NHMRC Guidelines and pathway specifications for future screening strategies under evaluation. It is acknowledged that clinical pathways are, in practice, also subject to a degree of clinical judgement; nevertheless it should be noted that the results of the modelled evaluation reflect the specified clinical pathways.

The economic evaluation report should be read in conjunction with the companion evidence review report, which concluded that 'a modelled analysis of cervical cancer screening, diagnosis and treatment is necessary to explore the potential long-term benefits and trade-offs of implementing new screening programs in the Australian screening program.'

Approach to addressing primary and secondary questions

In accordance with the DAP, three broad categories of potential changes were evaluated:

PRIMARY QUESTION 1 involves the retention of **conventional cytology**, but in the context of adopting International Agency for Research on Cancer (IARC) screening recommendations, which specify that cervical screening is performed 3-yearly in women age 25-49 years and 5-yearly in women aged 50-64 years;

PRIMARY QUESTION 2 involves replacement of conventional cytology with either **Manually-read** or **Automated Image-read Liquid-based Cytology (LBC)**, again in context of screening at the IARC intervals and age range; and

PRIMARY QUESTION 3 involved replacement of conventional cytology with **primary human papillomavirus (HPV) testing**, in the context of women aged 25-64 years having a recommended 5-yearly screening interval at all ages.

For Primary Question 3, three alternate approaches to using HPV for primary screening were evaluated. These were (i) cytology triaging of all oncogenic HPV-positive women, (ii) partial genotyping (i.e. differential management of HPV 16/18 positive women compared to women with other oncogenic type infections) and (iii) adjunctive co-testing (i.e. performing both cytology and HPV testing at the primary screening stage and managing on the basis of both tests).

Therefore, in total, six different primary screening approaches, using different technologies or technology combinations, were evaluated (one for conventional cytology, two LBC technologies, and three primary HPV technologies or technology combinations). For each of these six potential primary screening approaches, the effects of a number of possible variants, based on differences in screening behaviour and compliance assumptions and accounting for the secondary evaluation questions, were also evaluated. These included:

- (i) Moving from the current reminder-based screening system in which reminders are sent to eligible women who have not attended for screening at the recommended interval, to a call-and-recall system in which invitations are proactively sent before the re-screening due date (two different sets of attendance assumptions were used for future compliance in the context of longer intervals for reminder-based strategies and alternate assumptions were used for call-and-recall strategies);
- (ii) Moving from an assumed 'slower uptake' scenario for screening initiation after age 25 years (if the recommended age of starting was changed without issuing invitations to women on their 25th birthday) to a 'faster uptake' scenario which assumed women were sent invitations on their 25th birthday;
- (iii) For LBC options, use of reflex HPV triage testing for low grade cytology instead of management according to current NHMRC recommendations (which involve either cytology follow-up or immediate colposcopy depending on the age and screening history of the woman);
- (iv) For LBC options using HPV triage and for primary HPV testing options involving cytology triage, two different alternatives for managing triage-test-positive women thereafter (via either recommended 12 month follow-up ('Option A') or direct colposcopy referral ('Option B')); and
- (v) Introducing HPV 'exit testing' for women attending screening at age 64+ years, to assess and manage the group of women at very low risk of subsequent disease with a view to potential discharge of this group from screening.

Overview of model platform

The evaluation utilised a previously developed model platform which has been used for a number of HPV vaccination evaluations as well as screening technology, screening interval and screening management evaluations performed on behalf of national cervical screening programs in Australia, New Zealand and England. A schematic of the platform is shown in Figure E 2. This platform has previously been used, for example, to evaluate:

- The impact of the National HPV Vaccination Program on HPV infections in females in Australia (Smith *et al.* 2008);

- The impact of including males in the National HPV Vaccination Program on infection rates in females and males and cancer outcomes in males in Australia (Smith *et al.* 2011d);
- The effect of extending the recommended cervical screening interval in the national cervical screening programs in Australia (Creighton *et al.* 2010) and England (Canfell *et al.* 2004);
- The cost-effectiveness of LBC testing for cervical screening in Australia (MSAC 2009b, MSAC 2009a), New Zealand (Canfell *et al.* 2008) and England (Canfell *et al.* 2008, Legood *et al.* 2012);
- The cost-effectiveness of HPV triage testing for low grade cytology in Australia (MSAC 2009b, MSAC 2009a) and New Zealand (Canfell *et al.* 2008);
- The cost-effectiveness of automation-assisted and manual cervical screening in England (MAVARIC Trial study) (Canfell *et al.* 2011a)
- The cost-effectiveness of HPV as a test-of-cure in England using data from the NHS Sentinel Sites (Legood *et al.* 2012).
- The impact of HPV vaccination on the cost-effectiveness of the existing National Cervical Screening Program in New Zealand (Canfell *et al.* 2012b).
- The cost-effectiveness of alternative screening strategies, combined screening and vaccination approaches, and threshold per-dose vaccine price for HPV vaccination to be cost-effective in China (Canfell *et al.* 2011b, Shi *et al.* 2011, Shi *et al.* 2012);
- Costs and resource utilisation in the National Cervical Screening Program in Australia (Lew *et al.* 2012); and
- The cost-effectiveness of primary HPV screening in the context of HPV vaccination in England (Kitchener *et al.* 2013).

The platform, as adapted for Australia, consists of several elements, as follows:

- (i) A dynamic model of sexual behaviour, HPV transmission and HPV vaccination in females and males in the Australian population. This has been previously used to predict the impact of both female and male vaccination; predictions made at the start of the National HPV Vaccination Program using this model have recently been validated against observed post-vaccination HPV prevalence in Australia.
- (ii) A multi-HPV-type cohort model of the natural history of cervical HPV infection, progression, regression, the development of cervical intraepithelial neoplasia (CIN) and invasive cervical cancer.
- (iii) A model of cervical screening, management, diagnosis and treatment of CIN, and ‘test-of-cure’ after treatment of high grade CIN;
- (iv) A multiple-cohort implementation which separately models HPV exposure, CIN development, screening, and all downstream processes, for each single year age cohort of females, and
- (v) A population component that applies demographic data to the outputs to estimate cross-sectional results in each age group after the implementation of each potential new screening strategy.

This model platform incorporates the results of prior reviews of natural history parameters which were used to set *a priori* ranges for parameter values, and, after taking into account the

effect of screening, the platform has been previously calibrated across HPV prevalence and extensive national screening program data from three countries (Australia, New Zealand and England). The Australian version incorporates local data on screening behaviour and follow-up and management compliance over a 10-year period from analyses of the Victorian Cervical Cytology Register (VCCR). It has been updated for the purposes of the current evaluation and the model of current practice has been recently re-calibrated or validated against a large range of current screening program outputs and other national or nationally-representative data sources, including age-specific pre- and post-vaccination rates of HPV prevalence in Australia, observed post-vaccination reductions in age-specific HPV16 prevalence in Australia, age-specific rates of screen-detected high grade abnormalities, age-specific cervical cancer incidence and mortality, observed 'call rates' for low grade and high grade cytology, and the numbers of cytology, histology and high grade histology tests observed in the current program.

Approach to evaluation

We took a health services approach to the evaluation. Costs related to HPV vaccination were not included in the analysis, because the objective was to assess the costs and effects of new cervical screening strategies in the NCSP. NCSP overhead costs, including the overhead costs which would be associated with implementing new call-and-recall systems, were not included in the analysis, since these are likely to vary by state and territory, depend on existing cost structures, and are difficult to quantify in the context of the current evaluation. These costs should be considered as part of subsequent stages of the Renewal process.

As for prior evaluations (MSAC App.1122 and Ref. 39, 2009), out-of-pocket costs, costs related to Medicare safety net claims (including the Original and Extended Medicare Safety Nets) and incentive payments (such as the Service Incentive Payment (SIP) and the Practice Incentive Payment (PIP)) were not explicitly included in the effectiveness and economic model.

Current out-of-pocket costs are difficult to assess because a number of women choose to have adjunctive LBC testing with their conventional cytology test; the uptake of adjunctive LBC testing ranges from 4% in Victoria to 29% in NSW (Aminisani N, Armstrong BK, Canfell K., submitted 2013), and is not well characterised in all states. Additionally, health practitioners will potentially charge consultation rates in excess of the MBS scheduled fee, resulting in higher out-of-pocket costs, however the extent of and variation in these charges is also difficult to quantify.

Our main evaluation considered costs related to 100% of the MBS fee, but 85% reimbursement was considered in sensitivity analysis. This approach was chosen to be consistent with previous evaluations (MSAC 2009b, MSAC 2009a).

The Medicare Safety Net covers out-of-hospital visits and tests, and will reimburse a higher amount for these services once individuals or families reach various thresholds of expenditure (based on gap and out-of-pocket payments). The Original Medicare Safety Net will reimburse up to 100% of the scheduled fee once gap payments (the difference between the reimbursed amount and the scheduled fee) reach a minimum threshold. Although this was not explicitly considered in the detailed evaluation, aspects of the impact of changes to the NCSP on the Original Medicare Safety Net are potentially encompassed by our considering overall costs based on 100% of the MBS scheduled fee in this evaluation (as well as 85% in sensitivity analysis).

The impact on the Extended Medicare Safety Net (EMSN, based on out-of-pocket costs for out-of-hospital procedures) was not explicitly modelled. These out-of-pocket costs are variable and difficult to quantify. However, given that the majority of the costs in the NCSP relate to the delivery of primary screening tests in the general population (Lew *et al.* 2012), it is anticipated

that the impact on the EMSN from women attending for primary cervical screening tests will be minimal and generally positive, since all new strategies involved the delivery of fewer primary screening tests compared to current practice. For women referred for follow-up testing or diagnostic evaluation, the EMSN implications will depend on other MBS claims made during the same year and are difficult to quantify, since some of the most effective strategies identified in this evaluation resulted in more colposcopies but fewer treatments for CIN2/3 in the population overall. For women diagnosed with invasive cervical cancer the EMSN implications are expected to be positive (i.e. reduced numbers of ESNMB claims) since rates of invasive cervical cancer are predicted to be reduced for the most effective new strategies evaluated, compared to current practice.

We also did not explicitly include PIP or SIP incentive payments in the analysis. As part of the renewed national cervical screening policy, it is proposed that the practice PIP payments be tailored to the new longer recommended screening intervals (i.e. be tied to screening underscreened women who have not been screened by age 30 years or for whom more than 12 months has elapsed since their last recommended screening test would have occurred); since these payments will be tied to longer screening intervals they are not expected to increase overall. These PIP payments will also be supplemented with an MBS item encompassing processing for an HPV self-sample test collected within a health care setting for women who have never been screened by 30 years of age and for women who are underscreened.

Costs

Aggregate costs for screening, diagnostic and treatment procedures were derived using previously reported methods (MSAC 2009b, MSAC 2009a, Lew *et al.* 2012) and were based on the item cost of the component services, which were obtained from MBS Online for outpatient medical services, the National Hospital Cost Data Collection for inpatient services and the Pharmaceutical Benefits Schedule (PBS) Online where applicable. We updated the item costs to 2013 and re-calculated aggregate costs using the same methods as previously described. In brief, the aggregate cost of cytology comprised a medical consultation cost and a pathology cost. The consultation cost takes into account the range of practitioners who can collect cytology samples, and also that the purpose of consultation may be for multiple reasons. In the case where a second cytology test is performed after an unsatisfactory test, we assumed that the full cost of GP/specialist consultations was applicable. Abnormal cytology results were assumed to incur an additional consultation cost for conveying to the woman the cytology result. The cost of treatment for precancerous lesions was composed of the weighted-average of the costs of ablatational treatment, excisional treatment and hysterectomy. The weighting for each treatment type was informed by the MBS online database and RSC guidance. All cancer treatment costs, including the costs incurred in the year when cancer was diagnosed and the costs incurred over the subsequent years, were applied as a one-off cost in the year of diagnosis, with the exception of terminal care costs which were applied in the year a patient died from cervical cancer. The distribution of cancer stage at diagnosis was based on data provided by the Queensland Gynaecological Cancer Centre and the Royal Women's Hospital, Melbourne.

The assumed direct costs for screening tests (and range of costs used in sensitivity analysis) were determined with the guidance of the RSC and are shown in Table E 5 (it should be noted that the costs shown in this table reflect only direct test costs, but other costs related to primary screening, including practitioner visit costs and the patient episode initiation fee or PEI were taken into account in the modelled evaluation.) The current level of reimbursement for conventional cytology is \$19.60. For manually-read and image-read LBC a range of feasible costs were determined in consultation with the RSC, which were based on the requested price of the

technologies in the prior evaluation in 2009 (MSAC 2009a) but also included consideration of inflation and the underlying laboratory costs incurred. The assumed cost for an HPV test was based in the current 'lower volume' situation on the current reimbursement of \$64.00 when used as test-of-cure after treatment (the only currently approved indication) but HPV test costs for triage and primary screening applications also took into account the volume of tests conducted in the program and the consequent potential for economies of scale.

Costs associated with the National HPV Vaccination Program were not included, as they are the same for all strategies. The Australian Government provided more than \$537 million over the first four years of the vaccination program, which was implemented in 2007 and included females aged 12-26 years. The HPV vaccine is now being provided through a school-based program for females and males aged 12-13 years (ongoing) and males aged 14-15 years until the end of 2014. Additional funding of \$21.1 million over four years was allocated to extend the HPV immunisation program to include males from 2013.

Consideration of the effect of HPV vaccination

The population of women targeted for cervical screening in Australia has mixed exposure to HPV vaccination - most mid-adult and older women (those currently over 30 years of age) are unvaccinated, but younger cohorts have been offered vaccination in the National HPV Vaccination Program. Therefore, all evaluations of the cervical screening strategies under consideration were performed under two sets of assumptions. These were:

- That there was no effect of HPV vaccination in the population - a 'worst case' assumption with respect to the average population risk for developing cervical precancerous abnormalities and invasive cervical cancer, especially for younger women that have been offered vaccination; and
- That HPV vaccination decreases HPV incidence, average rates of low and high grade cervical abnormalities and average lifetime risk of developing cervical cancer in cohorts who have been offered vaccination (referred to as 'vaccinated cohort' or 'vaccinated population' in this report).

By performing evaluations of cervical screening in both groups, a range of possibilities for the costs and effects of particular screening strategies and their relationship to each other can be investigated, since it is possible that the relative effects and costs of the various strategies differ between unvaccinated and vaccinated cohorts. Conceptually, the optimal cervical screening strategies in the current era of HPV vaccination will be those which have higher effectiveness and lower costs compared to other potential strategies, across both unvaccinated and vaccinated women (since the same cervical screening strategy will be implemented across the whole population and include both groups).

Modelling of HPV vaccination against the vaccine-included oncogenic types 16 and 18 (implicated in ~70-80% of invasive cervical cancer) took into account the most recent data from the National HPV Vaccination Register on observed 3-dose coverage rates in 12-13 year old females since vaccination was implemented in 2007 (~72% coverage) (Australian Government 2013, Brotherton *et al.* 2013b). Modelling of the coverage achieved in the catch-up program in females aged 12-26 years (which took place from 2007-2009) was also performed, because the catch-up increases the level of 'herd' immunity experienced by later vaccinated cohorts (Brotherton *et al.* 2013a). Modelling of vaccination also took into account the 2013 inclusion of

12-13 year old males into the ongoing component of the National HPV Vaccination Program, and catch-up in males (aged 14-15) over 2013-2014, because this will also somewhat increase ongoing herd immunity in females and thus act to further reduce HPV incidence in females. The modelling of vaccination assumed that limited and/or short duration cross-protection was induced against non-vaccine-included oncogenic HPV types (consistent with the available clinical evidence). Therefore vaccinated women were modelled as remaining at risk of developing precancerous abnormalities and invasive cervical cancer due to infection with other oncogenic HPV types. The post-vaccination HPV natural history model also accounted for the effects of 'unmasking' of lesions associated with non-vaccine-included types, due to removal of concomitant HPV16 or 18 infections, for lesions previously attributed to HPV 16 or 18.

The 'vaccinated cohort' used for the current analysis represents the single year age cohort of females turning 18 years of age in 2015; therefore this is the group that will enter the cervical screening program in 2015-2017 if current screening recommendations for starting at 18-20 years are retained. This cohort were offered vaccination at school as 12 year olds in 2009 (i.e. they were offered vaccination at a young age, generally prior to HPV exposure, rather than being offered vaccination in the catch-up period). The 'vaccinated cohort' for the current evaluation thus represents a group who will experience the maximum benefits of the National HPV Vaccination Program, since HPV vaccination does not increase clearance of infections in women already exposed to a particular type and thus overall population effectiveness in catch-up cohorts is expected to be somewhat lower. The results for the 'vaccinated cohort' used for this evaluation should also be interpreted as applying to subsequent cohorts turning 18 years of age after 2015, under the assumption that current levels of vaccination coverage will be sustained (although the effect of alternate vaccination coverage assumptions were assessed in sensitivity analysis).

Screening test characteristics

Modelling of the underlying test characteristics for each screening test took into account the findings of the companion systematic review and evidence report. Where possible, data from high quality meta-analyses were used; however base case assumptions for the test characteristics for image-read cytology were mainly based on an Australian study comparing image-read and conventional cytology. As for prior evaluations (MSAC 2009b, MSAC 2009a), we made favourable assumptions for the test characteristics (sensitivity and specificity) of both manually-read and image-read cytology in terms of the relative performance of each of these tests compared to conventional cytology for detection of CIN2+ and CIN3+ lesions. The assumptions for screening test characteristics are summarised in Table E 6.

The unsatisfactory rate for each test was informed by national data for conventional cytology (AIHW 2013), by Australian data for image-read LBC (Davey *et al.* 2007) and by the international literature for HPV testing. The same unsatisfactory rate was used for manually read and image read LBC, based on findings that these rates are similar (Bolger *et al.* 2006). Women with an unsatisfactory test were assumed to be recalled and re-tested, incurring an additional cost.

For conventional cytology, we identified no local studies which assessed absolute cross-sectional sensitivity and specificity in the context of a screening population and including a comprehensive diagnostic assessment in screen-negative women (to assess the level of disease in this group, which is essential for an unbiased estimate of sensitivity). In the absence of this information, a fitting approach was used to derive the operating test characteristics of cytology in current practice in Australia. As described above, the model of current practice included an underlying natural history component which was extensively pre-calibrated to data across three countries. In the Australian context the test characteristics for conventional cytology were then re-calibrated to updated data for a number of screening program outcomes, including detected

high grade abnormalities and invasive cancer rates by age and cytology call rates for each grade of abnormality. In women with a satisfactory smear the observed and model-calibrated call rates for normal, pLSIL, dLSIL, pHSIL and dHSIL cytology were 94.5%, 2.3%, 1.8%, 0.7% and 0.8%, respectively (AIHW 2013). The calibrated model also yielded appropriate values for the observed correlation between high grade cytology and histology outcomes (AIHW 2013). The resulting estimated absolute sensitivity and specificity of conventional cytology in current practice in Australia for detection of histologically-confirmed CIN2/3 at a pLSIL threshold in the model was 74% and 96%, respectively (it should be noted that this cross-sectional estimate is not the same as the 'operating' sensitivity and specificity since in practice low grade abnormalities are managed via follow-up in many instances, rather than being referred directly to colposcopy). This estimate is broadly in accordance with international meta-analysis data for conventional cytology (Cuzick *et al.* 2006), but reflects an 'upper end' performance of conventional cytology which is consistent with the extensive quality assurance processes and health professional workforce for the implementation of cervical cytology in Australia.

For manually-read LBC, we used international meta-analysis data for the relative performance of conventional and manually-read LBC for primary screening (Arbyn *et al.* 2008). These data were predominantly based on cell filtration technology (six of nine studies) and thus the findings of this report should be considered to reflect that technology. This meta-analysis found no significantly significant difference in the sensitivity of the two tests, although the point estimate for the relative sensitivity of manually-read LBC was greater than unity when all international studies are considered together. Although in Australian context it is less likely that LBC will be associated with substantial gains in sensitivity because of the higher relative performance of conventional cytology, for the baseline test characteristics in the current evaluation we assumed an increase in sensitivity consistent with the point estimate in the international meta-analysis. The meta-analysis also found evidence that the specificity of LBC was decreased at the pLSIL threshold. Although we assumed that LBC was associated with a small (1%) loss in specificity at the pLSIL threshold compared to conventional cytology, we also assumed that the specificity relative to conventional cytology was higher than the upper end of the confidence interval estimated in the meta-analysis. The resulting estimated absolute sensitivity and specificity of manually-read LBC in Australia for detection of histologically-confirmed CIN2/3 at a pLSIL threshold in the model were 77% and 95%, respectively. For the reasons described above, these test characteristics of manually read LBC are considered to be *favourable assumptions*.

For image-read LBC, in the absence of high quality meta-analysis data, we based the test characteristic assumptions on local data (Davey *et al.* 2007). These data were based on cell filtration technology and thus the findings of this report reflect that technology. The whole-of-population model of current practice was calibrated to yield the additional pick-up of CIN2+ observed for image-read LBC in that study compared to conventional cytology (0.8 additional cases per 1,000 women screened, at a threshold of pHSIL). However, as described in the findings of the evidence review, data on the relative performance of image-read vs. manually-read LBC and image-read vs. conventional cytology are inconsistent and high quality evidence is lacking. The resulting estimated absolute sensitivity and specificity of image-read LBC in Australia for detection of histologically-confirmed CIN2/3 at a pLSIL threshold in the model was higher than for manually read LBC at 81% and 95%, respectively. For the reasons described above, these test characteristics for image-read LBC (filtration technology) are considered to be *highly favourable assumptions*.

For HPV testing, data from a recent meta-analysis was used to inform assumptions for the performance of the test in primary screening, as a triage test and as a test-of-cure after treatment of abnormalities (Arbyn *et al.* 2012). The data from the international meta-analysis were available as relative sensitivity and specificities for cytology and HPV testing (reflecting pooled values for

conventional and LBC cytology in the international data). However, we could not base our assumptions on the performance of primary HPV testing in the base case on the point summary estimate from the international data, because as described above the estimated performance of conventional cytology in Australia, is at the ‘upper end’ of the feasible range for absolute sensitivity. Therefore in order to avoid ‘ceiling effects’ for the estimated sensitivity of primary HPV testing in Australia (i.e. to avoid the assumption that the absolute sensitivity of HPV testing approaches 100%) we were required to use the lower end of the feasible international range for the relative sensitivity of HPV testing vs. cytology. The resulting estimated absolute sensitivity and specificity of HPV primary testing in Australia for detection of histologically-confirmed CIN2/3 at a pLSIL threshold in the model were 96% and 90%, respectively. For the reasons described above, these test characteristics for primary HPV testing are considered to be *conservative assumptions*.

Extensive sensitivity analysis was performed using a range of screening test characteristics for each test. These involved use of ‘best-case’ and ‘worst-case’ relative test performances compared to conventional cytology, which were consistent with the 95% CIs of the summary estimates of relative performance from the international meta-analyses for manually-read LBC and for HPV testing, and consistent with the range of outcomes observed in image-read LBC studies.

Outcomes

The calibrated model was used to simulate the various potential new strategies and to predict a range of outcomes for each strategy. These were in several broad categories, as follows:

1. **Health outcomes** (Discounted life years, Life Years Saved (LYS; i.e. difference in life years between a new strategy and current practice), predicted rates and case numbers of histologically-confirmed high grade abnormalities, invasive cervical cancer and cervical cancer deaths; age-specific rates of cervical cancer);
2. **Costs** (discounted lifetime costs; budget impact as total estimated program cost in 2015); and
3. **Resource utilisation** (predicted annual numbers of cytology tests, HPV tests, colposcopies, biopsies, and treatments for high grade CIN in the national cervical screening program).
4. **Relationship between health outcomes and resource utilisation** (increase in colposcopies versus decrease in mortality; relationship between numbers of colposcopies, numbers of treatments, and cancer mortality; interplay between overall treatment numbers and relative proportion of CIN2 vs. CIN3 treatments).

LYS vs. QALYs

Due to major uncertainties and inconsistencies in the available data for quality-of-life utility weights for HPV vaccination, cervical screening, diagnosis, and CIN and cancer treatment, the main effectiveness findings of this report are given in terms of life years and life years saved (LYS) and cervical cancer incidence and mortality. For clarity of presentation, the summary effectiveness findings are presented as changes in high grade abnormalities and cervical cancer incidence and mortality, but relative changes in overall life years compared to current practice followed similar patterns to the changes in cervical cancer mortality.

Supplementary analyses of Quality Adjusted Life Years (QALYs) were performed using two alternative sets of utility weights. The first of these (QALY Weight Set 1) utilised a new set of

weights from a study recently conducted by the UNSW group (formerly at CCNSW) in metropolitan Sydney, NSW, which was specifically designed to obtain weights relevant to cervical screening and HPV vaccination in an age-representative sample of women invited for screening. The second utility set (QALY Weight Set 2) was based on a commonly used set of weights; but it should be noted that these were obtained from a US study performed in a university clinic and is thus assumed to have mainly involved young women, although the age of the recruited women was not directly reported by the study authors. QALY Weight 2 was therefore not obtained in the age group primarily targeted by the new cervical screening strategies under consideration for the current evaluation.

Presentation of costs

For clarity of presentation, summary cost outcomes are presented as total annual screening program costs (standardised to the 2015 population), but changes in discounted lifetime costs compared to current practice followed similar patterns to the changes in total annual costs.

Relationship of these outcomes to those specified in the DAP

The original DAP for this evaluation specified a range of outcomes in three categories – health, diagnostic and patient outcomes. The DAP-specified outcomes and their relationship to the outcomes in this modelled evaluation are specified below.

1. Health outcomes:

- *(DAP) Incidence of cervical cancer:* Absolute values and relative changes in age-standardised cervical cancer incidence are given as a direct outcome of the modelled evaluation (and uncertainties in this outcome are calculated using probabilistic sensitivity analysis techniques).
- *(DAP) Cervical cancer mortality (age- and type-specific rates):* Absolute values and relative changes in age-standardised cervical cancer mortality are given as a summary outcome of the modelled evaluation (and uncertainties in this outcome are calculated using probabilistic sensitivity analysis techniques). Due to the large number of strategies evaluated, detailed information on age-specific mortality rates are presented for selected key (but not for all) strategies for each primary screening approach. The relatively smaller proportion of glandular (as opposed to squamous) abnormalities was not explicitly modelled in this evaluation, but the natural history of these abnormalities and the test performance for their detection was encompassed in the overall calibrated natural history and screening model, which was calibrated to overall rates of histologically confirmed high grade lesions (the majority of which are squamous CIN2/3) and invasive cervical cancer. This modelling approach is likely to favour cytology over primary HPV testing, because cytology is known to be less sensitive for glandular compared to squamous abnormalities, and is thus less effective at preventing adenocarcinoma compared to prevention of invasive squamous cervical cancer (Blomfield *et al.* 2008, Sasieni *et al.* 2009), whereas the majority of adenocarcinomas are associated with HPV 16/18 (IARC 2007).
- *(DAP) Morbidity and socio-economic effects of disease associated with oncogenic HPV types:* Morbidity outcomes would ideally be captured together with mortality outcomes by use of health state utility weightings and calculation of QALYs; as explained above this was performed for two QALY weight sets but results are presented as supplementary analyses due to limitations of the available source data on QALY weights.

2. Diagnostics:

- *(DAP) Accuracy of detecting cancer, histologically-confirmed CIN2/3, ACIS and glandular cell changes – sensitivity, specificity and associated test characteristics:* As described in the section on ‘Screening test characteristics’, these cross-sectional diagnostic test characteristics were based on the findings of the systematic review and were used as inputs for test performance in the overall population model.
- *(DAP) Accuracy of histologically-confirmed CIN1 – sensitivity, specificity and associated test characteristics:* As described in the section on ‘Screening test characteristics’, these cross-sectional diagnostic test characteristics were based on the findings of the systematic review and were used as inputs for test performance in the overall population model.
- *Proportion of lesions detected in each cytological category:* As described in the section on ‘Screening test characteristics’, these call rates acted as model calibration targets and were then used to estimate the cross-sectional test characteristics of conventional cytology in current practice in Australia. The predicted call rates for new strategies are given as an evaluation outcome.
- *Proportion of samples yielding unsatisfactory results:* As described in the section on ‘Screening test characteristics’, data on unsatisfactory rates for various tests acted as model inputs.

3. Patient outcomes

- *(DAP) Quality of life, patient preference, satisfaction/anxiety:* Ideally captured together by calculation of QALYs; performed for two QALY weight sets and results are presented as supplementary analyses.
- *(DAP) Patient compliance:* Used as an input, with the effect of a number of screening compliance assumptions assessed.
- *(DAP) Safety/adverse events such as complications, impact on fertility and/or obstetric complications, avoidance of unnecessary treatments:* Although we have previously presented preliminary estimates of the impact of cervical screening changes on obstetric complications in Australia (Canfell *et al.* 2012a), this requires consideration of treatment exposure time in relation to fertility and required use of a separate complex individual-based simulation model which is beyond the scope of the current analysis. Furthermore, data on the effect of treatment on obstetric complications are somewhat uncertain and applicability to Australian context is difficult to determine (Canfell *et al.* 2012a). For the purposes of the modelled evaluation we have presented a range of outcomes related to treatment exposure. These include rates of histologically-confirmed high grade lesions, treatment rates and numbers, and the relative proportion of treatments for CIN2 vs. CIN3. This latter proportion gives a measure of treatment for lesions more likely to progress (CIN3) vs. treatments for CIN2 which is a much more heterogeneous entity with lower overall progression potential (Schiffman *et al.* 2007).

Uncertainty and sensitivity analysis

Extensive uncertainty analysis was performed to assess the effect of changes to uncertain parameters. In particular, multiple scenarios for future screening behaviour (compliance) in the context of longer recommended intervals and for both reminder-based and call-and-recall organisational systems were investigated in order to assess the impact on the findings; these findings are presented as part of the main results section for each set of compliance assumptions.

In addition, extensive sensitivity analysis, using both one-way and probabilistic techniques, was also performed to assess the effect of changes in model assumptions on the findings. The effect of varying a wide range of assumptions were investigated, including, for example, further investigation around compliance (e.g. the effect of perfect compliance) with the recommended screening interval, screening initiation, and cessation of screening, test performance characteristics for screening and diagnostic tests, natural history parameters, and costs. The probabilistic sensitivity analysis involved multiple model runs (~300 runs for each screening strategy in each of unvaccinated and vaccinated populations) for which multiple parameters were varied with values sampled from feasible ranges. Results were estimated as 95% credible intervals (95% CrI: i.e. the range for which 95% of outputs were obtained); these can be interpreted as measure of the uncertainty in the final outcomes of the evaluation.

Results of the evaluation

Comparative safety from the evidence review

Conventional cytology, LBC with manual or automated slide reading and HPV testing are considered safe procedures.

The key safety concern about narrowing the age range and broadening the interval for screening to meet IARC recommendations is the potential for an increase in cervical cancer incidence and mortality due to the missed opportunity for earlier detection and treatment of precancerous lesions and invasive cancers. There are also potential safety benefits for adopting a less intensive screening strategy. The benefits of the consequent reduction in testing include reduced detection of cytological abnormalities that are ‘false positive’ (defined as detection of cervical intraepithelial neoplasia (CIN) requiring further investigation and monitoring that would not lead to clinically important consequences if left undiagnosed); a reduced risk of unnecessary treatment and associated reproductive complications and reductions in psychological harms. Potential harms would therefore need to be weighed against these potential benefits.

The key safety concern about HPV testing is a potential increase in the false positive rate and the downstream effect of this (additional colposcopies and potential psychological harms). HPV testing could also cause potential psychological harm; however, the Agency for Healthcare Research and Quality (AHRQ) HTA (Vesco *et al.* 2011) found the evidence on this to be limited.

Comparative effectiveness from the evidence review

The results of the systematic review are described here. The results of the second part of the assessment, the effectiveness and economic evaluation, are described in a following section of this summary.

Primary question 1: Cytology-based cervical screening

What is the comparative safety, effectiveness and cost-effectiveness of conventional cytology, using the IARC recommendations for age range and interval, compared with the protocol used in the current Australian cervical screening program?

Secondary questions:

1. What is the safety, effectiveness and cost-effectiveness of using one HPV test for women exiting the program at age 65 years and over, compared with the existing protocol?
2. What is the cost-effectiveness of the pathway if an invitation/recall system was introduced compared with the existing overdue reminder system without invitation?

Start age 25 years versus 20 years

Cervical cancer is very rare below the age of 25 years and cervical cancer mortality rates in women aged 20–24 years have not changed since the introduction of the national screening program. However, screening for unvaccinated women below the age of 25 is more likely to lead to further investigation than screening for older women.

In Australia, NCSP data from 2010 show that among women aged 20–69 years, women aged 20–24 years have the highest risk of abnormal cytology results, the second highest risk of high-grade histology after women aged 25–29 years, but the lowest risk of cervical cancer. Abnormalities are common in younger women due to HPV infections that occur frequently after sexual debut. However, most cervical HPV infections are cleared or suppressed within one to two years of exposure (Schiffman *et al.* 2007). These data indicate that screening women aged 20–24 years is more likely to lead to further investigation and potentially treatment than older age groups of women, despite their low risk of cancer.

Changing the commencement age for cervical screening to 25 years will reduce the rate of investigation in women aged less than 25 years. Observational studies indicate that most HPV infection and associated minor cervical changes will regress; however, some women will have persistent infection with CIN present when screening commences at age 25 years. This will increase the incidence of pre-invasive changes detected in unvaccinated women aged 25 years and older.

One large United Kingdom (UK) case control study has examined the impact of screening in unvaccinated women aged 20–24 years on cervical cancer incidence (Sasieni *et al.* 2009). This study found that screening women under the age of 25 years does not reduce the incidence of cervical cancer at ages 25–29 years.

The commencement age for screening in England increased from 20 to 25 years in 2004 and an increase in the incidence of cervical cancer and high-grade CIN in unvaccinated women aged 25–29 was observed. However, these cancer incidence trends were also observed in Scotland and Wales which continued to start screening at age 20 years, indicating the impact of factors other than screening age (Sasieni *et al.* 2012).

The national HPV vaccination program is anticipated to significantly reduce the risk of cervical cancer in young women. The early Australian data show a reduction in high-grade abnormalities between 2008 and 2011 among cohorts of women eligible to receive publicly funded HPV vaccination (VCCR 2011a).

Exit age 65 years versus 69 years

No studies were identified that directly compared the effectiveness of exiting screening at 65 versus 69 years of age.

Two case control studies provide evidence that screening beyond 65 years in unvaccinated women can reduce the risk of cervical cancer (Andrae *et al.* 2008, Lonnberg *et al.* 2012). However, neither of these studies reported on prior screening history to examine whether screening after 65 years offers any additional protection to that provided by adequate screening up to the age of 65 years.

A US health insurance plan member retrospective case series reported that 75% of women aged 65 and over that developed invasive cervical cancer did not meet their exit test criteria of three consecutive negative cytology tests or a single HPV co-test (Dinkelspiel *et al.* 2012).

Screening interval three years versus two years in women aged under 50 years; and five years versus two years in women aged 50 years and older

The current Australian screening program is considered intensive in comparison to those of other developed countries with successful cervical cancer prevention programs.

A UK case control study provides evidence that for unvaccinated women under 40 years of age, the risk reduction offered by screening is diminished substantially for screening intervals greater than three years (Sasieni *et al.* 2003). In contrast, for unvaccinated older women, screening intervals of five years offer risk reductions approaching those observed at three years (Sasieni *et al.* 2003). For women aged 55–69 years, 87% and 83% of cancers were prevented by three and five-yearly screening, respectively, in comparison to a reduction of 84% observed in women aged 40–54 years with three yearly screening.

A modelling study of the Australian NCSP predicts that extending the screening interval in unvaccinated women to three years will not substantially alter cervical cancer incidence or mortality rates but will lead to a reduction in the number of cytology tests and colposcopy procedures (Creighton *et al.* 2010). These results are consistent with results from a US modelled analysis (Kulasingam *et al.* 2011). They are based on data from unvaccinated women.

Primary question 2: Liquid-based cytology (LBC) cervical screening

What is the comparative safety, effectiveness and cost-effectiveness of either filtration or cell enrichment LBC (using the IARC recommendations for age range and interval for cytology), compared with the protocol used in the current Australian cervical screening program?

Secondary questions:

What is the comparative safety, effectiveness and cost-effectiveness of :

1. using automated image analysis under question 2 parameters, compared with the existing protocol?

2. adding an HPV test to triage women with pLSIL/LSIL, compared with the existing protocol?
3. using one HPV test for women exiting the program at age 65 years and over, compared with the existing protocol?
4. undertaking a colposcopy immediately in comparison to delaying the test in women who have pLSIL/LSIL cytology and a positive HPV test?

Manual LBC

No studies have assessed the impact of LBC with manual reading on incidence or mortality rates of invasive cervical cancer compared to conventional cytology. The potential long-term benefits and harms of this technology in the Australian setting using IARC recommendations in HPV vaccinated and unvaccinated populations is explored using an established model of cervical cancer screening, diagnosis and treatment, presented below (refer to following section on 'Effectiveness modelling and economic evaluation in the Australian setting').

Test accuracy

MSAC (2009) concluded that LBC provides no statistically significant difference in sensitivity (at high-grade squamous intraepithelial lesion (HSIL), LSIL or pLSIL thresholds) or specificity (at HSIL or LSIL thresholds) for the detection of CIN2+ compared to conventional cytology, but that LBC reduces the specificity for the detection of CIN2+ at a test threshold of pLSIL. This conclusion was based upon a high-quality systematic review by Arbyn et al. (2008).

The relative accuracy data from an applicable randomised controlled trial (RCT) published since the 2009 review (the Netherlands ThinPrep Versus Conventional Cytology (NETHCON) trial) are in accord with these conclusions.

Unsatisfactory rates and test yields

The MSAC (2009) report concluded that LBC reduces that rate of unsatisfactory smears in comparison with conventional cytology, and that LBC classifies significantly more slides as positive for low-grade lesions. This conclusion was based upon an HTA and meta-analysis by Krahn et al. (Krahn *et al.* 2008). The data presented in the current review from an applicable RCT published since the 2009 review (the NETHCON trial) are in accord with these conclusions.

Automated image analysis

No studies have assessed the impact of automated image analysis of LBC slides on incidence or mortality rates of invasive cervical cancer compared to manual reading. One excluded study of an obsolete system for automated reading of conventional cytology found no significant difference between slide reading techniques in terms of cancer incidence or mortality.

Test accuracy

Three diagnostic accuracy studies of fair to low quality and limited applicability provided data on the comparison of automated image analysis of LBC slides to manual LBC. These studies update the MSAC (2009) review that considered evidence from four studies (three of the ThinPrep Imager system and one of the outdated AutoPap system) providing level III-2 evidence of fair quality and limited or unclear applicability.

In the UK MAVARIC study (Kitchener *et al.* 2011) automated image analysis by two systems was less sensitive and more specific than manual reading of LBC for the detection of CIN2+ and CIN3+ by a histological reference standard. When individual systems were considered, the sensitivity of automated image analysis of either system was significantly lower than manual LBC for the detection of CIN2+.

A low-quality pseudorandomised trial of automated image analysis of cell filtration slides with the ThinPrep Imager system (Palmer *et al.* 2012) found no difference in the accuracy for classification of slides as HSIL according to an uncertain quality cytological reference standard. A partly retrospective, low-quality study of automated image analysis of cell enrichment LBC with the FocalPoint system (Wilbur *et al.* 2009) found an increase in the accuracy for slides to be classified as HSIL according to adjudicated cytology.

The overall body of evidence is considered poor (consisting of level III evidence which is inconsistent) and therefore conclusions on the relative accuracy of manual LBC and automated image analysis of LBC cannot be made.

MSAC (2009) concluded that automation-assisted image analysis with the ThinPrep Imager system detects as many CIN2+ lesions as conventional cytology, and may detect more. This conclusion was based upon two fair-quality level III-2 Australian studies (Davey *et al.* 2007, Roberts *et al.* 2007). The data presented in this review for the comparison to conventional cytology from two studies of the ThinPrep Imager system are either of lower quality or applicability than the studies considered in MSAC (2009), but nevertheless are in accord with this conclusion.

Unsatisfactory rates and test yields

In three studies conducted in countries with established screening programs, automated image analysis of cell filtration LBC slides yielded significantly lower unsatisfactory rates than manual slide reading of either LBC (MAVARIC, Kitchener *et al.* 2011; Palmer *et al.* 2012) or conventional slides (Halford *et al.* 2010). However, as the unsatisfactory rate for conventional slides is higher in the UK than in Australia, the applicability of the findings in comparison to manual LBC is uncertain.

HPV testing to triage women with pLSIL/LSIL

No studies have assessed the impact of HPV triage in women with pLSIL or LSIL cytology on incidence and mortality rates from invasive cervical cancer in comparison to repeat cytology. A modelled analysis of cervical cancer screening, diagnosis and treatment using the IARC recommendations for HPV-vaccinated and unvaccinated populations to explore the potential long-term benefits and harms of these triage options in the Australian setting is presented below (refer to following section on 'Effectiveness modelling and economic evaluation in the Australian setting').

Detection of precancerous cervical lesions

In three RCTs, in unvaccinated women there was no significant difference in the overall detection of CIN3+ by HPV triage in comparison to either repeat cytology or immediate colposcopy.

In the ASCUS-LSIL Triage Study Group (ALTS) trial (ASCUS-LSIL Triage Study Group 2003a, ASCUS-LSIL Triage Study Group 2003b), there were fewer CIN2 lesions detected in unvaccinated women referred with pLSIL in the repeat cytology arm compared to both HPV triage and immediate colposcopy. Similarly, in the Bjerre trial (2008), there were fewer CIN2 lesions detected in women younger than 35 years in the repeat cytology arm compared to the HPV triage arm (but not in women over 35). These data suggest that a statistically significant proportion of prevalent CIN2 lesions in trial participants, particularly younger women, regressed when a strategy of repeat cytology was followed, potentially avoiding unnecessary treatment and associated harms.

The colposcopy rate was higher in the HPV triage arms than the repeat cytology arms of trials and in women less than 35 years compared to older women.

Test accuracy

MSAC (2009) concluded that “if index cytology shows pLSIL, the HPV triage test is more sensitive than a single repeat cytology test for the detection of CIN2+ lesions and has similar specificity”.

The pooled accuracy data from Arbyn et al. (2013) are in accord with this conclusion and the same results were seen for the detection of CIN3+ lesions.

MSAC (2009) also concluded that “if index cytology shows LSIL, the HPV triage test is not more sensitive than a single repeat cytology test for the detection of CIN2+ lesions and has lower specificity”.

The pooled accuracy data from Arbyn et al. (2013) are in accord with this conclusion regarding specificity and the same finding was made for the detection of CIN3+.

The Arbyn et al. (2013) meta-analysis found that the HPV triage test for LSIL is more sensitive than a single repeat cytology test for the detection of CIN2+ lesions, but not CIN3+ lesions. Whether or not any additional CIN2+ lesions detected are destined to progress or regress cannot be determined from these data.

Age subgroups

MSAC (2009) concluded that “restricting the HPV triage test to older age groups is associated with a higher specificity and lower colposcopy referral rate and a corresponding smaller gain in sensitivity compared with its use in all age groups.”

The pooled accuracy data from Arbyn et al. (2013) found that the sensitivity of the Hybrid Capture 2 assay (HC2) for triage did not vary significantly by age but the specificity was always increased with age (three studies). Data from one included RCT demonstrated a higher colposcopy rate in women aged <35 compared to women aged ≥35 years following HPV triage.

Immediate versus delayed colposcopy

This question is considered under primary question 3.

Primary question 3: HPV testing

What is the comparative safety, effectiveness and cost-effectiveness of HPV testing as the primary screening test in women aged 25 to 65 years every five years, compared with the protocol used in the current Australian cervical screening program?

Secondary questions:

What is the comparative safety, effectiveness and cost-effectiveness of:

1. manually-read LBC or automated image analysis LBC as a co-test in the above scenario, compared with the existing protocol?
2. manually-read LBC or automated image analysis LBC as a reflex test to triage women with positive HPV test results, compared with the existing protocol?
3. undertaking a colposcopy immediately in comparison to delaying the test in women who have pLSIL/LSIL cytology and a positive HPV test?
4. including self-collected samples for HPV testing for underscreened and unscreened women to supplement the organised screening program using practitioner-collected HPV samples, compared with the existing protocol?
5. referring women positive for HPV 16/18 +/-45 using partial genotyping systems at primary screening immediately to colposcopy, and performing cytology triage on women positive for other oncogenic types?

Summary of RCTs of HPV screening strategies

One cluster RCT conducted in India (Sankaranarayanan *et al.* 2009) demonstrates that a single round of HC2 testing can significantly reduce both the cervical cancer incidence and mortality in comparison to a single cytology screen in a previously unscreened, unvaccinated population in a low-resource setting.

Evidence from seven RCTs (conducted in countries with established screening programs) that considered various HPV screening strategies, has been assessed in order to provide evidence for the questions posed for this review (Naucler *et al.* 2007, Kitchener *et al.* 2009, Ronco *et al.* 2010, Leinonen *et al.* 2012, Ogilvie *et al.* 2012, Rijkaart *et al.* 2012). All were regarded to be fair quality and were conducted in unvaccinated women. The studies assessed are as follows:

- One RCT (N =49 196) was of HPV primary screening.
- Two RCTs (N = 150,842) were of HPV screening with cytology triage.
- The remaining four RCTs (N =128,149) were of HPV and cytology co-testing.
- The HPV test used in the majority of studies was HC2; however, two studies used a polymerase chain reaction (PCR) test.
- Five RCTs provided a comparison with conventional cytology, one with LBC and one LBC with HPV triage.
- The RCTs varied in their characteristics, including the threshold for referral to colposcopy, follow-up testing procedures and included age ranges.
- No studies recruited women aged over 65 years.
- Five RCTs reported results over two screening rounds; the protocol for the second round differed from the first round in three of these.

Trials were not powered to detect a difference in invasive cervical cancer incidence. There was a broad trend of a reduction in the number of cervical cancer cases detected in the second round

in the intervention arm. This was significant in one trial of HPV and cytology co-testing (Population Based Screening Study Amsterdam (POBASCAM); RR 0.29, 0.10–0.87; $p=0.031$ (Rijkaart *et al.* 2012).

Cumulative detection ratios for CIN3+ did not differ significantly between arms in four of five trials in the older age group (unvaccinated women ≥ 30 or 35 years); one study comparing HPV primary testing alone to conventional cytology (New Technologies in Cervical Cancer (NTCC) Phase II) had a significantly increased cumulative detection of CIN3+ over two screening rounds (Ronco *et al.* 2010).

In the first screening round three of seven trials demonstrated a significantly greater detection of CIN3+ in unvaccinated women aged ≥ 30 –35 years with a HPV screening strategy compared with a cytology only screening strategy. This was also observed in two of four trials reporting data for women aged ≤ 30 –35 years. More trials reported increased detection of CIN2+ in the first screening round; five of seven trials in women ≥ 30 –35 years and three of four in women aged ≤ 30 –35 years. The extent to which additional detected precancerous lesions would progress to clinically significant disease is uncertain.

For five trials reporting data for an older age group (unvaccinated women ≥ 30 –35 years), a consistent reduction in the relative detection ratio of CIN3+ was seen in a second screening round and was statistically significant in three of four, despite differences in referral thresholds and follow up procedures. A similar trend was observed for the detection of CIN2+; there was a significant reduction in three of five trials.

The colposcopy referral rates for HPV-based screening strategies were increased in five of six RCTs in unvaccinated women aged ≥ 30 –35 years, and in all five studies in women aged ≤ 30 –35 years.

The overall body of evidence for the effectiveness of HPV based screening strategies (with or without triage or co-testing) is considered good consisting of several large RCTs (level II evidence) across multiple rounds whose findings are relatively consistent for the surrogate outcomes reported despite differences in design. The populations considered in these trials are similar to the target population and the results are likely to be applicable to unvaccinated women in the Australian context with some caveats.

In addition to the systematically reviewed RCTs of HPV-based screening, supportive data from two large cohort studies (Katki *et al.* 2011, Kitchener *et al.* 2011) suggest that longer screening intervals up to 5 years may be appropriate for women who are HPV negative due to the high negative predictive value of HPV.

Increased detection of precancerous lesions in a first screening round followed by decreased detection in the second round may indicate a benefit due to increased detection and treatment of progressive lesions, or simply earlier detection. Any potential harm in terms of increased colposcopy rates and the treatment of additional non-progressive lesions should also be considered. It appears that the balance of benefits and potential harms is more favourable in women ≥ 30 –35 years. A modelled analysis considering the potential long-term benefits and trade-offs of these screening strategies in the Australian setting is presented below (refer to following section on ‘Effectiveness modelling and economic evaluation in the Australian setting’)

HPV primary screening (without triage or co-testing)

Longitudinal outcomes from RCTs

In one RCT (NTCC Phase II (Ronco *et al.* 2010)), HPV primary screening (without cytology co-testing or triage) of unvaccinated women led to an increase in the detection of CIN2+ and CIN3+ in comparison to conventional cytology screening, which was greater in women <35 years than women ≥35 years. This trial was the only HPV trial that had a significant increase in the cumulative detection of CIN3+, which was observed in both younger and older age groups. It also had the greatest increase in cumulative detection of CIN2+. The extent to which this is due to the increased detection of clinically significant disease is unclear. However, the increase in the detection ratios in unvaccinated women younger than age 35 in comparison to older women suggests that an excess of regressive lesions (those destined to disappear or regress over time, without treatment) was identified in the HPV screening arm in this age group.

At round one, there were significantly more colposcopies in the HPV arm of the trial and the false positive proportion was significantly greater for the HPV strategy. The relative increase in CIN2+ and CIN3+ detection, the relative increase in colposcopy referral, and the relative false positive proportion was greater in unvaccinated younger women (<35 years) suggesting that HPV testing detects more clinically insignificant lesions in this age group.

This study was conducted in unvaccinated women and no triage strategy was employed. It is expected that the number of HPV positive tests and the number of colposcopies performed would be less in vaccinated women. A modelled analysis of cervical cancer screening, diagnosis and treatment using the IARC recommendations in HPV vaccinated and unvaccinated populations was undertaken to explore the long-term benefits and potential harms of these alternative screening strategies in the Australian setting.

Cross-sectional accuracy

A high-quality meta-analysis (Arbyn *et al.* 2012) of studies in unvaccinated women indicated that a primary HPV screening strategy is much more sensitive than cytology at the thresholds of LSIL+ and ASC-US+ for the detection of CIN2+ and CIN3+ with a small loss in specificity. Two studies included in the AHRQ review reporting on absolute accuracy measures also indicated that HPV screening was more sensitive than screening with cytology, but less specific. Relative specificity is reduced to a greater degree in younger women in one study identified by the AHRQ review.

HPV and cytology co-testing

Longitudinal outcomes from RCTs

Co-testing involves screening every woman with both a HPV test and a cytology test. The definition of a positive test (i.e. as both tests positive or either test positive) and the screening pathway following these tests varied greatly across the included studies.

Four RCTs in unvaccinated women were included, three of which provided a comparison to conventional cytology (NTCC Phase I (Ronco *et al.* 2010), Swedescreen (Naucner *et al.* 2007) and POBASCAM (Rijkaart *et al.* 2012) and one to LBC (ARTISTIC (Kitchener *et al.* 2009)). None of the trials showed any difference in the cumulative detection of CIN3+. One RCT (NTCC Phase I) comparing HPV and LBC co-testing to conventional cytology had increased cumulative detection of CIN2+ and suggests that excess regressive disease is being detected in this trial in

both younger and older age groups. This trial had a co-testing strategy that had a lower threshold for referral to colposcopy than the other trials and significantly more women were referred to colposcopy in the co-testing arm than the cytology arm.

Across trials there tended to be an increase in the detection of CIN2+ in round one followed by a decrease in detection of CIN3+ in round two.

A comparison of the intervention arms of NTCC Phase I (co-testing) and II (HPV primary) trials indicates similar sensitivity of these strategies, with higher colposcopy rates in the co-testing strategy. Such indirect comparisons are prone to bias but suggest no clear advantage of co-testing over HPV testing alone.

Cross-sectional accuracy

A high-quality meta-analysis (Arbyn *et al.* 2012) of studies in unvaccinated women indicated that co-testing is more sensitive, but less specific, than cytology alone at the threshold of pLSIL+ for the detection of CIN3+ when abnormalities on either test are considered positive. However, this gain in sensitivity is similar in magnitude to that for HPV testing alone.

In one study in unvaccinated women included in the AHRQ HTA (Kulasingam *et al.* 2002), a strategy in which both tests are required to show an abnormality for a positive test result demonstrated similar sensitivity to cytology alone (but lower than that for HPV testing alone), and increased specificity compared to either test alone. This approach is considered equivalent to a triage strategy.

Cytology triage of HPV testing

Longitudinal outcomes from RCTs

No RCTs were identified which provided a comparison of HPV primary screening with and without LBC triage.

Two RCTs of HPV with LBC triage providing comparisons to conventional cytology alone or LBC with HPV triage were included. Both trials only reported on one screening round and were conducted in unvaccinated populations.

The Finnish trial (Leinonen *et al.* 2012) demonstrated that HPV with LBC triage increases the detection of CIN2+ and CIN3+ lesions in comparison to conventional cytology. The trial found that:

- this was greater in women less than 35 years,
- younger women also had a greater number of referrals to colposcopy at the index screen (at a referral threshold of LSIL+) and repeat testing, with higher rates in the HPV with LBC triage arm,
- in contrast, colposcopy referrals (at a referral threshold of LSIL+) and repeat testing rates were similar for both testing strategies in older (≥ 35 years) women.

In the HPV FOCAL trial (Ogilvie *et al.* 2012), the detection of CIN2+ and CIN3+ lesions was non-significantly higher in the HPV with LBC triage arm compared to the LBC with HPV triage

arm after the first round. Referral to colposcopy was increased in the HPV with LBC triage arm of the trial, but these data were not age stratified.

These studies were conducted in unvaccinated women. It is expected that the number of positive tests and the number of colposcopies would decline in vaccinated women. This is explored in the modelled analysis presented below.

Cross-sectional accuracy

One study in unvaccinated women (Kulasingam *et al.* 2002) of HPV and cytology co-testing, in which an abnormal result on both tests is required for a positive result, provides accuracy data indicative of a triage approach. This study indicated that the sensitivity of the co- testing strategy for CIN3+ was lower than that of HPV testing alone while the specificity was increased. Results were similar for women aged less and more than 30 years.

Immediate versus delayed colposcopy

NOTE: Current Australian policy is to delay referral for colposcopy for pLSIL/LSIL for 12 months, repeat the Pap test, and if persistent (pLSIL+), refer to colposcopy. AIHW safety monitoring data show that the incidence of cervical cancer in women aged 20–69 has not changed since the introduction of this policy (AIHW 2013).

The Review sought to look at the effectiveness of delayed colposcopy versus immediate colposcopy in women with a positive HPV test and a pLSIL/LSIL result. For this comparison there was limited evidence.

Two included RCTs were of limited applicability so definitive conclusions cannot be made.

A modelled analysis explores the likely benefits and harms associated with immediate versus delayed colposcopy in women HPV positive with pLSIL/LSIL cytology in the Australian setting and is presented below (refer to following section on ‘Effectiveness modelling and economic evaluation in the Australian setting’).

HPV testing with partial genotyping

Accuracy

A subanalysis of the ATHENA trial (Castle *et al.* 2011) demonstrated that triage of unvaccinated HPV positive women with immediate referral to colposcopy for HPV 16 and/or 18 types had a similar sensitivity and positive predictive value (PPV) to triage of HPV by ASCUS+ cytology. Sensitivity was greater and PPV lower than triage by HSIL+ cytology. This does not take into account any effect of cytology triage of other HPV types, nor repeat testing and longitudinal follow-up. This study was considered a high-quality level III-2 diagnostic accuracy study.

An analysis of the intervention arm of the Swedescreen trial provided diagnostic accuracy data for alternative HPV-based screening strategies. In this analysis, a theoretical strategy of referring unvaccinated women positive for HPV16/18 immediately to colposcopy, and performing cytology triage on women positive for other oncogenic types had a similar sensitivity for the detection of CIN2+ and CIN3+ compared to HPV testing without triage or genotyping, with a higher positive predictive value. The potential for verification bias in this analysis was considered to be high.

Prognostic value of test results

Prognostic studies demonstrate that HPV types 16 and 18 are associated with a higher risk of development of CIN2+ and CIN3+ than other oncogenic HPV types. However, the effectiveness of management strategies based upon partial genotyping of women undergoing routine screening is uncertain.

HPV self-collection

Accuracy

Evidence for the accuracy of HPV self-collection was identified studies from the most recent comprehensive systematic review (Snijders *et al.* 2013). The authors did not report information about appraisal of included studies for classification of review quality, but the review met all other quality criteria. Evidence considered here is from 10 studies level III-2 diagnostic accuracy studies conducted in a screening setting. HPV self-collection showed moderate-high sensitivity and comparably high specificity for detecting CIN2+ compared to clinic HPV testing in 9 of 10 studies identified, with a relative sensitivity of 0.62–1.00 and relative specificity of 0.93–1.00. The evidence available from these studies suggests self-collection HPV accuracy varies for different types of sampling devices and HPV tests (Snijders *et al.* 2013).

Screening participation

There is strong consistent evidence that providing HPV self-collection kits to women who do not attend for cervical screening or are under-attenders improves screening participation (Snijders *et al.* 2013).

The size of improved participation rates achieved varies across different populations. Eight randomised controlled trials (level II evidence) have reported improvements in participation rates of between 4% and 24% compared to an additional recall letter.

Factors shown to have an impact on participation rates are: whether the self-collection kit is mailed with an invitation to screen or available on request, ethnicity, and screening history with one trial showing that women who were unscreened are more likely to respond than women who were not screened in accordance with the recommended screening interval.

Three studies that have examined adherence to screening follow-up for this population have reported high adherence (68–100%) to follow-up after a positive HPV test and very high adherence to colposcopy referral (Szarewski *et al.* 2007, Gok *et al.* 2010, Tamalet *et al.* 2013).

Effectiveness modelling and economic evaluation in the Australian setting

Primary Questions

In the base case evaluations, over 130 specific potential cervical screening strategies (varying from 12-48 for each of the primary questions, taking into account the range of primary screening approaches and a number of potential variants in each case), were evaluated and compared to current practice for cervical screening. Each of these new strategies were evaluated in both unvaccinated and vaccinated cohorts.

Health outcomes

The model of current practice predicts an age-standardised rate of 8.1 histologically-confirmed high grade (CIN 2/3) precancerous abnormalities per 1,000 women screened, compared to 8.5 (95% CI: 8.3-8.6) per 1,000 observed in 2010 (ASR 2001). The model of current practice predicts an age-standardised rate of 6.9 and 1.8 per 100,000 women for cervical cancer incidence and mortality, respectively, compared to observed rates of 6.7 (3-year range: 6.6-6.8) in 2007-9 and 2.0 (3-year range: 1.8-2.0) in 2005-2007, respectively. This corresponds to a predicted 762 and 202 cervical cancer cases and deaths in Australia in 2010, compared to 771 and 208 observed cases and deaths in 2009, respectively. The numbers of predicted and observed annual cytology tests are 2.2 million and 2.1 million, respectively, among women aged 20-69 years. The calibrated 'call rates' for low and high grade cytology abnormalities are 4.2% and 1.5%, respectively, compared to observed rates of 4.2% (95% CI: 4.2-4.3%) and 1.5% (95% CI: 1.4-1.5%) respectively, for satisfactory cytology tests from women aged 20-69 years in 2011. Therefore we concluded that the model of current practice adequately predicts outcome in the current screening practice, with close agreement between model predictions and a range of outcomes in the program.

The number of high grade abnormalities, cervical cancer cases and deaths in Australia in 2015, if current screening practice in the NCSP is retained, and if current cervical cancer incidence and death rates are maintained (but not taking into account the effect of vaccination), is predicted to be 17,800, 811 and 218, respectively, due to population growth and ageing. However, over the long term, as vaccinated cohorts age within the screening program, this is expected to decline to 10,100, 338 and 91 cases, respectively (calculated according to the age structure of the 2015 population), even if screening remains unchanged.

Figure E 3 and Figure E 4 show the cost-effectiveness plane for all strategies in the evaluation in unvaccinated and vaccinated populations; and Figure E 5 and Figure E 6 show more detailed results for the primary HPV strategies in unvaccinated and vaccinated populations. Some of the potential new cervical screening strategies are predicted to be associated with lower effectiveness than current practice. However, a number of the new screening strategies are predicted to be more effective than current practice in both unvaccinated (Figure E 3) and vaccinated cohorts (Figure E 4); i.e. to be associated with more life years and fewer cervical cancer cases and deaths than the current program. For each screening technology, a range of outcomes were obtained, which depended on the strategy variants assessed (as previously noted these strategy variants were based on differences in assumptions about the future compliance to longer-interval screening and the secondary questions).

Figure E 7 and Figure E 8 present the predicted cervical cancer incidence rate per 100,000 women for selected candidate strategies (one for each primary screening approach) by age group in the unvaccinated and vaccinated population, respectively; the selected strategies were among

the most effective for each primary screening approach. Figure E 9 and Figure E 10 present the predicted cervical cancer mortality rate per 100,000 women for selected candidate strategies by age group in the unvaccinated and vaccinated population, respectively. Excluding conventional cytology at IARC intervals, the overall predicted cancer incidence and mortality rates for the other selected strategies were lower than rates predicted for current practice - for women less than 35 years of age similar rates to current practice are predicted; for women aged 35-69 years rates significantly lower than current practice are predicted; but for women older than 69 years higher rates are predicted (due to the earlier age of stopping screening).

Table E 7 summarises the range of health outcomes, by primary screening approach, for all of the evaluated strategies in a unvaccinated population, and Table E 8 shows the findings for a population offered vaccination (referred to in this report as a ‘vaccinated population’). Table E 9 and Table E 10 give the health outcomes for selected strategies in unvaccinated and vaccinated populations along with the findings of the probabilistic sensitivity analysis for each strategy. Table E 11 and Table E 12 summarise the range of health outcome in selected candidate strategies in unvaccinated and vaccinated population, respectively. Table E 16 summarises the relative improvement in HPV strategies compared to LBC strategies (as distinct from the improvement compared to current practice).

For each screening technology, the main health outcomes were as follows:

Conventional cytology

- Retention of conventional cytology in the context of IARC age range and intervals would be associated with an increase in the age-standardised rate of cervical cancer mortality, ranging for the various specific strategies from between 8 to 20% (unvaccinated population, Table E 7) and from between 8 to 19% (vaccinated population, Table E 8), compared to current practice.
- Probabilistic sensitivity analysis demonstrated that these conventional cytology strategies are associated with a predicted increased age-standardised rate of cervical cancer mortality, compared to current practice, for all sets of feasible assumptions (Table E 9, Table E 10).
- One of the most effective conventional cytology strategies involves call-and-recall screening, sending women an invitation on their 25th birthday (‘fast uptake/initiation’) and exit HPV testing.
 - For this strategy, in an unvaccinated population (Table E 11);
 - The estimated decrease in histologically- confirmed high grade abnormalities compared to current practice is 12% (95% credible range(CrI: 7-13% in probabilistic sensitivity analysis);
 - The estimated increase in the age-standardised rate of cervical cancer incidence compared to current practice is 9% (95% CrI: 6-11%); and
 - The estimated increase in cervical cancer mortality compared to current practice is 12% (95% CrI: 9-15%).
 - In a vaccinated population (Table E 12);
 - The estimated decrease in high grade abnormalities compared to current practice is 14% (95% CrI: 9-15% in probabilistic sensitivity analysis);
 - The estimated increase in cervical cancer incidence compared to current practice is 8% (95% CrI: 6-10%); and
 - The estimated increase in cervical cancer mortality compared to current practice is 12% (95% CrI: 8-15%).

Further extensive exploratory analysis was performed to assess the underlying factors involved in the predicted incidence and mortality increase for IARC screening recommendations when

conventional cytology is retained. A previous study involving the current model platform had found that 2- and 3-yearly screening in Australia was predicted to have broadly similar outcomes (without any change to screening age range and without 5-yearly screening in women over 50 years of age) (Creighton *et al.* 2010). Similarly, analyses of comparative trends in incidence and mortality in Australia compared to England and New Zealand over in periods for which screening was predominantly 3-yearly in those countries, have concluded that 2-yearly and 3-yearly screening have broadly similar effectiveness (Canfell *et al.* 2006, Simonella *et al.* 2013).

It was confirmed that model predictions are in accordance with a key analysis of England data (Sasieni *et al.* 2003) which underpinned the IARC screening recommendations. Briefly, although both the observed data and modelled analysis found that 3-yearly screening at all ages is associated with broadly similar effectiveness to 2-yearly screening (only a small decrease in effectiveness if call-and-recall screening is used), the 5-yearly screening recommendation in women over 50 years of age is associated with some decrease in effectiveness overall (Sasieni *et al.* found 5-yearly screening in this age group to be of comparable effectiveness to more frequent screening in younger women but they did not find that it was of comparable effectiveness to more frequent screening in the same age group). Compliance to the screening interval recommendation, the rapidity of screening initiation, and the earlier age of stopping screening were also important factors in the current findings.

Manually-read LBC

- Under favourable test assumptions, strategies involving use of manually-read LBC in the context of the IARC age range and intervals could be either more or less effective than current practice, ranging from a 7% increase to a 13% decrease (unvaccinated cohort, Table E 7) and from a 6% increase to 12% decrease (vaccinated cohort, Table E 8) in age-standardised cervical cancer mortality, compared to current practice.
- The strategies that increased effectiveness generally involved HPV triage testing and for the specific selected (most effective) strategies, probabilistic sensitivity analysis demonstrated that these specific manually-read LBC strategies are associated with a predicted decreased age-standardised rate of cervical cancer mortality, compared to current practice, for all sets of feasible assumptions (Table E 9, Table E 10). However this finding does not necessarily apply to all scenarios involving HPV triage, in particular those with delayed follow up of triage test positives (Option A), as these were less effective than those with immediate follow-up (Option B), and so no Option A strategies were examined in the probabilistic sensitivity analysis.
- One of the most effective manually-read LBC strategies involves call-and-recall screening, sending women an invitation on their 25th birthday ('fast uptake/initiation'), exit HPV testing, and HPV triage of low grade abnormalities with immediate referral of HPV positive women to colposcopy ('Option B').
 - For this strategy, in an unvaccinated population (Table E 11);
 - The estimated decrease in high grade abnormalities compared to current practice is 5% (95% CrI: from a 7% decrease to a 4% increase in probabilistic sensitivity analysis);
 - The estimated decrease in cervical cancer incidence compared to current practice is 11% (95% CrI: 8-13%); and
 - The estimated decrease in cervical cancer mortality compared to current practice is 10% (95% CrI: 6-13%).
 - In a vaccinated population (Table E 12);
 - The estimated decrease in high grade abnormalities compared to current practice is 6% (95% from a 9% decrease to a 3% increase in probabilistic sensitivity analysis);

- The estimated decrease in cervical cancer incidence compared to current practice is 10% (95% CrI: 8-12%); and
- The estimated decrease in cervical cancer mortality compared to current practice is 9% (95% CrI: 5-12%).

Image-read LBC

- Under highly favourable test assumptions, strategies involving image-read LBC could be either more or less effective than current practice but the best strategies were associated with a greater improvement than for manually-read LBC, ranging from a 4% increase to a 14% decrease in cervical cancer mortality compared to current practice (unvaccinated cohort, Table E 7) and from a 4% increase to a 14% decrease (vaccinated cohort, Table E 8).
- The strategies that increased effectiveness generally involved HPV triage testing and for the specific selected strategies, probabilistic sensitivity analysis demonstrated that these image-read LBC strategies are associated with a predicted decreased age-standardised rate of cervical cancer mortality, compared to current practice, for most - but not all - sets of feasible assumptions (Table E 9, Table E 10).
- One of the most effective image-read LBC strategies involves call-and-recall screening, sending women an invitation on their 25th birthday ('fast uptake/initiation'), exit HPV testing, and HPV triage of low grade abnormalities with immediate referral of HPV positive women to colposcopy ('Option B').
 - For this strategy, in an unvaccinated population (Table E 11);
 - The estimated decrease in high grade abnormalities compared to current practice is 1% (95% CrI: from a 7% decrease to a 7% increase in probabilistic sensitivity analysis);
 - The estimated decrease in cervical cancer incidence compared to current practice is 13% (95% CrI: 2-17%); and
 - The estimated decrease in cervical cancer mortality compared to current practice is 12% (95% CrI: from a 18% decrease to a 1% increase in probabilistic sensitivity analysis).
 - In a vaccinated population (Table E 12);
 - The estimated decrease in high grade abnormalities compared to current practice is 2% (95% CrI: from a 9% decrease to a 7% increase in probabilistic sensitivity analysis);
 - The estimated decrease in cervical cancer incidence compared to current practice is 12% (95% CrI: 1-17%); and
 - The estimated decrease in cervical cancer mortality compared to current practice is 11% (95% CrI: from a 16% decrease to a 2% increase in probabilistic sensitivity analysis).

Primary HPV screening

- Under conservative test assumptions, all strategies involving 5-yearly primary HPV screening in women 25-64 years are predicted to be more effective than current practice, and the most effective of these strategies were associated with a greater improvement than was the case for either manually-read or image-read LBC - ranging from an 8 to 18% decrease in cervical cancer mortality for primary HPV screening compared to current practice (unvaccinated cohort, Table E 7) and from 8 to 17% (vaccinated cohort, Table E 8).

- Probabilistic sensitivity analysis demonstrated that these primary HPV strategies are associated with a predicted decreased age-standardised rate of cervical cancer mortality, compared to current practice, for all sets of feasible assumptions (Table E 9, Table E 10).
- One of the most effective strategies for primary HPV screening with cytology triage involved call-and-recall screening, sending women an invitation on their 25th birthday ('fast uptake/initiation'), exit HPV testing and immediate referral to colposcopy for women whose triage cytology result was p/dLSIL ('Option B').
 - For this strategy, in an unvaccinated population (Table E 11);
 - The estimated decrease in high grade abnormalities compared to current practice is 0% (i.e. no change predicted) (95% CrI: from a 3% decrease to a 6% increase in probabilistic sensitivity analysis);
 - The estimated decrease in cervical cancer incidence compared to current practice is 16% (95% CrI: 11-20%); and
 - The estimated decrease in cervical cancer mortality compared to current practice is 16% (95% CrI: 11-20%).
 - In a vaccinated population (Table E 12);
 - The estimated decrease in high grade abnormalities compared to current practice is 1% (95% CrI: from a 5% decrease to a 6% increase in probabilistic sensitivity analysis);
 - The estimated decrease in cervical cancer incidence compared to current practice is 15% (95% CrI: 10-18%); and
 - The estimated decrease in cervical cancer mortality compared to current practice is 16% (95% CrI: 11-19%).
- One of the most effective strategies for primary HPV and adjunctive cytology co-testing involved call-and-recall screening, sending women an invitation on their 25th birthday ('fast uptake/initiation'), exit HPV testing and immediate referral to colposcopy for women who are both HPV positive and cytology p/dLSIL ('Option B').
 - For this strategy, in an unvaccinated population (Table E 11);
 - The estimated increase in high grade abnormalities compared to current practice is 2% (95% CrI: from a 2% decrease to a 8% increase in probabilistic sensitivity analysis);
 - The estimated decrease in cervical cancer incidence compared to current practice is 17% (95% CrI: 12-22%); and
 - The estimated decrease in cervical cancer mortality compared to current practice is 17% (95% CrI: 12-22%).
 - In a vaccinated population (Table E 12);
 - The estimated increase in high grade abnormalities compared to current practice is 1% (95% CrI: from a 4% decrease to a 9% increase in probabilistic sensitivity analysis);
 - The estimated decrease in cervical cancer incidence compared to current practice is 17% (95% CrI: 11-20%); and
 - The estimated decrease in cervical cancer mortality compared to current practice is 17% (95% CrI: 11-20%).
- One of the most effective strategies, of any evaluated overall, involved primary HPV screening with partial genotyping for HPV 16 and 18. When this approach was implemented with call-and-recall screening, sending women an invitation on their 25th birthday ('fast uptake/initiation'), exit HPV testing and immediate referral to colposcopy for women positive for oncogenic HPV types other than HPV16/18 whose triage cytology result was p/dLSIL ('Option B'). The results were as follows:
 - For this strategy, in an unvaccinated population (Table E 11);

- The estimated increase in high grade abnormalities compared to current practice is 2% (95% CrI: from a 1% decrease to a 7% increase in probabilistic sensitivity analysis);
- The estimated decrease in cervical cancer incidence compared to current practice is 18% (95% CrI: 13-21%); and
- The estimated decrease in cervical cancer mortality compared to current practice is 18% (95% CrI: 14-21%).
- In a vaccinated population (Table E 12);
 - The estimated decrease in high grade abnormalities compared to current practice is 1% (95% CrI: from a 5% decrease to a 5% increase in probabilistic sensitivity analysis);
 - The estimated decrease in cervical cancer incidence compared to current practice is 16% (95% CrI: 11-18%); and
 - The estimated decrease in cervical cancer mortality compared to current practice is 16% (95% CrI: 11-19%).

Although primary HPV screening with partial genotyping was the most effective approach overall, the effectiveness of partial genotyping was approached by HPV and cytology co-testing and by HPV testing with cytology triage testing.

Supplementary analysis for QALYs

Supplementary analysis for QALYs showed that the QALY outcomes differed substantially from the main outcomes for LYS and cancer incidence and mortality, to the extent that in some cases the relative effectiveness compared to current practice was ‘reversed’ i.e. some strategies were associated with a *decrease* in effectiveness in terms of LYS (i.e. an increase in cervical cancer mortality or mortality shifted to a younger age), but with an *increase* in QALYs, compared to current practice). This was the case for example, for all strategies involving conventional cytology, and for some strategies for manually-read and image-read LBC. By contrast, in some cases, strategies that had an *increased* effectiveness compared to current practice in the main analysis, had *decreased* effectiveness in the QALY analysis; this was the case for most primary HPV strategies when QALY weight set 2 (but not QALY weight set 1) was used.

In general terms, effectiveness for conventional cytology and LBC strategies increased compared to current practice when comparing QALYs to life years outcomes for most strategies, and this was true when considering each of the QALY weight sets and for both unvaccinated and vaccinated populations. In broad terms this was due to the less frequent screening interval associated with all potential new strategies compared to current practice. However, the mechanisms by which the two QALY weight sets increased the calculated effectiveness differed. For QALY weight set 1 it appeared to be driven by the direct effect of reducing the number of screening tests, whereas for QALY weight set 2 it appeared to be driven by a decrease in the number of high grade abnormalities detected, which is generally a consequence of less frequent screening (although fewer high grade abnormalities is not necessarily associated with an increase in cancer since some abnormalities regress). These differences in QALY outcomes related to two major differences between the weight sets. The first of these is in terms of the health state (dis)utility weights for screen-normal health states (broadly equivalent to ‘the experience of being screened’, as distinct from the experience of a screen-positive outcome) for which QALY weight set 1 assigns a disutility but QALY weight set 2 does not. The second major difference is in the magnitude of the (dis)utility weight for high grade precancerous abnormalities, for which QALY weight set 2 assigned a far higher disutility. (It should be noted again that the methods to obtain QALY weight set 2 used the potentially less robust time-trade-off method in a study of US

University women whereas QALY weight set 1 was based on a study using standard gamble methods in an age-representative Australian population).

For cytology strategies, although both QALY weight sets generally acted to increase effectiveness, there were also important differences in relative effectiveness outcomes between the particular screening strategies when the two alternate QALY weight sets were used i.e. the relative ranking of strategy variants changed between the two weight sets.

For HPV strategies, strikingly disparate results were seen between the two QALY outcomes. For QALY weight set 1, all strategies were more effective than current practice, as was the case for the main analysis of LYS. However, for QALY weight set 2 most strategies became less effective than current practice. This appeared to be driven by the lack of disutility for the experience of being screened in QALY weight set 2 operating in conjunction with a third important difference between the two weight sets - the very high disutility assigned to a 'false positive' screening test result in QALY weight set 2. HPV testing is associated with a higher rate of test-positivity compared to cytology (which is why triaging of HPV positive women is an important aspect of the implementation of primary HPV screening); this resulted in accrual of QALY decrements for every HPV-positive result when this weight set was used.

Because of the uncertainties associated with the health state utilities, the lack of robustness of QALY findings to the use of alternate weight sets, and the consequent uncertainties in QALY outcomes, these findings were not used for the main effectiveness analysis.

However, this supplementary analysis demonstrated that when weights obtained from a study specifically designed to assess HPV screening in an appropriate population were used, the results for primary HPV screening supported the main LYS findings. More research into the appropriate health utility weights for cervical cancer screening (particularly for primary HPV screening), is required, and this research should focus on studies assessing health state utilities in an age-representative sample of the population.

Exploratory analysis of recommended age at stopping screening

Although the DAP specified that all new strategies assume that the recommended age of stopping screening was 64 years in accordance with the IARC recommendations, we performed extensive exploratory additional analyses to assess the impact of stopping screening at age 69 years vs. 64 years for all strategies. For these exploratory analyses, we assumed that screening behaviour if the recommended age remained at the current 69 years would be based on current attendance for women 65-69 years and over 70 years (since some women still attend screening over the recommended age). For the strategies that incorporate exit HPV testing, we assumed that this would be performed on women aged older than 69 years instead of those older than 64 years.

Retaining the recommended screening cessation age at 69 years was found to have a substantial impact on the predicted age-standardised rates (ASR) for incidence and mortality of all screening strategies as shown in Table E 13, such that there was between a 5-8% improvement in cancer mortality for each primary screening approach with the older recommended cessation age, in both unvaccinated and vaccinated populations. Table E 14 and Table E 15 show these outcomes when compared with current practice. The 'shift' in favour of effectiveness for all strategies is such that even the manually-read or image-read LBC strategies which were previously found to increase mortality were shifted to equivalent-or-better performance when compared to current practice.

Although a significant impact was predicted for age-standardised cancer incidence and mortality, changing the recommended screening cessation age from 64 to 69 years did not have a substantial impact on the predicted discounted life-years (detailed results not shown). This is because the discounting of life-years means that effects on cancer mortality in older age groups are not as pronounced as the effects in younger women when this measure is used.

Age-specific cancer incidence and mortality curves for selected strategies, assuming the recommended end age for screening is 69 rather than 64 years, are shown in Figure E 11 and Figure E 13 (unvaccinated cohorts) and Figure E 12 and Figure E 14 (vaccinated cohorts). All selected strategies (other than conventional cytology at IARC intervals) are predicted to have lower rates of cancer incidence and mortality in women aged 70+ when compared to current practice if the current recommended age of cessation remains at 69 years.

Cost outcomes and budget impact

The current annual cost of the NCSP in Australia is estimated to be ~\$215M (using 2013 costs and the projected 2015 population structure), excluding overheads. However, over the long term, the annual cost of the NCSP is expected to decline to ~\$184M, even if screening recommendations remain unchanged, due to the effect of HPV vaccination, which will act to reduce the underlying abnormality rates and thus reduce diagnostic referrals and their sequelae.

Many potential new screening strategies were found, in the base case, to be less costly than current screening practice in both unvaccinated and vaccinated cohorts, due in large part to the longer recommended screening interval for all of the potential new strategies considered, and also due in some part to narrower age range for screening in the new strategies. The most expensive strategies involved image-read LBC, for which some variants were considerably more expensive than current practice even at the longer IARC screening intervals, in both unvaccinated and vaccinated groups. Some of the co-testing strategies were also associated with costs greater than that of the current program, even at 5-yearly screening intervals, in unvaccinated (but not vaccinated) groups. Primary HPV screening with cytology triage or with genotyping yielded the least costly strategies overall for both unvaccinated and vaccinated groups.

Table E 7 summarises the budget impact, by primary screening approach, for all of the evaluated strategies in an unvaccinated population, and Table E 8 shows the findings for a vaccinated population. Table E 11 and Table E 12 also show the budget impact in selected candidate strategies in unvaccinated and vaccinated population, respectively. The budget increase or saving for each technology was as follows:

- For **conventional cytology** strategies, the total budget impact, in terms of the annual cost of the screening program (standardised to 2013 prices and the 2015 population structure), was a cost saving compared to current practice of between \$37.4M and \$66.8M in unvaccinated (Table E 7) and \$36.6M to \$65.8M in vaccinated (Table E 8) populations, respectively. The relative cost saving compared to current practice was 17-31% in unvaccinated and 20-36% in vaccinated populations, respectively.
- For **manually-read LBC** (under favourable test assumptions) the cost savings compared to current practice ranged from \$1.2 to \$50.2M in unvaccinated (Table E 7) and \$1.9M and \$47.8M in vaccinated (Table E 8) populations, respectively. The relative cost savings compared to current practice were highest in strategy variants without HPV triage for women with low-grade cytology (8-23% and 8-26% in unvaccinated and vaccinated population, respectively), and for HPV triage the strategy variants with immediate

colposcopy referral for women testing HPV triage positive were the most expensive (1-18% and 1-21% savings in unvaccinated and vaccinated population, respectively).

- For **automated image-read LBC** (under highly favourable test assumptions) the cost differential compared to current practice ranged from \$10.3M increase to a \$42.0M decrease, and from a \$8.5M increase to \$40.2M decrease, in unvaccinated (Table E 7) and vaccinated (Table E 8) populations, respectively. Strategy variants without HPV triage were predicted to be the most cost saving (3-20% and 3-22% in unvaccinated and vaccinated population, respectively). Strategy variants incorporating immediate colposcopy referral for women testing HPV triage positive were predicted to have between a 5% increase to a 14% decrease, and between a 5% increase to a 16% decrease, in unvaccinated and vaccinated populations, respectively.
- For **primary HPV strategies (conservative assumptions) with cytology triage of all oncogenic types**, the cost savings compared to current practice ranged from \$39.3M to \$58.5M, and from \$44.2M to \$60.6M, in unvaccinated (Table E 7) and vaccinated (Table E 8) populations, respectively. The relative cost saving compared to current practice was higher in strategy variants incorporating 12 months follow-up for women testing HPV triage positive (20-27% and 26-33% in unvaccinated and vaccinated populations, respectively) than those with immediate colposcopy referral (18-26% and 24-31% in unvaccinated and vaccinated populations, respectively).
- For **primary HPV strategies (conservative assumptions) with partial genotyping**, the cost savings compared to current practice ranged from \$33.8M to \$52.8M, and \$41.7M to \$58.5M, in unvaccinated (Table E 7) and vaccinated (Table E 8) populations, respectively. The relative cost saving compared to current practice was higher in strategy variants incorporating 12 months follow-up for women testing HPV triage positive (17-25% and 25-32% in unvaccinated and vaccinated population, respectively) than those with immediate colposcopy referral (16-23% and 23-30% in unvaccinated and vaccinated population, respectively).
- For **primary HPV strategies (conservative assumptions) with cytology co-testing**, the cost differential compared to current practice ranged from a \$2.3M increase to \$23.6M decrease, and \$1.4M decrease to \$24.7M decrease, in unvaccinated (Table E 7) and vaccinated (Table E 8) populations, respectively. The relative cost saving compared to current practice was higher in strategy variants incorporating 12 months follow-up for women testing HPV triage positive (1-11% decrease, and 3-13% decrease, in unvaccinated and vaccinated population, respectively) than those with immediate colposcopy referral (from a 10% decrease to a 1% increase, and 1-12% decrease, in unvaccinated and vaccinated population, respectively).

Overall, for strategies that resulted in cost savings, the relative cost savings compared with current practice were predicted to be slightly higher in vaccinated cohorts compared to unvaccinated cohorts, with these savings varying from 1-30% (saving of \$1.2-66.8M per annum) in unvaccinated cohorts and from 1-36% (saving of \$1.4-65.8M p.a.) in vaccinated cohorts.

Because most of the strategies were found to be cost saving, results for costs and effectiveness are generally presented in this report in a disaggregated form rather than as a cost per additional LYS (which is appropriate only if a new strategy increases costs compared to current practice).

Exploratory analysis of recommended age at stopping screening – impact on costs

As described above, we performed extensive exploratory additional analyses to assess the impact of stopping screening at age 69 years vs. 64 years for all strategies.

Table E 13 shows that there is an impact on total screening program cost when changing the recommended screening cessation age from 64 to 69 years of up to 3% and 4% increase in unvaccinated and vaccinated populations, respectively. Compared to current practice, the cost of the new strategies when the current recommended age of cessation was retained ranged from a 7% increase to a 30% decrease and 8% increase to a 34% decrease in unvaccinated (Table E 14) and vaccinated populations (Table E 15), respectively.

Health resource utilisation outcomes and relationship with health outcomes

If current practice for screening in the NCSP remains unchanged, and taking into account current levels of compliance with recommendations, the average lifetime number of cytology tests per woman in the population is predicted to be 15 for unvaccinated women (Table E 17); this will remain unchanged for women in vaccinated cohorts (Table E 18) (since the number of lifetime screening tests depends only on the recommendations for screening and compliance with those recommendations).

If current practice for screening in the NCSP remains unchanged, the total number of cytology tests, HPV tests, colposcopy examinations, histological evaluations and treatments for high grade CIN in Australia in 2015 is predicted to be 2.39 million, 54,700, 81,300, 40,000 and 21,485, respectively. However, over the long term, the number of these tests is expected to decline to 2.35 million, 31,100, 57,900, 28,200 and 13,203, respectively (adjusted to the 2015 population), even if screening recommendations remain unchanged, due to the effect of HPV vaccination. (Note that if current screening recommendations are retained the number of follow up cytology tests, diagnostic tests and treatments for CIN will be reduced due to the vaccination-induced falling rates of low and high grade abnormalities in the population).

Table E 17 summarises the range of health resource utilisation predictions, by primary screening approach, for all of the evaluated strategies in an unvaccinated population, and Table E 18 shows the findings for a vaccinated population. A number of the potential new strategies are predicted to increase the number of colposcopies in both unvaccinated and vaccinated cohorts, compared to current screening practice. However, for several key strategies this *increase* in colposcopies was actually associated with a concomitant *decrease* in biopsies and treatments for CIN, as well as a *decrease* in invasive cancer rates. This can occur when a new strategy has a higher rate of screen-and-triage positives, but these include a greater number of women at risk compared to current practice; colposcopy thus acts to rule out high grade disease in the larger pool of women referred, with treatment limited to the remaining at-risk group.

Resource utilisation outcomes

For each primary screening approach, the main resource utilisation outcomes were as follows:

- Retention of conventional cytology in the context of IARC intervals** would be associated with a reduction in the average lifetime number of screening or follow-up tests per woman in the population by 4-6 tests or 25% to 41% (unvaccinated population) and by 4-6 tests or 25% to 42% (vaccinated cohorts), compared to current practice. The total number of cytology tests, colposcopy examinations, histological evaluations and treatments for precancer per year in Australia would decrease by 23-41%, 12-22%, 12-22% and 13-23%, respectively (unvaccinated) and by 24-42%, 13-23%, 12-23% and 16-28%, respectively (vaccinated), compared to current practice. The number of HPV tests compared to current practice (where this is used for test-of-cure only) increases for strategies involving exit HPV testing (by up to 81% and 149% in unvaccinated and vaccinated populations, respectively), but decreases otherwise (up to a 21% decrease in unvaccinated populations, and a 24% decrease in vaccinated populations).

- Under *favourable* test assumptions, strategies involving use of **manually-read LBC** at IARC intervals would be associated with a decrease in the average lifetime number of screening or follow-up tests per woman in the population by 4-6 tests or by 24% to 41% (unvaccinated cohorts) and by 4-6 tests or 24% to 41% (vaccinated cohorts), compared to current practice. The total number of cytology tests and treatment for high grade CIN compared to current practice would decrease by 22-41% and 4-22%, respectively (unvaccinated) and by 22-41% and 6-27%, respectively (vaccinated), compared to current practice. Changes in the total number of HPV tests, colposcopy examinations and histological evaluations would range from a 538% increase to a 20% decrease, from a 20% increase to a 17% decrease and from a 24% increase to a 19% decrease, respectively (unvaccinated) and from a 866% increase to a 24% decrease, from a 21% increase to a 20% decrease and from a 25% increase to a 20% decrease, respectively (vaccinated), compared to current practice.
- Under *highly favourable* test assumptions, strategies involving **image-read LBC** would be associated with a decrease in the average lifetime number of screening or follow-up tests per woman in the population by 4-6 tests, by 24 to 41% (unvaccinated cohorts) and by 24% to 41% (vaccinated cohorts), compared to current practice. The total number of cytology tests and treatment for high grade CIN compared to current practice would decrease by 21-41% and 4-22%, respectively (unvaccinated) and by 22-41% and 7-27%, respectively (vaccinated), compared to current practice. Changes in the total number of HPV tests, colposcopy examinations and histological evaluations would range from a 561% increase to a 16% decrease, from a 23% increase to a 17% decrease and from a 29% increase to a 18% decrease, respectively (unvaccinated) and from a 895% increase to a 20% decrease, from a 22% increase to a 22% decrease and from a 28% increase to a 21% decrease, respectively (vaccinated), compared to current practice.
- Under *conservative* HPV test assumptions, strategies involving **primary HPV screening with cytology triage for all oncogenic types** would result in a decrease in the average lifetime number of screening or follow up tests per woman (calculated as the total number of either cytology or HPV tests for each strategy) in the population, by 7-8 tests or 44% to 50% (unvaccinated cohorts) and by 7-8 tests or 46 to 51% (vaccinated cohorts), compared to current practice. The total number of cytology tests and treatments for high grade CIN per year in Australia would reduce by 82-85% and 9-21%, respectively (unvaccinated) and 86-88% and 15-29%, respectively (vaccinated), compared to current practice. The total number of HPV tests would increase by 2061-2250% and 3591-3916% in unvaccinated and vaccinated population, respectively. Changes in the total number of colposcopy examinations and histological evaluations would range from a 20% increase to a 7% decrease and from a 28% increase to a 4% decrease, respectively (unvaccinated) and from a 13% increase to a 16% decrease and from a 22% increase to a 11% decrease (vaccinated), compared to current practice.
- Under *conservative* HPV test assumptions, strategies involving **primary HPV screening with cytology co-testing** would result in a decrease in the average lifetime number of screening or follow up tests per woman (calculated as the total number of either cytology or HPV tests for each strategy) in the population, by 44% to 48% (unvaccinated cohorts) and by 45 to 50% (vaccinated cohorts), compared to current practice. The total number of cytology tests and treatment for high grade CIN per year in Australia would decrease by 43-38% and 4-15%, respectively (unvaccinated) and by 45-50% and 8-21%, respectively (vaccinated), compared to current practice. The total number of HPV tests, colposcopy examinations and histological evaluation would increase by 2109-2300%, 6-33% and 9-40%, respectively (unvaccinated) and 3674-4001%, 1-29% and 5-37%, respectively (vaccinated), compared to current practice.
- Under *conservative* HPV test assumptions, strategies involving **primary HPV screening with partial genotyping** would result in a decrease in the average lifetime number of screening or follow up tests per woman (calculated as the total number of either cytology or HPV tests for

each strategy) in the population, by 45 to 49% (unvaccinated cohorts) and by 46 to 51% (vaccinated cohorts), compared to current practice. The total number of cytology tests and treatment for high grade CIN per year in Australia would decrease by 85-87% and 8-17%, respectively (unvaccinated) and by 89-91% and 16-29%, respectively (vaccinated), compared to current practice. The total number of HPV tests will increase by 2066-2255% and 3583-3909% in unvaccinated and vaccinated population, respectively. In an unvaccinated population, the total number of colposcopy examinations and histological evaluations would increase by 12-37% and 17-46%, respectively, compared to current practice. In a vaccinated population, the total number of colposcopy examinations and histological evaluation would range from a 13% increase to a 16% decrease and from a 22% increase to an 11% decrease, respectively (the decreases in the total number of colposcopy examinations in vaccinated populations were mainly for strategy variants incorporating 12 month follow-up for women testing HPV triage positive, as opposed to immediate colposcopy referral).

Colposcopies, treatments and cancer mortality

The relationship between the change in numbers of colposcopies, numbers of treatments, and cancer mortality for the selected key strategies (which are amongst the most effective for each primary screening approach) is shown in Table E 19. This shows that for the manually-read LBC, image-read LBC and primary HPV strategies, there is a predicted decrease in cancer mortality in the context of both a predicted increase in the number of colposcopies and a decrease in the number of treatments. In the unvaccinated population, the decrease in treatment rate is similar for all LBC and HPV strategies (except for co-testing), but HPV testing with genotyping and co-testing are associated with a greater relative increase in colposcopies. By contrast, in the vaccinated population the percentage increase in the number of colposcopies is similar for all LBC and primary HPV strategies (except co-testing) but primary HPV screening with either cytology triage or genotyping are associated with the greatest reductions in the number of treatments.

Age-specific treatment rates in selected strategies were investigated and these are shown in Table E 20 and Table E 21. For women aged 15-29 years, some strategies will have fewer treatments in compared with current practice, and some will have more treatments. In vaccinated women, however, all strategies are predicted to have fewer treatments than current practice in this age-group. Treatment numbers in the 30-64 year age-group vary - for the selected key strategies, 493-1145 fewer treatments are predicted when compared with current practice in unvaccinated cohorts (483-1215 in vaccinated cohorts). However, other strategies are predicted to have a *higher* number of treatments in this age-group compared with current practice, although this occurred in strategies that have high rates of early re-screening (specifically, IARC screening under Reminder R2). Treatment numbers in women aged 64+ years were predicted to be consistently lower than what is predicted for current practice, varying from 545 to 659 fewer treatments than current practice (511-584 less in vaccinated cohorts). This is likely due to the screening cessation age in all other strategies being 64 years, whereas current practice has a recommended cessation age of 69 years.

Changes in colposcopy referrals vs. changes in mortality

The trade-off between the increase in the overall effectiveness of a strategy and the increased number of diagnostic evaluations was also represented as the percentage improvement in cervical cancer mortality compared to the percentage increase in colposcopies for all strategies in the evaluation and is depicted in Figure E 15. This shows that the relative 'efficiency' of the various strategies in terms of the relationship between decrease in cervical cancer mortality and increase in number of colposcopies remained similar for most LBC and primary HPV strategies when unvaccinated populations and vaccinated populations were compared. However, the notable

exception was primary HPV screening with partial genotyping, which became more 'efficient' in the vaccinated population because as HPV 16/18 infections decreased, the number of colposcopy referrals dramatically declined (since HPV 16/18 positive women are referred directly to colposcopy in this strategy) but the relative mortality benefits were maintained.

Proportion of treatments for CIN2 vs. CIN3

Model predictions of the proportion of treatments for high grade abnormalities (CIN2/3) that are for CIN2 in current practice (40%) compares well with available data from Australia (AIHW 2013), New Zealand (Smith *et al.* 2011a, Smith *et al.* 2011b, Smith *et al.* 2011c, Smith *et al.* 2012b, Smith *et al.* 2012a), and England (Health and Social Care Information Centre Screening and Immunisations 2012).

The proportion of high grade treatments which were for CIN2 decreased for many of the new strategies compared to current practice. A summary of the results are shown in Table E 22 (unvaccinated cohorts) and Table E 23 (cohorts offered vaccination at age 12). All strategies that were predicted to be more effective than current practice were also predicted to have fewer treatments than current practice. For these strategies, the number of CIN3 treatments was higher than current practice, however the number of CIN2 treatments was substantially lower than current practice, and this reduction drove the overall reduction in treatments compared to current practice. Whereas CIN3 is now thought of as being a 'precancer', CIN2 is a more heterogeneous entity, representing a mix of precancer but also of productive HPV infections which do not generally have substantial potential to progress (Schiffman *et al.* 2007). Therefore, the shift towards treating proportionally more CIN3 represents a move towards more targeted treatments for precancer. Thus this is likely to represent a more optimal delivery of treatment in the new strategies, particularly given that for several key selected strategies for both LBC and primary HPV screening the shift towards CIN3 treatment occurs in context of both the overall treatment rate being lower than in current practice and the resulting invasive cancer incidence and mortality rates being reduced compared to current practice.

Effect of screening behaviour and compliance assumptions and secondary evaluations

The various screening behaviour and compliance assumptions, and other variants relating to the secondary questions, were found to have broadly consistent effects across all primary screening approaches and technologies. Furthermore, the effects of these changes in terms of their impact on overall effectiveness were found to be approximately 'additive', and thus the overall effectiveness of a particular screening approach can be maximised by incorporating most or all of the most effective secondary options.

In general terms, compliance with the recommended interval, compliance with age at initiation and the change to age at cessation had a substantial effect on outcomes. HPV triage testing for LBC strategies resulted in a substantial increase in effectiveness. HPV exit testing, as implemented in this evaluation, only slightly increased effectiveness.

Screening initiation

Currently, the recommended age of starting screening is 18-20 years in Australia, although in practice a small number of girls initiate screening before the age of 18 years; this behaviour was characterised via analysis of VCCR data and incorporated into the calibrated model of current practice. However, all potential new screening strategies involved initiating screening at age 25 years.

Because it is unlikely that there would be perfect population compliance to this recommendation, two sets of assumptions were used to model screening initiation after the change to the recommended age of starting screening, as follows:

- (1) A 'slow uptake' scenario assumed that the recommended age was changed but that in practice many women initiated screening between 25-29 years. This scenario assumed that the proportion of women having their first screening test at the age of 25 years was equivalent to the proportion of women who initiate screening at the age of 18 years in current practice.
- (2) A 'fast uptake' scenario assumed that women who currently have had their first screening test before and at the age of 25 years will in the future initially screen at the age of 25 years. This scenario assumed that the proportion initiating screening between 25-29 years would be the same as for current practice.

Both screening initiation patterns assumed that no women will initiate cervical screening before age of 25 years (a conservative assumption with respect to effectiveness) and that the overall proportion of women ever-screened by the age of 30 remains the same as in current practice.

In general terms, for all screening technologies, the fast uptake scenario was slightly more effective and somewhat more costly than the slow uptake scenario (Table E 24). This effectiveness finding is consistent with other evidence supporting the effectiveness of cervical screening between ages 25-29 years, and the cost increases relate to the increased number of screening tests, diagnostic evaluations and treatments in women in the age group from 25-29 years. The improvements for each primary screening technology were as follows:

- **For conventional cytology:**
 - *In an unvaccinated population*, when the outcomes for strategies with fast uptake scenarios were compared with the equivalent strategy with the slow uptake scenario, there was a 2% improvement in cervical cancer incidence and cervical cancer mortality. This was associated with a 4% relative increase in screening program cost.
 - *In a vaccinated population*, when the outcomes for strategies with fast uptake scenarios were compared with the equivalent strategy with the slow uptake scenario, there was a 1-2% improvement in cervical cancer incidence and a 1% improvement in cervical cancer mortality. This was associated with a 5% relative increase in screening program cost.
- **For manually-read LBC:**
 - *In an unvaccinated population*, when the outcomes for strategies with fast uptake scenarios were compared with the equivalent strategy with the slow uptake scenario, there was between a 2-3% relative improvement in cervical cancer incidence and a 2% improvement in cervical cancer mortality. This was associated with a 4-5% relative increase in screening program cost.
 - *In a vaccinated population*, when the outcomes for strategies with fast uptake scenarios were compared with the equivalent strategy with the slow uptake scenario, there was between a 1-2% relative improvement in cervical cancer incidence and a 1-2% improvement in cervical cancer mortality. This was associated with a 4-5% relative increase in screening program cost.
- **For image-read LBC:**
 - *In an unvaccinated population*, when the outcomes for strategies with fast uptake scenarios were compared with the equivalent strategy with the slow uptake scenario, there was between a 2-3% relative improvement in cervical cancer incidence and a

- 2% improvement in cervical cancer mortality. This was associated with a 4-5% relative increase in screening program cost.
- *In a vaccinated population*, when the outcomes for strategies with fast uptake scenarios were compared with the equivalent strategy with the slow uptake scenario, there was between a 1-2% relative improvement in cervical cancer incidence and a 1-2% improvement in cervical cancer mortality. This was associated with a 4-5% relative increase in screening program cost.
 - **For primary HPV screening with cytology triage for all oncogenic types:**
 - *In an unvaccinated population*, when the outcomes for strategies with fast uptake scenarios were compared with the equivalent strategy with the slow uptake scenario, there was between a 2-3% relative improvement in cervical cancer incidence and a 2% improvement in cervical cancer mortality. This was associated with a 5% relative increase in screening program cost.
 - *In a vaccinated population*, when the outcomes for strategies with fast uptake scenarios were compared with the equivalent strategy with the slow uptake scenario, there was 2% relative improvement in cervical cancer incidence and a 1% improvement in cervical cancer mortality. This was associated with a 5% relative increase in screening program cost.
 - **For primary HPV screening with cytology co-testing;**
 - *In an unvaccinated population*, when the outcomes for strategies with fast uptake scenarios were compared with the equivalent strategy with the slow uptake scenario, there was between a 2-3% relative improvement in cervical cancer incidence and a 2% improvement in cervical cancer mortality. This was associated with a 5% relative increase in screening program cost.
 - *In a vaccinated population*, when the outcomes for strategies with fast uptake scenarios were compared with the equivalent strategy with the slow uptake scenario, there was 2% relative improvement in cervical cancer incidence and a 1-2% improvement in cervical cancer mortality. This was associated with a 5% relative increase in screening program cost.
 - **For primary HPV screening with partial genotyping:**
 - *In an unvaccinated population*, when the outcomes for strategies with fast uptake scenarios were compared with the equivalent strategy with the slow uptake scenario, there was between a 2% relative improvement in cervical cancer incidence and a 2% improvement in cervical cancer mortality. This was associated with a 5-6% relative increase in screening program cost.
 - *In a vaccinated population*, when the outcomes for strategies with fast uptake scenarios were compared with the equivalent strategy with the slow uptake scenario, there was between a 2% relative improvement in cervical cancer incidence and a 1-2% improvement in cervical cancer mortality. This was associated with a 5% relative increase in screening program cost.

Therefore, in general terms, the use of a 'fast uptake' strategy for initiating screening in young women, is predicted to be associated with a ~1-3% increase in effectiveness, and a 4-6% increase in costs, irrespective of the particular primary screening approach and technology used.

Effect of varying assumptions for reminder-based and call-and-recall screening

Currently screening is recommended every 2 years, and reminders are sent if women have not attended for a routine screening test by 27 months. Screening behaviour in the context of current practice was characterised via analysis of VCCR data and incorporated into the calibrated model of current practice. However, all potential new screening strategies involved lengthening the screening interval, to at least three and up to five years. Additionally, the program may

remain a reminder-based one (as in current practice), or may potentially change to a system of call-and-recall, where women are proactively sent invitations prior to the re-screening due date. These changes required assumptions to be made about future screening behaviour, in the context of a longer screening interval, and potentially a different program design. While compliance with longer intervals and in the context of a different program design is uncertain, it is highly unlikely to be perfect (based on attendance observed for the current program), therefore for each program design (reminder-based and call-and-recall), we considered different sets of assumptions which were also explored further in sensitivity analysis. For a reminder-based program, the following sets of assumptions were considered for potential new screening strategies involving conventional cytology or LBC (either manually-read or image-read):

- (1) The 'Reminder 1 (R1)' scenario assumed that on-time screening is unchanged compared to current practice, and thus that the overall attendance achieved by 3 or 5 years (depending on the recommended interval) is the same as is currently observed at 2 years (approximately 52% overall, but with variation by age). Early and late re-screening rates were also assumed to be similar to what is currently observed.
- (2) The 'Reminder 2 (R2)' scenario assumed that more women would attend by 3 (or 5) years than currently attend by 2 years (70% overall attend within the recommended interval, but with variation by age), but that this would be accompanied by more early re-screening (42% overall attend more than a year earlier than recommended, but with variation by age).

For a call-and-recall based program, the following sets of assumptions were considered:

- (3) A 'Call-and-Recall 1 (CR or CR1)' scenario assumed high compliance with the recommended screening interval, with approximately 80% of those aged 25-49 years and 70% of those aged 50 years or older attending by the recommended interval (but with variations by age). Early re-screening was assumed to be very limited (<10%)
- (4) A 'Call-and-Recall 2 (CR2)' scenario which assumed less on-time screening (62-66% within five years, with variation by age) and also more early re-screening (approximately 30-33% overall screened a year or more earlier than recommended, but with variation by age). This scenario was only used for the primary HPV testing scenarios.

Evaluations of screening at IARC-recommended intervals considered both reminder-based call-and-recall options. However, for primary HPV testing, where a longer interval was recommended for all ages, a call-and-recall system was assumed. Thus cytology-based scenarios considered two possible 'reminder' scenarios for compliance and one call-and-recall scenario ('CR1'), whereas strategies involving HPV as the primary screening test considered two call-and-recall scenarios.

In general terms, for all cytology test technologies, the 'Reminder 1' scenario was the least effective and least costly; while the 'Reminder 2' scenario was the most effective and also the most costly. Call-and-recall had intermediate effectiveness and costs compared to the two reminder-based scenarios, however the predicted increase in costs between the call-and-recall scenario and 'Reminder 2' was generally much greater than the predicted increase in effectiveness (Table E 25). In the primary HPV scenarios, 'Call-and-Recall 2' was slightly more costly and slightly more effective than 'Call-and-Recall 1' (Table E 26).

- **For conventional cytology:**
 - *In an unvaccinated population*, when the outcomes for strategies with call-and-recall scenarios were compared with the equivalent strategy with the 'Reminder 1' uptake scenario, there was an approximately 3% improvement in cervical cancer incidence

and a 3% improvement in cervical cancer mortality. This was associated with a 4% relative increase in screening program cost. The 'Reminder 2' scenario (with higher on-time and early re-screening) was associated with both higher costs (9%) and effectiveness (2% improvement in incidence; 3-4% improvement in mortality) relative to the call-and-recall scenario.

- *In a vaccinated population*, when call-and-recall scenarios were compared with the equivalent strategy with the 'Reminder 1' uptake scenario, there was a 3% improvement in cervical cancer incidence and a 3-4% improvement in cervical cancer mortality. This was associated with a 5% relative increase in screening program cost. The 'Reminder 2' scenario was more effective than call-and-recall, and was associated with a 2% improvement in incidence and a 3-4% improvement in mortality compared to the call-and-recall scenario, but also higher costs (12%) than the call-and-recall scenario.
- **For LBC (manual and image-read):**
 - *In an unvaccinated population*, when the outcomes for strategies with call-and-recall scenarios were compared with the equivalent strategy with the 'Reminder 1' uptake scenario, there was an approximately 3% improvement in cervical cancer incidence and a 3-4% improvement in cervical cancer mortality. This was associated with a 4-5% relative increase in screening program cost. The 'Reminder 2' scenario had higher on-time and early re-screening, and so was associated with both higher costs (10-11%) and effectiveness (2-3% improvement in incidence; 3-4% improvement in mortality) relative to the call-and-recall scenario.
 - *In a vaccinated population*, when call-and-recall scenarios were compared with the equivalent strategy with the 'Reminder 1' uptake scenario, there was a 3-4% improvement in cervical cancer incidence and a 3-4% improvement in cervical cancer mortality. This was associated with a 5-6% relative increase in screening program cost. The 'Reminder 2' scenario was more effective than call-and-recall, and was associated with a 2-3% improvement in incidence and a 3-4% improvement in mortality compared to the call-and-recall scenario, but also higher costs (12-13%) than the call-and-recall scenario.
- **For primary HPV screening (including with and without partial genotyping, and with and without cytology co-testing):**
 - *In an unvaccinated population*, when the outcomes for strategies with 'Call-and-Recall 1' scenarios were compared with the equivalent strategy with the 'Call-and-Recall 2' scenario, there was consistently a 1% relative improvement in cervical cancer incidence and a 1% improvement in cervical cancer mortality. This was also associated with a 2-3% relative increase in screening program cost.
 - *In a vaccinated population*, when the outcomes for strategies with 'Call-and-Recall 1' scenarios were compared with the equivalent strategy with the 'Call-and-Recall 2' scenario, there was consistently a 1% relative improvement in cervical cancer incidence and a 1% improvement in cervical cancer mortality. This was also associated with a 3% relative increase in screening program cost.

Therefore, in general terms, the use of a call-and-recall strategy results in greater effectiveness than a reminder-based system where on-time screening remains similar to what is achieved for the current 2-yearly program. For cytology-based programs (irrespective of the particular technology used), call-and-recall strategies can improve cancer incidence by 1-3% and cancer mortality by 1-4%, but also increases costs by 4-6% (considering both vaccinated and unvaccinated populations).

A reminder-based system which can achieve higher on-time screening than current practice, but at the expense of more early re-screening, is predicted to be associated with a ~2-4% increase in effectiveness compared to what was assumed for call-and-recall. There is also an increase in costs compared to what was assumed for call-and-recall, and this increase in costs is greater for cohorts offered vaccination (12-13%) than for unvaccinated populations (9-11%).

Triage testing (HPV triage for LBC strategies; cytology triage for HPV strategies)

Two types of triage testing were assessed, depending on the primary screening test. In LBC-based strategies, HPV triage testing of low grade cytology was assessed. In HPV-based scenarios, cytology triage was assessed. Cytology triage was either used for women positive for any oncogenic HPV type, or for women positive for an oncogenic type other than HPV16 or 18 in the partial genotyping scenario (since women positive for HPV16/18 were referred directly to colposcopy in this scenario). In all cases, alternative scenarios for management of triage test positives were considered. The first scenario (Option A) assumed women who tested positive on their triage test were followed up with repeat testing in 12 months ('delayed follow-up'), while the second scenario (Option B) assumed that triage-test-positive women were referred immediately for colposcopy ('immediate follow-up').

HPV triage of low grade cytology

Currently, women with an initial low-grade cytological abnormality are generally managed by repeat cytology in 12 months according to the NHMRC 2006 Guidelines (although there are some exceptions, when women without a recent negative smear are followed up sooner). The LBC strategies considered involved either retaining current management of low-grade cytological abnormalities, or HPV triage of low-grade cytological abnormalities.

In general terms, for both manual and automated LBC, HPV triage (either immediate or delayed follow-up) was more effective and more costly than continuing current management of low grade cytology; and HPV triage with immediate follow-up was more costly but also more effective than delayed follow-up (Table E 27).

- **For manually-read LBC:**
 - *In an unvaccinated population*, when the outcomes for strategies with HPV triage were compared to the equivalent strategy without HPV triage, there was between a 3-11% relative improvement in cervical cancer incidence and a 3-10% improvement in cervical cancer mortality. This was associated with a 4-9% relative increase in screening program costs. When compared to the outcomes for strategies with delayed follow-up of triage test positives, strategies with immediate follow-up of triage positives was associated with a 7% improvement in cervical cancer incidence, a 6-7% improvement in cervical cancer mortality, and a 2-3% relative increase in screening program cost.
 - *In a vaccinated population*, when the outcomes for strategies with HPV triage were compared to the equivalent strategy without HPV triage, there was between a 2-10% relative improvement in cervical cancer incidence and a 3-9% improvement in cervical cancer mortality. This was associated with a 4-8% relative increase in screening program costs. When compared to the outcomes for strategies with delayed follow-up of triage test positives, strategies with immediate follow-up of triage positives was associated with a 6-7% improvement in cervical cancer incidence, a 6% improvement in cervical cancer mortality, and a 2-3% relative increase in screening program cost.
- **For image-read LBC:**

- *In an unvaccinated population*, when the outcomes for strategies with HPV triage were compared with the equivalent strategy without HPV triage, there was a 3-10% relative improvement in cervical cancer incidence and a 3-10% improvement in cervical cancer mortality. This was associated with a 4-9% relative increase in screening program costs. When compared to the outcomes for strategies with delayed follow-up of triage test positives, strategies with immediate follow-up of triage positives was associated with a 6-7% improvement in cervical cancer incidence, a 6% improvement in cervical cancer mortality, and a 3% relative increase in screening program costs.
- *In a vaccinated population*, when the outcomes for strategies with HPV triage were compared with the equivalent strategy without HPV triage, there was between a 2-9% relative improvement in cervical cancer incidence and a 3-9% improvement in cervical cancer mortality. This was associated with a 3-9% relative increase in screening program costs. When compared to the outcomes for strategies with delayed follow-up of triage test positives, strategies with immediate follow-up of triage positives was associated with a 6% improvement in cervical cancer incidence, a 5-6% improvement in cervical cancer mortality, and a 3% relative increase in screening program costs.

Therefore, the addition of HPV triage to LBC screening strategies is predicted to result in substantial improvements to cancer incidence and mortality, but also increases in program costs, compared to cytological follow-up both in unvaccinated and vaccinated groups. In an unvaccinated population, these would correspond to a 3-11% improvement in cervical cancer incidence, a 3-10% improvement in cervical cancer mortality, and a 4-9% relative increase in screening program costs. In a population offered vaccination as pre-adolescents these would correspond to a 2-10% improvement in cervical cancer incidence, a 3-9% improvement in cervical cancer mortality, and a 4-9% relative increase in screening program cost. Compared to strategies with delayed follow-up of triage test positives, strategies involving immediate follow-up improve incidence by 6-7%, improve mortality by 5-7%, but cost approximately 2-3% more. Frequently the inclusion of HPV triage was the key factor in whether the evaluated strategy was more or less effective than current practice.

Cytology triage of primary HPV test positives

The primary HPV screening strategies considered involved cytology triage of HPV-test positive women, with two follow-up options as in LBC scenarios, i.e. delayed follow-up (Option A) or immediate follow-up (Option B).

- **For primary HPV screening:**
 - *In an unvaccinated population*, when the outcomes for strategies with immediate follow-up of triage test positives were compared with the equivalent strategy with delayed follow-up, there was a 3-10% relative improvement in cervical cancer incidence and a 1-5% improvement in cervical cancer mortality. This was associated with a 2-3% relative increase in screening program costs.
 - In a vaccinated population, when the outcomes for strategies with immediate follow-up of triage test positives were compared with the equivalent strategy with delayed follow-up, there was a 3-5% relative improvement in cervical cancer incidence and a 3-5% improvement in cervical cancer mortality. This was associated with a 2-3% relative increase in screening program costs.

Exit HPV testing

The underlying basis of the idea of HPV exit testing is that it can be used to identify a group of older women who are at extremely low risk of cervical precancerous disease or of developing

invasive cervical cancer, because HPV testing has a very high negative predictive value. After identification of this group, such women can theoretically be safely 'discharged' from screening, thus minimising the attendance requirements in this group and also potentially reducing screening costs overall. Use of HPV exit testing is not, however, expected to substantially increase overall effectiveness, because a substantial proportion of the invasive cancers that arise in older women are likely to come from a group that are underscreened or unscreened, and thus are less likely to present for exit testing in their sixties, and this group remain at the same risk of developing invasive cervical cancer.

The use of HPV exit testing is predicted to reduce incidence and mortality by 1% (unvaccinated cohorts) and 1-2% (vaccinated cohorts) and increase total program cost by 0-1% for both unvaccinated and vaccinated cohorts (see Table E 28). The implementation of exit HPV does not impact health and cost outcomes as significantly as other scenario alterations (such as fast versus slow uptake, or routine screening compliance rates).

After extensive discussion with the RSC, it was determined that it would be important to offer ongoing screening to women who were HPV negative on 'exit' testing who continued to seek screening. Therefore, it was assumed that screening behaviour after 'exit' testing would be largely unchanged compared to a scenario where there was no 'exit' test (although it should be noted that behaviour in the 65-59 year old age group in all scenarios generally reflects lower uptake compared to current practice because of the change to the age of stopping screening from 69 to 65 years). It was therefore concluded that the incremental costs of HPV exit testing are highly dependent on the assumptions for post-exit testing behaviour. If women continue to seek screening after HPV exit testing, the cost savings associated with this option will not be substantial.

A complication in the current evaluation was the concomitant change to the recommended age of ceasing screening, which had an important overall impact on effectiveness (as previously discussed). Therefore whether or not exit testing was included as an 'add-on', there was an overall decrease in effectiveness compared to ceasing screening at 69 years. If the age of recommended cessation remained at 69 years, however, then exit testing could potentially be considered as a further 'add-on' to discharge women after that age.

Sensitivity analysis

Overview of results

In general terms, when compared to current practice, the one-way sensitivity analysis demonstrated that the relative effectiveness (relative change in life-years) of the new strategies were most sensitive to discount rate assumptions, the compliance assumptions for screening interval, compliance assumptions for follow-up management, and test characteristic assumptions for screening and triage tests. The findings were also sensitive to the assumptions around CIN natural history, and for some strategies were somewhat sensitive to assumptions around whether any women would initiate screening before the recommended age of starting at 25 years (in the base case we assumed no women would initiate screening before 25 years). The results were slightly sensitive to vaccination coverage assumptions but relatively insensitive to the 'unmasking' effect for other oncogenic HPV types for vaccinated scenarios. The relative effectiveness findings were comparatively insensitive to the specific assumptions for colposcopy accuracy and colposcopy attendance.

For manually-read and image-read LBC the effectiveness of strategies without HPV triage were highly sensitive to the cytology test characteristics assumptions, and for LBC strategies with HPV triage the effectiveness was moderately sensitive to LBC and relatively insensitive to HPV

test characteristics. For primary HPV screening the effectiveness of the strategies were moderately sensitive to cytology test characteristic assumptions and relatively insensitive to HPV test characteristics. Strategies involving primary HPV testing with partial genotyping were also found to be modestly sensitive to the accuracy of genotyping and assumptions related to the proportion of women who tested HPV 16/18 positive and then had a cytology test at colposcopy to inform in subsequent management. The effectiveness of both LBC and HPV strategies were more sensitive to the test characteristics of image-read LBC than for manually-read LBC, reflecting the greater uncertainty around the test accuracy of image-read LBC.

Results of the probabilistic sensitivity analysis demonstrated that for conventional cytology at IARC intervals, all strategies remain less effective (fewer life-years, more cervical cancer cases and cervical cancer deaths) and less costly than current practice under the full range of feasible model assumptions, in both unvaccinated and vaccinated populations. All such strategies were also predicted to be associated with fewer histologically-confirmed CIN2/3 abnormalities than for current practice, in both unvaccinated and vaccinated populations.

Results of the probabilistic sensitivity analysis for manually-read and image read LBC strategies show that the particular strategies examined which were more effective than current practice in the base case remained more effective in probability sensitivity analysis across a range of parameter set scenarios, in both unvaccinated and vaccinated populations (although there is a 'spread' of results with respect to the incremental increase in effectiveness). For these strategies, there are a large number of scenarios which result in an increase in costs compared to current practice (even if the costs were not increased in the base case). The findings related to health outcomes vary between strategies. For manually-read LBC, the particular strategies which were predicted to have fewer cervical cancer cases and cervical cancer deaths than current practice in the base case also have fewer cases and deaths in probabilistic sensitivity analysis. However, a number of these scenarios were predicted to have more cervical cancer cases and deaths than current practice even if cervical cancer cases and deaths were predicted to be less than current practice in the base case.

Results of the probabilistic sensitivity analysis for primary HPV strategies shows that all primary HPV strategies remain more effective than current practice in probability sensitivity analysis, in both unvaccinated and vaccinated populations (although there is a 'spread' of results with respect to the incremental increase in effectiveness). However, there are a number of strategies which result in an increase in costs compared to current practice (even if the costs were not increased in the base case). The particular strategies which were associated with fewer histologically-confirmed CIN2/3 abnormalities than for current practice in the base case were associated with fewer histologically-confirmed CIN2/3 abnormalities in probabilistic sensitivity analysis across a range of parameter set scenarios.

Cost outputs

Cost outputs were mainly sensitive to the discount rate, the compliance assumptions for the recommended screening interval, and compliance to follow-up and initiation of screening (because lower compliance to these recommendations results in more tests delivered at increased cost), test costs, test characteristics of the screening and triage tests, and natural history assumptions, but were comparatively insensitive to other model assumptions.

The effect of not taking a cytology at colposcopy in women who are referred without an accompanying cytology

For the primary analysis, we made the assumption that for primary HPV strategies, cytology would always be taken at colposcopy if women were referred to colposcopy on the basis of a

positive HPV test only, to inform subsequent management of these women. For example, this may occur in women who test positive for HPV 16/18 in the HPV genotyping strategy, and are referred immediately to colposcopy without cytology triage. In a sensitivity analysis, we explored the effect on health outcomes when women referred to colposcopy did not have a cytology taken to inform subsequent management. In particular, we explored the effects on three particular genotyping strategies in sensitivity analysis. For the sensitivity analysis, we assumed that management of women who attend colposcopy without an accompanying cytology would be equivalent to that for women referred with a low-grade (or less severe) cytology result, with or without an accompanying HPV test. The likelihood that a biopsy would be taken was unaffected during this sensitivity analysis, and women with histologically-confirmed CIN2/3 were treated, as in the primary analysis.

Table E 29 and Table E 30 show the difference in cancer cases in the three genotyping strategies in sensitivity analysis when women without a referring cytology do not have a cytology taken to inform management at colposcopy. The results indicate there is a slight increase in cancer incidence and mortality when cytology is not available to assist in the management of some women referred to colposcopy on the basis of a positive HPV test. The model predicted a 2% increase in cancer incidence (1-2% increase in a vaccinated population) and a 2-3% increase in cervical cancer mortality (2% increase in a vaccinated population). These increases most likely arise in the women who do not have a biopsy taken at colposcopy, since histology results were assumed to be the major factor in determining subsequent management in the clinical pathways modelled for this evaluation. These results suggest that cytology may play an important role in determining subsequent management in women referred on the basis of HPV test results when the colposcopic appearance is normal and for whom histology is not available. Performing this cytology test at colposcopy resulted in a less than 1% increase in program costs for both unvaccinated and vaccinated cohorts.

The effect of assuming that women who are discharged after a normal exit HPV test do not return for screening

Due to the magnitude of observed improvement in scenarios where the screening stopping age remained at 69 years compared to 64 years, we decided to further investigate the effects of reducing the rate of return to cervical screening when women are discharged after normal exit HPV test at 69 years of age. For this analysis, we assumed that women who attend an exit HPV test (and tested negative) will not return for screening. We compared the health and cost outcomes to equivalent scenarios where some women continue to return for screening even after being discharged. In all cases, we assume that the recommended screening end age is 69 instead of 64 years.

We investigated this scenario to determine whether it was safe to discharge women after their exit HPV test and results of this analysis compared to scenarios where women continue to return after being discharged are shown in Table E 31 and Table E 32. We found that if no women return for screening after being discharged from an exit test, the model predicts an additional 1-2 cancer cases (0-1 in vaccinated cohorts) and 0-1 cancer deaths (rounds to 0 cancer deaths in vaccinated cohorts). The ASR incidence and mortality both increase by 0.1-0.3% (0.1-0.4% in vaccinated cohorts). The model predicts an overall program cost decrease of 0.3-0.6% (0.3-0.7% in vaccinated cohorts) if no women return for screening after being discharged from their exit HPV test. Table E 33 and Table E 34 show comparisons of the scenarios with current practice management.

In summary, there is little impact on cancer cases, deaths or program cost if women who are discharged do not return for cervical screening.

The effect of lengthening the routine screening interval from 5 to 6 years for primary HPV screening strategies

Table E 35 and Table E 36 show the predicted health and cost outcomes if the routine screening interval is extended from 5 to 6 years in selected primary HPV screening scenarios. These results indicate that extending the screening interval from five to six years will result in a 3-4% increase in incidence (cases and age-standardised rates) for both unvaccinated and vaccinated cohorts, and a similar increase in cancer mortality (cases and age-standardised rates) relative to the same strategy with 5-yearly screening. This is similar to the magnitude of change in health outcomes predicted when the screening end-age was reduced from 69 years to 64 years. Extending the screening interval from five years to six is predicted to result in a further 10% decrease in program costs.

Table E 37 and Table E 38 show health and cost outcomes for selected primary HPV screening strategies compared to current practice. For all selected strategies, health outcomes are still predicted to be better than current practice if six yearly screening intervals are adopted. For unvaccinated cohorts, cost *savings* compared to current practice range from 25-32% for primary HPV screening with cytology triage, 23-30% for primary HPV with genotyping and 8-16% for adjunctive cytology co-testing. For vaccinated cohorts, cost *savings* compared to current practice range from 32-39% for primary HPV screening with cytology triage, 30-38% for primary HPV with genotyping and 12-19% for adjunctive cytology co-testing.

Self-collected HPV tests

Self-collected HPV tests for under-screened and unscreened women can supplement the organised screening program which uses health practitioner collected samples and examination.

In the 5-year period 2007–2011, 83.4% of women 20 to 69 years of age had at least one Pap test (AIHW 2013). Reaching unscreened and under-screened women will improve the early detection of cervical cancer. Within the context of the current NCSP, the Victorian Cervical Cytology Register estimates that over 80% of Victorian women diagnosed with invasive cervical cancer in 2009 had either never been screened or were lapsed screeners prior to their cancer diagnosis (VCCR 2011b).

Self-collected tests in Australian health care settings are thought to be a significant contributing factor to improved testing for sexually transmitted infections; however the future potential uptake of self-collected HPV tests in an Australian setting is unknown.

Currently there is a PIP Cervical Screening Incentive, of \$35 paid to GPs for each cervical smear on an under-screened woman aged 20 to 69 years of age (currently defined as a woman who has not had a cervical smear within the last four years). There are also practice sign on payments.

Irrespective of the primary screening technology chosen for the renewed program, as part of the renewed National Cervical Screening Policy, it is proposed that the practice PIP payments are adjusted to relate to use of HPV self-sampling testing in a health care setting and also adjusted to reflect the longer recommended intervals in the program (for the proposed new strategies underscreened women are considered to be women who have never been screened by 30 years of age or women on routine screening recall from whom it is 12 months or more since their screening test was due). It is also proposed that the MBS item for HPV testing is adjusted to reflect the possibility of self-sampled collection in a health care setting for underscreened women.

To ensure that the safety and efficacy of the test is maximised, use of the HPV test should be limited to use in healthcare settings that can provide:

- a) patient counselling and clinical interpretation of results
- b) patient follow-up and confirmatory testing for positive results when required
- c) testing in a safe environment with infection control procedures.

Figure E 2 Hybrid model of HPV transmission and vaccination; natural history of CIN and invasive cervical cancer; and cervical screening, diagnosis and treatment

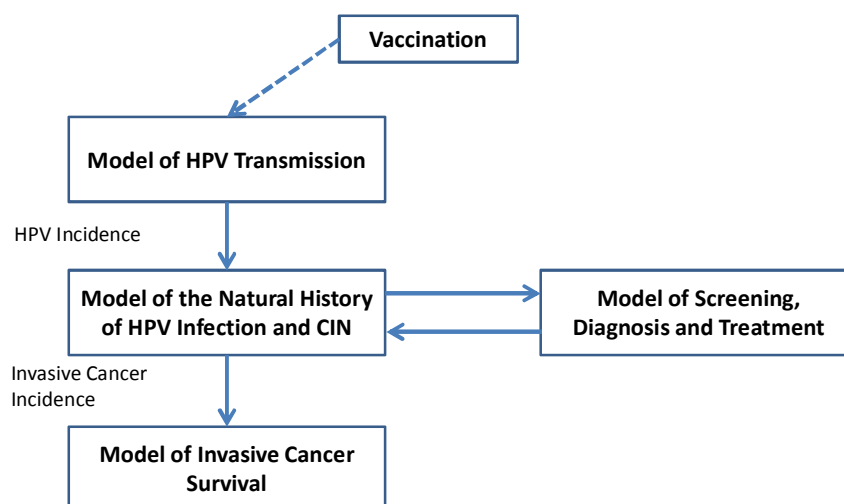


Table E 5 Direct test costs for screening (excluding related practitioner and PEI costs)

Screening test	Item cost assumed for base case	Range assessed in sensitivity analysis
Manually-read LBC	\$30.50	\$30.50-36.36
Image-read LBC	\$36.00	\$36.00-42.92
HPV test for low volume scenario (HPV test used only for TOC +/-exit test)	\$64.00	\$50.00-64.00
HPV test for medium volume scenario (HPV test used for triage, TOC +/-exit test)	\$40.00	\$40.00-64.00
HPV test for high volume scenario (HPV test is the primary screening test)	\$30.00	\$30.00-64.00

TOC: Test-of-cure

Table E 6 Summary of test characteristics modelled for conventional cytology, manually-read LBC, image-read LBC and HPV testing for different clinical applications for base case scenarios and sensitivity analysis, compared with observed data

Test characteristics	Histology and cytology test threshold - - -			
	Base case (range explored in sensitivity analysis)-			
	Histologically-confirmed CIN 2+ -		Histologically-confirmed CIN 3+ -	
	pLSIL	dLSIL	pLSIL	dLSIL
Conventional cytology				
Sensitivity	74.1%	71.0%	75.6%	74.6%
Specificity	95.7%	98.0%	95.3%	97.6%
Unsatisfactory rate (regardless of test threshold)	2.10% (1.20-2.60%)	2.10% (1.20-2.60%)	2.10% (1.20-2.60%)	2.10% (1.20-2.60%)
Manually-read LBC§§				
Sensitivity				
Sensitivity	77.0% (72.2-80.7%)	73.8% (68.4-78.5%)	83.9% (79.2-86.0%)	80.0% (74.2-83.0%)
Relative sensitivity compared to conventional cytology	1.04 (0.97-1.09)	1.04 (0.96-1.10)	1.11 (1.05-1.14)	1.07 (0.99-1.11)
Observed relative sensitivity compared to conventional cytology (Arbyn <i>et al.</i> 2008)	1.03 (95%CI: 0.97-1.09)	1.03 (95%CI: 0.96-1.11)	-	-
Specificity				
Specificity	94.7% (92.2-95.3%)	97.0% (95.9-97.6%)	94.3% (91.9-94.9%)	96.6% (95.5-97.1%)
Relative specificity compared to conventional cytology	0.99 (0.96-1.00)	0.99 (0.98-1.00)	0.99 (0.96-1.00)	0.99 (0.98-1.00)
Observed relative specificity compared to conventional cytology (Arbyn <i>et al.</i> 2008)	0.91 (95%CI: 0.84-0.98)	0.97 (95%CI: 0.94-1.01)	-	-
Unsatisfactory rate (regardless of threshold)	1.80% (0.31-2.57%)	1.80% (0.31-2.57%)	1.80% (0.31-2.57%)	1.80% (0.31-2.57%)
Image-read LBC §§, #				
Sensitivity				
Sensitivity	81.2% (70.6-85.5%)	80.3% (69.9-84.6%)	84.7% (73.7-89.2%)	84.5% (73.5-89.0%)
Relative sensitivity compared to conventional cytology	1.10 (0.95-1.15)	1.13 (0.98-1.19)	1.12 (0.97-1.18)	1.13 (0.99-1.19)
Specificity				
Specificity	94.5% (94.3-95.1%)	97.0% (96.8-97.3%)	94.1% (93.8-94.7%)	96.6% (96.3-96.9%)
Relative specificity to compared to conventional cytology	0.99 (0.99-0.99)	0.99 (0.99-0.99)	0.99 (0.98-0.99)	0.99 (0.99-0.99)
Unsatisfactory rate (regardless of threshold)	1.80% (0.22-1.90%)	1.80% (0.22-1.90%)	1.80% (0.22-1.90%)	1.80% (0.22-1.90%)
HPV testing for primary screening				
Sensitivity				
Sensitivity	96.4% (94.6-98.1%)	96.4% (94.6-98.1%)	98.4% (97.0-99.0%)	98.4% (97.0-99.0%)
Observed sensitivity (Arbyn <i>et al.</i> 2012)	96.0% (95%CI: 95.0-98.0)	96.0% (95%CI: 95.0-98.0)	91.0% (95%CI: 90.0-93.0)	91.0% (95%CI: 90.0-93.0)
Relative sensitivity compared to	-	-	-	-

Test characteristics	Histology and cytology test threshold Base case (range explored in sensitivity analysis)-			
	Histologically-confirmed CIN 2+		Histologically-confirmed CIN 3+	
	pLSIL	dLSIL	pLSIL	dLSIL
Base case conventional cytology	1.30 (1.28-1.32)	1.36 (1.33-1.38)	1.30 (1.28-1.31)	1.32 (1.30-1.33)
Base case manually-read LBC	1.25 (1.23-1.27)	1.31 (1.28-1.33)	1.17 (1.16-1.18)	1.23 (1.21-1.24)
Base case image-read LBC	1.19 (1.17-1.21)	1.20 (1.18-1.22)	1.16 (1.15-1.17)	1.16 (1.15-1.17)
Observed relative sensitivity compared to cytology test (Arbyn <i>et al.</i> 2012)	1.37 (95% CI: 1.22-1.54)	1.40 (95% CI: 1.27-1.54)	1.43 (95% CI: 1.15-1.77)	1.36 (95% CI: 1.21-1.53)
Specificity				
Specificity	90.1% (88.6-93.3%)	90.1% (88.6-93.3%)	89.6% (88.1-92.7%)	89.6% (88.1-92.7%)
Observed specificity (Arbyn <i>et al.</i> 2012)	91.0% (95%CI: 90.0-93.0)	91.0% (95%CI: 90.0-93.0)	-	-
Relative specificity compared to				
Base case conventional cytology	0.94 (0.93-0.97)	0.92 (0.90-0.95)	0.94 (0.92-0.97)	0.92 (0.90-0.95)
Base case manually-read LBC	0.95 (0.94-0.98)	0.93 (0.91-0.96)	0.95 (0.93-0.98)	0.93 (0.91-0.96)
Base case image-read LBC	0.95 (0.94-0.99)	0.93 (0.91-0.96)	0.95 (0.94-0.99)	0.93 (0.91-0.96)
Observed relative specificity compared to cytology test (Arbyn <i>et al.</i> 2012)	0.97 (95% CI: 0.96-0.98)	0.92 (95% CI: 0.90-94)	0.97 (95% CI: 0.96-0.98)	0.93 (95% CI: 0.91-96)
Unsatisfactory rate (regardless of threshold)	0% (0-1%)	0% (0-1%)	0% (0-1%)	0% (0-1%)
HPV triage test of women with low-grade cytology				
Sensitivity				
Sensitivity for women with pLSIL	90.4% (88.9-92.2%)	90.4% (88.9-92.2%)	95.9% (90.4-97.0%)	95.9% (90.4-97.0%)
Sensitivity for women with dLSIL	94.6% (90.0-95.8%)	94.6% (90.0-95.8%)	95.9% (90.4-97.0%)	95.9% (90.4-97.0%)
Observed sensitivity for women with pLSIL (Arbyn <i>et al.</i> 2012, Arbyn <i>et al.</i> 2013)	90.4% (95%CI: 88.1-92.3)	90.4% (95%CI: 88.1-92.3)	93.7% (95%CI: 90.4-95.9)	93.7% (95%CI: 90.4-95.9)
Observed sensitivity for women with dLSIL (Arbyn <i>et al.</i> 2012, Arbyn <i>et al.</i> 2013)	95.4% (95%CI: 94.0-96.5)	95.4% (95%CI: 94.0-96.5)	96.4% (95%CI: 90.5-98.7)	96.4% (95%CI: 90.5-98.7)
Specificity				
Specificity for women with pLSIL	59.0% (53.8-59.7%)	59.0% (53.8-59.7%)	58.0 (53.0-58.7%)	58.0 (53.0-58.7%)
Specificity for women with dLSIL	27.8% (27.0-29.5%)	27.8% (27.0-29.5%)	(Arbyn <i>et al.</i> 2013) 26.6% (26.0-28.2%)	(Arbyn <i>et al.</i> 2013) 26.6% (26.0-28.2%)
Observed specificity for women with pLSIL (Arbyn <i>et al.</i> 2012, Arbyn <i>et al.</i> 2013)	58.3% (95% CI: 53.6-62.9)	58.3% (95% CI: 53.6-62.9)	52.3% (95% CI: 45.7-58.7)	52.3% (95% CI: 45.7-58.7)
Observed specificity for women with dLSIL (Arbyn <i>et al.</i> 2012, Arbyn <i>et al.</i> 2013)	27.8% (95% CI: 23.8-32.1)	27.8% (95% CI: 23.8-32.1)	23.7% (95% CI: 19.4-28.7)	23.7% (95% CI: 19.4-28.7)
HPV test for follow-up after treatment of high-grade CIN				
Sensitivity	93.2% (85.5-97.4%)	93.2% (85.5-97.4%)	94.0% (87.0-98.0%)	94.0% (87.0-98.0%)
Observed sensitivity (Arbyn <i>et al.</i> 2012)	93.0% (95% CI: 85.0-97.0)	93.0% (95% CI: 85.0-97.0)	-	-

Test characteristics	Histology and cytology test threshold - - -			
	Base case (range explored in sensitivity analysis)-			
	Histologically-confirmed CIN 2+		Histologically-confirmed CIN 3+	
	pLSIL	dLSIL	pLSIL	dLSIL
Specificity	80.8% (74.1-85.6%)	80.8% (74.1-85.6%)	80.1% (73.6-84.8%)	80.1% (73.6-84.8%)
Observed specificity (Arbyn <i>et al.</i> 2012)	81.0% (95% CI: 74.0-86.0)	81.0% (95% CI: 74.0-86.0)	-	-

CI – confidence interval; pLSIL - possible low-grade squamous intraepithelial lesion; dLSIL - definite low-grade squamous intraepithelial lesion

The modelled test characteristics of image-read LBC assumed image-read LBC would detect an 0.88 additional CIN2+ and 0.07 less false positive at cytological threshold of pHSIL per 1,000 women screened compared to conventional cytology. This assumption is consistent with the findings of Davey *et al.* (2007), which observed 0.82 addition CIN2+ and 0.07 less false positive cases detected by image-read LBC versus conventional cytology for CIN2+ at cytological threshold of pHSIL per 1,000 women screened.

§§ Test characteristics for LBC is predominantly derived from cell filtration technology

Figure E 3 Cost-effectiveness plane showing current practice and potential screening scenarios with life-years as an outcome – unvaccinated cohort

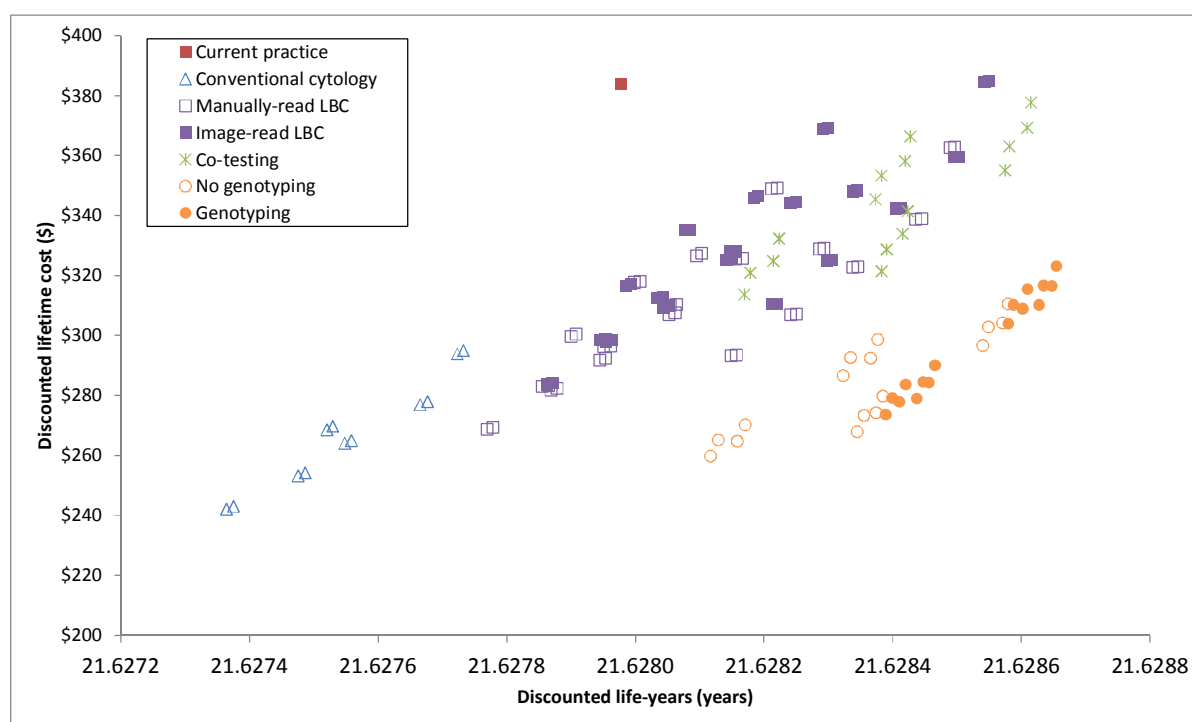


Figure E 4 Cost-effectiveness plane showing current practice and potential screening scenarios with life-years as an outcome – cohort offered vaccination at age 12 years

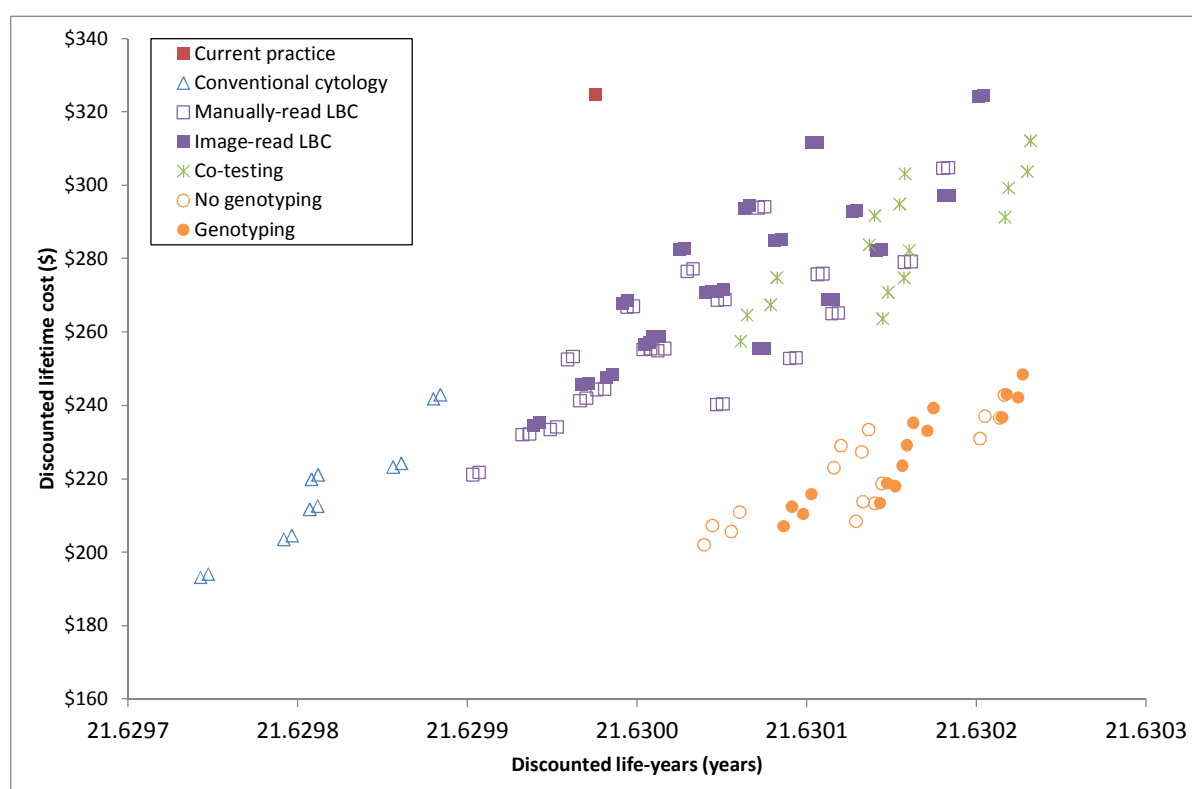


Figure E 5 Cost-effectiveness plane showing current practice and primary HPV strategies with life-years as an outcome - unvaccinated cohort

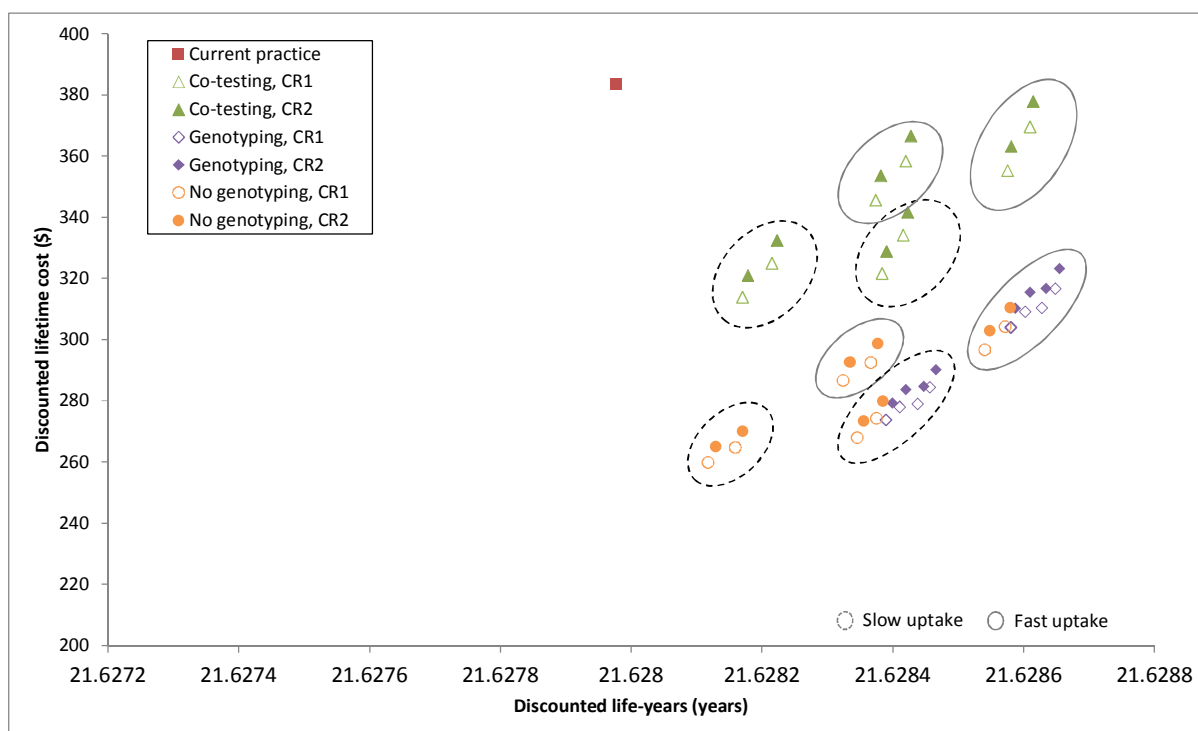


Figure E 6 Cost-effectiveness plane showing current practice and primary HPV strategies with life-years as an outcome - cohort offered vaccination at age 12 years

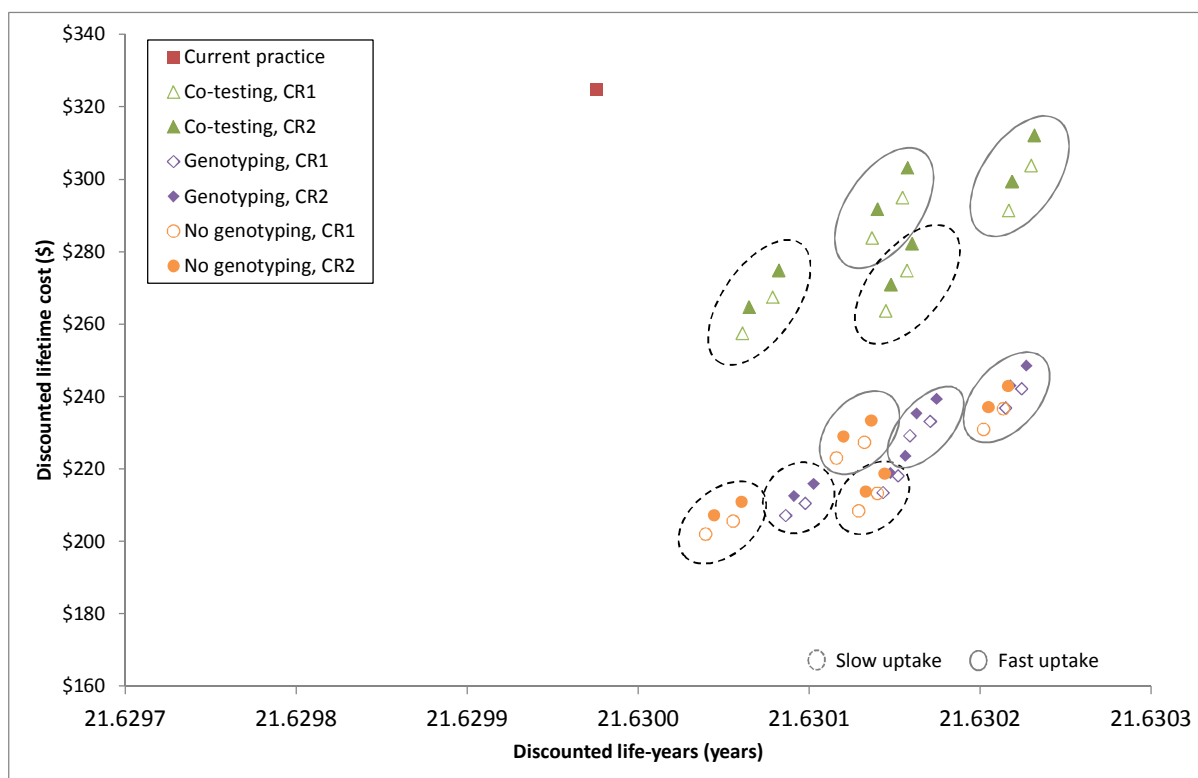


Figure E 7 Predicted cancer incidence per 100,000 women for current practice and selected candidate strategies (base case results) – unvaccinated population

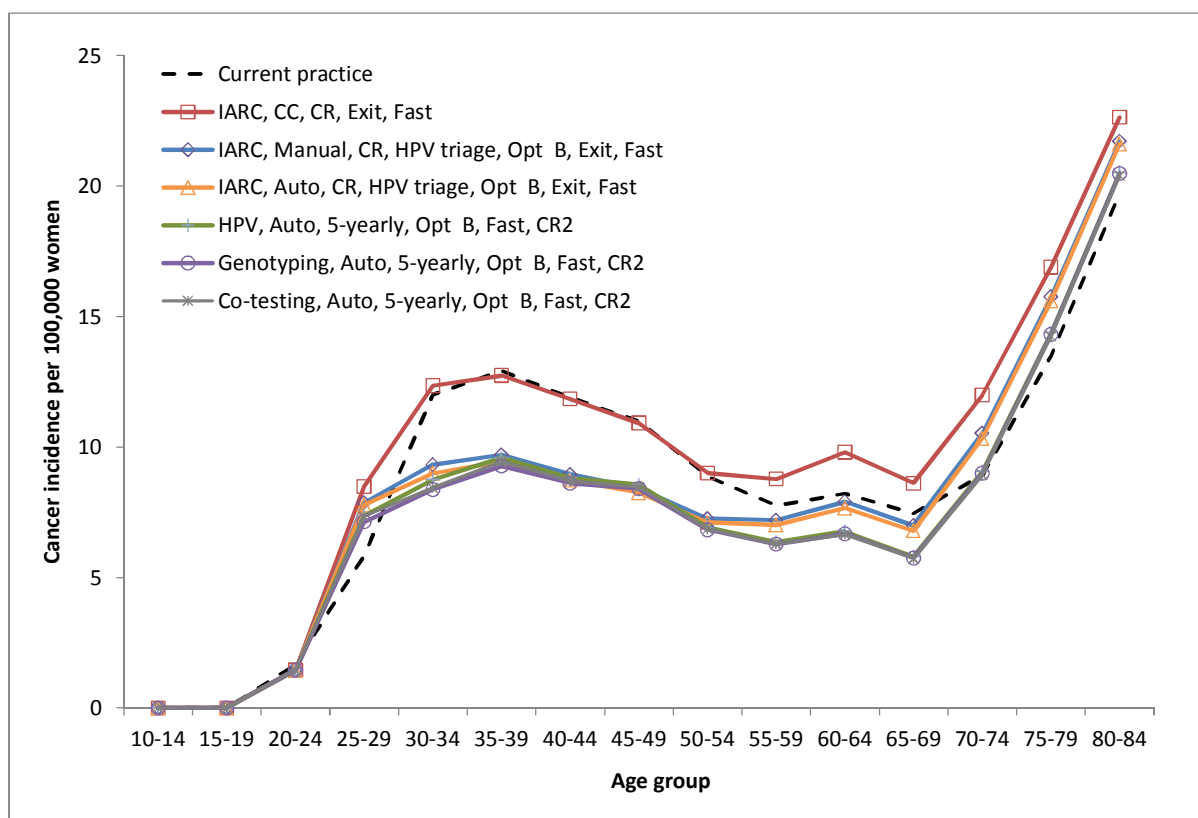


Figure E 8 Predicted cancer incidence per 100,000 women for current practice and selected candidate strategies (base case results) – cohort offered vaccination at age 12 years

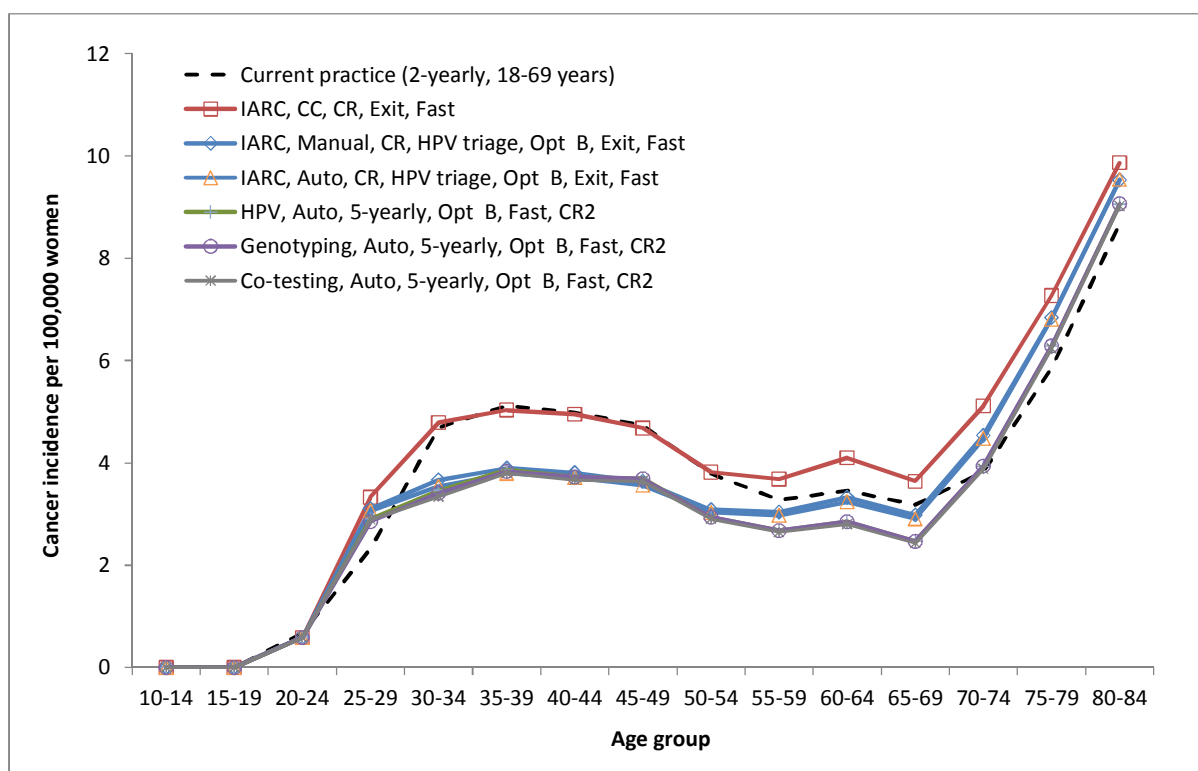


Figure E 9 Predicted cancer mortality per 100,000 women for current practice and selected candidate strategies (base case results) – unvaccinated population

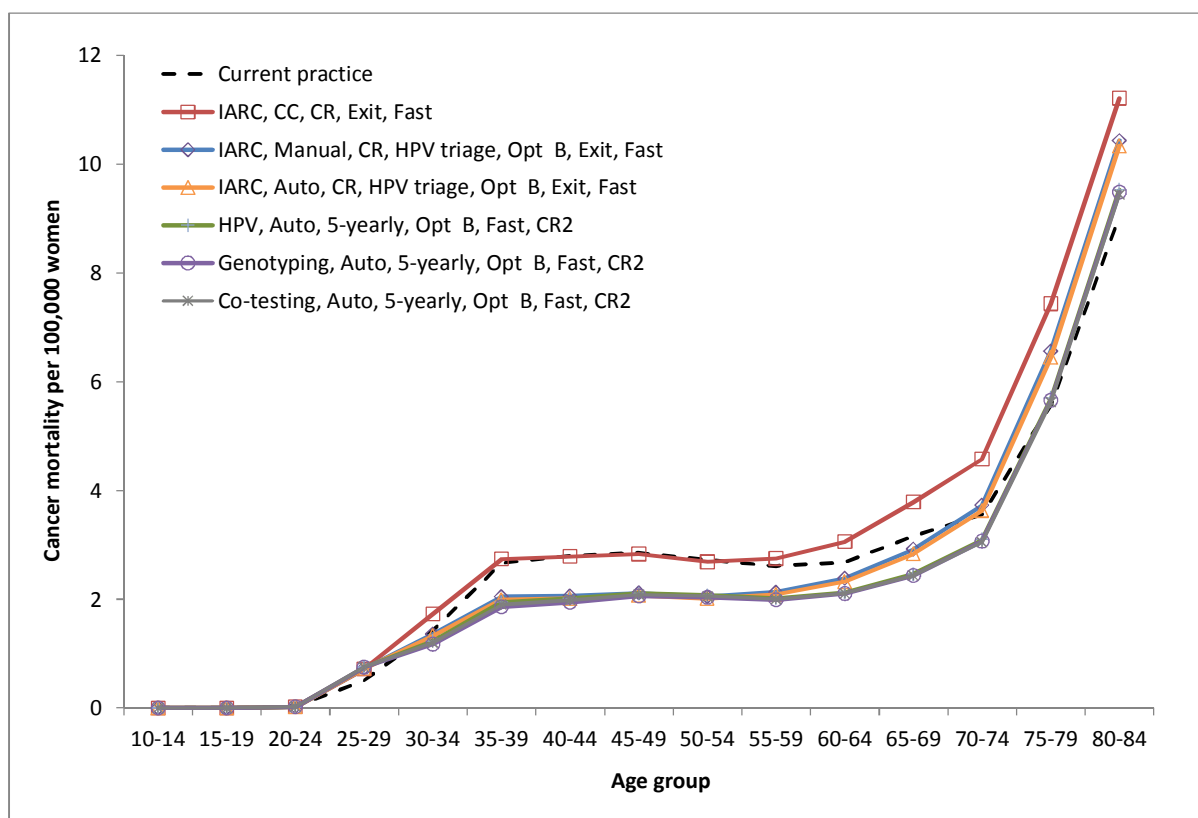


Figure E 10 Predicted cancer mortality per 100,000 women for current practice and selected candidate strategies (base case results) – cohort offered vaccination at age 12 years

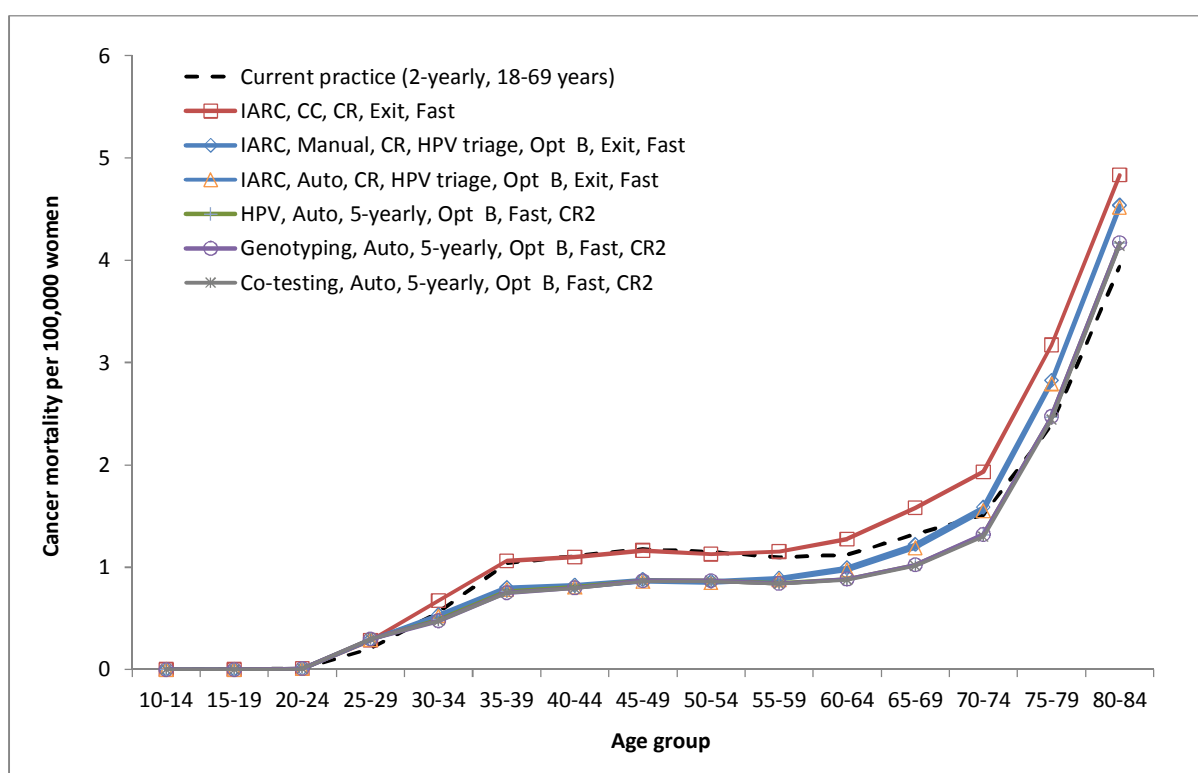


Table E 7 Summary of health outcomes and budget impact for all potential screening scenarios compared to current practice - unvaccinated population

Test technology	High grade abnormalities -		Cancer incidence -		Cancer mortality -		Total cost associated with screening program -		
	No. (range)*	% change compared to CP (range‡)††	ASR§ (range)	% change in ASR§ compared to CP (range‡)††	ASR§ (range)	% change in ASR§ compared to CP (range‡)††	Total screening program cost (\$ M) (range‡)	Difference in program cost compared to CP (\$ M) (range‡)	% change compared to CP (range‡)††
Current practice (model predicted)**	17800	-	6.9	-	1.8	-	214.7	-	-
Conventional cytology	(14300, 15900)	(-20%, -11%)	(7.4, 8)	(6%, 16%)	(2, 2.2)	(8%, 20%)	(148, 177.4)	(-66.8, -37.4)	(-31%, -17%)
Manually-read LBC§§	(14200, 17200)	(-20%, -3%)	(6, 7.3)	(-13%, 6%)	(1.6, 1.9)	(-13%, 7%)	(164.6, 213.5)	(-50.2, -1.2)	(-23%, -1%)
Image-read LBC§§	(14800, 17900)	(-17%, 1%)	(5.9, 7.1)	(-15%, 3%)	(1.5, 1.9)	(-14%, 4%)	(172.7, 225.1)	(-42, 10.3)	(-20%, 5%)
Primary HPV screening with cytology triage	(15400, 17800)	(-13%, 0%)	(5.8, 6.4)	(-16%, -7%)	(1.5, 1.7)	(-16%, -8%)	(156.2, 175.5)	(-58.5, -39.3)	(-27%, -18%)
Primary HPV screening with partial genotyping	(16100, 18100)	(-10%, 2%)	(5.7, 6)	(-18%, -13%)	(1.5, 1.6)	(-18%, -14%)	(162, 181)	(-52.8, -33.8)	(-25%, -16%)
Primary HPV and adjunctive cytology co-testing	(15700, 18100)	(-12%, 2%)	(5.8, 6.3)	(-17%, -9%)	(1.5, 1.6)	(-17%, -9%)	(191.2, 217.1)	(-23.6, 2.3)	(-11%, 1%)

CP – current practice; \$ M - costs represent millions of dollars; * Using female Australian population as predicted for 2015; § Age-standardised (0-84 years) using 2001 Australian population as the standard population; **Predicted values under current practice management using female Australian population as predicted for 2015; ‡ Minimum and maximum % change across all strategies within each test technology were used as the range; †† Negative values represent a decrease; §§ Test characteristics for LBC is based on cell filtration technology

Table E 8 Summary of health outcomes and budget impact for all potential screening scenarios compared to current practice - cohort offered vaccination at age 12 years

Test technology	High grade abnormalities -		Cancer incidence -		Cancer mortality -		Total cost associated with screening program -		
	No. (range)*	% change compared to CP (range‡)††	ASR§ (range)	% change in ASR§ compared to CP (range‡)††	No. (range)*	% change compared to CP (range‡)††	ASR§ (range)	% change in ASR§ compared to CP (range‡)††	No. (range)*
Current practice (model predicted)**	10,100	-	2.9	-	0.7	-	184.4	-	-
Conventional cytology	(7800, 8900)	(-23%, -12%)	(3.1, 3.3)	(6%, 15%)	(0.8, 0.9)	(8%, 19%)	(118.6, 147.7)	(-65.8, -36.6)	(-36%, -20%)
Manually-read LBC§§	(7700, 9700)	(-24%, -4%)	(2.5, 3)	(-13%, 5%)	(0.7, 0.8)	(-12%, 6%)	(136.6, 182.4)	(-47.8, -1.9)	(-26%, -1%)
Image-read LBC§§	(8100, 10100)	(-20%, 0%)	(2.5, 2.9)	(-14%, 2%)	(0.6, 0.8)	(-14%, 4%)	(144.1, 192.9)	(-40.2, 8.5)	(-22%, 5%)
Primary HPV screening with cytology triage	(8400, 10000)	(-17%, -1%)	(2.4, 2.7)	(-15%, -7%)	(0.6, 0.7)	(-16%, -8%)	(123.7, 140.2)	(-60.6, -44.2)	(-33%, -24%)
Primary HPV screening with partial genotyping	(8400, 10000)	(-17%, -1%)	(2.4, 2.6)	(-16%, -10%)	(0.6, 0.7)	(-16%, -11%)	(125.9, 142.6)	(-58.5, -41.7)	(-32%, -23%)
Primary HPV and adjunctive cytology co-testing	(8600, 10200)	(-15%, 1%)	(2.4, 2.6)	(-17%, -9%)	(0.6, 0.7)	(-17%, -10%)	(159.6, 183)	(-24.7, -1.4)	(-13%, -1%)

CP – current practice; \$ M - costs represent millions of dollars; * Using female Australian population as predicted for 2015; § Age-standardised (0-84 years) using 2001 Australian population as the standard population; **Predicted values under current practice management using female Australian population as predicted for 2015; ‡ Minimum and maximum % change across all strategies within each test technology were used as the range; †† Negative values represent a decrease; §§ Test characteristics for LBC is based on cell filtration technology

Table E 9 Summary of health outcomes for selected strategies and probabilistic sensitivity analysis (PSA) findings- unvaccinated population

Test technology	Key strategies used in PSA	High grade abnormalities	-	Cancer incidence ,	Baseline (95% credible interval)	Cancer mortality,	Baseline (95% credible interval)
		Number of cases*	% change compared to CP††	ASR§	% change in ASR§ compared to CP††	ASR§	% change in ASR§ compared to CP††
Conventional cytology	IARC, CC, R1, Slow	14259 (12162, 16251)	-20% (-21%, -17%)	8 (6.5, 10)	16% (12%, 19%)	2.2 (1.7, 2.7)	20% (14%, 24%)
	IARC, CC, R2, Slow	14744 (12571, 16834)	-17% (-18%, -14%)	7.6 (6.1, 9.5)	10% (7%, 12%)	2 (1.6, 2.6)	12% (8%, 14%)
	IARC, CC, R2, Exit, Fast	15876 (13644, 18352)	-11% (-11%, -6%)	7.4 (5.9, 9.2)	6% (4%, 8%)	2 (1.6, 2.5)	8% (6%, 10%)
	IARC, CC, CR, Exit, Fast	15664 (13463, 18092)	-12% (-13%, -7%)	7.6 (6.1, 9.4)	9% (6%, 11%)	2 (1.6, 2.6)	12% (9%, 15%)
Manually-read LBC§§	IARC, Manual, R1, Slow	14164 (11753, 16248)	-20% (-24%, -15%)	7.3 (6, 9.4)	6% (0%, 12%)	1.9 (1.6, 2.5)	7% (0%, 15%)
	IARC, Manual, R2, Slow	14567 (12105, 16744)	-18% (-22%, -12%)	7 (5.6, 9)	0% (-5%, 5%)	1.8 (1.5, 2.4)	1% (-5%, 6%)
	IARC, Manual, R2, HPV triage, Opt B, Exit, Fast	17230 (14601, 19805)	-3% (-6%, 5%)	6 (4.9, 7.7)	-13% (-15%, -11%)	1.6 (1.3, 2)	-13% (-16%, -10%)
	IARC, Manual, CR, HPV triage, Opt B, Exit, Fast	16965 (14372, 19490)	-5% (-7%, 4%)	6.2 (5, 7.9)	-11% (-13%, -8%)	1.6 (1.3, 2.1)	-10% (-13%, -6%)
Image-read LBC§§	IARC, Auto, R1, Slow	14754 (11797, 16630)	-17% (-24%, -12%)	7.1 (5.6, 9.4)	3% (-6%, 20%)	1.9 (1.5, 2.6)	4% (-6%, 25%)
	IARC, Auto, R2, Slow	15169 (12229, 17080)	-15% (-21%, -9%)	6.8 (5.4, 8.9)	-2% (-9%, 12%)	1.8 (1.4, 2.4)	-2% (-10%, 14%)
	IARC, Auto, R2, HPV triage, Opt B, Exit, Fast	17877 (14962, 20366)	1% (-6%, 8%)	5.9 (4.7, 7.6)	-15% (-19%, -5%)	1.5 (1.2, 2)	-14% (-19%, -4%)
	IARC, Auto, CR, HPV triage, Opt B, Exit, Fast	17624 (14718, 20056)	-1% (-7%, 7%)	6.1 (4.9, 7.9)	-13% (-17%, -2%)	1.6 (1.3, 2.1)	-11% (-18%, 1%)
Primary HPV screening with cytology triage	HPV, Manual, 5-yearly, Opt A, Slow, CR1	15402 (12949, 17695)	-13% (-16%, -9%)	6.4 (5.1, 8.3)	-7% (-9%, -5%)	1.7 (1.3, 2.2)	-8% (-10%, -6%)
	HPV, Manual, 5-yearly, Opt A, Slow, CR2	15473 (13006, 17766)	-13% (-16%, -8%)	6.4 (5.1, 8.2)	-8% (-10%, -6%)	1.7 (1.3, 2.1)	-9% (-11%, -7%)
	HPV, Auto, 5-yearly, Opt A, Slow, CR1	15675 (13156, 17826)	-12% (-15%, -8%)	6.4 (5.1, 8.1)	-8% (-12%, -4%)	1.6 (1.3, 2.1)	-9% (-13%, -5%)
	HPV, Auto, 5-yearly, Opt A, Slow, CR2	15749 (13219, 17902)	-11% (-14%, -8%)	6.3 (5.1, 8.1)	-9% (-13%, -5%)	1.6 (1.3, 2.1)	-10% (-14%, -5%)
	HPV, Auto, 5-yearly, Opt B, Fast, CR2	17833 (15022, 20324)	0% (-3%, 6%)	5.8 (4.7, 7.5)	-16% (-20%, -11%)	1.5 (1.2, 2)	-16% (-20%, -11%)
Primary HPV screening with partial genotyping	Genotyping, Manual, 5-yearly, Opt A, Slow, CR1	16090 (13582, 18338)	-10% (-12%, -5%)	6 (4.8, 7.7)	-13% (-14%, -12%)	1.6 (1.2, 2)	-14% (-15%, -12%)
	Genotyping, Manual, 5-yearly, Opt A, Slow, CR2	16161 (13638, 18405)	-9% (-12%, -5%)	6 (4.8, 7.7)	-14% (-15%, -12%)	1.5 (1.2, 2)	-15% (-16%, -13%)
	Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	18107 (15396, 20620)	2% (-1%, 7%)	5.7 (4.6, 7.4)	-18% (-21%, -13%)	1.5 (1.2, 2)	-18% (-21%, -13%)
Primary HPV and adjunctive cytology co-testing	Co-testing, Auto, 5-yearly, Opt A, Slow, CR1	15969 (13404, 18134)	-10% (-14%, -6%)	6.2 (5, 8)	-10% (-14%, -5%)	1.6 (1.3, 2.1)	-11% (-16%, -6%)
	Co-testing, Auto, 5-yearly, Opt B, Fast, CR2	18099 (15218, 20737)	2% (-2%, 8%)	5.8 (4.6, 7.5)	-17% (-21%, -12%)	1.5 (1.2, 2)	-17% (-22%, -12%)

IARC – IARC recommended screening age and interval; CC – conventional cytology; Manual – manually-read LBC; Auto – image-read LBC; Slow – women will not receive an invitation to attend their first cervical screen; Fast – women will receive an invitation to attend their first cervical screen; CR – call-and-recall program (proactive invitation) for strategies incorporating conventional cytology and LBC (either manually-read or image-read); R1 - reminder-based program (with the lower proportion of the overall participation rate); R2 - reminder-based program (with the higher proportion of the overall participation rate); CR1- call-and-recall program (assuming high compliance with the recommended screening interval and limited early re-screening) for primary HPV testing strategies; CR2 - call-and-recall program (assuming a higher proportion of early re-screening and a lower proportion of women who screen in-time) for primary HPV testing strategies; Opt A – 12 months follow-up for women with low-grade cytology and testing HPV positive using reflex HPV triage; Opt B – direct colposcopy referral for women with low-grade cytology and testing HPV positive using reflex HPV triage; Exit –HPV exit testing for women exiting the program at age 65 years (Note: all primary HPV screening strategies incorporate HPV exit testing for women 65+ years of age therefore not specified in the above table);

§§ Test characteristics for LBC is based on cell filtration technology;* Using female Australian population as predicted for 2015; § Age-standardised (0-84 years) using 2001 Australian population as the standard population; †† Negative values represent a decrease

Table E 10 Summary of health outcomes for selected strategies and probabilistic sensitivity analysis (PSA) findings - cohort offered vaccination at age 12 years

Test technology	Key strategies used in PSA	High grade abnormalities		Cancer incidence, ASR§	Baseline (95% credible interval) % change in ASR§ compared to CP††	Cancer mortality, ASR§	Baseline (95% credible interval) % change in ASR§ compared to CP††
		Number of cases*	% change compared to CP††				
Conventional cytology	IARC, CC, R1, Slow	7800 (6400, 9000)	-23% (-24%, -20%)	3.3 (2.5, 4.2)	15% (11%, 17%)	0.9 (0.7, 1.2)	19% (13%, 23%)
	IARC, CC, R2, Slow	8100 (6700, 9400)	-20% (-21%, -16%)	3.1 (2.3, 4)	9% (6%, 10%)	0.8 (0.6, 1.1)	11% (7%, 13%)
	IARC, CC, R2, Exit, Fast	8900 (7400, 10400)	-13% (-13%, -7%)	3.1 (2.3, 3.9)	6% (4%, 7%)	0.8 (0.6, 1.1)	8% (5%, 10%)
	IARC, CC, CR, Exit, Fast	8700 (7300, 10300)	-14% (-15%, -9%)	3.1 (2.3, 4)	8% (6%, 10%)	0.8 (0.6, 1.1)	12% (8%, 15%)
Manually-read LBC§§	IARC, Manual, R1, Slow	7700 (6200, 9000)	-24% (-28%, -18%)	3 (2.2, 3.9)	5% (0%, 10%)	0.8 (0.6, 1.1)	6% (0%, 14%)
	IARC, Manual, R2, Slow	7900 (6400, 9300)	-22% (-25%, -15%)	2.9 (2.1, 3.8)	-1% (-5%, 4%)	0.7 (0.5, 1)	0% (-5%, 5%)
	IARC, Manual, R2, HPV triage, Opt B, Exit, Fast	9700 (8100, 11400)	-5% (-7%, 5%)	2.5 (1.9, 3.3)	-13% (-14%, -10%)	0.7 (0.5, 0.9)	-12% (-15%, -10%)
	IARC, Manual, CR, HPV triage, Opt B, Exit, Fast	9500 (7900, 11200)	-6% (-9%, 3%)	2.6 (1.9, 3.4)	-10% (-12%, -8%)	0.7 (0.5, 0.9)	-9% (-12%, -5%)
Image-read LBC§§	IARC, Auto, R1, Slow	8100 (6300, 9300)	-21% (-28%, -15%)	2.9 (2.2, 4.1)	2% (-6%, 18%)	0.8 (0.6, 1.1)	4% (-6%, 24%)
	IARC, Auto, R2, Slow	8300 (6600, 9600)	-18% (-25%, -12%)	2.8 (2, 3.9)	-3% (-10%, 10%)	0.7 (0.5, 1)	-3% (-11%, 13%)
	IARC, Auto, R2, HPV triage, Opt B, Exit, Fast	10100 (8200, 11800)	0% (-7%, 9%)	2.5 (1.8, 3.3)	-14% (-18%, -5%)	0.6 (0.5, 0.9)	-14% (-19%, -3%)
	IARC, Auto, CR, HPV triage, Opt B, Exit, Fast	10000 (8000, 11600)	-2% (-9%, 7%)	2.5 (1.9, 3.4)	-12% (-17%, -1%)	0.7 (0.5, 0.9)	-11% (-16%, 2%)
Primary HPV screening with cytology triage	HPV, Manual, 5-yearly, Opt A, Slow, CR1	8400 (6800, 9800)	-17% (-21%, -11%)	2.7 (2, 3.5)	-7% (-9%, -6%)	0.7 (0.5, 0.9)	-8% (-10%, -7%)
	HPV, Manual, 5-yearly, Opt A, Slow, CR2	8400 (6800, 9900)	-17% (-20%, -11%)	2.6 (1.9, 3.5)	-8% (-10%, -6%)	0.7 (0.5, 0.9)	-9% (-11%, -7%)
	HPV, Auto, 5-yearly, Opt A, Slow, CR1	8600 (6900, 9900)	-15% (-19%, -11%)	2.6 (1.9, 3.6)	-9% (-12%, -4%)	0.7 (0.5, 0.9)	-10% (-13%, -5%)
	HPV, Auto, 5-yearly, Opt A, Slow, CR2	8600 (7000, 10000)	-15% (-18%, -11%)	2.6 (1.9, 3.5)	-9% (-12%, -5%)	0.7 (0.5, 0.9)	-10% (-14%, -6%)
	HPV, Auto, 5-yearly, Opt B, Fast, CR2	10000 (8200, 11600)	-1% (-5%, 6%)	2.4 (1.8, 3.3)	-15% (-18%, -10%)	0.6 (0.5, 0.9)	-16% (-19%, -11%)
Primary HPV screening with partial genotyping	Genotyping, Manual, 5-yearly, Opt A, Slow, CR1	8400 (6800, 9800)	-17% (-20%, -11%)	2.6 (1.9, 3.4)	-10% (-10%, -8%)	0.7 (0.5, 0.9)	-11% (-12%, -9%)
	Genotyping, Manual, 5-yearly, Opt A, Slow, CR2	8500 (6900, 9900)	-16% (-20%, -11%)	2.6 (1.9, 3.4)	-10% (-11%, -8%)	0.7 (0.5, 0.9)	-11% (-12%, -9%)
	Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	10000 (8300, 11600)	-1% (-5%, 5%)	2.4 (1.8, 3.3)	-16% (-18%, -11%)	0.6 (0.5, 0.9)	-16% (-19%, -11%)
Primary HPV and adjunctive cytology co-testing	Co-testing, Auto, 5-yearly, Opt A, Slow, CR1	8800 (7100, 10200)	-13% (-17%, -9%)	2.6 (1.9, 3.5)	-10% (-14%, -6%)	0.7 (0.5, 0.9)	-11% (-15%, -6%)
	Co-testing, Auto, 5-yearly, Opt B, Fast, CR2	10200 (8400, 11800)	1% (-4%, 9%)	2.4 (1.8, 3.3)	-17% (-20%, -11%)	0.6 (0.5, 0.9)	-17% (-20%, -11%)

IARC – IARC recommended screening age and interval; CC – conventional cytology; Manual – manually-read LBC; Auto – image-read LBC; Slow – women will not receive an invitation to attend their first cervical screen; Fast – women will receive an invitation to attend their first cervical screen; CR – call-and-recall program (proactive invitation) for strategies incorporating conventional cytology and LBC (either manually-read or image-read); R1 - reminder-based program (with the lower proportion of the overall participation rate); R2 - reminder-based program (with the higher proportion of the overall participation rate); CR1- call-and-recall program (assuming high compliance with the recommended screening interval and limited early re-screening) for primary HPV testing strategies; CR2 - call-and-recall program (assuming a higher proportion of early re-screening and a lower proportion of women who screen in-time) for primary HPV testing strategies; Opt A – 12 months follow-up for women with low-grade cytology and testing HPV positive using reflex HPV triage; Opt B – direct colposcopy referral for women with low-grade cytology and testing HPV positive using reflex HPV triage; Exit –HPV exit testing for women exiting the program at age 65 years (Note: all primary HPV screening strategies incorporate HPV exit testing for women 65+ years of age therefore not specified in the above table);

§§ Test characteristics for LBC is based on cell filtration technology;* Using female Australian population as predicted for 2015; § Age-standardised (0-84 years) using 2001 Australian population as the standard population; †† Negative values represent a decrease

Table E 11 Summary of health and cost outcomes in selected candidate strategies – results of the probabilistic sensitivity analyses in unvaccinated cohort

Strategy	High grade abnormalities	Baseline (95% credible interval)	Cervical cancer incidence	Baseline (95% credible interval)	-	-	Cervical cancer mortality	Baseline (95% credible interval)	-	-	Total cost associated with screening program	-
	Annual no. of cases	% change compared to CP	ASR\$	% change in ASR\$ compared to CP	Annual no. of cases*	% change in no. of cases compared to CP*	ASR\$	% change in ASR\$ compared to CP	Annual no. of cases*	% change in no. of cases compared to CP*	Total screening program cost*	Total cost difference (%) compared to CP††
Current practice (model predicted)**	17,800	-	6.9	-	811	-	1.8	-	218	-	\$ 214.7 M	-
IARC, CC, CR, Exit, Fast	15,700 (13,500 ,18,100)	-12% (-13%, -7%)	7.6 (6.1, 9.4)	9% (6%, 11%)	891 (715, 1112)	10% (7%, 12%)	2 (1.6, 2.6)	12% (9%, 15%)	246 (196, 311)	13% (9%, 16%)	\$ 162.3 M	\$ -52.4 M (-24.4 %)
IARC, Manual, CR, HPV triage, Opt B, Exit, Fast	17,000 (14,400 ,19,500)	-5% (-7%, 4%)	6.2 (5, 7.9)	-11% (-13%, -8%)	732 (592, 933)	-10% (-13%, -7%)	1.6 (1.3, 2.1)	-10% (-13%, -6%)	198 (159, 257)	-9% (-13%, -6%)	\$ 193.1 M	\$ -21.7 M (-10.1 %)
IARC, Auto, CR, HPV triage, Opt B, Exit, Fast	17,600 (14,700 ,20,100)	-1% (-7%, 7%)	6.1 (4.9, 7.9)	-13% (-17%, -2%)	716 (574, 930)	-12% (-17%, -1%)	1.6 (1.3, 2.1)	-11% (-18%, 1%)	194 (155, 255)	-11% (-17%, 2%)	\$ 203.5 M	\$ -11.2 M (-5.2 %)
HPV, Auto, 5-yearly, Opt B, Fast, CR2	17,800 (15,000 ,20,300)	0% (-3%, 6%)	5.8 (4.7, 7.5)	-16% (-20%, -11%)	684 (549, 887)	-16% (-20%, -10%)	1.5 (1.2, 2)	-16% (-20%, -11%)	183 (145, 243)	-16% (-20%, -11%)	\$ 175.5 M	\$ -39.3 M (-18.3 %)
Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	18,100 (15,400 ,20,600)	2% (-1%, 7%)	5.7 (4.6, 7.4)	-18% (-21%, -13%)	671 (540, 867)	-17% (-21%, -13%)	1.5 (1.2, 2)	-18% (-21%, -13%)	179 (142, 238)	-18% (-21%, -13%)	\$ 181 M	\$ -33.8 M (-15.7 %)
Co-testing, Auto, 5-yearly, Opt B, Fast, CR2	18,100 (15,200 ,20,700)	2% (-2%, 8%)	5.8 (4.6, 7.5)	-17% (-21%, -12%)	675 (537, 876)	-17% (-21%, -11%)	1.5 (1.2, 2)	-17% (-22%, -12%)	181 (141, 240)	-17% (-22%, -12%)	\$ 217.1 M	\$ 2.3 M (1.1 %)

CP – current practice; \$ M - costs represent millions of dollars; IARC – IARC recommended screening age and interval; CC – conventional cytology; Manual – manually-read LBC; Auto – image-read LBC

Slow – women will not receive an invitation to attend their first cervical screen; Fast – women will receive an invitation to attend their first cervical screen

CR – call-and-recall program (proactive invitation) for strategies incorporating conventional cytology and LBC (either manually-read or image-read); CR2 - call-and-recall program (assuming a higher proportion of early re-screening and a lower proportion of women who screen in-time) for primary HPV testing strategies

Opt B – direct colposcopy referral for women with low-grade cytology and testing HPV positive using reflex HPV triage

Exit –HPV exit testing for women exiting the program at age 65 years (Note: all primary HPV screening strategies incorporate HPV exit testing for women 65+ years of age therefore not specified in the above table)

* Using female Australian population as predicted for 2015

**Predicted values under current practice management using female Australian population as predicted for 2015

§ Age-standardised (0-84 years) using 2001 Australian population as the standard population per 100,000 women

†† Negative values represent a decrease

Table E 12 Summary of health and cost outcomes in selected candidate strategies – results of the probabilistic sensitivity analyses in cohort offered vaccination at age 12 years

Strategy	High grade abnormalities	Baseline (95% credible interval)	Cervical cancer incidence	Baseline (95% credible interval)	-	-	Cervical cancer mortality	Baseline (95% credible interval)	-	-	Total cost associated with screening program	-
	Annual no. of cases	% change compared to CP	ASR§	% change in ASR§ compared to CP	Annual no. of cases*	% change in no. of cases compared to CP*	ASR§	% change in ASR§ compared to CP	Annual no. of cases*	% change in no. of cases compared to CP*	Total screening program cost*	Total cost difference (%) compared to CP††
Current practice (model predicted)**	10100	-	2.9	-	338	-	0.7	-	91	-	\$ 184.4 M	-
IARC, CC, CR, Exit, Fast	8700 (7300, 10300)	-14% (-15%, -9%)	3.1 (2.3, 4)	8% (6%, 10%)	369 (274, 475)	9% (6%, 11%)	0.8 (0.6, 1.1)	12% (8%, 15%)	102 (75, 133)	12% (8%, 16%)	\$ 132.4 M	\$ -52 M (-28.2 %)
IARC, Manual, CR, HPV triage, Opt B, Exit, Fast	9500 (7900, 11200)	-6% (-9%, 3%)	2.6 (1.9, 3.4)	-10% (-12%, -8%)	306 (229, 403)	-9% (-12%, -7%)	0.7 (0.5, 0.9)	-9% (-12%, -5%)	83 (61, 111)	-9% (-12%, -5%)	\$ 161.9 M	\$ -22.4 M (-12.2 %)
IARC, Auto, CR, HPV triage, Opt B, Exit, Fast	10000 (8000, 11600)	-2% (-9%, 7%)	2.5 (1.9, 3.4)	-12% (-17%, -1%)	300 (223, 407)	-11% (-16%, 0%)	0.7 (0.5, 0.9)	-11% (-16%, 2%)	81 (60, 111)	-10% (-16%, 3%)	\$ 171.3 M	\$ -13 M (-7.1 %)
HPV, Auto, 5-yearly, Opt B, Fast, CR2	10000 (8200, 11600)	-1% (-5%, 6%)	2.4 (1.8, 3.3)	-15% (-18%, -10%)	287 (212, 391)	-15% (-18%, -10%)	0.6 (0.5, 0.9)	-16% (-19%, -11%)	76 (56, 106)	-16% (-19%, -11%)	\$ 140.2 M	\$ -44.2 M (-24 %)
Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	10000 (8300, 11600)	-1% (-5%, 5%)	2.4 (1.8, 3.3)	-16% (-18%, -11%)	285 (212, 387)	-16% (-18%, -11%)	0.6 (0.5, 0.9)	-16% (-19%, -11%)	76 (56, 105)	-16% (-19%, -11%)	\$ 142.6 M	\$ -41.7 M (-22.6 %)
Co-testing, Auto, 5-yearly, Opt B, Fast, CR2	10200 (8400, 11800)	1% (-4%, 9%)	2.4 (1.8, 3.3)	-17% (-20%, -11%)	283 (208, 388)	-16% (-20%, -11%)	0.6 (0.5, 0.9)	-17% (-20%, -11%)	75 (55, 105)	-17% (-20%, -11%)	\$ 183 M	\$ -1.4 M (-0.8 %)

CP – current practice; \$ M - costs represent millions of dollars; IARC – IARC recommended screening age and interval; CC – conventional cytology; Manual – manually-read LBC; Auto – image-read LBC

Slow – women will not receive an invitation to attend their first cervical screen; Fast – women will receive an invitation to attend their first cervical screen

CR – call-and-recall program (proactive invitation) for strategies incorporating conventional cytology and LBC (either manually-read or image-read); CR2 - call-and-recall program (assuming a higher proportion of early re-screening and a lower proportion of women who screen in-time) for primary HPV testing strategies

Opt B – direct colposcopy referral for women with low-grade cytology and testing HPV positive using reflex HPV triage

Exit –HPV exit testing for women exiting the program at age 65 years (Note: all primary HPV screening strategies incorporate HPV exit testing for women 65+ years of age therefore not specified in the above table)

* Using female Australian population as predicted for 2015

**Predicted values under current practice management using female Australian population as predicted for 2015

§ Age-standardised (0-84 years) using 2001 Australian population as the standard population per 100,000 women

†† Negative values represent a decrease

Table E 13 **Summary of the effect of changing the screening end-age from 64 to 69 years on health and cost outcomes**

Test technology	% change when screening end-age is 69 years compared to the equivalent strategy when the screening end-age is 64 years †† (unvaccinated)			% change when screening end-age is 69 years compared to the equivalent strategy when the screening end-age is 64 years †† (vaccinated)		
	Cancer incidence (ASR§) (range‡)	Cancer mortality (ASR§) (range‡)	Total screening programming cost (range‡)	Cancer incidence (ASR§) (range‡)	Cancer mortality (ASR§) (range‡)	Total screening programming cost (range‡)
-						
Conventional cytology	(-4%, -3%)	(-7%, -5%)	(1%, 2%)	(-4%, -3%)	(-8%, -5%)	(1%, 2%)
Manually-read LBC§§	(-5%, -3%)	(-8%, -5%)	(2%, 2%)	(-5%, -3%)	(-8%, -5%)	(2%, 3%)
Image-read LBC§§	(-5%, -3%)	(-8%, -5%)	(2%, 2%)	(-5%, -3%)	(-8%, -5%)	(2%, 3%)
Primary HPV screening with cytology triage	(-4%, -3%)	(-6%, -5%)	(2%, 2%)	(-4%, -3%)	(-6%, -5%)	(2%, 2%)
Primary HPV screening with partial genotyping	(-4%, -3%)	(-6%, -5%)	(2%, 2%)	(-4%, -3%)	(-6%, -5%)	(2%, 2%)
primary HPV and adjunctive cytology co-testing	(-4%, -3%)	(-6%, -5%)	(3%, 3%)	(-4%, -3%)	(-6%, -5%)	(3%, 4%)

§ Age-standardised (0-84 years) using 2001 Australian population as the standard population

‡ % changes represent the relative change in each of the outcomes from strategies incorporating screening stopping age at 69 years compared to equivalent strategies (i.e. same strategy variants except for screening stopping age). Minimum and maximum % change across all strategies within each test technology were used as the range. The upper and the lower range sometimes appears to be the same, however this is because these numbers have been rounded to the nearest integer.

†† Negative values represent a decrease

§§ Test characteristics for LBC is based on cell filtration technology

Table E 14 Summary of health outcomes and budget impact for all screening scenarios when the screening end-age is changed to 69 years compared to current practice – unvaccinated population

Test technology	Cancer incidence -		Cancer mortality -		Total cost associated with screening program -		
	ASR§ (range)	% change in ASR§ compared to CP (range‡)††	ASR§ (range)	% change in ASR§ compared to CP (range‡)††	Total screening program cost (\$ M) (range‡)	Difference in program cost compared to CP (\$ M) (range‡)	% change compared to CP (range‡)††
Current practice (model predicted)**	6.9	-	1.8	-	214.7	-	-
Conventional cytology	(7.2, 7.7)	(4%, 12%)	(1.9, 2)	(4%, 13%)	(151.2, 180.5)	(-63.5, -34.3)	(-30%, -16%)
Manually-read LBC§§	(5.8, 7)	(-16%, 1%)	(1.5, 1.8)	(-18%, -1%)	(168.6, 218.3)	(-46.2, 3.5)	(-22%, 2%)
Image-read LBC§§	(5.7, 6.8)	(-18%, -2%)	(1.5, 1.7)	(-20%, -3%)	(176.9, 230.1)	(-37.9, 15.3)	(-18%, 7%)
Primary HPV screening with cytology triage	(5.6, 6.2)	(-19%, -11%)	(1.4, 1.6)	(-21%, -14%)	(160, 179.2)	(-54.7, -35.5)	(-25%, -17%)
Primary HPV screening with partial genotyping	(5.5, 5.8)	(-21%, -17%)	(1.4, 1.5)	(-23%, -20%)	(166, 184.9)	(-48.8, -29.9)	(-23%, -14%)
Primary HPV and adjunctive cytology co-testing	(5.5, 6.1)	(-20%, -12%)	(1.4, 1.5)	(-22%, -15%)	(197.5, 223.5)	(-17.2, 8.8)	(-8%, 4%)

§ Age-standardised (0-84 years) using 2001 Australian population as the standard population

‡ % changes represent the relative change in each of the outcomes from strategies incorporating screening stopping age at 69 years compared to equivalent strategies (i.e. same strategy variants except for screening stopping age). Minimum and maximum % change across all strategies within each test technology were used as the range. The upper and the lower range sometimes appears to be the same, however this is because these numbers have been rounded to the nearest integer.

†† Negative values represent a decrease

§§ Test characteristics for LBC is based on cell filtration technology

Table E 15 Summary of health outcomes and budget impact for all screening scenarios when the screening end-age is changed to 69 years compared to current practice – cohort offered vaccination at age 12 years

Test technology	Cancer incidence -		Cancer mortality -		Total cost associated with screening program -		
	ASR§ (range)	% change in ASR§ compared to CP (range‡)††	ASR§ (range)	% change in ASR§ compared to CP (range‡)††	Total screening program cost (\$ M) (range‡)	Difference in program cost compared to CP (\$ M) (range‡)	% change compared to CP (range‡)††
Current practice (model predicted)**	2.9	-	0.7	-	184.4	-	-
Conventional cytology	(3, 3.2)	(3%, 10%)	(0.8, 0.8)	(3%, 11%)	(122.2, 151.1)	(-62.2, -33.2)	(-34%, -18%)
Manually-read LBC§§	(2.4, 2.9)	(-16%, 0%)	(0.6, 0.7)	(-18%, -2%)	(141, 187.5)	(-43.4, 3.1)	(-24%, 2%)
Image-read LBC§§	(2.4, 2.8)	(-18%, -3%)	(0.6, 0.7)	(-19%, -4%)	(148.7, 198.2)	(-35.6, 13.8)	(-19%, 8%)
Primary HPV screening with cytology triage	(2.3, 2.6)	(-19%, -11%)	(0.6, 0.6)	(-22%, -14%)	(127.7, 144.1)	(-56.6, -40.3)	(-31%, -22%)
Primary HPV screening with partial genotyping	(2.3, 2.5)	(-19%, -13%)	(0.6, 0.6)	(-22%, -17%)	(130, 146.6)	(-54.4, -37.7)	(-29%, -20%)
Primary HPV and adjunctive cytology co-testing	(2.3, 2.5)	(-20%, -13%)	(0.6, 0.6)	(-23%, -16%)	(166.2, 189.6)	(-18.1, 5.2)	(-10%, 3%)

§ Age-standardised (0-84 years) using 2001 Australian population as the standard population

‡ % changes represent the relative change in each of the outcomes from strategies incorporating screening stopping age at 69 years compared to equivalent strategies (i.e. same strategy variants except for screening stopping age). Minimum and maximum % change across all strategies within each test technology were used as the range. The upper and the lower range sometimes appears to be the same, however this is because these numbers have been rounded to the nearest integer.

†† Negative values represent a decrease

§§ Test characteristics for LBC is based on cell filtration technology

Table E 16 Health outcomes of primary HPV testing strategies compared to selected candidate strategies from both manually-read and image-read LBC

Test technology	Selected candidate strategy	ASR§ (% change compared to LBC) in unvaccinated cohort		ASR§ (% change compared to LBC) in vaccinated cohort	
		Incidence††	Mortality††	Incidence††	Mortality††
-	-				
Manually-read LBC§§ (Comparator)	IARC, Manual, CR, HPV triage, Opt B, Exit, Fast	6.2	1.63	2.6	0.68
Primary HPV screening with cytology triage	HPV, Auto, 5-yearly, Opt B, Fast, CR2	5.8 (-6 %)	1.5 (-7 %)	2.4 (-2 %)	0.6 (-3 %)
Primary HPV screening with partial genotyping	Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	5.7 (-8 %)	1.5 (-9 %)	2.4 (-3 %)	0.6 (-3 %)
primary HPV and adjunctive cytology co-testing	Co-testing, Auto, 5-yearly, Opt B, Fast, CR2	5.8 (-7 %)	1.5 (-8 %)	2.4 (-3 %)	0.6 (-4 %)
Image-read LBC§§ (Comparator)	IARC, Auto, CR, HPV triage, Opt B, Exit, Fast	6.1	1.60	2.5	0.67
Primary HPV screening with cytology triage	HPV, Auto, 5-yearly, Opt B, Fast, CR2	5.8 (0 %)	1.5 (0 %)	2.4 (-2 %)	0.6 (-3 %)
Primary HPV screening with partial genotyping	Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	5.7 (-2 %)	1.5 (-2 %)	2.4 (-3 %)	0.6 (-3 %)
primary HPV and adjunctive cytology co-testing	Co-testing, Auto, 5-yearly, Opt B, Fast, CR2	5.8 (-1 %)	1.5 (-1 %)	2.4 (-3 %)	0.6 (-4 %)

CP – current practice; IARC – IARC recommended screening age and interval; CC – conventional cytology; Manual – manually-read LBC; Auto – image-read LBC

Slow – women will not receive an invitation to attend their first cervical screen; Fast – women will receive an invitation to attend their first cervical screen

CR – call-and-recall program (proactive invitation) for strategies incorporating conventional cytology and LBC (either manually-read or image-read); CR2 - call-and-recall program (assuming a higher proportion of early re-screening and a lower proportion of women who screen in-time) for primary HPV testing strategies

Opt B – direct colposcopy referral for women with low-grade cytology and testing HPV positive using reflex HPV triage

Exit –HPV exit testing for women exiting the program at age 65 years (Note: all primary HPV screening strategies incorporate HPV exit testing for women 65+ years of age therefore not specified in the above table)

§ Age-standardised rate per 100,000 women (0-84 years) using 2001 Australian population as the standard population

†† Negative values represent a decrease

§§ Test characteristics for LBC is based on cell filtration technology

Figure E 11 Predicted age-specific cancer incidence per 100,000 women for current practice and selected candidate strategies (recommended screening end age 69 years) – unvaccinated cohort

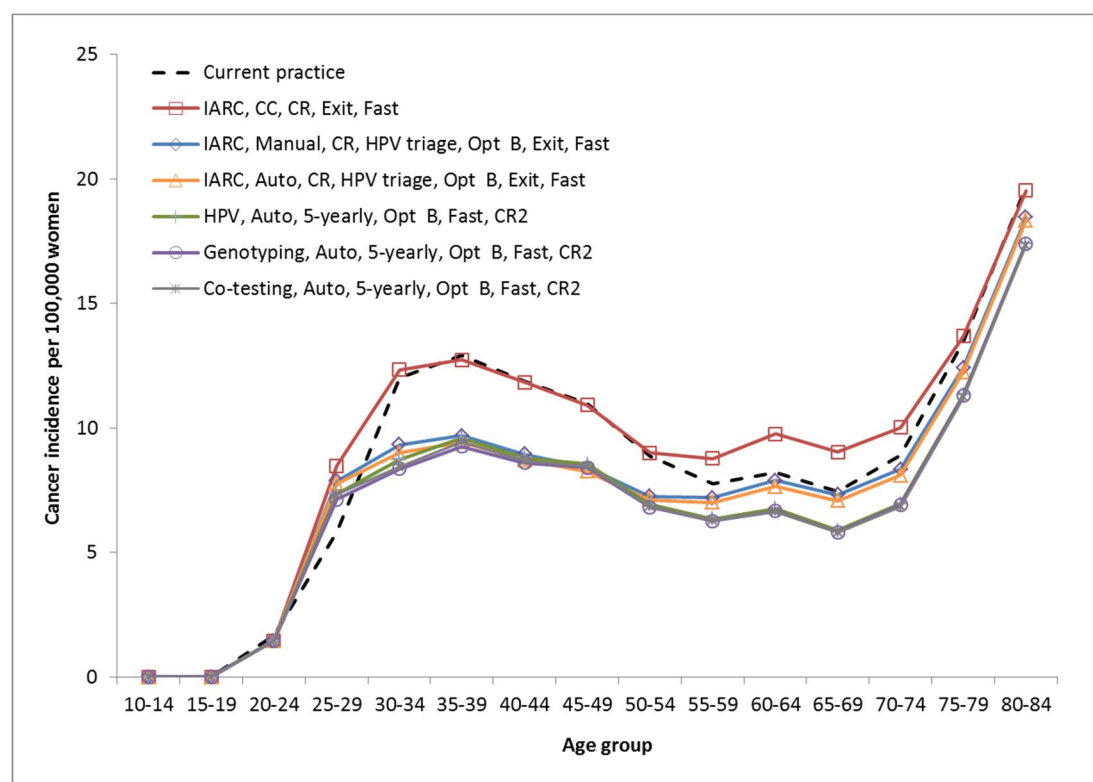


Figure E 12 Predicted age-specific cancer mortality per 100,000 women for current practice and selected candidate strategies (recommended screening end age 69 years) – unvaccinated cohort

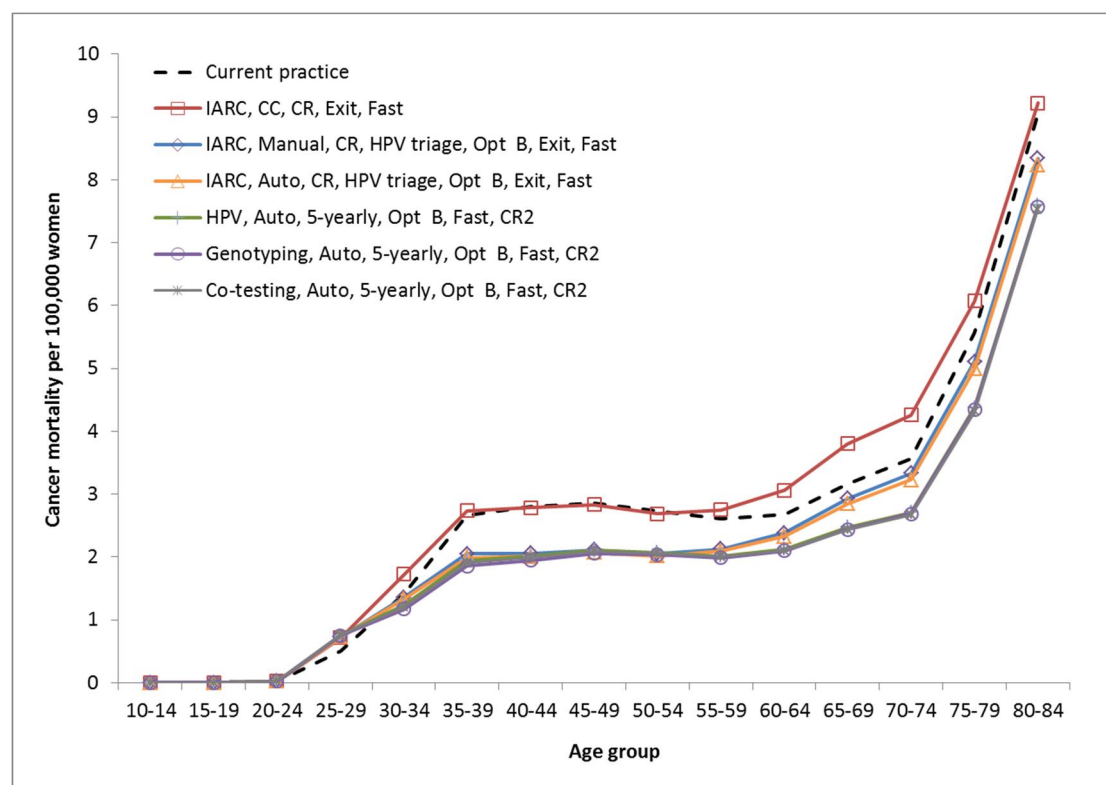


Figure E 13 Predicted age-specific cancer incidence per 100,000 women for current practice and selected candidate strategies (recommended screening end age 69 years) – cohort offered vaccination at age 12 years

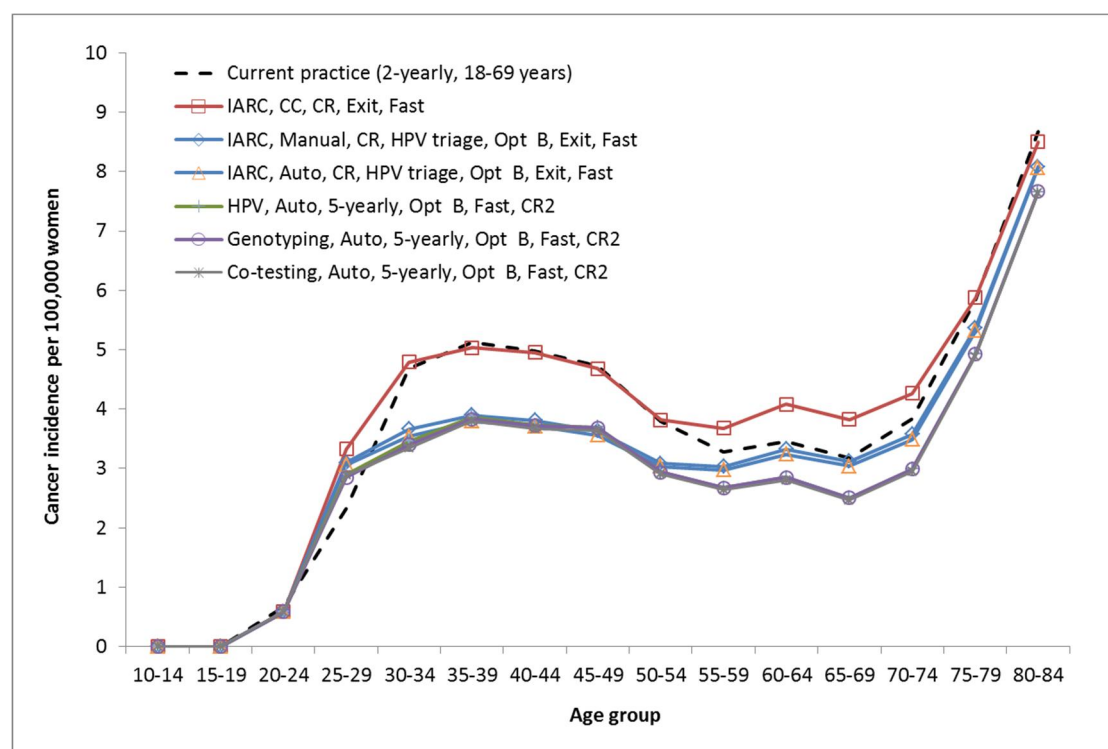


Figure E 14 Predicted age-specific cancer mortality per 100,000 women for current practice and selected candidate strategies (recommended screening end age 69 years) – cohort offered vaccination at age 12 years

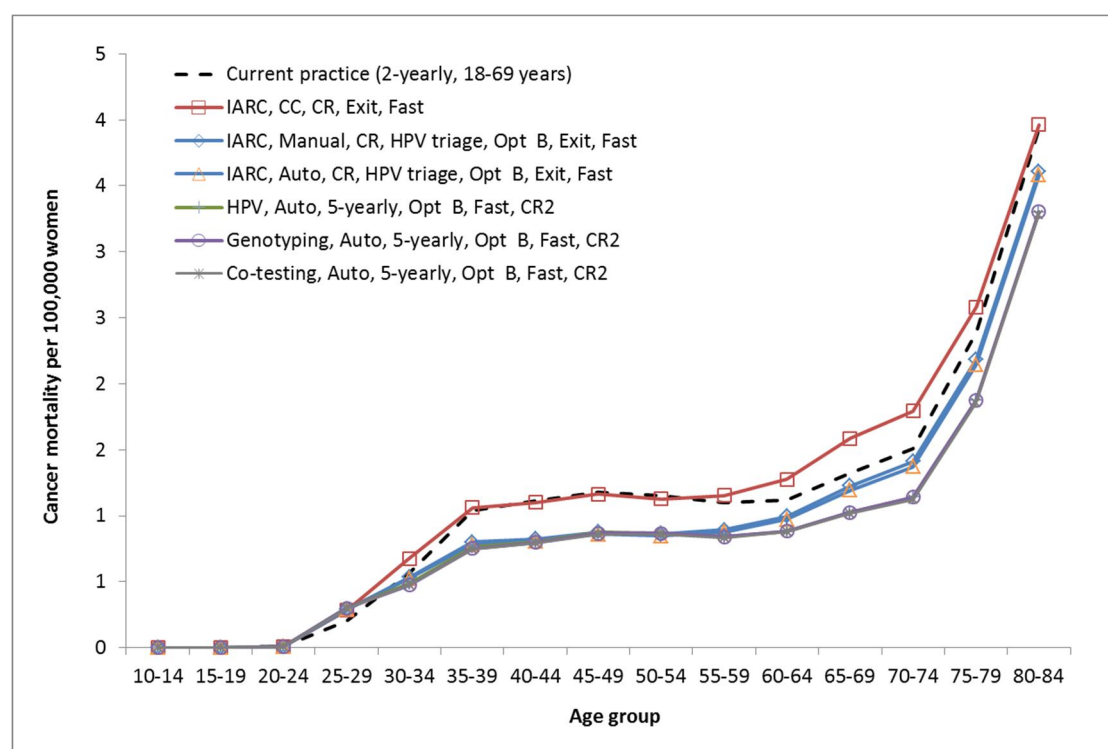


Table E 17 Summary of health resources utilisation for all potential screening scenarios compared to current practice – unvaccinated cohort

Test technology	-	% change in annual number* of tests compared to current practice††	-	-	-	-
	Average number* of lifetime screening episode^ per woman (range‡)	Cytology test# (% range‡)	HPV test (% range‡)	Colposcopies¶ (% range‡)	No. of women with histology evaluation (% range‡)	TreatmentΩ (% range‡)
Current practice (model predicted)**	15	2.39 million	54700	81300	40000	21485
Conventional cytology	(9, 11)	(-41%, -23%)	(-21%, 81%)	(-22%, -12%)	(-22%, -12%)	(-23%, -13%)
Manually-read LBC§§	(9, 11)	(-41%, -22%)	(-20%, 538%)	(-17%, 20%)	(-19%, 24%)	(-22%, -4%)
Image-read LBC§§	(9, 11)	(-41%, -21%)	(-16%, 561%)	(-17%, 23%)	(-18%, 29%)	(-22%, -4%)
Primary HPV screening with cytology triage	(7, 8)	(-85%, -82%)	(2061%, 2250%)	(-7%, 20%)	(-4%, 28%)	(-21%, -9%)
Primary HPV screening with partial genotyping	(7, 8)	(-87%, -85%)	(2066%, 2255%)	(12%, 37%)	(17%, 46%)	(-17%, -8%)
primary HPV and adjunctive cytology co-testing	(8, 8)	(-48%, -43%)	(2109%, 2300%)	(6%, 33%)	(9%, 40%)	(-15%, -4%)

^ Episode is defined as the sequence of events within 12 month (e.g. cytology with HPV triage with or without colposcopy)

includes unsatisfactory tests

* Using female Australian population as predicted for 2015

**Predicted values under current practice management using female Australian population as predicted for 2015

‡ Minimum and maximum % change across all strategies within each test technology were used as the range

†† Negative values represent a decrease

¶ Colposcopies predicted by the model represent total number of colposcopies, including investigative procedures performed on women referred with an abnormal test, colposcopies performed at treatment and colposcopies performed during post-treatment follow-up

Ω Treatment numbers predicted by the model include re-treatments after a failed treatment procedure. As the model includes the possibility of referral to excisional biopsy without a histologically confirmed high grade lesion, a small number of treatments are performed on women without advanced (CIN2+) disease

§§ Test characteristics for LBC is based on cell filtration technology

Table E 18 Summary of health resources utilisation for all potential screening scenarios compared to current practice – cohort offered vaccination at age 12 years

Test technology	Average number* of lifetime screening episode [^] per woman (range‡)	% change in annual number* of tests compared to current practice††				
		Cytology test# (% range‡)	HPV test (% range‡)	Colposcopies¶ (% range‡)	No. of women with histology evaluation (% range‡)	TreatmentΩ (% range‡)
Current practice (model predicted)**	15	2.35 million	31100	57900	28200	13203
Conventional cytology	(9, 11)	(-42%, -24%)	(-24%, 149%)	(-23%, -13%)	(-23%, -12%)	(-28%, -16%)
Manually-read LBC§§	(9, 11)	(-41%, -22%)	(-24%, 866%)	(-20%, 21%)	(-20%, 25%)	(-27%, -6%)
Image-read LBC§§	(9, 11)	(-41%, -22%)	(-20%, 895%)	(-22%, 22%)	(-21%, 28%)	(-27%, -7%)
Primary HPV screening with cytology triage	(7, 8)	(-88%, -86%)	(3591%, 3916%)	(-16%, 13%)	(-11%, 22%)	(-29%, -15%)
Primary HPV screening with partial genotyping	(7, 8)	(-91%, -89%)	(3583%, 3909%)	(-16%, 13%)	(-11%, 22%)	(-29%, -16%)
primary HPV and adjunctive cytology co-testing	(7, 8)	(-50%, -45%)	(3674%, 4001%)	(1%, 29%)	(5%, 37%)	(-21%, -8%)

[^] Episode is defined as the sequence of events within 12 month (e.g. cytology with HPV triage with or without colposcopy)

includes unsatisfactory tests

* Using female Australian population as predicted for 2015

**Predicted values under current practice management using female Australian population as predicted for 2015

‡ Minimum and maximum % change across all strategies within each test technology were used as the range

†† Negative values represent a decrease

¶ Colposcopies predicted by the model represent total number of colposcopies, including investigative procedures performed on women referred with an abnormal test, colposcopies performed at treatment and colposcopies performed during post-treatment follow-up

Ω Treatment numbers predicted by the model include re-treatments after a failed treatment procedure. As the model includes the possibility of referral to excisional biopsy without a histologically confirmed high grade lesion, a small number of treatments are performed on women without advanced (CIN2+) disease

§§ Test characteristics for LBC is based on cell filtration technology

Table E 19 Summary of health resources utilisation and the effect on mortality from the selected candidate strategies compared to current practice

Selected candidate strategy	Changes on the outcome in the selected strategies compared to current practice (unvaccinated)††				Changes on the outcome in the selected strategies compared to current practice (vaccinated)††			
	No* of additional colposcopies¶	% change in colposcopies¶	% change in Treatment for precancerΩ	% change in ASR§ mortality	No* of additional colposcopies¶	% change in colposcopies¶	% change in Treatment for precancerΩ	% change in ASR§ mortality
Current practice (model predicted)**	81,300	-	-	-	57,900	-	-	-
IARC, CC, CR, Exit, Fast	71,400	-12%	-16%	12%	50,500	-13%	-20%	12%
IARC, Manual, CR, HPV triage, Opt B, Exit, Fast	91,500	13%	-8%	-10%	64,800	12%	-11%	-9%
IARC, Auto, CR, HPV triage, Opt B, Exit, Fast	94,300	16%	-7%	-11%	66,000	14%	-11%	-11%
HPV, Auto, 5-yearly, Opt B, Fast, CR2	97,600	20%	-9%	-16%	65,400	13%	-15%	-16%
Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	111,000	37%	-8%	-18%	65,500	13%	-16%	-16%
Co-testing, Auto, 5-yearly, Opt B, Fast, CR2	107,800	33%	-4%	-17%	74,800	29%	-9%	-17%

IARC – IARC recommended screening age and interval; CC – conventional cytology; Manual – manually-read LBC; Auto – image-read LBC

Slow – women will not receive an invitation to attend their first cervical screen; Fast – women will receive an invitation to attend their first cervical screen

CR – call-and-recall program (proactive invitation) for strategies incorporating conventional cytology and LBC (either manually-read or image-read); CR2 - call-and-recall program (assuming a higher proportion of early re-screening and a lower proportion of women who screen in-time) for primary HPV testing strategies

Opt B – direct colposcopy referral for women with low-grade cytology and testing HPV positive using reflex HPV triage

Exit –HPV exit testing for women exiting the program at age 65 years (Note: all primary HPV screening strategies incorporate HPV exit testing for women 65+ years of age therefore not specified in the above table)

* Using female Australian population as predicted for 2015

**Predicted values under current practice management using female Australian population as predicted for 2015

§ Age-standardised (0-84 years) using 2001 Australian population as the standard population

†† Negative values represent a decrease

¶ Colposcopies predicted by the model represent total number of colposcopies, including investigative procedures performed on women referred with an abnormal test, colposcopies performed at treatment and colposcopies performed during post-treatment follow-up

Ω Treatment numbers predicted by the model include re-treatments after a failed treatment procedure. As the model includes the possibility of referral to excisional biopsy without a histologically confirmed high grade lesion, a small number of treatments are performed on women without advanced (CIN2+) disease

Table E 20 Age-specific total number of treatments from the selected candidate strategies compared to current practice – unvaccinated cohort

Test technology	Selected candidate strategy	Total number* of treatments Ω				Additional number* of treatmentsΩ compared to current practice††			
		15-29 years	30-64 years	65+ years	Total	15-29 years	30-64 years	65+ years	Total
-	-	-	-	-	-	-	-	-	-
Current practice	Current practice (model predicted)**	8,182	12,194	1,109	21,485	-	-	-	-
Conventional cytology	IARC, CC, CR, Exit, Fast	6,368	11,187	450	18,005	-1,814	-1,007	-659	-3,480
Manually-read LBC	IARC, Manual, CR, HPV triage, Opt B, Exit, Fast	8,106	11,382	484	19,972	-76	-812	-625	-1,513
Image-read LBC	IARC, Auto, CR, HPV triage, Opt B, Exit, Fast	7,707	11,577	505	19,789	-475	-617	-604	-1,696
Primary HPV screening with cytology triage	HPV, Auto, 5-yearly, Opt B, Fast, CR2	8,017	11,083	504	19,604	-165	-1,111	-605	-1,881
Primary HPV screening with partial genotyping	Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	8,305	11,049	506	19,860	123	-1,145	-603	-1,625
primary HPV and adjunctive cytology co-testing	Co-testing, Auto, 5-yearly, Opt B, Fast, CR2	8,279	11,702	564	20,545	97	-493	-545	-941

CP – current practice; IARC – IARC recommended screening age and interval; CC – conventional cytology; Manual – manually-read LBC; Auto – image-read LBC

Slow – women will not receive an invitation to attend their first cervical screen; Fast – women will receive an invitation to attend their first cervical screen

CR – call-and-recall program (proactive invitation) for strategies incorporating conventional cytology and LBC (either manually-read or image-read); CR2 - call-and-recall program (assuming a higher proportion of early re-screening and a lower proportion of women who screen in-time) for primary HPV testing strategies

Opt B – direct colposcopy referral for women with low-grade cytology and testing HPV positive using reflex HPV triage

Exit –HPV exit testing for women exiting the program at age 65 years (Note: all primary HPV screening strategies incorporate HPV exit testing for women 65+ years of age therefore not specified in the above table)

* Using female Australian population as predicted for 2015

**Predicted values under current practice management using female Australian population as predicted for 2015

†† Negative values represent a decrease

Ω Treatment numbers predicted by the model include re-treatments after a failed treatment procedure. As the model includes the possibility of referral to excisional biopsy without a histologically confirmed high grade lesion, a small number of treatments are performed on women without advanced (CIN2+) disease

Table E 21 Age-specific total number of treatments from the selected candidate strategies compared to current practice – cohort offered vaccination at age 12 years

Test technology	Selected candidate strategy	Total number* of treatments Ω				Additional number* of treatments Ω compared to current practice††			
		15-29 years	30-64 years	65+ years	Total	15-29 years	30-64 years	65+ years	Total
-	-	-	-	-	-	-	-	-	-
Current practice	Current practice (model predicted)**	4,552	7,782	869	13,203	-	-	-	-
Conventional cytology	IARC, CC, CR, Exit, Fast	3,389	6,849	285	10,523	-1,163	-933	-584	-2,680
Manually-read LBC	IARC, Manual, CR, HPV triage, Opt B, Exit, Fast	4,334	7,087	303	11,724	-218	-695	-566	-1,479
Image-read LBC	IARC, Auto, CR, HPV triage, Opt B, Exit, Fast	4,089	7,303	328	11,720	-463	-478	-542	-1,483
Primary HPV screening with cytology triage	HPV, Auto, 5-yearly, Opt B, Fast, CR2	4,221	6,647	300	11,168	-331	-1,135	-569	-2,035
Primary HPV screening with partial genotyping	Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	4,250	6,567	297	11,114	-303	-1,215	-573	-2,091
primary HPV and adjunctive cytology co-testing	Co-testing, Auto, 5-yearly, Opt B, Fast, CR2	4,377	7,299	359	12,035	-175	-483	-511	-1,169

IARC – IARC recommended screening age and interval; CC – conventional cytology; Manual – manually-read LBC; Auto – image-read LBC

Slow – women will not receive an invitation to attend their first cervical screen; Fast – women will receive an invitation to attend their first cervical screen

CR – call-and-recall program (proactive invitation) for strategies incorporating conventional cytology and LBC (either manually-read or image-read); CR2 - call-and-recall program (assuming a higher proportion of early re-screening and a lower proportion of women who screen in-time) for primary HPV testing strategies

Opt B – direct colposcopy referral for women with low-grade cytology and testing HPV positive using reflex HPV triage

Exit –HPV exit testing for women exiting the program at age 65 years (Note: all primary HPV screening strategies incorporate HPV exit testing for women 65+ years of age therefore not specified in the above table)

* Using female Australian population as predicted for 2015

**Predicted values under current practice management using female Australian population as predicted for 2015

†† Negative values represent a decrease

Ω Treatment numbers predicted by the model include re-treatments after a failed treatment procedure. As the model includes the possibility of referral to excisional biopsy without a histologically confirmed high grade lesion, a small number of treatments are performed on women without advanced (CIN2+) disease

Figure E 15 The relative trade-off between the percent increase in the mortality and the percent increase in colposcopies compared to current practice for all of the strategies considered (unvaccinated cohorts and cohorts offered vaccination are shown together on this graph)

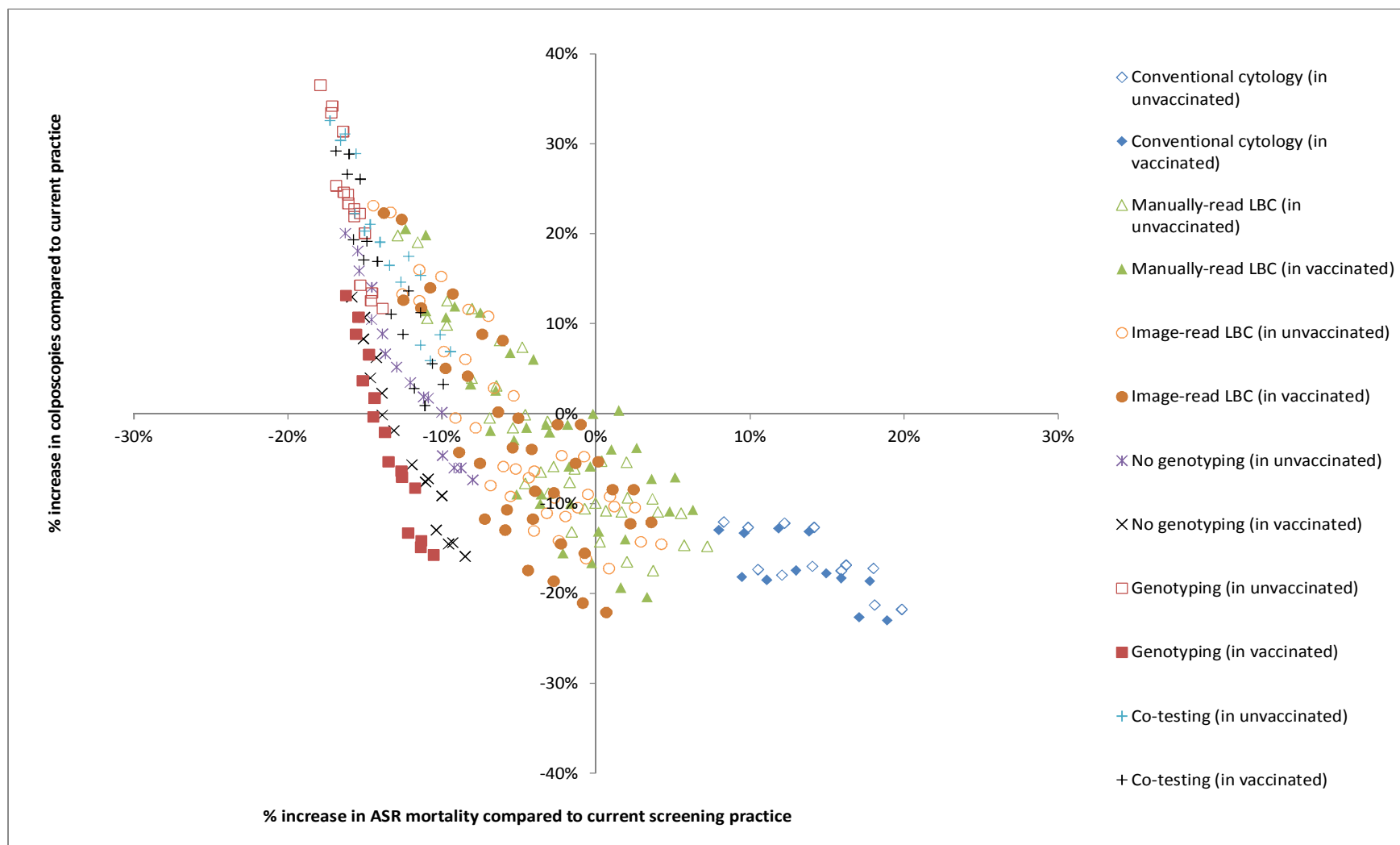


Table E 22 **Summary of treatment breakdown for high grade abnormalities (CIN 2 or CIN 3) - unvaccinated cohort**

Test technology	Difference in high grade squamous abnormalities* (CIN2 or CIN3) detected compared to CP††			Percentage of high-grade treatments that are for CIN2* (range‡)	% change in ASR§ mortality compared to CP (range‡)††
	Difference in overall cases of CIN 2 or CIN 3 (range‡)	Difference in CIN 2 cases (range‡)	Difference in CIN 3 cases (range‡)		
Current Practice	-	-	-	40%	-
Conventional cytology	(-3528, -1911)	(-2851, -1632)	(-677, -279)	(30%, 34%)	(8%, 20%)
Manually-read LBC	(-3623, -557)	(-3755, -1463)	(132, 906)	(24%, 33%)	(-13%, 7%)
Image-read LBC	(-3033, 91)	(-3146, -703)	(113, 794)	(27%, 36%)	(-14%, 4%)
Primary HPV screening with cytology triage	(-2385, 46)	(-2908, -862)	(492, 997)	(27%, 35%)	(-16%, -8%)
Primary HPV screening with partial genotyping	(-1696, 320)	(-2332, -564)	(606, 935)	(30%, 36%)	(-18%, -14%)
primary HPV and adjunctive cytology co-testing	(-2135, 312)	(-2687, -596)	(516, 1001)	(28%, 36%)	(-17%, -9%)

CP – current practice

* Using female Australian population as predicted for 2015

§ Age-standardised (0-84 years) using 2001 Australian population as the standard population

‡ Minimum and maximum values across all strategies within each test technology were used as the range

†† Negative values represent a decrease

Table E 23 **Summary of treatment breakdown for high grade abnormalities (CIN 2 or CIN 3) - cohort offered vaccination at age 12 years**

Test technology	Difference in high grade squamous abnormalities* (CIN2 or CIN3) detected compared to CP††			Percentage of high-grade treatments that are for CIN2* (range‡)	% change in ASR§ mortality compared to CP (range‡)††
	Difference in overall cases of CIN 2 or CIN 3 (range‡)	Difference in CIN 2 cases (range‡)	Difference in CIN 3 cases (range‡)		Difference in overall cases of CIN 2 or CIN 3 (range‡)
Current Practice	-	-	-	44%	-
Conventional cytology	(-2346, -1300)	(-1833, -1049)	(-513, -251)	(34%, 39%)	(8%, 19%)
Manually-read LBC	(-2482, -470)	(-2398, -927)	(-84, 457)	(27%, 37%)	(-12%, 6%)
Image-read LBC	(-2080, -1)	(-2005, -419)	(-74, 418)	(31%, 40%)	(-14%, 4%)
Primary HPV screening with cytology triage	(-1761, -107)	(-1941, -603)	(173, 532)	(30%, 39%)	(-16%, -8%)
Primary HPV screening with partial genotyping	(-1711, -116)	(-1892, -597)	(175, 508)	(31%, 39%)	(-16%, -11%)
primary HPV and adjunctive cytology co-testing	(-1586, 86)	(-1792, -423)	(199, 546)	(32%, 40%)	(-17%, -10%)

CP – current practice

* Using female Australian population as predicted for 2015

§ Age-standardised (0-84 years) using 2001 Australian population as the standard population

‡ Minimum and maximum values across all strategies within each test technology were used as the range

†† Negative values represent a decrease

Table E 24 **Summary of the effect of screening initiation (fast vs slow uptake) on health and cost outcomes**

Test technology	% change in the outcome from strategies incorporating fast uptake compared to equivalent strategies incorporating slow uptake (range‡) in unvaccinated cohort††			% change in the outcome from strategies incorporating fast uptake compared to equivalent strategies incorporating slow uptake (range‡) in vaccinated cohort††		
	Cancer incidence (ASR§) (range‡)	Cancer mortality (ASR§) (range‡)	Total screening programming cost (range‡)	Cancer incidence (ASR§) (range‡)	Cancer mortality (ASR§) (range‡)	Total screening programming cost (range‡)
-						
Conventional cytology	(-2%, -2%)	(-2%, -2%)	(4%, 4%)	(-2%, -1%)	(-1%, -1%)	(5%, 5%)
Manually-read LBC§§	(-3%, -2%)	(-2%, -2%)	(4%, 5%)	(-2%, -1%)	(-2%, -1%)	(4%, 5%)
Image-read LBC§§	(-3%, -2%)	(-2%, -2%)	(4%, 5%)	(-2%, -1%)	(-2%, -1%)	(4%, 5%)
Primary HPV screening with cytology triage	(-3%, -2%)	(-2%, -2%)	(5%, 5%)	(-2%, -2%)	(-2%, -1%)	(5%, 5%)
Primary HPV screening with partial genotyping	(-2%, -2%)	(-2%, -2%)	(5%, 6%)	(-2%, -2%)	(-1%, -1%)	(5%, 5%)
primary HPV and adjunctive cytology co-testing	(-3%, -2%)	(-2%, -2%)	(5%, 5%)	(-2%, -2%)	(-2%, -1%)	(5%, 5%)

Slow – women will not receive an invitation to attend their first cervical screen; Fast – women will receive an invitation to attend their first cervical screen

§ Age-standardised rate per 100,000 women (0-84 years) using 2001 Australian population as the standard population

‡ % changes represent the relative change in each of the outcomes from strategies incorporating fast uptake compared to equivalent strategies (i.e. same strategy variants except for screening initiation) incorporating slow uptake. Minimum and maximum % change across all strategies within each test technology were used as the range. The upper and the lower range sometimes appears to be the same, however this is because these numbers have been rounded to the nearest integer.

†† Negative values represent a decrease.

§§ Test characteristics for LBC is based on cell filtration technology

Table E 25 Summary of the effect of screening program (call-and-recall program vs reminder-based program) on health and cost outcomes

Test technology	% change in outcomes under a call-and-recall program compared to the equivalent strategy that utilises a reminder based system (range‡)†† (unvaccinated cohort)			% change in outcomes under a call-and-recall program compared to the equivalent strategy that utilises a reminder based system (range‡)†† (vaccinated cohort)		
	Cancer incidence (ASR§) (range‡)	Cancer mortality (ASR§) (range‡)	Total screening programming cost (range‡)	Cancer incidence (ASR§) (range‡)	Cancer mortality (ASR§) (range‡)	Total screening programming cost (range‡)
Conventional cytology	-	-	-	-	-	-
Reminder (R2) compared to call-and-recall (CR)	(-2%, -2%)	(-4%, -3%)	(9%, 9%)	(-2%, -2%)	(-4%, -3%)	(12%, 12%)
Call-and-recall (CR) compared to reminder (R1)	(-3%, -3%)	(-3%, -3%)	(4%, 4%)	(-3%, -3%)	(-4%, -3%)	(5%, 5%)
Manually-read LBC§§	-	-	-	-	-	-
Reminder (R2) compared to call-and-recall (CR)	(-3%, -2%)	(-4%, -3%)	(10%, 11%)	(-3%, -2%)	(-4%, -3%)	(12%, 13%)
Call-and-recall (CR) compared to reminder (R1)	(-3%, -3%)	(-4%, -3%)	(4%, 4%)	(-4%, -3%)	(-4%, -3%)	(5%, 5%)
Image-read LBC§§	-	-	-	-	-	-
Reminder (R2) compared to call-and-recall (CR)	(-3%, -2%)	(-4%, -3%)	(10%, 11%)	(-3%, -2%)	(-4%, -3%)	(12%, 13%)
Call-and-recall (CR) compared to reminder (R1)	(-3%, -3%)	(-3%, -3%)	(4%, 5%)	(-3%, -3%)	(-4%, -3%)	(5%, 6%)

CR – call-and-recall program (proactive invitation); R1 - reminder-based program (with the lower proportion of the overall participation rate); R2 - reminder-based program (with the higher proportion of the overall participation rate)

§ Age-standardised rate per 100,000 women (0-84 years) using 2001 Australian population as the standard population

‡ % changes represent the relative change in each of the outcomes from strategies incorporating fast uptake compared to equivalent strategies (i.e. same strategy variants except for screening initiation) incorporating slow uptake. Minimum and maximum % change across all strategies within each test technology were used as the range. The upper and the lower range sometimes appears to be the same, however this is because these numbers have been rounded to the nearest integer.

†† Negative values represent a decrease

§§ Test characteristics for LBC is based on cell filtration technology

Table E 26 Summary of the effect of poor compliance with 5-yearly call-and-recall (high proportion of early re-screening, CR2) compared with the equivalent strategy under assumptions of better compliance with 5-yearly screening (low proportion of early re-screening, most women re-attending on time (CR1)) for primary HPV testing strategies

Test technology	% change in outcomes comparing strategies under CR2 with the equivalent strategy under CR1†† (unvaccinated cohort)			% change in outcomes comparing strategies under CR2 with the equivalent strategy under CR1†† (vaccinated cohort)		
	Cancer incidence (ASR§) (range‡)	Cancer mortality (ASR§) (range‡)	Total screening programming cost (range‡)	Cancer incidence (ASR§) (range‡)	Cancer mortality (ASR§) (range‡)	Total screening programming cost (range‡)
Primary HPV screening with cytology triage	(-1%, -1%)	(-1%, -1%)	(2%, 3%)	(-1%, -1%)	(-1%, -1%)	(3%, 3%)
Primary HPV screening with partial genotyping	(-1%, -1%)	(-1%, -1%)	(2%, 3%)	(-1%, -1%)	(-1%, -1%)	(3%, 3%)
primary HPV and adjunctive cytology co-testing	(-1%, -1%)	(-1%, -1%)	(3%, 3%)	(-1%, -1%)	(-1%, -1%)	(3%, 3%)

CR1- call-and-recall program (assuming high compliance with the recommended screening interval and limited early re-screening); CR2 - call-and-recall program (assuming a higher proportion of early re-screening and a lower proportion of women who screen in-time)

§ Age-standardised rate per 100,000 women (0-84 years) using 2001 Australian population as the standard population

‡ % changes represent the relative change in each of the outcomes from strategies incorporating fast uptake compared to equivalent strategies (i.e. same strategy variants except for screening initiation) incorporating slow uptake. Minimum and maximum % change across all strategies within each test technology were used as the range. The upper and the lower range sometimes appears to be the same, however this is because these numbers have been rounded to the nearest integer.

†† Negative values represent a decrease

Table E 27 Summary of the effect of HPV triage testing for women with low-grade cytology on health and cost outcomes – comparison among strategies incorporating HPV triage testing with different follow-up options (Option A, B) for women testing HPV positive and not incorporating HPV triage (no triage)

Test technology	% change in the outcome among strategies incorporating HPV triage testing with different follow-up options and not incorporating triage†† (unvaccinated cohort)			% change in the outcome among strategies incorporating HPV triage testing with different follow-up options and not incorporating triage†† (vaccinated cohort)		
	Cancer incidence (ASR§) (range‡)	Cancer mortality (ASR§) (range‡)	Total screening program cost (range‡)	Cancer incidence (ASR§) (range‡)	Cancer mortality (ASR§) (range‡)	Total screening program cost (range‡)
Manually-read LBC§§	-	-	-	-	-	-
HPV triage option B compared to no triage ^a	(-11%, -9%)	(-10%, -10%)	(6%, 9%)	(-10%, -9%)	(-9%, -9%)	(6%, 8%)
HPV triage option B compared to HPV triage option A ^b	(-7%, -7%)	(-7%, -6%)	(2%, 3%)	(-7%, -6%)	(-6%, -6%)	(2%, 3%)
HPV triage option A compared to no triage ^c	(-4%, -3%)	(-4%, -3%)	(4%, 6%)	(-3%, -2%)	(-4%, -3%)	(4%, 6%)
Image-read LBC§§	-	-	-	-	-	-
HPV triage option B compared to no triage ^a	(-10%, -9%)	(-10%, -9%)	(7%, 9%)	(-9%, -8%)	(-9%, -8%)	(6%, 9%)
HPV triage option B compared to HPV triage option A ^b	(-7%, -6%)	(-6%, -6%)	(3%, 3%)	(-6%, -6%)	(-6%, -5%)	(3%, 3%)
HPV triage option A compared to no triage ^c	(-4%, -3%)	(-4%, -3%)	(4%, 6%)	(-3%, -2%)	(-4%, -3%)	(3%, 5%)
Primary HPV screening with cytology triage	-	-	-	-	-	-
HPV triage option B compared to HPV triage option A ^b	(-6%, -5%)	(-5%, -5%)	(2%, 3%)	(-5%, -5%)	(-5%, -4%)	(2%, 3%)
Primary HPV screening with partial genotyping	-	-	-	-	-	-
HPV triage option B compared to HPV triage option A ^b	(-1%, -1%)	(-1%, -1%)	(2%, 2%)	(-4%, -3%)	(-4%, -3%)	(2%, 3%)
Primary HPV and adjunctive cytology co-testing	-	-	-	-	-	-
HPV triage option B compared to HPV triage option A ^b	(-5%, -5%)	(-5%, -4%)	(2%, 2%)	(-5%, -4%)	(-5%, -4%)	(2%, 2%)

HPV triage option A – 12 months follow-up for women with low-grade cytology and testing HPV positive using reflex HPV triage; HPV triage option B – direct colposcopy referral for women with low-grade cytology and testing HPV positive using reflex HPV triage; no triage – not incorporating HPV triage testing for women with low-grade cytology

§ Age-standardised rate per 100,000 women (0-84 years) using 2001 Australian population as the standard population.

‡ % changes represent the relative change in each of the outcomes as following: ^a strategies incorporating HPV triage testing with immediate colposcopy referral for women testing HPV positive compared to strategies not incorporating HPV triage testing for women with low-grade cytology; ^b strategies incorporating immediate colposcopy referral compared to strategies incorporating 12 months follow-up for women

testing HPV positive using reflex HPV triage testing for women with low-grade cytology; ° strategies incorporating 12 months follow-up for women testing HPV positive compared to strategies not incorporating HPV triage testing for women with low-grade cytology. Minimum and maximum % change across all strategies within each test technology were used as the range. The upper and the lower range sometimes appears to be the same, however this is because these numbers have been rounded to the nearest integer.

†† Negative values represent a decrease; §§ Test characteristics for LBC is based on cell filtration technology

Table E 28 **Summary of the effect of HPV exit testing for women 65+ years of age on health and cost outcomes**

Test technology	% change compared to the equivalent strategy without exit HPV testing†† (unvaccinated cohort)			% change compared to the equivalent strategy without exit HPV testing†† (vaccinated cohort)		
	Cancer incidence (ASR§) (range‡)	Cancer mortality (ASR§) (range‡)	Total screening programming cost (range‡)	Cancer incidence (ASR§) (range‡)	Cancer mortality (ASR§) (range‡)	Total screening programming cost (range‡)
Conventional cytology	(-1%, -1%)	(-2%, -1%)	(1%, 1%)	(-1%, -1%)	(-2%, -1%)	(1%, 1%)
Manually-read LBC§§	(-1%, -1%)	(-2%, -1%)	(0%, 1%)	(-1%, -1%)	(-2%, -1%)	(0%, 1%)
Image-read LBC§§	(-1%, -1%)	(-2%, -1%)	(0%, 1%)	(-1%, -1%)	(-2%, -1%)	(0%, 1%)

Note) all primary HPV screening strategies incorporate HPV exit testing for women 65+ years of age therefore not included in the above table

§ Age-standardised rate per 100,000 women (0-84 years) using 2001 Australian population as the standard population

‡ % changes represent the relative change in each of the outcomes from strategies incorporating HPV exit testing compared to equivalent strategies (i.e. same strategy variants except for HPV exit testing) without incorporating HPV exit testing. Minimum and maximum % change across all strategies within each test technology were used as the range. The upper and the lower range sometimes appears to be the same, however this is because these numbers have been rounded to the nearest integer.

†† Negative values represent a decrease.

§§ Test characteristics for LBC is based on cell filtration technology

Table E 29 Changes in predicted health outcomes when no cytology is taken at colposcopy for women referred with 16/18 positive directly to colposcopy when compared to the baseline strategy where women always have a cytology available for management at colposcopy – unvaccinated cohort

Strategy	Changes in cancer incidence compared to current practice††		Changes in cancer mortality compared to current practice††		Changes in total screening program cost††
	Additional cancer cases (% increase in cases)††	% change in ASR§ incidence††	Additional cancer deaths (% increase in cases)††	% change in ASR§ mortality	% Change in costs
Genotyping, Manual, 5-yearly, Opt A, Slow, CR1	17 (2%)	2%	5 (3%)	2%	-0.37%
Genotyping, Manual, 5-yearly, Opt A, Slow, CR2	17 (2%)	2%	5 (3%)	2%	-0.38%
Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	16 (2%)	2%	4 (2%)	2%	-0.52%

§ Age-standardised (0-84 years) using 2001 Australian population as the standard population

†† Negative values represent a decrease.

Table E 30 Changes in predicted health outcomes when no cytology is taken at colposcopy for women referred with 16/18 positive directly to colposcopy when compared to the baseline strategy where women always have a cytology available for management at colposcopy – cohort offered vaccination at age 12

Strategy	Changes in cancer incidence compared to current practice††		Changes in cancer mortality compared to current practice††		Changes in total screening program cost††
	Additional cancer cases (% increase in cases)††	% change in ASR§ incidence††	Additional cancer deaths (% increase in cases)††	% change in ASR§ mortality	% Change in costs
Genotyping, Manual, 5-yearly, Opt A, Slow, CR1	6 (2%)	2%	2 (2%)	2%	-0.10%
Genotyping, Manual, 5-yearly, Opt A, Slow, CR2	6 (2%)	2%	2 (2%)	2%	-0.10%
Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	4 (1%)	2%	1 (2%)	2%	-0.16%

§ Age-standardised (0-84 years) using 2001 Australian population as the standard population

†† Negative values represent a decrease.

Table E 31 Health and cost outcomes in strategies where women never return for more cervical screening after being completely discharged after a normal HPV exit test (compared to the equivalent strategy where some women continue to return after an exit test at rates as observed under current practice) and assuming screening ends at 69 instead of 64 years for both sets of scenarios – unvaccinated cohort

Test technology	Key strategies used in PSA that include HPV exit testing	Changes in cancer incidence compared to equivalent strategy where some women continue to return after being discharged after an exit HPV test ††		Changes in cancer mortality compared to equivalent strategy where some women continue to return after being discharged after an exit HPV test ††		% Changes in total screening program cost compared to equivalent strategy where some women continue to return after being discharged after an exit HPV test †
		Additional cancer cases (% increase in cases)††	% change in ASR§ incidence††	Additional cancer deaths (% increase in cases)††	% change in ASR§ incidence††	
Conventional cytology	IARC, CC, R2, Exit, Fast	1, (0.1%)	0, (0.1%)	0.1%	0.1%	-0.3%
	IARC, CC, CR, Exit, Fast	2, (0.2%)	0, (0.2%)	0.2%	0.2%	-0.6%
Manually-read LBC§§	IARC, Manual, R2, HPV triage, Opt B, Exit, Fast	1, (0.2%)	0, (0.2%)	0.2%	0.2%	-0.3%
	IARC, Manual, CR, HPV triage, Opt B, Exit, Fast	1, (0.2%)	0, (0.2%)	0.2%	0.2%	-0.3%
Image-read LBC§§	IARC, Auto, R2, HPV triage, Opt B, Exit, Fast	2, (0.3%)	1, (0.3%)	0.3%	0.3%	-0.6%
	IARC, Auto, CR, HPV triage, Opt B, Exit, Fast	2, (0.3%)	1, (0.3%)	0.3%	0.3%	-0.6%
Primary HPV screening with cytology triage	HPV, Manual, 5-yearly, Opt A, Slow, CR1	1, (0.2%)	0, (0.2%)	0.2%	0.2%	-0.3%
	HPV, Manual, 5-yearly, Opt A, Slow, CR2	1, (0.2%)	0, (0.2%)	0.2%	0.2%	-0.4%
	HPV, Auto, 5-yearly, Opt A, Slow, CR1	2, (0.2%)	0, (0.3%)	0.2%	0.3%	-0.5%
	HPV, Auto, 5-yearly, Opt A, Slow, CR2	2, (0.3%)	0, (0.3%)	0.3%	0.3%	-0.5%
	HPV, Auto, 5-yearly, Opt B, Fast, CR2	2, (0.3%)	1, (0.3%)	0.3%	0.3%	-0.5%
Primary HPV screening with partial genotyping	Genotyping, Manual, 5-yearly, Opt A, Slow, CR1	1, (0.2%)	0, (0.2%)	0.2%	0.2%	-0.4%
	Genotyping, Manual, 5-yearly, Opt A, Slow, CR2	2, (0.3%)	1, (0.3%)	0.3%	0.3%	-0.5%
	Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	2, (0.3%)	1, (0.3%)	0.3%	0.3%	-0.5%
Primary HPV and adjunctive cytology co-testing	Co-testing, Auto, 5-yearly, Opt A, Slow, CR1	1, (0.2%)	0, (0.2%)	0.2%	0.2%	-0.4%
	Co-testing, Auto, 5-yearly, Opt B, Fast, CR2	2, (0.3%)	1, (0.3%)	0.3%	0.3%	-0.5%

IARC – IARC recommended screening age and interval; CC – conventional cytology; Manual – manually-read LBC; Auto – image-read LBC; Slow – women will not receive an invitation to attend their first cervical screen; Fast – women will receive an invitation to attend their first cervical screen; CR – call-and-recall program (proactive invitation) for strategies incorporating conventional cytology and LBC (either manually-read or image-read); R1 - reminder-based program (with the lower proportion of the overall participation rate); R2 - reminder-based program (with the higher proportion of the overall participation rate); CR1 - call-and-recall program (assuming high compliance with the recommended screening interval and limited early re-screening) for primary HPV testing strategies; CR2 - call-and-recall program (assuming a higher proportion of early re-screening and a lower proportion of women who screen in-time) for primary HPV testing strategies; Opt A – 12 months follow-up for women with low-grade cytology and testing HPV positive using reflex HPV triage; Opt B – direct colposcopy referral for women with low-grade cytology and testing HPV positive using reflex HPV triage; Exit – HPV exit testing for women exiting the program at age 65 years (Note: all primary HPV screening strategies incorporate HPV exit testing for women 69+ years of age therefore not specified in the above table);

§§ Test characteristics for LBC is based on cell filtration technology;* Using female Australian population as predicted for 2015; § Age-standardised (0-84 years) using 2001 Australian population as the standard population; †† Negative values represent a decrease

Table E 32 Health and cost outcomes in strategies where women never return for more cervical screening after being completely discharged after a normal HPV exit test (compared to the equivalent strategy where some women continue to return after an exit test at rates as observed under current practice) and assuming screening ends at 69 instead of 64 years for both sets of scenarios – cohort offered vaccination at age 12

Test technology	Key strategies used in PSA that include HPV exit testing	Changes in cancer incidence compared to equivalent strategy where some women continue to return after being discharged after an exit HPV test ††		Changes in cancer mortality compared to equivalent strategy where some women continue to return after being discharged after an exit HPV test ††		% Changes in total screening program cost compared to equivalent strategy where some women continue to return after being discharged after an exit HPV test †
		Additional cancer cases (% increase in cases)††	% change in ASR§ incidence††	Additional cancer deaths (% increase in cases)††	% change in ASR§ mortality	
Conventional cytology	IARC, CC, R2, Exit, Fast	0, (0.1%)	0, (0.1%)	0.1%	0.1%	-0.4%
	IARC, CC, CR, Exit, Fast	1, (0.2%)	0, (0.2%)	0.2%	0.2%	-0.7%
Manually-read LBC§§	IARC, Manual, R2, HPV triage, Opt B, Exit, Fast	1, (0.2%)	0, (0.2%)	0.2%	0.2%	-0.4%
	IARC, Manual, CR, HPV triage, Opt B, Exit, Fast	1, (0.3%)	0, (0.3%)	0.3%	0.3%	-0.7%
Image-read LBC§§	IARC, Auto, R2, HPV triage, Opt B, Exit, Fast	1, (0.2%)	0, (0.2%)	0.2%	0.2%	-0.4%
	IARC, Auto, CR, HPV triage, Opt B, Exit, Fast	1, (0.3%)	0, (0.4%)	0.3%	0.4%	-0.7%
Primary HPV screening with cytology triage	HPV, Manual, 5-yearly, Opt A, Slow, CR1	1, (0.2%)	0, (0.2%)	0.2%	0.2%	-0.4%
	HPV, Manual, 5-yearly, Opt A, Slow, CR2	1, (0.2%)	0, (0.2%)	0.2%	0.2%	-0.4%
	HPV, Auto, 5-yearly, Opt A, Slow, CR1	1, (0.3%)	0, (0.3%)	0.3%	0.3%	-0.6%
	HPV, Auto, 5-yearly, Opt A, Slow, CR2	1, (0.3%)	0, (0.3%)	0.3%	0.3%	-0.6%
	HPV, Auto, 5-yearly, Opt B, Fast, CR2	1, (0.3%)	0, (0.3%)	0.3%	0.3%	-0.6%
Primary HPV screening with partial genotyping	Genotyping, Manual, 5-yearly, Opt A, Slow, CR1	1, (0.2%)	0, (0.2%)	0.2%	0.2%	-0.4%
	Genotyping, Manual, 5-yearly, Opt A, Slow, CR2	1, (0.3%)	0, (0.3%)	0.3%	0.3%	-0.6%
	Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	1, (0.3%)	0, (0.3%)	0.3%	0.3%	-0.6%
Primary HPV and adjunctive cytology co-testing	Co-testing, Auto, 5-yearly, Opt A, Slow, CR1	1, (0.2%)	0, (0.2%)	0.2%	0.2%	-0.5%
	Co-testing, Auto, 5-yearly, Opt B, Fast, CR2	1, (0.3%)	0, (0.3%)	0.3%	0.4%	-0.7%

IARC – IARC recommended screening age and interval; CC – conventional cytology; Manual – manually-read LBC; Auto – image-read LBC; Slow – women will not receive an invitation to attend their first cervical screen; Fast – women will receive an invitation to attend their first cervical screen; CR – call-and-recall program (proactive invitation) for strategies incorporating conventional cytology and LBC (either manually-read or image-read); R1 - reminder-based program (with the lower proportion of the overall participation rate); R2 - reminder-based program (with the higher proportion of the overall participation rate); CR1- call-and-recall program (assuming high compliance with the recommended screening interval and limited early re-screening) for primary HPV testing strategies; CR2 - call-and-recall program (assuming a higher proportion of early re-screening and a lower proportion of women who screen in-time) for primary HPV testing strategies; Opt A – 12 months follow-up for women with low-grade cytology and testing HPV positive using reflex

HPV triage; Opt B – direct colposcopy referral for women with low-grade cytology and testing HPV positive using reflex HPV triage; Exit –HPV exit testing for women exiting the program at age 65 years (Note: all primary HPV screening strategies incorporate HPV exit testing for women 69+ years of age therefore not specified in the above table);

§§ Test characteristics for LBC is based on cell filtration technology;* Using female Australian population as predicted for 2015; § Age-standardised (0-84 years) using 2001 Australian population as the standard population; †† Negative values represent a decrease

Table E 33 Health and cost outcomes in strategies where women never return for cervical screening after being discharged after a normal HPV exit test and assuming screening ends at 69 instead of 64 years – unvaccinated cohort

Test technology	Key strategies used in PSA that include HPV exit testing	Changes in cancer incidence compared to CP††		Changes in cancer mortality compared to CP††		% Changes in total screening program cost compared to CP††
		Difference in cancer deaths (% change in cases)††	% change in ASR§ incidence††	Difference in cancer deaths (% change in cases)††	% change in ASR§ mortality††	
Conventional cytology	IARC, CC, CR, Exit, Fast	55, (6.3%)	17, (7.2%)	6.0%	7.2%	-23.5%
	IARC, CC, R2, Exit, Fast	32, (3.8%)	8, (3.7%)	3.7%	3.8%	-16.4%
Manually-read LBC§§	IARC, Manual, CR, HPV triage, Opt B, Exit, Fast	-122, (-17.6%)	-36, (-19.8%)	-15.8%	-17.0%	-3.7%
	IARC, Manual, R2, HPV triage, Opt B, Exit, Fast	-105, (-14.9%)	-32, (-17.2%)	-13.8%	-15.1%	-8.6%
Image-read LBC§§	IARC, Auto, CR, HPV triage, Opt B, Exit, Fast	-127, (-18.5%)	-38, (-21.3%)	-16.0%	-17.7%	1.0%
	IARC, Auto, R2, HPV triage, Opt B, Exit, Fast	-141, (-21%)	-42, (-23.7%)	-17.8%	-19.3%	6.5%
Primary HPV screening with cytology triage	HPV, Manual, 5-yearly, Opt A, Slow, CR1	-85, (-11.7%)	-30, (-16.2%)	-10.4%	-13.5%	-25.7%
	HPV, Auto, 5-yearly, Opt A, Slow, CR1	-95, (-13.3%)	-33, (-17.9%)	-11.6%	-14.7%	-24.6%
	HPV, Manual, 5-yearly, Opt A, Slow, CR2	-87, (-12%)	-31, (-16.2%)	-10.6%	-13.5%	-24.1%
	HPV, Auto, 5-yearly, Opt A, Slow, CR2	-97, (-13.6%)	-33, (-17.9%)	-11.8%	-14.7%	-22.9%
	HPV, Auto, 5-yearly, Opt B, Fast, CR2	-152, (-23%)	-46, (-26.8%)	-18.9%	-21.2%	-16.9%
Primary HPV screening with partial genotyping	Genotyping, Manual, 5-yearly, Opt A, Slow, CR1	-133, (-19.6%)	-43, (-24.2%)	-16.5%	-19.4%	-23.0%
	Genotyping, Manual, 5-yearly, Opt A, Slow, CR2	-134, (-19.8%)	-43, (-24.2%)	-16.7%	-19.4%	-21.3%
	Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	-165, (-25.6%)	-49, (-29.2%)	-20.6%	-22.8%	-14.3%
Primary HPV and adjunctive cytology co-testing	Co-testing, Auto, 5-yearly, Opt A, Slow, CR1	-109, (-15.5%)	-36, (-19.9%)	-13.3%	-16.2%	-5.4%
	Co-testing, Auto, 5-yearly, Opt B, Fast, CR2	-161, (-24.8%)	-48, (-28.3%)	-20.1%	-22.2%	3.5%

CP – current practice; IARC – IARC recommended screening age and interval; CC – conventional cytology; Manual – manually-read LBC; Auto – image-read LBC; Slow – women will not receive an invitation to attend their first cervical screen; Fast – women will receive an invitation to attend their first cervical screen; CR – call-and-recall program (proactive invitation) for strategies incorporating conventional cytology and LBC (either manually-read or image-read); R1 – reminder-based program (with the lower proportion of the overall participation rate); R2 – reminder-based program (with the higher proportion of the overall participation rate); CR1 – call-and-recall program (assuming high compliance with the recommended screening interval and limited early re-screening) for primary HPV testing strategies; CR2 – call-and-recall program (assuming a higher proportion of early re-screening and a lower proportion of women who screen in-time) for primary HPV testing strategies; Opt A – 12 months follow-up for women with low-grade cytology and testing HPV positive using reflex HPV triage; Opt B – direct colposcopy referral for women with low-grade cytology and testing HPV positive using reflex HPV triage; Exit – HPV exit testing for women exiting the program at age 65 years (Note: all primary HPV screening strategies incorporate HPV exit testing for women 69+ years of age therefore not specified in the above table);

§§ Test characteristics for LBC is based on cell filtration technology; * Using female Australian population as predicted for 2015; § Age-standardised (0-84 years) using 2001 Australian population as the standard population; †† Negative values represent a decrease

Table E 34 Health and cost outcomes in strategies where women never return for cervical screening after being discharged after a normal HPV exit test and assuming screening ends at 69 instead of 64 years – cohort offered vaccination at age 12

Test technology	Key strategies used in PSA that include HPV exit testing	Changes in cancer incidence compared to CP††		Changes in cancer mortality compared CP††		% Changes in total screening program cost compared to CP††
		Difference in cancer deaths (% change in cases)††	% change in ASR§ incidence††	Difference in cancer deaths (% change in cases)††	% change in ASR§ mortality††	
Conventional cytology	IARC, CC, CR, Exit, Fast	20, (5.7%)	6, (6.7%)	5.3%	6.5%	-27.0%
	IARC, CC, R2, Exit, Fast	11, (3.2%)	3, (3.2%)	3.1%	3.2%	-18.6%
Manually-read LBC§§	IARC, Manual, CR, HPV triage, Opt B, Exit, Fast	-43, (-14.6%)	-13, (-17%)	-13.6%	-15.0%	-10.3%
	IARC, Manual, R2, HPV triage, Opt B, Exit, Fast	-52, (-18.1%)	-16, (-21.2%)	-15.7%	-17.6%	1.0%
Image-read LBC§§	IARC, Auto, CR, HPV triage, Opt B, Exit, Fast	-49, (-17.1%)	-15, (-19.3%)	-15.3%	-16.6%	-5.1%
	IARC, Auto, R2, HPV triage, Opt B, Exit, Fast	-57, (-20.4%)	-17, (-23.3%)	-17.3%	-19.0%	6.7%
Primary HPV screening with cytology triage	HPV, Manual, 5-yearly, Opt A, Slow, CR1	-38, (-12.6%)	-13, (-17.5%)	-11.0%	-14.3%	-31.0%
	HPV, Auto, 5-yearly, Opt A, Slow, CR1	-42, (-14.1%)	-14, (-19%)	-12.1%	-15.4%	-30.0%
	HPV, Manual, 5-yearly, Opt A, Slow, CR2	-38, (-12.8%)	-13, (-17.5%)	-11.2%	-14.4%	-29.2%
	HPV, Auto, 5-yearly, Opt A, Slow, CR2	-42, (-14.3%)	-14, (-19%)	-12.3%	-15.5%	-28.1%
	HPV, Auto, 5-yearly, Opt B, Fast, CR2	-62, (-22.7%)	-19, (-26.9%)	-18.6%	-21.2%	-22.3%
Primary HPV screening with partial genotyping	Genotyping, Manual, 5-yearly, Opt A, Slow, CR1	-45, (-15.2%)	-15, (-20.1%)	-13.2%	-16.4%	-29.8%
	Genotyping, Manual, 5-yearly, Opt A, Slow, CR2	-45, (-15.5%)	-15, (-20.2%)	-13.4%	-16.5%	-27.9%
	Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	-64, (-23.2%)	-20, (-27.5%)	-19.0%	-21.6%	-20.9%
Primary HPV and adjunctive cytology co-testing	Co-testing, Auto, 5-yearly, Opt A, Slow, CR1	-47, (-16.3%)	-16, (-21.1%)	-13.8%	-16.9%	-7.1%
	Co-testing, Auto, 5-yearly, Opt B, Fast, CR2	-66, (-24.4%)	-20, (-28.4%)	-19.8%	-22.2%	2.2%

CP – current practice; IARC – IARC recommended screening age and interval; CC – conventional cytology; Manual – manually-read LBC; Auto – image-read LBC; Slow – women will not receive an invitation to attend their first cervical screen; Fast – women will receive an invitation to attend their first cervical screen; CR – call-and-recall program (proactive invitation) for strategies incorporating conventional cytology and LBC (either manually-read or image-read); R1 - reminder-based program (with the lower proportion of the overall participation rate); R2 - reminder-based program (with the higher proportion of the overall participation rate); CR1- call-and-recall program (assuming high compliance with the recommended screening interval and limited early re-screening) for primary HPV testing strategies; CR2 - call-and-recall program (assuming a higher proportion of early re-screening and a lower proportion of women who screen in-time) for primary HPV testing strategies; Opt A – 12 months follow-up for women with low-grade cytology and testing HPV positive using reflex HPV triage; Opt B – direct colposcopy referral for women with low-grade cytology and testing HPV positive using reflex HPV triage; Exit – HPV exit testing for women exiting the program at age 65 years (Note: all primary HPV screening strategies incorporate HPV exit testing for women 69+ years of age therefore not specified in the above table);

§§ Test characteristics for LBC is based on cell filtration technology; * Using female Australian population as predicted for 2015; § Age-standardised (0-84 years) using 2001 Australian population as the standard population; †† Negative values represent a decrease

Table E 35 Health and cost outcomes in primary HPV screening strategies if the routine screening interval is lengthened out to 6 years compared to the equivalent screening strategy under 5 yearly screening intervals – unvaccinated cohort

Test technology	Key primary HPV screening strategies used in PSA	Changes in cancer incidence compared to 5 yearly routine screening interval††		Changes in cancer mortality compared to 5 yearly routine screening interval ††		% Changes in total screening program cost compared to 5 yearly routine screening interval ††
		Difference in cancer cases* (% change in cases)††	% change in ASR§ incidence††	Difference in cancer deaths* (% change in deaths)††	% change in ASR§ mortality††	
-	-					-
Primary HPV screening with cytology triage	HPV, Manual, 5-yearly, Opt A, Slow, CR1	24 (3%)	3.2%	6 (3%)	3.1%	-7.5%
	HPV, Manual, 5-yearly, Opt A, Slow, CR2	25 (3%)	3.4%	7 (3%)	3.3%	-8.5%
	HPV, Auto, 5-yearly, Opt A, Slow, CR1	24 (3%)	3.2%	6 (3%)	3.1%	-7.5%
	HPV, Auto, 5-yearly, Opt A, Slow, CR2	25 (3%)	3.4%	6 (3%)	3.3%	-8.5%
	HPV, Auto, 5-yearly, Opt B, Fast, CR2	25 (4%)	3.7%	6 (3%)	3.4%	-8.5%
Primary HPV screening with partial genotyping	Genotyping, Manual, 5-yearly, Opt A, Slow, CR1	22 (3%)	3.1%	5 (3%)	2.9%	-7.6%
	Genotyping, Manual, 5-yearly, Opt A, Slow, CR2	23 (3%)	3.3%	6 (3%)	3.1%	-8.5%
	Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	24 (4%)	3.6%	6 (3%)	3.3%	-8.5%
Primary HPV and adjunctive cytology co-testing	Co-testing, Auto, 5-yearly, Opt A, Slow, CR1	21 (3%)	2.9%	5 (3%)	2.7%	-8.4%
	Co-testing, Auto, 5-yearly, Opt B, Fast, CR2	22 (3%)	3.2%	5 (3%)	2.9%	-9.4%

Slow – women will not receive an invitation to attend their first cervical screen; Fast – women will receive an invitation to attend their first cervical screen; CR1- call-and-recall program (assuming high compliance with the recommended screening interval and limited early re-screening); CR2 - call-and-recall program (assuming a higher proportion of early re-screening and a lower proportion of women who screen in-time; Opt A – 12 months follow-up for women with low-grade cytology and testing HPV positive using reflex HPV triage; Opt B – direct colposcopy referral for women with low-grade cytology and testing HPV positive using reflex HPV triage; Exit –HPV exit testing for women exiting the program at age 65 years (Note: all primary HPV screening strategies incorporate HPV exit testing for women 65+ years of age therefore not specified in the above table).

* Using female Australian population as predicted for 2015

§ Age-standardised (0-84 years) using 2001 Australian population as the standard population

†† Negative values represent a decrease

Table E 36 Health and cost outcomes in primary HPV screening strategies if the routine screening interval is lengthened out to 6 years compared to the equivalent screening strategy under 5 yearly screening intervals – cohort offered vaccination at age 12

Test technology	Key primary HPV screening strategies used in PSA	Changes in cancer incidence compared to 5 yearly routine screening interval††		Changes in cancer mortality compared to 5 yearly routine screening interval ††		% Changes in total screening program cost compared to 5 yearly routine screening interval ††
		Difference in cancer cases* (% change in cases)††	% change in ASR§ incidence††	Difference in cancer deaths* (% change in deaths)††	% change in ASR§ mortality††	
-	-	-	-	-	-	-
Primary HPV screening with cytology triage	HPV, Manual, 5-yearly, Opt A, Slow, CR1	11 (4%)	3.5%	3 (3%)	3.3%	-9.4%
	HPV, Manual, 5-yearly, Opt A, Slow, CR2	11 (4%)	3.7%	3 (4%)	3.6%	-10.6%
	HPV, Auto, 5-yearly, Opt A, Slow, CR1	11 (4%)	3.5%	3 (3%)	3.3%	-9.4%
	HPV, Auto, 5-yearly, Opt A, Slow, CR2	11 (4%)	3.7%	3 (4%)	3.6%	-10.5%
	HPV, Auto, 5-yearly, Opt B, Fast, CR2	11 (4%)	4.0%	3 (4%)	3.7%	-10.5%
Primary HPV screening with partial genotyping	Genotyping, Manual, 5-yearly, Opt A, Slow, CR1	11 (4%)	3.5%	3 (3%)	3.4%	-9.4%
	Genotyping, Manual, 5-yearly, Opt A, Slow, CR2	11 (4%)	3.7%	3 (4%)	3.6%	-10.6%
	Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	11 (4%)	4.0%	3 (4%)	3.7%	-10.5%
Primary HPV and adjunctive cytology co-testing	Co-testing, Auto, 5-yearly, Opt A, Slow, CR1	10 (3%)	3.2%	2 (3%)	2.9%	-10.0%
	Co-testing, Auto, 5-yearly, Opt B, Fast, CR2	10 (3%)	3.6%	2 (3%)	3.1%	-11.2%

Slow – women will not receive an invitation to attend their first cervical screen; Fast – women will receive an invitation to attend their first cervical screen; CR1- call-and-recall program (assuming high compliance with the recommended screening interval and limited early re-screening); CR2 - call-and-recall program (assuming a higher proportion of early re-screening and a lower proportion of women who screen in-time; Opt A – 12 months follow-up for women with low-grade cytology and testing HPV positive using reflex HPV triage; Opt B – direct colposcopy referral for women with low-grade cytology and testing HPV positive using reflex HPV triage; Exit –HPV exit testing for women exiting the program at age 65 years (Note: all primary HPV screening strategies incorporate HPV exit testing for women 65+ years of age therefore not specified in the above table).

* Using female Australian population as predicted for 2015

§ Age-standardised (0-84 years) using 2001 Australian population as the standard population

†† Negative values represent a decrease

Table E 37 Health and cost outcomes in primary HPV screening strategies if the routine screening interval is lengthened out to 6 years compared to current practice – unvaccinated cohort

Test technology	Key primary HPV screening strategies used in PSA	Changes in cancer incidence compared to 5 yearly routine screening interval††		Changes in cancer mortality compared to 5 yearly routine screening interval ††		% Changes in total screening program cost compared to 5 yearly routine screening interval ††
		Difference in cancer cases (% change in cases)††	% change in ASR§ incidence††	Difference in cancer deaths (% change in deaths)††	% change in ASR§ mortality††	
-	-	-	-	-	-	-
Primary HPV screening with cytology triage	HPV, Manual, 5-yearly, Opt A, Slow, CR1	-34 (-4%)	-4.1%	-13 (-6%)	-5.2%	-32.7%
	HPV, Manual, 5-yearly, Opt A, Slow, CR2	-38 (-5%)	-4.6%	-14 (-6%)	-5.8%	-31.7%
	HPV, Auto, 5-yearly, Opt A, Slow, CR1	-44 (-5%)	-5.3%	-15 (-7%)	-6.4%	-31.6%
	HPV, Auto, 5-yearly, Opt A, Slow, CR2	-48 (-6%)	-5.8%	-17 (-8%)	-7%	-30.7%
	HPV, Auto, 5-yearly, Opt B, Fast, CR2	-102 (-13%)	-12.7%	-29 (-13%)	-13.4%	-25.2%
Primary HPV screening with partial genotyping	Genotyping, Manual, 5-yearly, Opt A, Slow, CR1	-83 (-10%)	-10.5%	-25 (-12%)	-11.3%	-30.3%
	Genotyping, Manual, 5-yearly, Opt A, Slow, CR2	-87 (-11%)	-10.9%	-27 (-12%)	-11.9%	-29.3%
	Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	-117 (-14%)	-14.7%	-33 (-15%)	-15.2%	-22.9%
Primary HPV and adjunctive cytology co-testing	Co-testing, Auto, 5-yearly, Opt A, Slow, CR1	-60 (-7%)	-7.4%	-19 (-9%)	-8.4%	-15.8%
	Co-testing, Auto, 5-yearly, Opt B, Fast, CR2	-115 (-14%)	-14.4%	-33 (-15%)	-14.9%	-8.4%

Slow – women will not receive an invitation to attend their first cervical screen; Fast – women will receive an invitation to attend their first cervical screen; CR1- call-and-recall program (assuming high compliance with the recommended screening interval and limited early re-screening); CR2 - call-and-recall program (assuming a higher proportion of early re-screening and a lower proportion of women who screen in-time; Opt A – 12 months follow-up for women with low-grade cytology and testing HPV positive using reflex HPV triage; Opt B – direct colposcopy referral for women with low-grade cytology and testing HPV positive using reflex HPV triage; Exit – HPV exit testing for women exiting the program at age 65 years (Note: all primary HPV screening strategies incorporate HPV exit testing for women 65+ years of age therefore not specified in the above table).

* Using female Australian population as predicted for 2015

§ Age-standardised (0-84 years) using 2001 Australian population as the standard population

†† Negative values represent a decrease

Table E 38 Health and cost outcomes in primary HPV screening strategies if the routine screening interval is lengthened out to 6 years compared to current practice – cohort offered vaccination at age 12

Test technology	Key primary HPV screening strategies used in PSA	Changes in cancer incidence compared to 5 yearly routine screening interval††		Changes in cancer mortality compared to 5 yearly routine screening interval ††		% Changes in total screening program cost compared to 5 yearly routine screening interval ††
		Difference in cancer cases (% change in cases)††	% change in ASR§ incidence††	Difference in cancer deaths (% change in deaths)††	% change in ASR§ mortality††	
-	-	-	-	-	-	-
Primary HPV screening with cytology triage	HPV, Manual, 5-yearly, Opt A, Slow, CR1	-15 (-4%)	-4.2%	-6 (-6%)	-5.4%	-39.2%
	HPV, Manual, 5-yearly, Opt A, Slow, CR2	-17 (-5%)	-4.7%	-6 (-7%)	-6%	-38.1%
	HPV, Auto, 5-yearly, Opt A, Slow, CR1	-19 (-6%)	-5.3%	-7 (-7%)	-6.6%	-38.3%
	HPV, Auto, 5-yearly, Opt A, Slow, CR2	-20 (-6%)	-5.8%	-7 (-8%)	-7.2%	-37.2%
	HPV, Auto, 5-yearly, Opt B, Fast, CR2	-40 (-12%)	-11.9%	-12 (-13%)	-12.8%	-31.9%
Primary HPV screening with partial genotyping	Genotyping, Manual, 5-yearly, Opt A, Slow, CR1	-22 (-6%)	-6.4%	-7 (-8%)	-7.5%	-38.2%
	Genotyping, Manual, 5-yearly, Opt A, Slow, CR2	-23 (-7%)	-6.9%	-8 (-9%)	-8.1%	-37%
	Genotyping, Auto, 5-yearly, Opt B, Fast, CR2	-41 (-12%)	-12.4%	-12 (-13%)	-13.2%	-30.8%
Primary HPV and adjunctive cytology co-testing	Co-testing, Auto, 5-yearly, Opt A, Slow, CR1	-25 (-8%)	-7.4%	-8 (-9%)	-8.5%	-19.3%
	Co-testing, Auto, 5-yearly, Opt B, Fast, CR2	-45 (-13%)	-13.6%	-13 (-14%)	-14.3%	-11.8%

Slow – women will not receive an invitation to attend their first cervical screen; Fast – women will receive an invitation to attend their first cervical screen; CR1- call-and-recall program (assuming high compliance with the recommended screening interval and limited early re-screening); CR2 - call-and-recall program (assuming a higher proportion of early re-screening and a lower proportion of women who screen in-time; Opt A – 12 months follow-up for women with low-grade cytology and testing HPV positive using reflex HPV triage; Opt B – direct colposcopy referral for women with low-grade cytology and testing HPV positive using reflex HPV triage; Exit – HPV exit testing for women exiting the program at age 65 years (Note: all primary HPV screening strategies incorporate HPV exit testing for women 65+ years of age therefore not specified in the above table).

* Using female Australian population as predicted for 2015

§ Age-standardised (0-84 years) using 2001 Australian population as the standard population

†† Negative values represent a decrease

Discussion

Comparative safety from the evidence review

All tests under review are considered safe procedures in themselves, however, there is uncertainty as to how to weight factors including test-related discomfort, test-related anxiety and patient inconvenience associated with both screening and follow-up tests such as colposcopy and biopsy (many of which will be found to be normal) against reductions in cervical cancer incidence and mortality.

Comparative effectiveness from the systematic review

No included studies were conducted in vaccinated populations.

The evidence for the effectiveness of screening age ranges and interval is limited to observational evidence. In addition, two observational studies providing evidence of the effectiveness of screening beyond 65 years do not report whether prior screening history in these women was adequate or not.

The evidence for the accuracy of liquid based cytology (LBC) is limited to comparative accuracy data and test performance measures. Accuracy conclusions are based upon a meta-analysis predominantly consisting of studies of cell filtration LBC (six of nine included studies; Arbyn *et al.* 2008), plus two additional studies of cell filtration LBC included in this update (Siebers *et al.* 2009; Klug *et al.* 2013). Comparisons of automated image analysis of LBC slides to manual reading of conventional cytology slides are based entirely on studies of cell filtration LBC. The body of evidence for a comparison of automated image analysis and manual reading of LBC slides is poor and inconsistent and comprises studies of both cell filtration and cell enrichment.

The evidence base for the effectiveness of HPV based screening strategies (with or without triage or co-testing) is good consisting of several large RCTs whose findings are relatively consistent for the outcomes reported despite differences in design.

Many of these trials demonstrate an increased detection of high grade CIN in the first round, followed by a decrease in detection in the second round with one RCT also demonstrating a significant decrease in the detection of cervical cancer in the second screening round, although the number of cases is small (POBASCAM). Interpretation is complex in the absence of a decrease in the cumulative detection rate of cervical cancer or its surrogate CIN3+. Increased detection in round one may represent earlier diagnosis (of uncertain benefit) and/or detection of additional disease, of which the proportion destined to progress is uncertain. Strategies in the second round differed across trials limiting the ability to interpret second round results.

Many of the HPV based screening strategies show an increase in the colposcopy rates in the first screening round. The colposcopy rates may decrease in later rounds; however these data are generally not available. Reporting of full data from these trials, including referrals to colposcopy for each round and overall, and longer follow up to allow for more complete ascertainment, may reduce the level of uncertainty regarding the trade-offs between the benefits and harms of these screening strategies.

Uncertainties regarding the lack of studies in vaccinated populations and the use of surrogate and accuracy outcomes in the existing literature are addressed by modelling long-term benefits and harms, using an established model of cervical cancer screening, diagnosis and treatment in HPV vaccinated and unvaccinated populations in the Australian setting.

Effectiveness modelling and economic evaluation

Overview

Since the introduction of the organised National Cervical Screening Program (NCSP) in Australia in 1991, rates of cervical cancer incidence and mortality have declined substantially, and the rates in Australia are now among the lowest in the world. From the mid-1990s to the mid-2000s, cervical cancer incidence declined by 36% and mortality decreased by 44% (Simonella *et al.* 2013). However, in recent years, both the incidence and mortality rates for cervical cancer in Australia appear to have stabilised, with no further substantial declines evident after about 2002-4 (AIHW 2012). This plateauing is likely to be due, in part, to the inherent difficulties involved in regularly screening all eligible women. As for any screening approach, these difficulties are likely to be increased in the context of the currently recommended relatively short screening interval, which at two years is shorter than in almost all other countries.

The International Agency for Research on Cancer (IARC) recommends screening women aged 25-29 years every 3 years, and screening women 50-65 years every 5 years if cytology is used. For primary HPV screening, intervals of no less than 5 years are generally recommended. The current evaluation has assessed a number of future options for cervical screening in Australia which utilise conventional cytology or newer technologies for screening, and which also involve increasing the recommended screening interval.

This evaluation has found that, if conventional cytology is retained, longer-interval IARC screening is predicted to be associated with an increase in cervical cancer incidence and mortality by ~8-20%; with much of the increase deriving from the 5-yearly screening component in women over 50 years (i.e. a part-reversal of the gains made by the organised program since 1991). These predicted increases in cervical cancer rates could be minimised if high compliance to the recommended age of initiating screening and screening interval can be achieved. Although conventional cytology with the IARC recommendations is predicted to be associated with a ~\$37-66M cost saving per annum (depending on the particular strategy and whether vaccination is considered), the findings of this evaluation do not suggest that conventional cytology at IARC intervals would have either equivalent or improved effectiveness overall compared to the current program.

However, the evaluation identified a number of potential screening strategies which are predicted to reduce cervical cancer incidence and mortality rates in Australia even further than the current levels. All of the strategies which would further improve cervical cancer rates involve the adoption of newer technologies as a replacement to conventional cytology for the primary screening test. The greatest gains in effectiveness would be associated with the implementation of primary HPV screening (for which all evaluated strategies are predicted to be more effective than current practice) but effectiveness gains could potentially also be made in the context of the adoption of either manually-read and image-read LBC, provided that LBC screening is implemented with HPV triage testing for low grade cytology; this is most effectively done if HPV triage-positive women are referred directly to colposcopy. The scale of the potential further reductions in cervical cancer rates compared to current practice is up to ~13% for manually read LBC with HPV triage strategies (favourable assumptions), up to ~14% for image-read LBC with

HPV triage strategies (highly favourable assumptions) and up to ~18% for primary HPV screening strategies (conservative assumptions).

With respect to changes in recommended screening age range, the findings of this evaluation suggest that the change in age of cessation has an important effect on outcomes for cancer incidence and mortality, and that this effect is considerably larger than the effect associated with raising the age of starting to 25 years (provided that adequate compliance to a screening start age of 25 years can be achieved). A further reassuring consideration for younger women is that although we modelled an ‘unvaccinated’ scenario, in practice all women under 30 years of age have now been offered HPV vaccination in the National HPV Vaccination Program, and this has already been associated with a reduction in rates of high grade abnormalities in women aged 20-24 years (AIHW 2013), which will act to further increase safety in this group. However, because the absolute rates of invasive cervical cancer are considerably higher in older women, retaining the currently recommended screening cessation age of 69 years, rather than lowering it to the IARC-recommended 64 years, would substantially improve the predicted cervical cancer mortality for all the new screening strategies evaluated, by ~5-8%. Therefore, consideration might be given to retaining the currently recommended age of cessation. If this occurs, then the results of the current evaluation can be considered to have included an additional ‘safety margin’ in terms of the estimated effectiveness of all new strategies, since the change to the age of cessation is predicted to have a similar relative impact for all the new strategies evaluated. If the age of recommended cessation remained at 69 years, then exit testing could be considered as a further ‘add-on’ to safely discharge women after that age, and the findings of this evaluation suggest that the use of exit testing in this context would not be associated with a loss of effectiveness.

We also found in exploratory analysis of conventional cytology at IARC-recommended intervals, that 5-yearly screening in older women was an important factor in the effectiveness of screening. Although not explicitly evaluated here, retaining 3-yearly screening for LBC cytology strategies across the whole target age group for screening would consequently be expected to further increase the effectiveness of these strategies and thus provide a further ‘safety margin’. However, it should be noted that this would be likely to considerably increase costs, and given that the most effective LBC strategies were some of the most expensive evaluated overall, this approach has the potential to considerably increase overall program costs compared to current practice.

Although the primary HPV strategies, and some of the LBC strategies, are associated with an effectiveness improvement compared to current practice, the cost trade-offs differ somewhat between the two new technology alternatives. The annual cost of the NCSP in 2015 is estimated to be ~\$215M. The most expensive of the new strategies involved use of image-read LBC. If a reminder-based system of screening organisation is retained, this has the potential to be more expensive than current practice even at the longer IARC screening intervals, in both unvaccinated and vaccinated groups. Therefore, for the LBC strategies, maintaining compliance to the new IARC screening initiation and interval recommendations is critical to containing costs within the NCSP. If, however, image-read LBC with HPV triage testing was implemented using a ‘fast uptake’ initiation strategy, and call-and-recall screening with HPV triage and immediate referral of triage-positive women to colposcopy (one of the most effective LBC strategies overall), the cost savings compared to current practice would still be of the order of \$10M per annum in an unvaccinated population, increasing over time to savings of more than \$12M per annum as more vaccinated women enter the population.

Some of the HPV/cytology co-testing strategies were also associated with costs greater than that of the current program, even at 5-yearly screening intervals, in unvaccinated (but not vaccinated) groups, but these increased costs were not associated with substantial improved effectiveness

compared to alternate strategies involving use of HPV as the sole primary screening test. Therefore, these findings suggest that primary HPV and cytology co-testing would be neither the most effective or least costly option for the NCSP.

Primary HPV screening with cytology triage or with genotyping in the context of call-and-recall screening was associated both with the most effective and also the least costly strategies overall, for both unvaccinated and vaccinated groups. As for LBC strategies, maintaining compliance with the recommended interval is expected to be of major importance in containing costs in the program. For primary HPV strategies with cytology triage of all oncogenic types, the cost savings compared to current practice ranged from ~\$39-59M per annum, with savings increasing over time to ~\$44-61M, as more vaccinated women enter the population. For primary HPV strategies with partial genotyping, the cost savings compared to current practice ranged from ~\$34-53M per annum, with savings increasing over time to \$42-59M per annum. Therefore, this evaluation found that primary HPV testing with either cytology triage or partial genotyping would be associated with cost savings of the order of \$50M per annum within the current national cervical screening program, that these savings would be achieved in the context of a substantial further improvement in the effectiveness of the program.

The relative 'efficiency' of the various strategies in terms of the relationship between decrease in cervical cancer mortality and the number of colposcopies required, remained similar for most LBC and primary HPV strategies when unvaccinated populations and vaccinated populations were compared. However, the notable exception was primary HPV screening with partial genotyping, which became more 'efficient' in the vaccinated population because as HPV 16/18 infections decreased, the number of colposcopy referrals dramatically declined (since HPV 16/18 positive women are referred directly to colposcopy in this strategy) but the relative mortality benefits were maintained.

Key uncertainties

The findings of this evaluation should be considered to be favourable for manually-read and image-read LBC testing and conservative with respect to primary HPV testing, for the following reasons: (i) the assumptions used for HPV test characteristics were more conservative than those chosen for either manually-read or image-read LBC; (ii) the evaluation did not explicitly account for any potential degradation in manually or image-read LBC test performance in the post-vaccination era due either to HPV 16/18 depletion and its subsequent impact on cytology accuracy or cytology de-training effects (Schiffman *et al.* 2007) (HPV testing is expected to be subject to such effects to a lesser degree since it involves automated analysis using molecular methods); (iii) The impact of HPV vaccination on the test characteristics of image-read LBC has not been assessed (iv) We did not explicitly model differential test performance for glandular lesions, which is expected to be relatively higher for HPV testing compared to cytology; (v) sensitivity analysis demonstrated that the LBC findings were highly sensitive to the assumed test characteristics, whereas findings for primary HPV strategies were less sensitive to assumed test characteristics (within the feasible range reported in the literature); and (vi) Results of the probabilistic sensitivity analysis for all HPV strategies suggested that they would have improved cancer mortality outcomes compared to current practice; this was the case for some, but not all, LBC strategies.

Overall conclusion

Comparative safety

- Narrowing the screening age range and extending the screening interval will provide potential safety benefits by reducing the harms of tests and procedures for abnormalities that may otherwise regress. Estimates of these benefits need to be weighed against uncertainty about the potential impact on cervical cancer incidence and mortality.
- LBC with manual or automated slide reading is considered a safe procedure.
- HPV testing is a safe procedure

Comparative clinical effectiveness

Cytology-based screening

- Cervical cancer is very rare before the age of 25 years.
- HPV vaccination is anticipated to substantially reduce the risk of cervical cancer in young women.
- There are limited comparative data on the age at which to start and stop screening.
- The available data do not demonstrate a benefit of screening women aged less than 25 years. However, screening in this age group does result in increased investigations, treatments and potential harms, without decreasing mortality.
- The majority of cervical cancer cases in women aged 65 and over are in women not meeting the criteria for an exit test.
- Extending the screening interval from two to three years is unlikely to substantially alter cervical cancer incidence or mortality rates but will lead to a reduction in the number of cytology tests and colposcopy procedures (based on two modelling studies).
- For women aged over 50 years screening intervals of five years offer risk reductions approaching those observed at three years in younger women (based on an analysis of cancer in women aged 55 to 69 years).

LBC-based screening

- LBC provides no statistically significant difference in sensitivity (at HSIL, LSIL or pLSIL thresholds) or specificity (at HSIL or LSIL thresholds) when compared with conventional cytology (MSAC 2009).
- LBC reduces the rate of unsatisfactory smears in comparison with conventional cytology (MSAC 2009).
- There is limited evidence regarding the effectiveness of automated image analysis when compared with manual reading of LBC.
- Automated image analysis with the ThinPrep Imager system detects as many CIN2+ lesions as conventional cytology, and may detect more (MSAC 2009).
- There is no evidence of an advantage, disadvantage or equivalence of the accuracy of the FocalPoint system compared to conventional cytology (MSAC 2009).

- Automated image analysis with the ThinPrep Imager system yields lower unsatisfactory rates than manual slide reading of conventional slides.
- The HPV triage test is more sensitive than a single repeat cytology test for the detection of CIN2+ and CIN3+ lesions in women with pLSIL, and has similar specificity.
- The HPV triage test is more sensitive than a single repeat cytology test for the detection of CIN2+ lesions (but not CIN3+) in women with LSIL, and has lower specificity.
- A significant proportion of additional CIN2+ lesions that would be detected by HPV triage of pLSIL and LSIL are likely to regress when a strategy of repeat cytology is used.
- The colposcopy rate following HPV triage is higher in women aged <35 years compared to women aged ≥35 years.

HPV-based screening

- HPV testing has a high negative predictive value (the probability that a negative test result is a true negative).
- The balance of benefits from increased detection of precancerous cervical lesions and potential harms from increased colposcopy referrals is more favourable for women aged ≥30–35 years for all HPV based screening strategies
- HPV testing alone (without triaging) for primary screening is more sensitive and less specific than cytology screening for CIN2+ and CIN3+.
- HPV testing alone (without triaging) for primary screening increases colposcopy referrals in comparison to cytology-based screening.
- The high rate of detection of CIN2+ and CIN3+ in unvaccinated women younger than age 35 suggests that an excess of regressive lesions is identified with HPV screening in this age group (NTCC HPV testing alone trial) in unvaccinated populations.
- Co-testing (adjunctive or dual HPV and cytology testing) for either HPV or cytology positivity is marginally (but significantly) more sensitive than HPV testing alone.
- Co-testing for either HPV or cytology positivity is significantly less specific than HPV testing alone.
- HPV and cytology co-testing does not demonstrate a clear advantage over HPV testing alone (based on indirect comparisons which are prone to bias).
- Cytology triage of HPV primary testing has a higher colposcopy and retesting rate than cytology screening alone (at a referral threshold of LSIL+) in unvaccinated women <35 years.
- Cytology triage of HPV primary testing has a similar colposcopy and retesting rate to cytology screening alone (at a referral threshold of LSIL+) in women ≥35 years.
- HPV types 16 and 18 are associated with a higher risk of subsequent development of high-grade CIN than other oncogenic HPV types.
- HPV self-collection has a moderate-high sensitivity and comparably high specificity for detecting CIN2+ compared to clinic HPV testing.
- The accuracy of HPV self-collection varies for different types of sampling devices and HPV tests.
- Providing HPV self-collection kits to women who do not attend for cervical screening or who are under-attenders improves screening participation. The magnitude of this is uncertain.

Effectiveness modelling and economic evaluation in the Australian setting

In this evaluation we have identified specific options for either LBC-based or primary HPV screening which are predicted to result in both cost and life years savings, compared to current practice for cervical screening in Australia. The greatest gains in both effectiveness and cost savings would be associated with primary HPV testing with either cytology triage of all oncogenic types or partial genotyping for HPV 16/18. However, under favourable or highly favourable assumptions, some LBC-based screening strategies could also be associated with increased effectiveness and lower costs compared to the current program, provided that HPV triage testing for low grade cytology is implemented. However, the findings for primary LBC strategies should be considered to be more uncertain than for primary HPV strategies, because of uncertainties in LBC test performance (given limited data sources for image-read LBC and lack of data on LBC performance in a vaccinated population), and also because the LBC findings were more equivocal overall (i.e. some LBC strategies are predicted to decrease cervical cancer mortality and some to increase mortality; whereas all HPV strategies are predicted to decrease mortality compared to current practice).

For both primary LBC and primary HPV strategies these findings critically depend on the maintenance of compliance with longer-interval screening and with initiating screening at 25 years. Retaining the currently recommended age of screening cessation would have an important further impact to increase the overall effectiveness of any new screening approach and HPV exit testing could be considered as a further 'add-on' to discharge women after that age.

In conclusion, the findings of this evaluation suggest that improved cost and effectiveness outcomes could be achieved within the National Cervical Screening Program in Australia, by either primary HPV screening with either cytology triage for all oncogenic types or with partial genotyping, or by LBC with HPV triage testing. The improvements in costs and effectiveness outcomes are optimal for the primary HPV testing strategies (excluding co-testing) and have the advantage of being underpinned by a stronger evidence base and more conservative assumptions about test performance characteristics. Moreover, the superiority of primary HPV testing over LBC based screening is predicted to become more significant as more vaccinated cohorts enter the screening program with time.

Other relevant factors

Program related factors

As part of the implementation of a renewed National Cervical Screening Program (NCSP), the following projects will be undertaken by the Renewal Steering Committee and will be considered by the Standing Committee on Screening of the Australian Health Ministers' Advisory Council (AHMAC).

1. **Quality Management Framework.** A new framework will be developed in line with the AHMAC Population Based Screening Framework (2008) and will include evidence based systems and processes for quality management and safety monitoring. This framework will include key standards and performance measures that will support quality improvement in the NCSP.
2. **Quality and Safety Monitoring Committee.** This committee will provide a national focus for leadership and governance for the renewed NCSP. It will monitor the safety and quality of the NCSP; continue to monitor the safety of the 2005 NHMRC Guidelines; provide advice on any new statistical analyses that will be required to monitor the safety of a renewed NCSP and revised NHMRC Guidelines; and report to Standing Committee on Screening immediately if there are any potential safety or quality concerns. Cervical Cancer Prevention Register/s. Options for improving data collection systems and registry functions will be considered. Cervical cancer prevention register/s will support policy planning, service delivery, quality management and research.
3. **Stakeholder Communication and Program Acceptability.** A communication strategy will be developed to support the implementation of a renewed NCSP.

In addition, the Renewal Steering Committee will consider issues related to the workforce and capacity of colposcopy services and patient access and equity.

References

AIHW (2012) "ACIM (Australian Cancer Incidence and Mortality) Books."

<http://www.aihw.gov.au/aihw-national-mortality-database/>.

AIHW (2013). Cervical screening in Australia 2010-2011. Cancer series 76. Cat no. CAN 72. Cancer series. Canberra, AIHW.

Andrae, B., Kemetli, L., Sparen, P., Silfverdal, L., Strander, B., Ryd, W., Dillner, J. and Tornberg, S. (2008). "Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden." J Natl Cancer Inst **100**(9).

Arbyn, M., Bergeron, C., Klinkhamer, P., Martin-Hirsch, P., Siebers, A. G. and Bulten, J. (2008). "Liquid compared with conventional cervical cytology: a systematic review and meta-analysis." Obstetrics & Gynecology **111**(1): 167-177.

Arbyn, M., Roelens, J., Simoons, C., Buntinx, F., Paraskevaidis, E., Martin-Hirsch, P. P. and Prendiville, W. J. (2013). "Human papillomavirus testing versus repeat cytology for triage of minor cytological cervical lesions." Cochrane Database of Systematic Reviews **3**: CD008054.

Arbyn, M., Ronco, G., Anttila, A., Meijer, C. J., Poljak, M., Ogilvie, G., Koliopoulos, G., Naucler, P., Sankaranarayanan, R. and Peto, J. (2012). "Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer." Vaccine **30 Suppl 5**: F88-99.

ASCUS-LSIL Triage Study Group (2003a). "A randomized trial on the management of low-grade squamous intraepithelial lesion cytology interpretations." American Journal of Obstetrics and Gynecology **188**(6): 1393-1400.

ASCUS-LSIL Triage Study Group (2003b). "Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance." American Journal of Obstetrics and Gynecology **188**(6): 1383-1392.

Australian Government. (2013). "Immunise - Human Papillomavirus (HPV)." from <http://www.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-hpv>.

Blomfield, P. and Saville, M. (2008). "Outstanding problems - glandular lesions." CancerForum **32** **32**(Number 2): 81-84.

Bolger, N., Heffron, C., Regan, I., Sweeney, M., Kinsella, S., McKeown, M., Creighton, G., Russell, J. and O'Leary, J. (2006). "Implementation and evaluation of a new automated interactive image analysis system.[see comment]." Acta Cytologica **50**(5): 483-491.

Brotherton, J. M. L., Liu, B., Donovan, B., Kaldor, J. M. and Saville, M. (2013a). "Human papillomavirus (HPV) vaccination coverage in young Australian women is higher than previously estimated: independent estimates from a nationally representative mobile phone survey (Submitted)." Vaccine.

Brotherton, J. M. L., Murray, S. L., Hall, M., Andrewartha, L. K., Banks, C. A., Meijer, D., Pitcher, H. C., Scully, M. M. and Molchanoff, L. (2013b). "Human papillomavirus vaccine coverage among female Australian adolescents: success of the school based approach (in press)." MJA.

Canfell, K., Barnabas, R., Patnick, J. and Beral, V. (2004). "The predicted effect of changes in cervical screening practice in the UK: results from a modelling study." Br J Cancer **91**(3): 530-536.

Canfell, K., Clements, M. and Harris, J. (2008). Cost-effectiveness of proposed changes to the national cervical screening program.

Canfell, K., Lew, J. B., Caruana, M., Smith, M., Howard, K., Shi, J. F., Lord, S., Saville, M. and Gertig, D. (2012a). The impact of raising the age of starting cervical screening on both cervical cancer and obstetric complication rates: Example from Australia. Selected for Oral Presentation. 28th International Human Papillomavirus Conference & Clinical and Public Health Workshops, San Juan, Puerto Rico.

Canfell, K., Lew, J. B., Clements, M., Smith, M., Harris, J., Simonella, L., Nickson, C., Waler, R., Neal, H. and Lewis, H. (2012b). Impact of HPV vaccination on cost-effectiveness of existing screening programs: Example from New Zealand. 28th International Human Papillomavirus Conference & Clinical and Public Health Workshops, San Juan, Puerto Rico.

Canfell, K., Lew, J. B., Smith, M. and Walker, R. (2011a). "Cost-effectiveness modelling beyond MAVARIC study end-points, in: HC Kitchener, R Blanks, H Cubie, M Desai, G Dunn, R Legood, A Gray, Z Sadique and S Moss, on behalf of the MAVARIC Trial Study Group. MAVARIC - a comparison of automation-assisted and manual cervical screening: a randomised controlled trial." Health Technology Assessment **15**(3).

Canfell, K., Shi, J. F., Lew, J. B., Walker, R., Zhao, F. H., Simonella, L., Chen, J. F., Legood, R., Smith, M. A., Nickson, C. and Qiao, Y. L. (2011b). "Prevention of cervical cancer in rural China: evaluation of HPV vaccination and primary HPV screening strategies." Vaccine **29**(13): 2487-2494.

Canfell, K., Sitas, F. and Beral, V. (2006). "Cervical cancer in Australia and the United Kingdom: comparison of screening policy and uptake, and cancer incidence and mortality." Med J Aust **185**(9): 482-486.

Castle, P. E., Stoler, M. H., Wright, T. C., Sharma, A., Wright, T. L. and Behrens, C. M. (2011). "Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: A subanalysis of the ATHENA study." The Lancet Oncology **12**(9): 880-890.

Creighton, P., Lew, J. B., Clements, M., Smith, M., Howard, K., Dyer, S., Lord, S. and Canfell, K. (2010). "Cervical cancer screening in Australia: modelled evaluation of the impact of changing the recommended interval from two to three years." BMC Public Health **10**: 734.

Cuzick, J., Clavel, C., Petry, K. U., Meijer, C. J., Hoyer, H., Ratnam, S., Szarewski, A., Birembaut, P., Kulasingam, S., Sasieni, P. and Iftner, T. (2006). "Overview of the European and North American studies on HPV testing in primary cervical cancer screening." *Int J Cancer* **119**(5): 1095-1101.

Davey, E., d'Assuncao, J., Irwig, L., Macaskill, P., Chan, S. F., Richards, A. and Farnsworth, A. (2007). "Accuracy of reading liquid based cytology slides using the ThinPrep Imager compared with conventional cytology: prospective study." *BMJ* **335**(7609): 31.

Dinkelspiel, H., Fetterman, B., Poitras, N., Kinney, W., Cox, J. T., Lorey, T. and Castle, P. E. (2012). "Screening history preceding a diagnosis of cervical cancer in women age 65 and older." *Gynecologic Oncology* **126**(2): 203-206.

Gok, M., Heideman, D. A., van Kemenade, F. J., Berkhof, J., Rozendaal, L., Spruyt, J. W., Voorhorst, F., Belien, J. A., Babovic, M., Snijders, P. J. and Meijer, C. J. (2010). "HPV testing on self collected cervicovaginal lavage specimens as screening method for women who do not attend cervical screening: cohort study." *BMJ* **340**: c1040.

Health and Social Care Information Centre Screening and Immunisations. (2012, 18/10/2012). "Cervical Screening Programme - England, 2011-2012 Data Tables." Retrieved 20/8/2013, 2013, from http://www.hscic.gov.uk/catalogue/PUB07990/cerv_scre_prog_eng_2011-12_tab_v2.xls.

IARC (2007). IARC Monographs on the evaluation of carcinogenic risk to humans: Human Papillomaviruses. Lyon, France, IARC. **Vol. 90**.

Katki, H. A., Kinney, W. K., Fetterman, B., Lorey, T., Poitras, N. E., Cheung, L., Demuth, F., Schiffman, M., Wacholder, S. and Castle, P. E. (2011). "Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: A population-based study in routine clinical practice." *The Lancet Oncology* **12**(7): 663-672.

Kitchener, H. C., Almonte, M., Thomson, C., Wheeler, P., Sargent, A., Stoykova, B., Gilham, C., Baysson, H., Roberts, C., Dowie, R., Desai, M., Mather, J., Bailey, A., Turner, A., Moss, S. and Peto, J. (2009). "HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial." *The Lancet Oncology* **10**: 672-682.

Kitchener, H. C., Blanks, R., Dunn, G., Gunn, L., Desai, M., Albrow, R., Mather, J., Rana, D. N., Cubie, H., Moore, C., Legood, R., Gray, A. and Moss, S. (2011). "Automation-assisted versus manual reading of cervical cytology (MAVARIC): A randomised controlled trial." *The Lancet Oncology* **12**(1): 56-64.

Kitchener, H. C., Canfell, K., Gilham, C., Sargent, A., Roberts, C., Desai, M., Peto, J. and on behalf of the ARTISTIC Trial Study Group (2013). The clinical effectiveness and cost effectiveness of primary HPV cervical screening in England; extended follow-up of the ARTISTIC cohort through three screening rounds (report to the HTA).

Klug, S. J., Neis, K. J., Harlfinger, W., Malter, A., K'nig, J., Spieth, S., Brinkmann-Smetanay, F., Kommos, F., Weyer, V. and Ikenberg, H. (2013). "A randomized trial comparing conventional

cytology to liquid-based cytology and computer assistance." International Journal of Cancer **132**(12): 2849-2857.

Krahn, M., McLachlin, M., Pham, B., Rosen, B., Sander, B., Grootendorst, P., Tomlinson, G., John-Baptiste, A., Frikemerid, M., Hong, C. M., Woo, G., Anonychuk, A., Carcone, S., Witteman, H., Chen, W., Liu, K., Sampson, M. and Tricco, A. (2008). Liquid-based techniques for cervical cancer screening: systematic review and cost-effectiveness analysis.

Kulasingam, S. L., Havrilesky, L., Ghebre, R. and Myers, E. R. (2011). Screening for cervical cancer. A decision analysis for the US Preventative Services Task Force. Rockville (MD), Agency for Healthcare Research and Quality (US). **Report No.: 11-05157-EF-1.**

Kulasingam, S. L., Hughes, J. P., Kiviat, N. B., Mao, C., Weiss, N. S., Kuypers, J. M. and Koutsky, L. A. (2002). "Evaluation of human papillomavirus testing in primary screening for cervical abnormalities: Comparison of sensitivity, specificity, and frequency of referral." JAMA - Journal of the American Medical Association **288**(14): 1749-1757.

Legood, R., Smith, M., Lew, J. B., Walker, R., Moss, S., Kitchener, H., Patnick, J. and Canfell, K. (2012). "Cost effectiveness of human papillomavirus test of cure after treatment for cervical intraepithelial neoplasia in England: economic analysis from NHS Sentinel Sites Study." BMJ **345**: e7086.

Leinonen, M. K., Nieminen, P., Lonnberg, S., Malila, N., Hakama, M., Pokhrel, A., Laurila, P., Tarkkanen, J. and Anttila, A. (2012). "Detection rates of precancerous and cancerous cervical lesions within one screening round of primary human papillomavirus DNA testing: prospective randomised trial in Finland." BMJ **345**: e7789.

Lew, J. B., Howard, K., Gertig, D., Smith, M., Clements, M., Nickson, C., Shi, J. F., Dyer, S., Lord, S., Creighton, P., Kang, Y. J., Tan, J. and Canfell, K. (2012). "Expenditure and resource utilisation for cervical screening in Australia." BMC Health Services Research: 12;446.

Lonnberg, S., Anttila, A., Luostarinen, T. and Nieminen, P. (2012). "Age-specific effectiveness of the Finnish cervical cancer screening programme." Cancer Epidemiol Biomarkers Prev **21**(8).

Lonnberg, S., Nieminen, P., Luostarinen, T. and Anttila, A. (2013). "Mortality audit of the Finnish cervical cancer screening program." Int J Cancer **132**(9).

Meijer, C. J. L. M., Berkhof, J., Castle, P. E., Hesselink, A. T., Franco, E. L. and Ronco, G. (2009). "Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older." Int J Cancer **124**(3): 516-520.

MSAC (2009a). Automation Assisted and Liquid Based Cytology for Cervical Cancer Screening. MSAC reference 1122, Assessment report. Canberra, Australia.

MSAC (2009b). Human Papillomavirus Triage Test For Women With Possible or Definite Low-Grade Squamous Intraepithelial Lesions. MSAC reference 39, Assessment report. Canberra, Australia.

MSAC (2013). "National Cervical Screening Program Renewal. Draft report for public consultation. MSAC application no 1276."

Naucler, P., Ryd, W., TÇörnberg, S., Strand, A., Wadell, G. Ç., Elfgrén, K., RÇ³dberg, T., Strander, B., Johansson, B., Forslund, O., Hansson, B. G., Rylander, E. and Dillner, J. (2007). "Human Papillomavirus and Papanicolaou Tests to Screen for Cervical Cancer." New England Journal of Medicine **357**(16): 1589-1597.

Ogilvie, G. S., Krajden, M., van Niekerk, D. J., Martin, R. E., Ehlen, T. G., Ceballos, K., Smith, L. W., Kan, L., Cook, D. A., Peacock, S., Stuart, G. C., Franco, E. L. and Coldman, A. J. (2012). "Primary cervical cancer screening with HPV testing compared with liquid-based cytology: results of round 1 of a randomised controlled trial - the HPV FOCAL Study." Br J Cancer **107**(12): 1917-1924.

Palmer, T. J., Nicoll, S. M., McKean, M. E., Park, A. J., Bishop, D., Baker, L. and Imrie, J. E. A. (2012). "Prospective parallel randomized trial of the MultiCyte(trademark) ThinPrep(registered trademark) imaging system: The Scottish experience." Cytopathology.

Patel, A., Galaal, K., Burnley, C., Faulkner, K., Martin-Hirsch, P., Bland, M. J., Leeson, S., Beer, H., Paranjothy, S., Sasieni, P. and Naik, R. (2012). "Cervical cancer incidence in young women: a historical and geographic controlled UK regional population study." Br J Cancer **106**(11).

Peirson, L., Fitzpatrick-Lewis, D., Ciliska, D., Warren, R. and Elit, L. (2012). Screening for Cervical Cancer, Canadian Task Force on Preventive Health Care.

Queensland Cervical Screening Program. (2008). from <http://www.health.qld.gov.au/qhpolicy/docs/gdl/qh-gdl-314.pdf>.

Rijkaart, D. C., Berkhof, J., Rozendaal, L., van Kemenade, F. J., Bulkman, N. W. J., Heideman, D. A. M., Kenter, G. G., Cuzick, J., Snijders, P. J. F. and Meijer, C. J. L. M. (2012). "Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: Final results of the POBASCAM randomised controlled trial." The Lancet Oncology **13**(1): 78-88.

Roberts, J. M., Thurloe, J. K., Bowditch, R. C., Hyne, S. G., Greenberg, M., Clarke, J. M. and Biro, C. (2007). "A three-armed trial of the thinprep imaging system." Diagnostic Cytopathology **35**(2): 96-102.

Ronco, G., Giorgi-Rossi, P., Carozzi, F., Confortini, M., Palma, P. D., Del Mistro, A., Ghiringhello, B., Girlando, S., Gillio-Tos, A., De Marco, L., Naldoni, C., Pierotti, P., Rizzolo, R., Schincaglia, P., Zorzi, M., Zappa, M., Segnan, N. and Cuzick, J. (2010). "Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial." The Lancet Oncology **11**(3): 249-257.

Ronco, G., Segnan, N., Giorgi-Rossi, P., Zappa, M., Casadei, G. P., Carozzi, F., Palma, P. D., Del Mistro, A., Folicaldi, S., Gillio-Tos, A., Nardo, G., Naldoni, C., Schincaglia, P., Zorzi, M., Confortini, M., Cuzick, J., Rizzolo, R., Mari, D., De Marco, L., Ghiringhello, B., Parisio, F., Volante, R., Berardengo, E., Andron, A., Coverlizza, S., Taraglio, S., Accinelli, M. G., Polla, E.,

Pojer, A., Girlando, S., Aldovini, D., Vettorazzi, M., Minucci, D., Matteucci, M., Onnis, L., Insacco, E., Lestani, M., Vignato, A., Manfredi, M., Pierotti, P., Collina, G., Serafini, M., Sintoni, C., Aldi, M., Bondi, A., Galanti, G., Iossa, A., Ciatto, S., Cariaggi, M. P., Cecchini, S., Sani, C., Taddie, G. L., Brezzi, S., Raggi, P., Gomes, E., Pellegrini, A. and Schiboni, M. L. (2006). "Human papillomavirus testing and liquid-based cytology: Results at recruitment from the new technologies for cervical cancer randomized controlled trial." Journal of the National Cancer Institute **98**(11): 765-774.

Sankaranarayanan, R., Nene, B. M., Shastri, S. S., Jayant, K., Muwonge, R., Budukh, A. M., Hingmire, S., Malvi, S. G., Thorat, R., Kothari, A., Chinoy, R., Kelkar, R., Kane, S., Desai, S., Keskar, V. R., Rajeshwarkar, R., Panse, N. and Dinshaw, K. A. (2009). "HPV Screening for Cervical Cancer in Rural India." New England Journal of Medicine **360**(14): 1385-1394.

Sasieni, P., Adams, J. and Cuzick, J. (2003). "Benefit of cervical screening at different ages: evidence from the UK audit of screening histories." Br J Cancer **89**(1).

Sasieni, P. and Castanon, A. (2012). "Dramatic increase in cervical cancer registrations in young women in 2009 in England unlikely to be due to the new policy not to screen women aged 20-24." J.Med.Screen. **19**(3): 127-132.

Sasieni, P., Castanon, A. and Cuzick, J. (2009). "Screening and adenocarcinoma of the cervix." Int J Cancer **125**(3): 525-529.

Saslow, D., Solomon, D., Lawson, H. W., Killackey, M., Kulasingam, S. L., Cain, J., Garcia, F. A. R., Moriarty, A. T., Waxman, A. G., Wilbur, D. C., Wentzensen, N., Downs, Jr., Spitzer, M., Moscicki, A. B., Franco, E. L., Stoler, M. H., Schiffman, M., Castle, P. E. and Myers, E. R. (2012). "American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer." American Journal of Clinical Pathology **137**(4): 516-542.

Schiffman, M., Castle, P. E., Jeronimo, J., Rodriguez, A. C. and Wacholder, S. (2007). "Human papillomavirus and cervical cancer." Lancet **370**(9590): 890-907.

Shi, J. F., Canfell, K., Lew, J. B., Zhao, F. H., Legood, R., Ning, Y., Simonella, L., Ma, L., Kang, Y. J., Zhang, Y. Z., Smith, M. A., Chen, J. F., Feng, X. X. and Qiao, Y. L. (2011). "Evaluation of primary HPV-DNA testing in relation to visual inspection methods for cervical cancer screening in rural China: an epidemiologic and cost-effectiveness modelling study." BMC Cancer **11**(1): 239.

Shi, J. F., Chen, J. F., Canfell, K., Feng, X. X., Ma, J. F., Zhang, Y. Z., Zhao, F. H., Li, R., Ma, L., Li, Z. F., Lew, J. B., Ning, Y. and Qiao, Y. L. (2012). "Estimation of the costs of cervical cancer screening, diagnosis and treatment in rural Shanxi Province, China: a micro-costing study." BMC Health Services Research **12**: 123.

Siebers, A. G., Klinkhamer, P. J. J. M., Grefte, J. M. M., Massuger, L. F. A. G., Vedder, J. E. M., Beijers-Broos, A., Bulten, J. and Arbyn, M. (2009). "Comparison of liquid-based cytology with conventional cytology for detection of cervical cancer precursors: A randomized controlled trial." JAMA - Journal of the American Medical Association **302**(16): 1757-1764.

Simonella, L. and Canfell, K. (2013). "The impact of a two- versus three-yearly cervical screening interval recommendation on cervical cancer incidence and mortality: an analysis of trends in Australia, New Zealand, and England." Cancer Causes Control.

Smith, M., Walker, R. and Canfell, K. (2012a). National Cervical Screening Programme Monitoring Report Number 33.

Smith, M., Walker, R. and Canfell, K. (2012b). National Cervical Screening Programme Monitoring Report Number 34.

Smith, M., Walker, R., Clements, M. and Canfell, K. (2011a). National Cervical Screening Programme Monitoring Report Number 31. Wellington, New Zealand.

Smith, M., Walker, R., Clements, M. and Canfell, K. (2011b). National Cervical Screening Programme Monitoring Report Number 32. Wellington, New Zealand.

Smith, M., Walker, R., Clements, M., Canfell, K., Lewis, H., Neal, H. and Maxwell, A. (2011c). National Cervical Screening Programme Monitoring Report Number 30. Wellington, New Zealand.

Smith, M. A., Canfell, K., Brotherton, J. M., Lew, J. B. and Barnabas, R. V. (2008). "The predicted impact of vaccination on human papillomavirus infections in Australia." Int J Cancer **123**(8): 1854-1863.

Smith, M. A., Lew, J. B., Walker, R. J., Brotherton, J. M., Nickson, C. and Canfell, K. (2011d). "The predicted impact of HPV vaccination on male infections and male HPV-related cancers in Australia." Vaccine **29**(48): 9112-9122.

Snijders, P. J., Verhoef, V. M., Arbyn, M., Ogilvie, G., Minozzi, S. and Banzi, R. (2013). "High-risk HPV testing on self-sampled versus clinician-collected specimens: a review on the clinical accuracy and impact on population attendance in cervical cancer screening." Int J Cancer **132**(10).

Szarewski, A., Cadman, L., Mallett, S., Austin, J., Londesborough, P., Waller, J., Wardle, J., Altman, D. G. and Cuzick, J. (2007). "Human papillomavirus testing by self-sampling: assessment of accuracy in an unsupervised clinical setting." Journal of Medical Screening **14**(1): 34-42.

Tamalet, C., Le Retraite, L., Leandri, F. X., Heid, P., Sancho Garnier, H. and Piana, L. (2013). "Vaginal self-sampling is an adequate means of screening HR-HPV types in women not participating in regular cervical cancer screening." Clin Microbiol Infect JID - 9516420 **19**(1).

VCCR (2011a). Statistical Report, Victorian Cervical Cytology Registry.

VCCR (2011b). Victorian Cervical Cytology Registry.

Vesco, K. K., Whitlock, E. P., Eder, M., Lin, J., Burda, B. U., Senger, C. A., Holmes, R. S., Fu, R. and Zuber, S. (2011). Screening for Cervical Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force. AHRQ Report No.: 11-05156-EF-1, Agency for Healthcare Research and Quality.

Wilbur, D. C., Black-Schaffer, W. S., Luff, R. D., Abraham, K. P., Kemper, C., Molina, J. T. and Tench, W. D. (2009). "The Becton Dickinson focalpoint GS imaging system: Clinical trials demonstrate significantly improved sensitivity for the detection of important cervical lesions." American Journal of Clinical Pathology **132**(5): 767-775.