Cell Enrichment Liquid-Based Cytology

in routine screening for the prevention of cervical cancer

Submission to MSAC

MSAC Application 1157

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MAIN BODY OF THE SUBMISSION

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Executive Summary

This application is seeking Medicare Benefits Schedule (MBS) listing of cell enrichment liquid-based cytology (LBC) for cervical cancer screening.

In Australia, cervical cytology is routinely undertaken using the conventional Papanicolaou (Pap) smear or test (also referred to as conventional cytology, CC, in this document). The cell enrichment LBC test is an alternative method of preparing a Pap test.

The Australian Medical Services Advisory Committee (MSAC) has reviewed LBC for cervical screening twice before. The finding of the second review (MSAC 1122 assessment report March 2009) was that LBC was "*safe, at least as effective, not cost effective at the price requested*". The 2009 review was not based on randomised controlled trial evidence but rather the best evidence available at the time. The detailed conclusion drawn in the review was that LBC compared with conventional cytology was not statistically significantly different with the exception of reduced specificity for the detection of CIN 2+ at a threshold of pLSIL, more slides classified as positive for LSIL and reduced rates of unsatisfactory tests. The cost-effectiveness ratio was high and unfavourable at the price requested.

MSAC's conclusions from the 2009 review were as follows:

> "With respect to Liquid Based Cytology (LBC), MSAC finds that in comparison to the Papanicolaou (Pap) test that LBC:
> - is safe,
> - is at least as effective,
> - is not cost effective at the price requested."

The current submission contains new clinical evidence and also requests MBS listing at the same fee as for CC which represents a reduction in cost versus previous submissions.

Description of new technology

A conventional Pap test involves the collection of cells from the uterine cervix using a small cytobrush/broom or spatula which is then smeared onto a glass slide. LBC uses a different method for collecting and preparing cervical cells for cytological examination. The BD SurePath™ cell enrichment LBC is a proprietary, sample collection, preservation, transport and slide preparation system that consists of the BD SurePath™ sample collection vial containing proprietary preservative solution and sample collection. Cells are collected using a brush, broom or spatula in the same way as they are collected for a conventional Pap test, but the head of the brush or spatula is detached into a vial of preservative fluid to produce a cell suspension which is sent to the laboratory where a large

number of slides are prepared together using standardised protocols. Conversely, conventional cytology slides are prepared at the point of collection which inevitably introduces variability as to the quality of the specimen. Another benefit of cell enrichment LBC is that 100% of the sampled material is captured. The more material collected and the better the standardisation in the quality of the specimen collected, the greater the chance of both achieving a satisfactory sample for review and finding any abnormal cells.

In the SurePath™ vial the ethanol-based preservative immediately fixes the cells, preserving the morphology (thereby removing air-drying artefact) as well as breaking down the mucus releasing the cells. The sample is vortexed in the laboratory and the cells are released from the collection device. The cell enrichment LBC process consists of centrifugal sedimentation through Density Reagent, partially removing non-diagnostic debris such as blood, mucus and inflammatory cells. The vial is then centrifuged and the resultant enriched cell pellet is then placed on the BD PrepStain™ where it is re-suspended in de-ionised water. An aliquot is then transferred to a settling chamber and the suspension of cervical cells is allowed to settle via Gravity Sedimentation, producing a homogenised, well-distributed thin layer slide for cytologic interpretation.

The cell enrichment process results in a well distributed thin layer of cells on the slide which enables quicker visualisation of clinically relevant cells versus CC. The removal of non-diagnostic debris is achieved without the need for additional processing steps (which may be the case under cell filtrationLBC) and together with the initial high cell capture results in a consistently low unsatisfactory test rate.

The main indication and proposed MBS item descriptions

The final Decision Analytic Protocol 'DAP' (DAP, May 2012) stated that SurePath™ LBC Pap test will be an alternative method of preparing a conventional Pap test and would therefore be listed in category 6 Pathology Services, Group P6 Cytology of the MBS as is the conventional Pap test (MBS item number 73053, 73055 and 73057).

As per the DAP the proposed change to the MBS items 73053, 73055 and 73057 allows cell enrichment LBC techniques to be used. Alternatively new item numbers specifically for LBC using cell enrichment could be used for for each circumstance. As advised in the DAP, the following statement is proposed in the listing to ensure that other methods cannot be claimed using the below item, "cell enrichment liquid based techniques utilising centrifugal sedimentation through density reagent". This application presents evidence to support the differentiation of cell enrichment from other methods of LBC (e.g. cell filtration) thereby justifying the explicit inclusion of cell enrichment on the MBS.

Evidence is also presented in this submission to show that cell enrichment LBC can be reviewed "using manual or automated methods".

The explanatory notes reflect that on any one screening occasion only one of the available Pap test techniques, cell enrichment or CC, should be used.

Category 6—Pathology services (cytology)
MBS 73053, 73055, 73057 (or alternatively a new item number for each circumstance)
Cytology of a smear from cervix or vagina where the smear is prepared by direct application of the specimen to a slide or using cell enrichment liquid based techniques utilising centrifugal sedimentation through density reagent and the smear is microscopically examined by or on behalf of a pathologist using manual or automated methods.
Fee: $19.60 Benefit: 75% = $14.70 85% = $16.70
Explanatory notes for above items:
P16.11: 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.
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:
(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
(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.
(iii) that on any one occasion only a direct application of the specimen to a slide or a cell enrichment liquid based technique should be used
The Health Insurance Act 1973 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.
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.
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.
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.
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.
Related Items: 73053, 73055, 73057

Rationale for the proposed listing and clinical management algorithm

Liquid based cytology by any method is not reimbursed by the MBS, and is currently explicitly excluded.

LBC is commonly offered to women as an additional test performed on the same occasion as the conventional Pap test using the split sample technique whereby a slide is prepared for CC and the

remainder of the same sample is then used for LBC. In this case the laboratories receive the MBS schedule fee for CC and charge the patient out-of-pocket for the LBC test. The LBC out-of-pocket charge varies however the average charge is $45. Approximately 18% of the population receiving MBS funded cervical cancer screening services also pay for an LBC Pap test. It is of note that in the case of discordant results from split sample testing the LBC result is likely to inform the treatment algorithm. Hence a proportion of the population already receives follow-up under the National Cervical Screening Program based on a technology only available to those women with access to LBC.

Although cell enrichment LBC offers benefits over conventional Pap test in terms of lower unsatisfactory rates, a conservative position has been taken in this application with the requested MBS item fee being the same as that for conventional cytology.

Cell enrichment LBC is proposed to be a direct substitute for the current conventional Pap smear (see Figure 1). It is not proposed that cell enrichment LBC be used in conjunction with conventional cytology. The conventional Pap test would still be available on the MBS however its utilisation would be expected to decrease with the introduction of cell enrichment LBC.

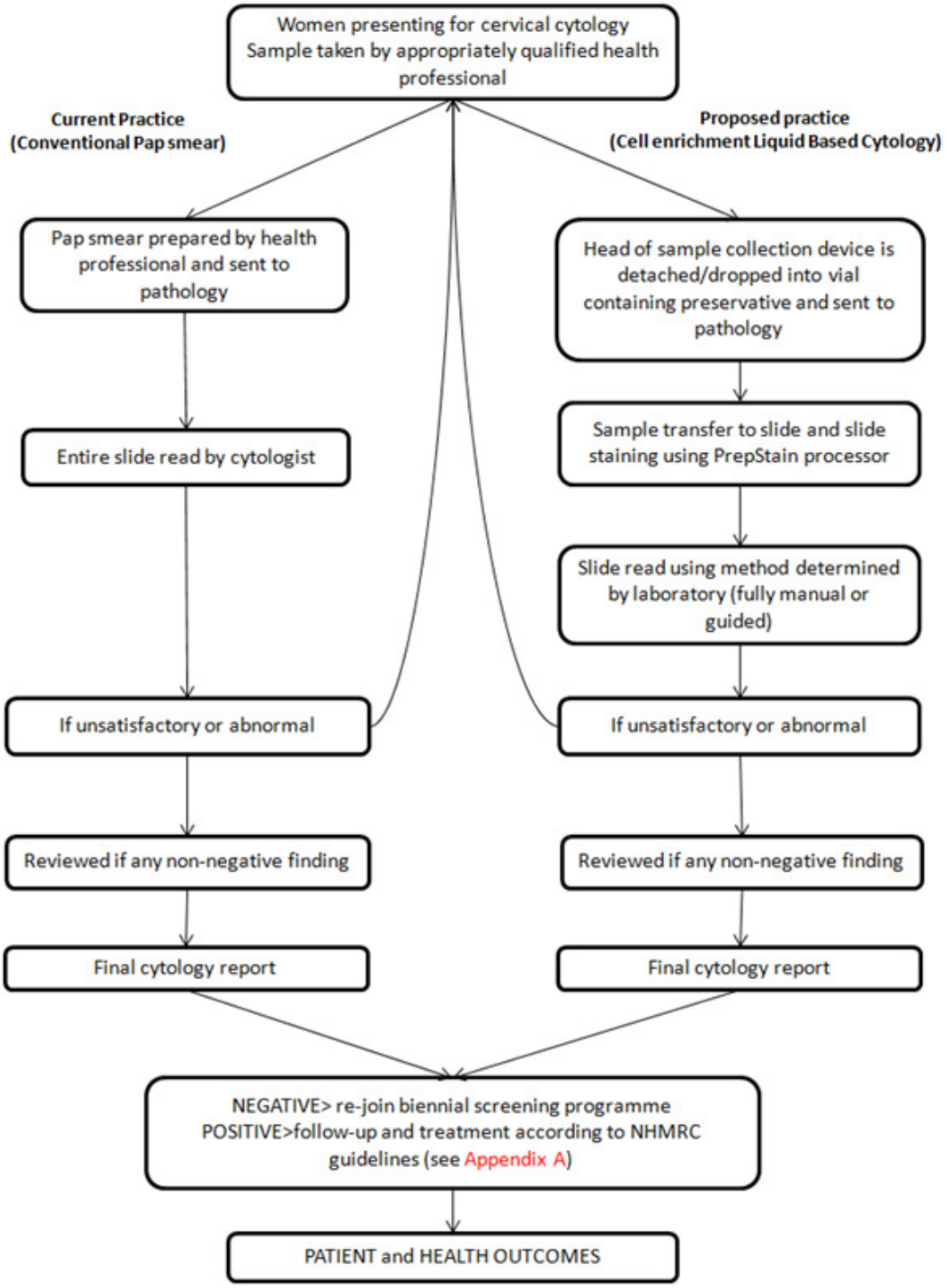

Figure 1 Current practice on the MBS compared with the proposed practice for cervical cancer screening

Comparator

The most appropriate test to inform the comparative effectiveness and cost-effectiveness of cell enrichment LBC is manual screening of conventional Pap smear cytology. The conventional Pap test is the primary comparator required by the final DAP recommendations (May 2012).

Individual laboratories currently make the decision about whether to review slides using manual or automated methods and both methods are currently used in Australia. Whichever method of review is implemented, laboratories are still required to meet quality standards. Nevertheless, the final DAP (May 2012) requires that a secondary comparison be "undertaken to examine the issue of automated versus manual reading of slides" as in the 2009 MSAC review of LBC.

As recommended in the DAP, cell enrichment LBC will also be compared with cell filtration LBC in order to justify the explicit inclusion of cell enrichment LBC in the MBS item descriptor.

Source of clinical evidence

Ten direct head to head randomised controlled trials (RCTs) in a cervical cancer screening population provide the pivotal evidence for the submission (Table 1). There were no RCTs that compared cell enrichment LBC and cell filtration LBC, therefore indirect comparisons are provided where possible.

Table 1 Summary of RCT evidence and limitations

Trial	Sample size	Study limitations
Cell enrichment versus conventional cytology		
Beerman 2009 (Netherlands) July 1997—June 2002	CC=51,154 LBC=35,315	Reference standard not described Uneven distribution of patients within trial
RODEO Study (Brazil) May 2010–December 2010	CC=6047 LBC=6001	Reference standard not described Represents a different geographical location and type of health service (recruitment through mobile units)
Cell filtration versus conventional cytology		
NTCC trial (Ronco 2006a, b) (Italy) 2002–2003	CC=22,547 LBC=22,760	Performed HPV triage on LBC samples only
NETHCON Trial (Siebers 2008, 2009) (Netherlands) April 2003–July 2006	CC=40,047 LBC=48,941	Uneven distribution of patients within trial
Strander 2007(Sweden) May 2002–Dec 2003	CC=8810 LBC=4676	Uneven distribution of patients within trial
Maccallini 2008 (Italy) 2001–2002	CC=4299 LBC=4355	
Obwegeser 2001 (Switzerland) July 1998–Sep 1998	CC=1002 LBC=997	Used different collection instruments between arms
RHINE-SAAR Study (Germany) August 2007 –October 2008	CC=9296 LBC=11,331	Uneven distribution of patients within trial
Manual verses automated		
MAVARIC Study (Kitchener 2011a, b) (UK) Mar 2006–Feb 2009	Manual=24,668 Auto=48,578	performed HPV triage on LBC samples only
Palmer 2012(Scotland) Oct 2008+	Manual=90,551 Auto=79,366	Uneven distribution of patients within trial

Across all trials, where reported, colposcopy and/or biopsy were used as the reference standard. The test threshold at which the reference standard was uniformly applied was either ASCUS+ or HSIL+. Generally the outcome assessor, colposcopist and where relevant histologist, were not blinded to the index/screening test result. Although in four trials—NETHCON; Strander 2009, Maccallini 2008; MAVARIC—the outcome assessors were blinded to the cytology test type.

Beerman 2009 and Strander 2007 were the only trials to follow up all randomised patients by review of any histology results in a national database and report the true false negative rates.

The mean age of participants across the trials ranged from 37 to 44 years of age. Similar collection tools were used between the arms within each trial except Obwegeser 2001.

For most trials the implementation of LBC was new and as such training was reportedly provided to collectors of the LBC specimen and cytology reviewers.

Comparative clinical efficacy

Despite variation in baseline rates of unsatisfactory slides across the studies LBC consistently results in:

- less unsatisfactory tests versus CC
- significantly decreased rate of unsatisfactory tests occur with cell enrichment LBC than cell filtration LBC

There was substantial variation the baseline rated of normal, ASCUS, LSIL and HSIL cytological test yield results across the studies. Nonetheless cell enrichment was consistently associated with:

- decreased rates of normal outcomes and increased rates of ASCUS outcomes.

The direction of the point estimates for each cytological outcome is more variable with the six cell filtration LBC trials, although there is a trend for more LSIL detected with cell filtration LBC compared with CC. No indirect comparison was able to be performed.

Sensitivity and specificity traditionally represent diagnostic accuracy but are only available from two trials and for CIN1+ endpoint. Therefore positive predictive value for CIN 2+ and CIN 3+, are relied on for the assessment of diagnostic accuracy.

Upon application of the reference standard, compared to CC, cell enrichment liquid based cytology LBC demonstrates:

- a significantly greater sensitivity to detect CIN 1+ at a test threshold of ASCUS (pLSIL) (96.3% vs. 92.0%, P=0.0244; an absolute increase of 4.3%)
- a significantly reduced specificity to detect CIN 1+ at a test threshold of ASCUS (pLSIL) (97.7% vs. 98.2%, P < 0.0001, an absolute decrease of 0.5%).

CIN 1 is the histopathologic manifestation of a carcinogenic or non-carcinogenic HPV infection that rarely progresses to cancer (Arbyn 2009). The Australian cervical screening guidelines take the conservative approach whereby the clinical investigation for a pLSIL outcome is follow up CC in 12 months (NHMRC 2005). Although false positives are undesirable in a screening program, the follow up investigation in this circumstance does not expose patients to a high risk of adverse outcome.

Given the transient nature of much CIN1, Arbyn recommends that surrogate outcomes such as reduction of incidence of CIN 3+, increased detection rate of CIN 3+ or CIN 2+, or increased, similar or hardly reduced positive predictive provide more robust comparative assessment of the screening technology. CIN 3 in particular is the direct precursor of invasive cancer, and therefore a good proxy outcome of trials evaluating new technologies.

Cell enrichment LBC demonstrated no significant difference in the detection of CIN2+ or CIN3+ at a test threshold of ASCUS+ (pLSIL), LSIL+ or HSIL+compared with conventional cytology.

These conclusions are similar to those reached in MSAC's second review of LBC in 2009 (MSAC 2009).

Importantly given the level of evidence and the number of trials now available it was possible to pool the numbers of cervical cancers or CIN 3+ detected thereby increasing the power to detect any difference between LBC and CC. The pooled OR (OR 0.69, 95% CI 0.50 to -0.95) indicates that the odds of detecting CIN3+ with conventional cytology is 31% lower than with LBC.

The DAP requires review of outcomes including those related to glandular abnormalities however the trial evidence did not distinguish cervical glandular abnormalities. Retrospective evidence provides data to support the increased detection of glandular abnormalities with cell enrichment LBC. Technical features of cell enrichment LBC provide a plausible rationale supporting this claim.

Table 2 Summary of the evidence base supporting the therapeutic claims

Comparison	Therapeutic claim	The level and quality of the evidence	Statistical precision and size of the effect	Consistency of the results over the trials presented
Cell enrichment LBC v conventional cytology	Cell enrichment LBC results in less unsatisfactory tests	Single head-to-head RCT of over 80,000 slides (Beerman 2009)	% of tests (n/N) LBC: 0.1% (46/35315) CC: 0.9% (435/51132) OR (95%CI): 0.15 (0.11, 0.21) (Table 24)	Not applicable (only one trial with evidence). applicable. Although unsatisfactory tests consistently lower with LBC (of either method compared with CC,)
	Cell enrichment demonstrates a ***significantly greater sensitivity*** to detect CIN 1+ at a test threshold of ASCUS (pLSIL)	As above	Sensitivity [95% CI] LBC: 96.24% [93.54, 97.84] CC: 92.04% [88.87, 94.37] p=0.0244 (Table 50)	Not applicable (only one trial with evidence). applicable. Although greater sensitivity with LBC (of either method compared with CC)
	Cell enrichment demonstrates a ***significantly reduced specificity*** to detect CIN 1+ at a test threshold of ASCUS (pLSIL).	As above	Specificity (n/N) [95% CI] LBC: 97.75% [97.58, 97.90] CC: 98.17% [98.05, 98.28] p<0.0001 (Table 50)	Not applicable (only one trial with evidence). applicable. Although reduced specificity with LBC (of either method compared with CC)
	Higher detection of ASCUS (pLSIL)	As above	Test yield comparison LBC: 2.07% (730/35,315) CC: 0.87% (443/51132) P<0.0001 (Table 32)	Consistent increase in ASCUS reported in RODEO trial
	No difference in the detection of LSIL	As above	Test yield comparison LBC: 0.27% (94/35,315) CC: 0.22% (110/51132) p=0.13 (Table 32)	RODEO trial reported LBC= 0.7%(42/6001) CC=0.3%(18/6047) P<0.001*
	No difference in the detection of HSIL	As above	Test yield comparison LBC: 0.64% (226/35,315) CC: 0.56% (288/51132) p=0.15 (Table 32)	Consistent with no difference reported in RODEO trial
	No difference in PPV at various test thresholds	As above	Comparative PPV RR (95%CI) ASCUS+:1.04[0.91,1.18] LSIL+:0.98[0.9,1.07] HSIL+: 1[0.92,1.07] SCC: 1.33[0.76,2.35] (RR <1 indicates performance of CC is better than LBC)	Not applicable (only one trial with evidence). applicable.

Comparison	Therapeutic claim	The level and quality of the evidence	Statistical precision and size of the effect	Consistency of the results over the trials presented
Cell enrichment LBC v Cell filtration LBC	Cell enrichment LBC results in less unsatisfactory tests	Indirect comparison via conventional cytology with a single RCT of each LBC method compared with CC (Beerman and Strander for cell enrichment and cell filtration respectively)	Indirect estimate of effect OR (95%CI) 0.3586 (0.19, 0.69), p=0.0022 (Table 31)	Not applicable.
	No difference in the detection of CIN 1+	As above	Sensitivity: Indirect OR (95%): 0.3319 (0.0165, 6.6684), p=0.47 Specificity: Indirect OR (95%): 1.2596 (0.9542, 1.6627), p=0.10 (An OR >1 indicates performance of cell enrichment LBC is better than cell filtration LBC)	As above

* The sample size in the RODEO trial is much smaller than the Beerman 2009 trial and the trial represents a different geographical location (remote areas of Brazil) and type of health service (recruitment through mobile units). As such the results are seen to be less comparable with Beerman 2009 and viewed with caution.

In regard to the comparison of manual versus automated review, the results of the MAVARIC trial are confounded due to triage HPV testing, the results of which dictated the application of the reference standard. The results from the study by Palmer 2012 showed that image-assisted screening is at least as good as screening with conventional cytology and is significantly more specific than manual screening. Automated slide review in Palmer 2012 averaged 17 slides per hour, a statistically significant increase of 70% compared to manual review.

The therapeutic conclusion and type of economic evaluation presented

For the purpose of economic evaluation differences between cell enrichment LBC and conventional cytology are taken as being confined to differences in detection of pLSIL (more with cell enrichment LBC) and differences in rates of unsatisfactory tests (more with conventional cytology). The NCSP guidelines provide almost identical guidance with respect to the follow-up of pLSIL and unsatisfactory smears. That is, repeat the test in 12 months (within 6 to 12 weeks in the case of unsatisfactory smears). As such, a cost-minimisation analysis which incorporates the costs of following up these repeat tests (whether for pLSIL or unsatisfactory tests) is sufficient to determine

the cost-effectiveness of cell enrichment LBC relative to conventional cytology. A cost-effectiveness model is provided as a supplementary analysis in accordance with the DAP.

The above is a conservative approach to the economic evaluation in that it excludes the pooled data indication of higher detection of CIN3+ with LBC and also the higher probability of greater findings of abnormalities within tests otherwise categorised as unsatisfactory by conventional cytology.

Assessment of applicability issues

The reference standards applied in the majority of trials are not applicable to the Australian context. For those that are representative of Australian practice the timing of repeat cytology is not known nor the outcome of the repeat test. Furthermore the participant baseline characteristics and test yield outcomes from the trials are not representative of the Australian population. Nonetheless across varying reference standards, patient characteristics and test yield outcomes the same conclusions that cell enrichment LBC demonstrates superior reduction in unsatisfactory slides and non inferior accuracy compared with cell filtration LBC and conventional cytology are maintained.

The lower unsatisfactory outcomes associated with cell enrichment LBC are expected to outweigh the lower ASCUS outcomes associated with conventional cytology. However the outcomes of repeat testing in both situations are not known. There is a high likelihood that unsatisfactory slides harbour cervical abnormalities (OR 2.78, 95% CI: 2.31 to 3.35) however the follow up testing is conservatively assumed to be the same in the cost-minimisation calculations in section D and E.

The cost per patient

The proposed MBS fee for cell enrichment LBC is $19.60. This equates to the current fee for conventional cytology. This reflects that the outcomes associated with cell enrichment LBC is at least as accurate as conventional cytology.

Evidence presented in Section D.1 indicates that should a laboratory choose to offer LBC services, the proposed benefit will be sufficient for meeting the commercial incentives, thereby ensuring LBC is a sustainable service item on the MBS.

Sustainability of the proposed MBS fee for LBC with cell enrichment

The addition of cell enrichment LBC to the MBS as proposed in this application will lead to a substantial reduction in out-of-pocket costs. Currently, most private laboratories in Australia provide Pap test collection kits using LBC. Internal market research by BD estimates that approximately 18% of MBS funded Pap tests are collected as a split sample. In these cases, the cost of conventional cytology is met by the MBS, while the cost of LBC is paid for by the patient. Referring

practitioners and laboratories currently charge an average of $45 for LBC tests with the market leading pathologies charging between $45 and $55 per LBC service.

It is estimated that over $14.0 million is currently being paid by Australian women for LBC tests each year. That is, 18% of 1.74 million tests annually at an average cost to patients of $45 per test. It is important to note that this means 310,000 to 320,000 cervical specimens are being reviewed twice (once with conventional cytology paid for by the MBS, once with LBC paid for by patients) which represents an unnecessary societal cost. Despite the known resource constraint (as noted MSAC 2009) of an increasing shortage of trained cytotechnologists, the current system whereby approximately 18% of slides are read twice means six cytotechnologists are required to do the job of five. This puts pressure on the wages of cytotechnologists and eventually the MBS fee for conventional cytology will need to increase (or the costs will be passed on to patients) because of this unnecessary, inefficient, duplication.

The duplication of LBC and conventional cytology would be significantly reduced (if not eliminated) by an MBS listing of cell enrichment LBC – a saving to patients of over $14.0 million annually. From a financial and economic perspective, the flexibility and efficiency of the added alternative with cell enrichment LBC is the sustainable option for the MBS and the NCSP in the long term.

The other types of resources affected by this proposed MBS listing

The requested MBS fee represents a cost-minimising fee for cell enrichment LBC compared with conventional cytology, thereby reflecting the available clinical evidence that cell enrichment LBC is at least as accurate as conventional cytology. This approach however omits any resource and thus cost implications possible due to lower rates of unsatisfactory smears (thus re-tests) with cell enrichment LBC relative to conventional cytology. Equally, it does not necessarily account for potentially higher rates of follow-up of possible low-grade findings with cell enrichment LBC. After accounting for the expected reduction in the number of re-tests due to unsatisfactory smear and the expected increase in the number of follow-up tests due to pLSIL results, cell enrichment LBC is estimated to offer an overall saving to the MBS of $0.29 per test when compared with conventional test (see Section D.2 for further details). Here, it is important to note that the cost of following up high grade abnormalities is not included in the analysis because there is no difference in the rate of detection of these abnormalities between these tests and thus no further resource cost implications will occur.

It should be noted that the practice of split sample is prevalent in the current clinical practice, affecting approximately 18% of MBS funded Pap test collections. The costs of these LBC tests are currently met by out-of-pocket payment (~$45 per test; an estimated total of $14 million each year). This practice will be addressed by the proposed listing and the potential cost savings to the patients

can be calculated as -$8.10 per patient, further improving 'value for money' offered by the proposed listing of cell enrichment LBC.

Estimated extent of Use and Financial Implications

The listing of cell enrichment LBC can be achieved with no additional costs to the MBS, given the cost-minimising benefit amount requested in the submission. In fact, the listing of cell enrichment LBC generates cost savings to the MBS. These savings are due to the lower rate of unsatisfactory Pap test given by cell enrichment LBC, offsetting potential additional follow-up costs (reflecting its higher sensitivity for pLSIL than conventional cytology; as shown in the cost analysis above). Assuming 100% uptake (i.e., all conventional cytology tests are replaced by cell enrichment LBC after listing), the net financial implications to the MBS is estimated to be a saving of approximately $115,000 each year (see Section E.4). In addition, women will save in excess of $14 million per annum in out of pocket expenses.

Other relevant considerations

In addition to the clinical and financial attributes of cell enrichment LBC as discussed in detail in this submission other relevant considerations as also highlighted in the 2009 MSAC review (Assessment report #1122 Executive Summary page xiv) are that:

"The collection of cervical cytology into an LBC medium provides the opportunity for reflex testing of a range of pathogens, including HPV, Chlamydia trachomatis and Neisseria gonorrhoea" ,

"There is an increasing shortage of trained cytotechnologists in Australia. Technologies which decrease cytology screening time and increase productivity may aid in addressing workforce shortages by decreasing staff requirements", and

"With the recent introduction of the HPV vaccine in Australia, the expected impact is a decrease in the prevalence of HPV and pre-cancerous cytological abnormalities and also alteration of the distribution of cytological abnormalities, increasing technical difficulties for cytotechnologists manually screening slides even further".

Consideration of the role of LBC in the future NCSP Guidelines is beyond the scope of this submission however the general observation is made that to list cell enrichment LBC on the MBS increases the flexibility and sustainability of the NCSP.

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Attachment 4	Section B statistical calculations (RevMan database and excel spread sheets electronic only)	Electronic only
Attachment 5	Cost-minimisation calculations (excel spread sheets electronic only)	Electronic only
Attachment 6	*Commercial-in-confidence.* Cost-effectiveness model technical report and Australian model inputs (including Excel spread sheet model)	4 (Excel sheets electronic only)
Attachment 7	Financial implications (excel spread sheets electronic only)	Electronic only

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Abbreviations

Abbreviation	Full term
AGC	Atypical glandular cells
AGUS	Atypical glandular cells of undetermined significance
AIS	Adenocarcinoma in situ
AMBS	Australian modified Bethesda System
APV	Abnormal Predictive Value
ASC-H	Atypical squamous cells, possible high-grade lesion
ASCUS	Atypical squamous cells of undetermined significance/pLSIL
ASCUS+	Atypical squamous cells of undetermined significance grade or higher
BD	Becton Dickinson Pty Limited
BSCC	British Society for Clinical Cytology
CC	Conventional cytology
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CIN 1	Cervical intraepithelial neoplasia grade 1
CIN 1+	Cervical intraepithelial neoplasia grade 1 or higher
CIN 2	Cervical intraepithelial neoplasia grade 2
CIN 2+	Cervical intraepithelial neoplasia grade 2 or higher
CIN 3	Cervical intraepithelial neoplasia grade 3
CIN 3+	Cervical intraepithelial neoplasia grade 3 or higher
CISOE-A	Cytology Classification System: composition (C), inflammation (I), squamous epithelium (S), other and endometrium (O), endocervical columnar epithelium (E)
CPS	Conventional Pap smear
CV	Conventional cytology
DAP	Decision Analytical Protocol
DoHA	Department of Health and Ageing
DR	Detection Rate
FAR	Final automated result
FDA	US Food and Drug Administration
FMR	Final manual result
FN	False negative
FP	False positive
FPGS	FocalPoint Guided Screening
FPSP	FocalPoint SurePath
GAA	Glacial acetic acid
GP	General practitioner
HPV	Human papillomavirus
HSIL	High-grade squamous intraepithelial lesions
HSIL+	High-grade squamous intraepithelial lesions grade or higher

HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IVD	In vitro diagnostic
KOPAC-B	Dutch Cytology Classification System: kompositie (K), ontsteking (O), plaveisel epitheel (P), andere en endometrium afwijkingen (A), cylinder epitheel (C)
LBC	Liquid-based cytology
LSIL	Low-grade squamous intraepithelial lesions
LSIL+	Low-grade squamous intraepithelial lesions or higher
MAVARIC	Manual Assessment Versus Automated Reading In Cytology trial
MBS	Medicare Benefits Scheme
MCID	Minimal clinically important difference
MR1	Manual result 1
MSAC	Medical Services Advisory Committee
NA	Not applicable
NATA	National Association of Testing Authorities
NC	Not calculated
NCSP	National Cervical Screening Program
NETHCON	Netherlands ThinPrep Versus Conventional Cytology trial
NHMRC	National Health Medical Research Council
NHSPC	National Health Service Cervical Screening program
NPV	Negative predictive value
NR	Not reported
NS	Not significant
NTCC	New Technology in Cervical Cancer trial
NZ NCSP	New Zealand National Cervical Screening Program
OR	Odds ratio
PALGA	Dutch Network and National Database for Pathology
Pap	Papanicolaou
PASC	Protocol Advisory Subcommittee
pHSIL	Possible high-grade squamous intraepithelial lesions
pLSIL	Possible low-grade squamous intraepithelial lesions/ASCUS
PPV	Positive predictive value
QALY	quality adjusted life year
QC	Quality control
RCPA	Royal College of Pathologists Australia
RCT	Randomised controlled trial
RD	Risk difference
RevMan	Review Manager Version 5
SBLB	Significant but limited by
SCC	Squamous cell carcinoma
SIL	Squamous intraepithelial lesion

SE	Standard error
SP	SurePath
TIS	ThinPrep Imaging system
TN	True negative
TP	True positive
TPV	Total predictive value
WHO	World Health Organization

A. Details of the proposed intervention and its intended use on the MBS

A.1 Requested MBS listing and details of the intervention

This application is seeking Medicare Benefits Schedule (MBS) listing of cell enrichment liquid-based cytology (LBC) for cervical cancer screening.

In Australia, cervical cytology is routinely undertaken using the conventional Papanicolaou (Pap) smear or test (also referred to as conventional cytology, CC, in this document). In line with the National Cervical Screening Program (NSCP) cervical cytology tests are recommended every two years starting at 18 years of age (or two years after first sexual intercourse, whichever occurs first) and ceasing at 69 years of age.

The cell enrichment LBC test is an alternative method of preparing a Pap smear test. This submission refers to the assessment of cell enrichment LBC system, also referred to in the document as SurePath™. It encompasses both manual and automated reading methods of the slides.

A.1.1 Health technology assessment background

The Australian Medical Services Advisory Committee (MSAC) has reviewed LBC for cervical screening twice before. The first review concluded that "there is currently insufficient evidence pertaining to liquid-based cytology for cervical screening"' (MSAC 12a assessment report August 2002). The second review (MSAC 1122 assessment report March 2009) concluded that LBC compared with conventional cytology:

- is safe
- provides no statistically significant increase in sensitivity or specificity
- provides no statistically significant difference in sensitivity (high-grade squamous intraepithelial lesion (HSIL), low-grade squamous intraepithelial lesion (LSIL) or possible low-grade squamous intraepithelial lesion (pLSIL) thresholds) or specificity (HSIL or LSIL thresholds)) for the detection of cervical intraepithelial neoplasia grade 2 or higher (CIN 2+)+
- reduces the specificity for the detection of CIN 2+ at a threshold of pLSIL
- classifies more slides as positive for LSIL
- reduces the rate of unsatisfactory smears; and

- has a high cost-effectiveness ratio which appears to be unfavourable in the current Australian setting.

Furthermore the MSAC review found that Automation-assisted reading of LBC slides with the ThinPrepImager system compared to manual reading of conventional cytology

- is safe
- detects at least as many CIN 2+ lesions, and may detect more
- increases the number of slides classified as having low-grade lesions on cytology
- reduces the rate of unsatisfactory slides
- reduces slide processing time
- has a high cost-effectiveness ratio which appears to be unfavourable in the current Australian setting

In addition, other international health technology assessment (HTA) agencies have reviewed LBC for cervical cancer screening.

The first UK HTA report for LBC in cervical cancer screening was published in January 2000 (Payne 2000). The National Institute for Excellence (NICE) rejected the report on the basis that although LBC "could provide significant and important benefits… [The] quality of the evidence is variable and… there is insufficient evidence to justify the nationwide introduction of LBC technology at this time" (Karnon 2004). A second HTA report was subsequently published resulting in a positive recommendation by NICE in October 2003. LBC is the primary means of processing samples in the cervical screening program in England and Wales. No distinction between automated and manual processing was documented in the guidance published by NICE, although evaluation of automated technologies for the analysis of cervical samples was recommended for future research (NICE Guidance on LBC 2003).

In November 2003, the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) published a HTA report reviewing both LBC and human papillomavirus (HPV) in comparison with conventional Pap smears for cervical cancer screening. A secondary systematic review and cost-effectiveness analysis was published in February 2008 by the Canadian Agency for Drugs and Technologies in Health (CADTH). These reports were considered by provincial and territorial health ministries in Canada and formed the evidence-base for the recommendations on the delivery of cervical cancer screening within the Canadian health system. Whilst the use of semi-automated LBC screening is discussed in the Canadian HTA assessments, no formal recommendation is given for either manual or semi-automated cytology processing.

A.1.2 Cervical cancer and screening background

The NCSP was established in Australia in 1991 to identify and treat women with precancerous cervical intraepithelial neoplasia (CIN) before it progresses to invasive cancer. Cervical cytology tests are recommended every two years starting at age 18 to 20 years for asymptomatic, sexually active women (or within 1 to 2 years of becoming sexually active) and ceasing at age 69 years. If the cytology results are suggestive of precancerous changes, women are referred for specialist histological diagnosis, further follow up and appropriate treatment.

Different systems are used for classifying cytological and histological abnormalities in cervical screening. In Australia, cytological abnormalities are classified by using the Australian Modified Bethesda System (AMBS). Under this system, cytological abnormalities of squamous cells are classified as high-grade squamous intraepithelial lesion (HSIL), possible HSIL (pHSIL), LSIL or possible LSIL (pLSIL) (Table 3). Cytological abnormalities of glandular cells are classified as atypical endocervical cells of undetermined significance, atypical glandular cells of undetermined significance (AGUS), possible high-grade glandular lesion, endocervical adenocarcinoma in situ (AIS), and adenocarcinoma. The international literature most commonly uses the US Bethesda System for classifying cervical cytology, which uses a slightly different terminology. Importantly, pLSIL is equivalent to atypical squamous cells of undetermined significance (ASCUS) under the US Bethesda System (Table 3).

As per the Australian National Health and Medical Research Council (NHMRC) Screening to Prevent Cervical Cancer Guidelines (NHMRC 2005), women with HSIL are referred to a specialist for examination of the cervix using a colposcope (colposcopy). Abnormal lesions identified at colposcopy are biopsied and classified as CIN grades 1 to 3 on the basis of the histological findings (Table 4). Although it was originally believed that neoplastic cellular changes occurred along a continuum from CIN 1 to 2 to 3, CIN 1 is now regarded as a manifestation of the HPV infective process, rather than as the first step in the neoplastic process.

HPV infection of the cervix is usually asymptomatic, and most infections are transient. HPV infection may not cause any change in cell morphology or it may cause the cytopathic effect previously recognised as mild dysplasia and classified as CIN 1. Thus, CIN 1 lesions are now monitored by repeat cytology with the expectation that the cellular changes will regress when HPV infection resolves. In a small proportion of women, persistent HPV infection may occur.

Persistent infection with oncogenic HPV genotypes precedes precancerous changes, which are classified as CIN 2 (moderate dysplasia) or CIN 3 (severe dysplasia) (Table 4). These lesions are treated by ablative therapy to prevent progression to invasive cancer. It is now accepted that CIN 2 or CIN 3 can occur de novo, rather than as a continuum from CIN 1 lesions. A trial-based quality

control assessment of community pathology biopsy diagnoses has demonstrated that the detection of CIN 2 has poor reproducibility compared to the detection of CIN 3, with 56% of 523 CIN 2 cases reclassified as CIN 3 (27%) or ‹ CIN 2 (29%) at the quality control assessment (Castle 2007). The authors suggested that this evidence indicates that CIN 2 represents a mix of HPV infection and CIN 3, and that CIN 3 is the true precursor to cancer (Castle 2007). Women with CIN 3 have a 12% chance of progression and should therefore be treated to reduce their risk of developing squamous cell carcinoma (SCC) (NHMRC 2005 p.53).

In Australia, women with cytological findings of pLSIL or LSIL are managed more conservatively; cervical cytology is repeated at 12 and 24 months and referral for colposcopy is made only if these lesions are persistent[1], because the majority represent an infective process due to HPV and will resolve spontaneously without treatment(Appendix A). However, around 20% of women with LSIL will be confirmed as CIN 2 to CIN 3 at histology if immediate colposcopy and biopsy are performed (pooled prevalence from 10 studies: 18.8% [95% CI 1.24% to 25.2%]; Arbyn 2006).

Table 3 Comparison of the Australian Modified Bethesda System (2004) and the US Bethesda System (2001)

AMBS	US Bethesda System
Squamous abnormalities	
Possible low-grade squamous intraepithelial lesion (pLSIL)	Atypical squamous cells, undetermined significance (ASCUS)
Low-grade squamous intraepithelial lesion (LSIL)	Low-grade squamous intraepithelial lesion
Possible high-grade squamous intraepithelial lesion (pHSIL)	Atypical squamous cells, possible high-grade lesion (ASC-H)
High-grade squamous intraepithelial lesion (HSIL)	High-grade squamous intraepithelial lesion
Squamous cell carcinoma (SCC)	Squamous cell carcinoma
Glandular abnormality	
Atypical endocervical cells of undetermined significance	Atypical endocervical cells, undetermined significance
Atypical glandular cells of undetermined significance (AGUS)	Atypical glandular cells of undetermined significance
Possible high-grade glandular lesion	Atypical endocervical cells, possibly neoplastic
Endocervical adenocarcinoma in situ (AIS)	Endocervical adenocarcinoma in situ
Adenocarcinoma	Adenocarcinoma
Source: Australian NHMRC Screening to Prevent Cervical Cancer Guidelines, 2005	

[1] The NHMRC Guidelines suggest that LSIL's may be managed more aggressively in women aged 30 years or more without a history of normal smears in the preceding two to three years (that is, repeat test within 6 months or immediate colposcopy), although the guidance for "all ages" is a repeat test in 12 months. Management following this guidance is expected to affect a small minority of women (on the basis that only a small minority of women over 30 experience persistent low grade abnormalities). Also in such circumstances a LSIL finding is more likely to be clinically significant. For the purpose of this submission it is assumed that the follow-up for pLSIL and LSIL findings is a repeat test at 12 months.

Table 4 Classification of histological abnormalities as grades of CIN

Grade	Definition
CIN 1	Mild dysplasia involving the basal 1/3 of the epithelium; an infective process
CIN 2	Moderate dysplasia involving the basal 2/3 of the epithelium
CIN 3	Severe dysplasia involving more than 2/3 of the cervical epithelium; also referred to as cervical cancer in situ
Source: MSAC 1122 assessment report March 2009	

A.2 Indications and requested restrictions

A.2.1. Existing arrangements

Conventional Pap smears are reimbursed by Medicare (MBS item numbers 73053, 73055, 73057) and are a stand-alone primary screening test commonly administered within the context of a medical consultation (MBS Item 3, 23, 36, 44), administered by qualified health professionals (MBS Item 52, 53, 54, 57) or provided in the context of a specialist appointment (MBS Item 104 ,105). A colposcopy and referral to a specialist may be indicated following any abnormal test result from the initial screen.

Table 5 lists the current MBS item descriptors for conventional Pap smears.

Table 5 Current MBS item descriptor for conventional Pap smears

Category 6—Pathology Services (Cytology)
MBS 73053 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 (a) for the detection of precancerous or cancerous changes in women with no symptoms, signs or recent history suggestive of cervical neoplasia; or (b) if a further specimen is taken due to an unsatisfactory smear taken for the purposes of paragraph; or (c) if there is inadequate information provided to use item 73055; (See para P16.11 of explanatory notes to this Category) Fee: $19.60 Benefit: 75%=$14.70 85%=$16.70
MBS 73055 Cytology of a smear from cervix, not associated with item 73053, 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 test (a) for the management of previously detected abnormalities including precancerous or cancerous conditions; or (b) for the investigation of women with symptoms, signs or recent history suggestive of cervical neoplasia; (see para 16.11 of explanatory notes to this Category) Fee: $19.60 Benefit: 75%=$14.70 85%=$16.70
MBS 73057 Cytology of smears from vagina, not associated with item 73053 or 73055 and not to monitor hormone replacement therapy, 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 test. (See para P16.11 of explanatory notes to this Category) Fee: $19.60 Benefit: 75%=$14.70 85%=$16.70
Explanatory notes for above items: P16.11: 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. 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: (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

(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.

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.

The Health Insurance Act 1973 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.

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.

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.

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.

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.

Related Items: 73053, 73055, 73057

A.2.2 Marketing status of LBC

The only cell enrichment LBC product available in Australia is SurePath™ (supplied by Becton Dickinson Pty Ltd [BD]). All products supplied in Australia by BD are done so in accordance with the requirements of the Therapeutic Goods Act (1989) and the Therapeutic Goods (Medical Devices) Regulations 2002. In vitro diagnostic (IVD) medical devices, such as the cell enrichment LBC test, were exempt IVDs prior to 1 July 2010. The introduction of a revised regulatory framework for IVDs from 1 July 2010 means that all devices supplied before that date are covered by a four year transition period (to 30 June 2014) to be integrated into the new regulatory framework.

A.2.3 Reimbursement status of liquid-based cytology (LBC)

Liquid-based cytology (LBC) by any method is not reimbursed on the MBS, and is explicitly excluded from the MBS. LBC is however currently provided by most private pathology laboratories for a fee additional to the MBS fee for conventional Pap smear tests, and is collected using the split-sample technique in conjunction with conventional Pap smear tests. The additional fee is paid by the patient and averages $45.

LBC was first introduced to Australia by private laboratories in 1997 in response to demand by referring practitioners (Farnsworth 2003). Farnsworth notes that "the total number of smears read in the laboratory in the calendar year (January 2000–December 2000) was 147 181 of which 21 100 were accompanied by a ThinPrep test" (Farnsworth 2003. p49). This is a prevalence of split sampling of 14% (21,100/147,181).

The practice of split-sampling continues in 2012, it is estimated that 18% of women receive conventional cytology, funded by the MBS, in combination with LBC, funded by the patient. This is a significant proportion of the population paying for additional cervical screening service. This has equity implications as it is reasonable to conclude that women with the means and access are receiving better health care than the general population. It is of note that in the case of discordant results from split sample testing the LBC result is likely to inform the treatment algorithm. Hence a proportion of the population already receives follow-up under the National Cervical Screening Program based on a technology only available to those women with access to LBC.

LBC can also be used for adjunctive testing for a range of pathogens including HPV, *Chlamydia trachomatis* and *Neisseria gonorrhoea.* This is not routinely performed in Australia.

A.2.4 Proposed listing of liquid-based cytology

Rationale for the proposed listing

In the laboratory, the BD SurePath™ proprietary cell enrichment process separates and reduces obscuring debris (such as blood and mucus) and inflammatory cells, preserving background interpretation, and thereby reducing unsatisfactory rates. This method therefore provides better and quicker visualisation of clinically relevant cells versus CC (Sweeney 2006). There is no need for additional processing steps dedicated to handling bloody or mucoid samples, resulting in greater standardisation of sample processing and clarity of results (Sweeney 2006).

Although cell enrichment LBC offers benefits over conventional Pap smears in terms of lower unsatisfactory rates, a conservative position has been taken in this application with the requested MBS item fee being the same as that for conventional cytology.

Proposed MBS listing(s)

The final Decision Analytic Protocol (DAP, May 2012) stated that SurePath™ LBC Pap test would be an alternative method of preparing a conventional Pap smear and would therefore be listed in category 6 Pathology Services, Group P6 Cytology of the MBS as is the conventional Pap smear (MBS item number 73053, 73055 and 73057).

Table 2 of the DAP proposes a change to the MBS items 73053, 73055 and 73057 whereby cell enrichment LBC techniques can be used. AS per the DAP the proposed change to the MBS items 73053, 73055 and 73057 allows cell enrichment LBC techniques to be used. Alternatively a new item number may be listed for each circumstance. As advised in the DAP, the following statement is proposed in the restriction to ensure that other methods cannot be claimed using the below item, "cell enrichment liquid based techniques utilising centrifugal sedimentation through density reagent". This application presents evidence to support the differentiation of cell enrichment from

other methods of LBC (e.g. cell filtration) thereby justifying the explicit inclusion of cell enrichment on the MBS.

Similarly, evidence presented in this submission will be used to show that the term "using manual or automated methods" in the proposed MBS item descriptor of the DAP can be justified. That is to say, there is no evidence to suggest that the alternative methods of reading cell enrichment LBC are different.

The explanatory notes reflect that on any one screening occasion only one of the techniques available should be used.

Category 6—Pathology services (cytology)

MBS 73053, 73055, 73057 (or alternatively a new item number for each circumstance)

Cytology of a smear from cervix or vagina where the smear is prepared by direct application of the specimen to a slide or using cell enrichment liquid based techniques utilising centrifugal sedimentation through density reagent and the smear is microscopically examined by or on behalf of a pathologist using manual or automated methods.

Fee: $19.60 Benefit: 75%=$14.70 85%=$16.70

Explanatory notes for above items:

P16.11: 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.

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:

(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

(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.

(iii) that on any one occasion only a direct application of the specimen to a slide or a cell enrichment liquid-based technique should be used

The Health Insurance Act 1973 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.

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.

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.

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.

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.

Related Items: 73053, 73055, 73057

A.3 Intervention details

A.3.1 Slide collection and preparation

A conventional Pap smear involves the collection of cells from the uterine cervix. Cells are collected from the cervix using a small cytobrush/broom or spatula and smeared onto a glass slide. There are proposed differences between the different collection devices. Cotton swabs and Ayre spatula are quoted as being insufficient to harvest adequate endocervical cells for full investigation of squamous and glandular abnormalities, unlike the Szalay spatula (Obwegeser 2001). Rovers Cervex Brush, is the most common collection device in use in Australia (BD personal communication).Sampling of the endocervix can be performed under the guidance of a colposcopy or, as occurs generally, the cervix is well visualised with an adequate light source. In any case, the intention is to collect cells 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 of the endocervical canal meet). The entire transformation zone should be sampled since most high-grade lesions develop in this region. The cells are spread onto a glass slide and the slide is sprayed with fixative and then sent to the laboratory for staining and examination under the microscope by a cytologist.

LBC uses a different method for collecting and preparing cervical cells for cytological examination than the conventional Pap smear. There are currently two marketed LBC preparation systems available in Australia, the SurePath™ LBC system (Becton Dickinson [BD] Pty Ltd) and ThinPrep® Pap system (Hologic [Australia] Pty Ltd). These systems use different technical methods for storing and preparing the cervical cytology sample, some of which are patented.

The BD SurePath™ cell enrichment LBC is a proprietary, sample collection, preservation and transport system that consists of the BD SurePath™ sample collection vial containing proprietary preservative fluid and sample collection devices (all of which are provided by the pathology companies). Cells are collected using a brush, broom or spatula in the same way as they are collected for a conventional Pap smear, but the head of the brush or spatula is detached into a vial of preservative fluid to produce a cell suspension which is sent to the laboratory. In the direct-to-vial collection method, instead of smearing the cells directly onto a glass slide, cells collected from the cervical scraping are transferred directly to the LBC preservative fluid. The collection method benefit of cell enrichment LBC is that 100% of the sampled material is captured providing a more representative sample of the cervix and increasing the chance of finding abnormal material. The more material collected the greater the chance of finding any abnormal cells. Part of the material includes mucus and endocervical cells which are often trapped in the mucus, this will often stick to the collection device of conventional Pap smears and be discarded. Furthermore, the immediate fixation preserves morphology and removes air drying artefact (Hoda 2012).

In the SurePath™ vial the mucus slowly softens and breaks down in the ethanol-based preservative fluid, releasing the cells. The sample is vortexed in the laboratory and the cells are released from the collection device. The cell enrichment LBC process consists of centrifugal sedimentation through Density Reagent, removing non-diagnostic debris such as blood, mucus and inflammatory cells. The vial is then centrifuged; the enriched cell pellet is then placed on the BD PrepStain™ re-suspended in de-ionised water. The specimen is then homogenised and a randomised aliquot is transferred to a settling chamber. The suspension of cervical cells is then allowed to settle via Gravity Sedimentation, producing a thin layer slide for cytologic interpretation.

Glandular abnormalities are often in large groups, which can be quite heavy. The Cell enrichment cell enrichment and gravity sedimentation processes both actively select for heavier elements, meaning that large groups of cells and tissue fragments are more likely to be present with cell enrichment LBC.

Instructions are provided for cell enrichment LBC specimen collection with the collection devices. Training is required for LBC processing and specimen review. Specimen review training is intensive, involving training over four days.

The ThinPrep® cell filtration LBC system (Hologic [Australia] Pty Ltd) requires that the head of the brush or spatula be rinsed into a vial of liquid to produce a cell suspension. ThinPrep® is a filter-based processing technique in which a filter is inserted into the vial and which is then spun at high speed, with the resulting centrifugal forces helping to break up mucus and to homogenise the specimen. The specimen is then aspirated through the filter until the computer registers that the filter is occluded. The filter is then applied to a slide and the cells are pressed onto the surface using mechanical and positive air pressure, creating a thin layer slide. Non-squamous cell particles, such as white and red blood cells and mucin compete with diagnostic material for space on the membrane filter, and the cervical cell residue which adheres to the filter s transferred to the slide (Hoda 2012). The ThinPrep® Pap system will be referred to in this document as cell filtration LBC.

Slide review

LBC slides can be reviewed using standard manual practices on typical microscopes common in all pathology laboratories. Alternatively laboratories can choose to implement a guided slide reading system. Guided systems are commonly referred to as 'automated'; however, automation is partial only in the sense of directing the attention of the screener to fields of view that are most likely to contain abnormalities. The aim of automated slide reading is to reduce cytology reading time and detection error. Both the cell enrichment LBC system and the cell filtration LBC system can be reviewed using either manual or automated reading methods.

In the 1990s two United States (US) Food and Drug Administration (FDA)-approved automated machines were developed to review cervical smears. They were the AutoPap® 300 QC (NeoPath,

Redmond, WA, USA) and the PapNet® (Neuromedical Systems Inc. Suffern, NY, USA), both systems being designed to work with conventional Pap smears. AutoCyte had also developed a machine known as the AutoCyte-Screen which was able to read AutoCyte-Prep slides (now BD SurePath LBC). Despite the initial promise of the technology none of these machines is now available (Kitchener 2011).

The BD FocalPoint™ Guided Screening (GS) Imaging System and the ThinPrep Imaging System (Hologic™, Bedford, MA, USA) are FDA approved for primary screening of SurePath and ThinPrep samples respectively. Use of these systems in Australia is subject to the pathology laboratory validation processes; both systems are currently in use in Australia

The BD FocalPoint™ GS Imaging System is a system which directs the cytotechnologist (screening cytologist) to areas on the specimen most likely to contain abnormalities. When using this system the cytotechnologist is able to review the selected areas of the specimen and confirm whether or not abnormalities are present. With manual review, the cytotechnologist is required to examine the entire specimen. This guided screening system therefore decreases the time required to complete the assessment.

The BD FocalPoint™ GS Imaging System also ranks each slide according to its likelihood of containing an abnormality, effectively directing internal quality control within the laboratory and potentially minimising false negatives.

Australian pathology laboratories are required to maintain quality standards in line with mandatory quality assurance program. The reporting of cervical cytology differs from most areas of pathology, where machines or test kits can be calibrated against control specimens. The reporting of cervical cytology is entirely a human experience and is subject to error. Consequently, both the purchasers and providers of cervical cytology services are accountable for the quality of the service and responsible for minimising error levels. The same quality assurance procedures apply irrespective of whether laboratories choose to review cervical smears using manual or automated methods.

The National Association of Testing Authorities (NATA) has the responsibility for performing a triennial inspection of each laboratory in Australia and for assessing annual reports of laboratories in relation to the performance standards (DoHA Performance measures for Australian laboratories reporting cervical cytology 2006). There are six mandatory performance measures for Australian laboratories reporting cervical cytology (DoHA 2006). The Royal College of Pathologists of Australasia (RCPA) maintains the Cytopathology Quality Assurance Program across Australia and laboratories are required to submit data against the mandated performance measure twice a year (DoHA 2006).

The current MBS listings of conventional Pap smear preparation and proposed future listings specific to LBC do not stipulate the type of smear review to be used by laboratories. Importantly, the same fee is proposed as is currently reimbursed irrespective of the type of smear review performed at the laboratory. The DAP proposed listing states, "microscopically examined by or on behalf of a pathologist using manual or automated methods". Individual laboratories currently make the decision whether to review slides using manual or automated methods, with LBC primary slide reading automation in place in several large laboratory sites. The aim of automated slide reading is to reduce cytology reading time and detection error. There is an increasing shortage of trained cytotechnologists in Australia therefore automated technologies, which increase productivity, may aid in addressing workforce shortages by decreasing staff requirement. Whichever method of review is implemented by laboratories they are still required to meet quality standards, with the method of slide review at the discretion of the laboratory. Generally it is the larger laboratories with highest throughput which are able to generate the efficiencies from automated guided screening to offset the additional investment required for automation.

A.3.2 Other healthcare resources

Other healthcare resources implemented in association with cervical screening are medical consultation, colposcopy, biopsy, surgical, and nonsurgical treatments.

Medical consultation

Conventional Pap smears are a stand-alone primary screening test commonly administered within the context of a medical consultation (MBS Item 3, 23, 36, 44). The test can also be administered by qualified health professionals (MBS Item 52, 53, 54, 57) or in the context of a specialist appointment (MBS Item 104, 105).

Colposcopy

Colposcopic examination is performed after the insertion of a vaginal speculum. It enables magnified inspection of the cervix and vagina to guide biopsy (when required) of the most abnormal areas for histological diagnosis. The procedure is usually performed by a gynaecologist, and can be undertaken in about 10 minutes. Colposcopic examination is more accurate than cervical cytology although false negatives may still occur due to failure to visualise abnormal lesions (Schiffman & Solomon 2003). The main disadvantage of colposcopy is that it is an expensive test and thus not suitable for population screening. It also causes minimal to moderate discomfort (MSAC 2009 p.10).

Should the cell enrichment LBC receive approval for listing on the MBS, there are expected to be differences in resource usage, such as a reduction in repeat testing due to unsatisfactory results. Differences in test performance, such as classifying more slides as positive for low-grade lesions, may also change follow-up investigations (primarily cytological surveillance). In addition, the listing of

the technology will reduce the use of healthcare resources and costs borne outside the MBS associated with any duplication of both LBC and conventional Pap smear being performed.

A.4 Main comparator

The most appropriate test to inform the comparative effectiveness and cost-effectiveness of cell enrichment LBC is manual screening of conventional Pap smear cytology. The conventional Pap smear test is the primary comparator required by the final DAP recommendations (May 2012).

Individual laboratories currently make the decision about whether to review slides using manual or automated methods. Whichever method of review is implemented, laboratories are still required to meet quality standards. Nevertheless, the final DAP (May 2012) requires that a secondary comparison be "undertaken to examine the issue of automated versus manual reading of slides" as in the 2009 MSAC review of LBC.

As recommended in the DAP, cell enrichment LBC will also be compared with cell filtration LBC in order to justify the explicit inclusion of cell enrichment LBC in the MBS item descriptor.

The comparisons made in this submission are summarised in Table 6:

Table 6 Summary of research questions that the assessment will investigate

Research questions proposed in the DAP	Intervention	Comparator	Rationale/justification
What is the safety, effectiveness and cost effectiveness of cell enrichment liquid-based cytology using manual reading of slides compared with manual reading of conventionally prepared Pap smear cytology? What is the safety, effectiveness and cost effectiveness of cell enrichment liquid-based cytology using automated image analysis systems compared with manual reading of conventionally prepared Pap smear cytology?	Cell enrichment LBC	Conventional cytology	This is the primary comparison of the proposed intervention with the agreed main comparator. In this comparison if it is not possible to locate trials that compare LBC read using automated review and CC read manually than manual versus automation is proposed as a separate comparison.
What is the safety, effectiveness and cost effectiveness of cell enrichment liquid-based cytology compared with cell filtration liquid-based cell cytology?	Cell enrichment LBC	Cell filtration LBC	This is to justify the explicit inclusion of cell enrichment over other forms of LBC in the MBS item descriptor
To what extent, if at all, do these comparisons vary according to whether either method of cytology is assessed using manual reading or automated image analysis systems?	Manual reading	Automated reading	This is to understand whether comparative outcomes are influenced by manual reading or automated image analysis

Abbreviations: LBC, liquid-based cytology; MBS, Medicare Benefits Schedule

A.5 Clinical management algorithms

Cell enrichment LBC is proposed to be a direct substitute for the current conventional Pap smear (see Figure 2). It is not proposed that cell enrichment LBC be used in conjunction with conventional cytology. Conventional Pap smear would still be available on the MBS but its use would be expected to decrease with the introduction of cell enrichment LBC.

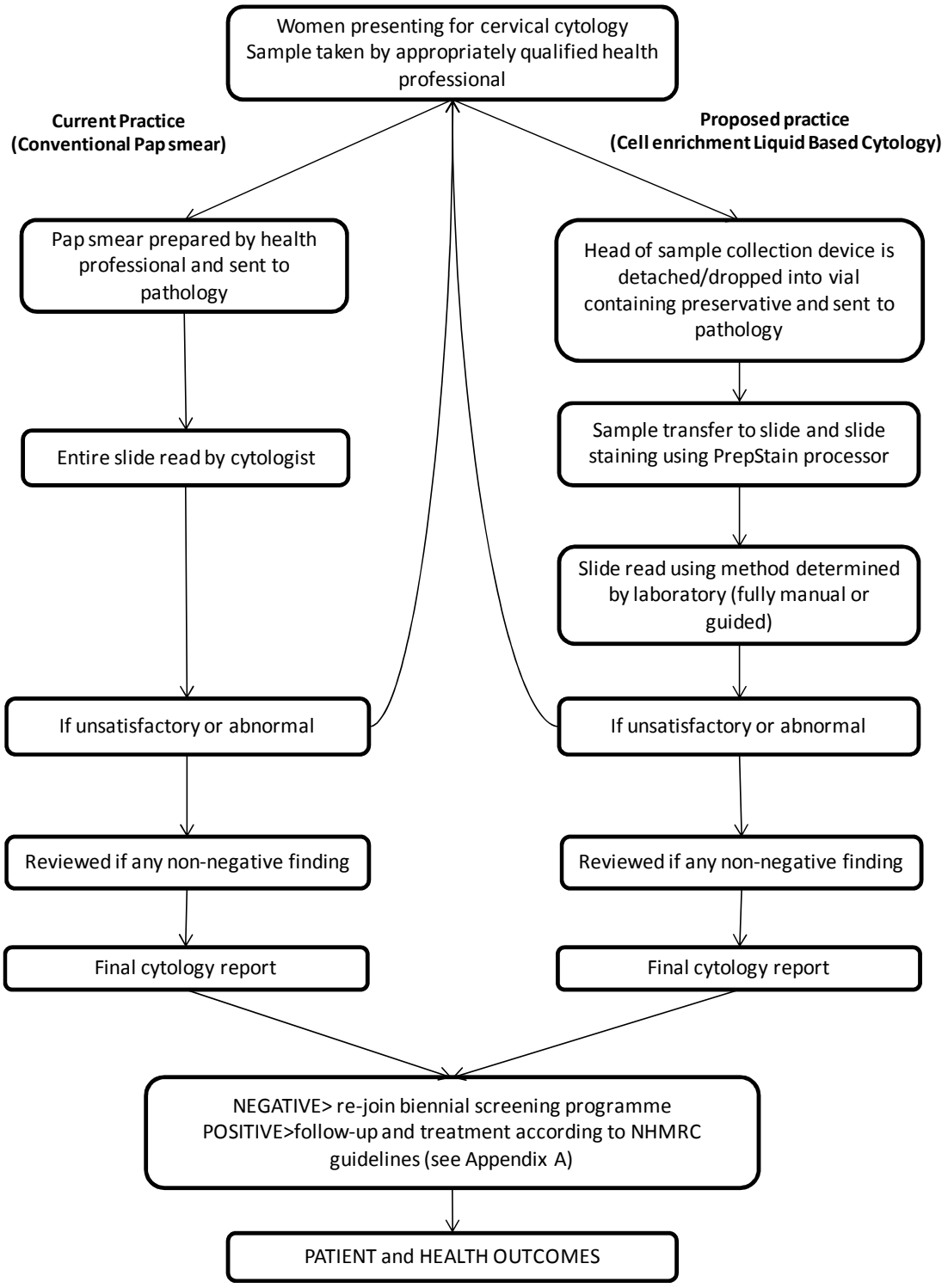

Figure 2 Current practice on the MBS compared with the proposed practice for cervical cancer screening

A.6 Differences between the proposed intervention and main comparator

Technical and general cytological features of cell enrichment LBC vs. conventional cytology and cell filtration LBC, and are summarised in Table 7. Technical details are provided in Attachment 1.

Table 7 Technical and general cytological differences between LBC (cell enrichment and filtration) and conventional cytology

	Conventional cytology	Cell enrichment LBC (SurePath™)	Cell filtration LBC (ThinPrep®)
Sample collection	Head of sampling device is discarded	Head of sampling device is submitted	Head of sampling device is discarded
Sample transfer	< 80%	Entire	Almost entire
Fixation	Varies	Immediate	Immediate
Transport	Easy-difficult	Easy	Easy
Slide preparation	Manual	Fully automated[a]	Fully automated
Number of cells	> 300,000	~50,000	~50,000
Slide evaluation	Cells diffusely smeared in a 25 x 75 mm area	Cells in a defined 13 mm diameter area	Cells in a well-defined 20 mm diameter area
Image guided screening	Yes, FPSP and FPGS	Yes, FPSP and FPGS	Yes, TIS
Cell preservation	Variable	Good	Good
Obscuring factors (obscuring red blood cells, acute inflammatory cells, and mucin)	Usually present	None	Some[b]
Air drying artefact	Usually present	None	None
Screening time	Always long	Reduced	Reduced
Interobserver Reproducibility	No	Yes	Yes
Ancillary studies (e.g. HPV test)	+/-	Possible	Possible
Source: Hoda 2012. Table 1.			

Abbreviations: CPS, conventional Pap smear; LBC, liquid-based cytology; TIS, ThinPrep Imaging System; FPSP, FocalPoint SurePath; FPGS, FocalPoint Guided Screening.

a.Hoda describes SurePath™ LBC automation as 'partial' however subsequently Becton Dickinson internationally has released enhanced front end automation for slide preparation enhancing the BD automation offering such that 'full automation' becomes an appropriate descriptor based on the Hoda comparisons.

b.Hoda describes that the most frequent cause of unsatisfactory slide with ThinPrep is due to too few squamous cells, followed by obscuring factors (Hoda 2012 p. 3)

B. Clinical evaluation for the main indication

The evidence base for this submission was drawn from 10 randomised controlled trials (RCTs) to evaluate the comparison of:

- Cell enrichment liquid-based cytology (LBC) versus conventional cytology (Beerman 2009 and the RODEO study)
- Cell enrichment LBC versus cell filtration LBC (NTCC; NETHCON; Strander 2007; Maccallini 2008; Obwegeser 2001; RHINE-SAAR trial)

These trials used the same slide reading method in both the LBC arm and conventional cytology. Two trials—MAVARIC and Palmer 2012—provide comparative evidence for manual versus automated reading. There are no head-to-head comparisons of the two different LBC systems.

The clinical evaluation for this submission is limited to randomised controlled trials (RCTs), where possible, in a cervical screening population. The rationale for relying on RCT evidence is provided below.

The accuracy of cervical screening techniques has been investigated using a range of clinical trial designs. However, evaluations of the comparative sensitivity and specificity using alternative trial designs, such as non-randomised populations or a split-sample design, have severe limitations. One limitation is that few studies compute relative sensitivity and false-positives in a primary screening setting using high-grade histology (CIN2+ or CIN3+) as the endpoint.

A limitation of the split sample design is the compromise of the accuracy of liquid-based cytology (LBC) performed on the second sample because the diagnostic cells can be removed when taking the first sample (Ronco 2006a).

Studies using a two-cohort design (in which conventional tests and LBC samples are taken from women belonging to separate but similar populations) frequently find higher test positivity rates for LBC. The higher detection rates reported with the LBC technique in other studies may be caused by the introduction of the LBC technique, creating a higher awareness and enthusiasm for the new technique (intention bias). Improved quality control, coinciding with the introduction of the new technique, may also have resulted in an increased detection of cytologic abnormalities

reflecting a learning curve. Finally, when using historical data as a control group, differences in the study populations may have biased the results (Siebers 2008).

A publication regarding evaluating technologies for cervical cancer screening by a leading authority in the field, Arbyn 2009, provides a list of indicators for screening effectiveness, assessed by different study methods, The authors ranked studies from high to low according to the level of evidence that such studies provide. RCTs designed to demonstrate a reduction in invasive cervical cancer provide the highest level of evidence of efficacy of screening. However, it is acknowledged that conducting such studies requires enormous financial resources and huge study populations to be followed for many years. Therefore, it is proposed to study intermediate or surrogate outcomes such as reduction of incidence of CIN 3 or worse disease (CIN 3+), increased detection rate of CIN 3+ or CIN 2+, or increased, similar or hardly reduced positive predictive value be evaluated. CIN 1 is the histopathologic manifestation of a carcinogenic or non-carcinogenic HPV infection that rarely progresses on a per event basis to cancer. Its detection is not clinically useful, possibly leading to over-treatment, and should not be targeted by any screening test (Arbyn 2009). CIN 3 is the direct precursor of invasive cancer, and therefore, reduced incidence of CIN 3+ is considered as an acceptable a proxy outcome of trials evaluating new preventive strategies.

The 2009 MSAC assessment report was well conducted however relied on non-RCT trial designs, because at the time only two RCTs were available—NTCC and Obwegeser 2001—both of which were confounded, the NTCC trial by human papillomavirus (HPV) testing in the LBC arm only, and Obwegeser 2001 by incomplete follow up.

The MSAC report relied on a comprehensive systematic review of the comparative accuracy of LBC and conventional cytology (Arbyn 2008), a health technology assessment (HTA) of comparative unsatisfactory rates (Krahn 2008) and the NTCC RCT reporting unsatisfactory rates (Ronco 2007). The MSAC report relied on evidence about the relative accuracy of manual or automated LBC to detect precancerous cervical lesions to draw conclusions about its relative effectiveness. This linked evidence approach was justified by existing evidence that early detection and treatment of precancerous cervical lesions leads to a reduction in the incidence and mortality of cervical cancer (AIHW 2007a; Peto 2004).

Given the guidance provided by leading experts in the field of cervical screening and the advent of RCT evidence since the 2009 MSAC evaluation the trial design for the current review of comparative effectiveness of LBC will be limited to RCTs in a cervical screening population if possible.

B.1 Description of search strategies

The research questions to be addressed and comparisons performed in the submission are described in Table 6.

The aim of the literature search was to identify all comparative studies that include LBC for the screening of cervical cancer. Such a broad search would enable identification of RCTs comparing cell enrichment LBC with conventional cytology (CC) and cell enrichment LBC versus cell filtration LBC. The search captured trials using automated and/or manual review of cytology.

The broad search enabled identification of RCTs that compared cell filtration LBC with CC. This permitted an indirect comparison to be made of cell enrichment LBC to cell filtration LBC with CC as the common comparator, should there be no head-to-head comparisons between cell enrichment LBC and cell filtration LBC found.

A pragmatic approach was taken to rely on previous health technology assessments and systematic reviews for the identification of RCTs prior to 2002. The most recent searches undertaken by health technology assessors NICE, MSAC and CADTH covered the following periods; 1966-2002, 2000-2007 and 1997-2006 respectively. The two HTA's (Payne 2000 and Karnon 2004) that informed NICE covered a wide search period (1966-2002). These two systematic reviews provided a complete and thorough search of the relevant literature through 2002. We used these reviews as source documents to locate relevant studies from before 2002 and bridged the search with one tailored for this submission. A similar pragmatic approach was taken in a recently published systematic review of Screening for Cervical Cancer for the U.S. Preventive Services Task Force (Vesco et al. 2011).

The literature search for this submission was performed in two stages. First, a retrospective review was conducted of the included studies in the Payne (2000) and Karnon (2004) systematic reviews. This was then followed by a prospective search to identify all RCTs from 2002 onwards.

A prospective search was undertaken in 2011; the search was performed from 2002 to 6 September 2011 in MEDLINE; EMBASE; and *The Cochrane Library*. To update the systematic review before the HTA submission, a second search was conducted on June 20, 2012. The updated searches were limited to articles published from 2011 or to records added since 7 September 2011, the date of the previous search.

Conference web sites were also searched for abstracts. We limited the scope of searches of conference abstracts to the authors of studies identified in the prospective literature search. This

step was undertaken to capture evidence not yet be published in peer reviewed journals, and for which subsequent data would likely only be available in abstract form.

A search of registers of randomised trials—ClinicalTrials.gov and ANZCTR—was also performed . A search of the sponsor's (BD) database for additional trial data was also performed.

A full description of the search strategies used in the submission is provided in Attachment 2. The outputs from the original and additional searches were extracted into two separate Reference Manager databases and reviewed (Attachment 2).

B.2 Listing of all direct randomised trials

The citations identified by the literature search were evaluated using predefined inclusion/exclusion criteria. To be included, a reference had to report a study that met all of the following criteria:

a. The trial included a randomisation procedure in its design (opinion pieces, letter, editorials, reviews and non-randomised trials were excluded)

b. The study compared liquid-based cytology (LBC: cell enrichment or cell filtration) with conventional cytology (CC) or cell enrichment with cell filtration in separate arms or compared manual with semi-automated screening

c. The study reported at least one of the health related and/or patient related outcomes as specified in the final DAP

d. The study participants were representative of a cervical cancer screening population

e. The study was applied to the detection of cervical cancer

f. The study was in English.

The results of the literature searches for RCTs are presented in Table 8. The published searches identified a total of 220 unique citations, of which 22 citations described 10 RCTs included in this submission. Given there was sufficient RCT evidence to address the research questions (Table 6), the literature search output for nonrandomised trials and clinical studies as reported in the description of the search strategies and provided in the Reference Manager databases denoted as 'Studies' was not reviewed.

The Reference Manager databases (denoted by suffix "_RCT") contain each citation annotated with the reasons for exclusion (Attachment 2). An evaluation of the studies included in the systematic reviews by Payne 2000 and Karnon 2004 did not locate any new RCTs. A manual search for relevant studies identified a total of 7 citations but did not result in any new included trials. The search of the sponsor's (BD) database resulted in no additional trial data.

Table 8 Summary of identification of randomised trials of LBC from the search of the published literature

	MEDLINE/EMBASE	Cochrane						Manual search
		Reviews	Protocols	DARE	Central	HTA	NHSEED	
Number of citations retrieved by original search	173	1	0	0	20	0	0	7
Number of unique citations (removing duplicates within and across databases)	167	1	-	-	5	-	-	7
Number of unique citations retrieved in updated search	39	0	0	0	2	0	0	-
Consolidated number of unique citations (original + updated search)	206	1	0	0	7	0	0	7[a]
Number of citations excluded after title/abstract review:								
— not RCT	87	0	-	-	1	-	-	1
— wrong intervention	69	0	-	-	4	-	-	-
— wrong outcome	6	0	-	-	-	-	-	-
— wrong population	2	0	-	-	1	-	-	-
— wrong indication	11	0	-	-	-	-	-	-
TOTAL EXCLUDED	175	0			6			1[a]
Number of citations excluded after full text review:								
— not RCT	3	0	-	-	0	-	-	0
— wrong intervention	2	1	-	-	0	-	-	0
— wrong population	4	0	-	-	0	-	-	0
— article not in English	1	0	-	-	0	-	-	0
— technology no longer available	6	0	-	-	0	-	-	0
TOTAL EXCLUDED	16	1			0			0
Number of meta-analyses and systematic reviews	6							
Number of multiple citations of direct randomised trials	22							
Number of published direct randomised trials included	10							
Number of included RCTs	10							

a. Citation excluded because it is not an RCT but included as a systematic review (discussed below). The other 6 citations represent RCT's already identified (also discussed below).

Manual searches

A manual search of conference abstracts and systematic reviews located five conference abstracts, four of which supplemented data for the RHINE-SAAR study (Ikenberg 2010b, 2010c and 2011a, 2011b). One additional abstract was found for the RODEO study (Fregnani 2012).

An additional full length article was identified from the full text review of Confortini 2010, which referenced an NTCC trial publication (Dalla Palma 2008) not identified in the original search.

A total of six (6) citations identified from manual searches are included in this submission.

Second round exclusions

After the first round of exclusions, 33 papers from MEDLINE; EMBASE; and The Cochrane Library were retrieved for review. From the full text review of these articles 3 papers were excluded because they were not RCTs, and 1 paper was not available in English. Five studies used a semi-automated pre-screening technology for conventional Pap smears known as Papnet. Papnet is no longer commercially available in Australia or internationally and these trials were subsequently excluded from analyses (http://www.eurocytology.eu/static/eurocytology/eng/cervical/LP1ContentKcontD.html).Two studies were excluded because the results reported did not allow for the comparison of LBC with CC in the absence of HPV testing.

Four studies (Sykes 2008, Jesdapatarakul 2010, Mount 2004, Taylor 2006) were further excluded as the participants did not represent a cervical cancer screening population.

Randomised controlled trials

A list of all direct randomised trials of LBC is presented (Table 9). A hard copy of the trials is located in Attachment 3. There are no RCTs that compare cell enrichment LBC and cell filtration LBC. There are, however, cell enrichment LBC versus conventional cytology RCTs and cell filtration LBC versus conventional cytology RCTs. Data from these trials are tabulated separately throughout sections B.3 to B. 6, with an indirect comparison provided where possible in section B.6. Comparisons between manual versus semi-automated screening of cervical cytology are tabulated separately throughout the document with results discussed separately.

Table 9 RCTs (and associated reports) of cervical cancer screening methodologies

Trial	Reports
Cell enrichment LBC versus conventional cytology	
Beerman 2009	Beerman H, van Dorst EB, Kuenen-Boumeester V, Hogendoorn PC. Superior performance of liquid-based versus conventional cytology in a population-based cervical cancer screening program. Gynecol Oncol. 2009 Mar; 112(3):572-6
RODEO Study	Longatti-Filho A, Fregnani JH, Scapulatempo C, Haikel R, Carloni AC, Souza NC, Campacci N, Mauad. SurePath liquid-based cytology improved the detection of high grade lesions in remote rural areas. Preliminary results of RODEO study. Abstract presented at the 17th International Meeting of the European Society of Gynaecological Oncology. International Journal of Gynecological Cancer, 2011; 21Suppl 3
	Fregnani JH, Scapulatempo C, Haikel RL, Mauad EC, Campacci N, Longatto-Filho A. Liquid-based cytology improves detection of cervical intraepithelial lesion in Low and High-risk women for HPV related diseases. Abstract presented at the Global Academic Program (GAP), 14-16 May 2012, Oslo, Norway
Cell filtration LBC versus conventional cytology	
NTCC Trial	Ronco G, Segnan N, Giorgi-Rossi P, Zappa M, Casadei GP, Carozzi F, Dalla Palma P, Del Mistro A, Folicaldi S, Gillio-Tos A, Nardo G, Naldoni C, Schincaglia P, Zorzi M, Confortini M, Cuzick J. New Technologies for Cervical Cancer Working Group. Human papillomavirus testing and liquid-based cytology: results at recruitment from the new technologies for cervical cancer randomized controlled trial. J Natl Cancer Inst, 2006; 98(11):765-774
	Ronco G, Giorgi-Rossi P, Carozzi F, Dalla Palma P, Del Mistro A, De Marco L, De Lillo M, Naldoni C, Pierotti P, Rizzolo R, Segnan N, Schincaglia P, Zorzi M, Confortini M, Cuzick J. New Technologies for Cervical Cancer screening Working Group. Human papillomavirus testing and liquid-based cytology in primary screening of women younger than 35 years: results at recruitment for a randomised controlled trial. Lancet Oncol, 2006; 7(7):547-555
	Ronco G, Cuzick J, Pierotti P, Cariaggi MP, Dalla Palma P, Naldoni C, Ghiringhello B, Giorgi-Rossi P, Minucci D, Parisio F, Pojer A, Schiboni ML, Sintoni C, Zorzi M, Segnan N, Confortini M. Accuracy of liquid-based versus conventional cytology: overall results of new technologies for cervical cancer screening: randomised controlled trial. BMJ, 2007; 335(7609):28. Epub May 21 2007
	Giorgi-Rossi P, Segnan N, Zappa M, Naldoni C, Zorzi M, Confortini M, Merito M, Cuzick J, Ronco G; NTCC Working Group. The impact of new technologies in cervical cancer screening: results of the recruitment phase of a large randomised controlled trial from a public health perspective. Int J Cancer, 2007; 121(12):2729-2734
	Dalla Palma P, Giorgi Rossi P, Collina G, Buccoliero AM, Ghiringhello B, Lestani M, Onnis G, Aldovini D, Galanti G, Casadei G, Aldi M, Gomes V, Giubilato P, Ronco G; NTCC Pathology Group. 2008 The risk of false-positive histology according to the reason for colposcopy referral in cervical cancer screening: a blind revision of all histologic lesions found in the NTCC trial. Am J Clin Pathol, 2008; 129(1):75-80
	Confortini M, Bergeron C, Desai M, Negri G, Dalla Palma P, Montanari G, Pellegrini A, Ronco G; New Technologies for Cervical Cancer Screening Study Cytology Group. Accuracy of liquid-based cytology: comparison of the results obtained within a randomized controlled trial (the New Technologies for Cervical Cancer Screening Study) and an external group of experts. Cancer Cytopathology, 2010; 118(4):203-208
NETHCON Trial	Siebers AG, Klinkhamer PJ, Arbyn M, Raifu AO, Massuger LF, Bulten J. Cytologic Detection of Cervical Abnormalities Using Liquid-Based Compared With Conventional Cytology: A Randomized Controlled Trial. Obstetrics & Gynecology, 2008; 112(6):1327-1334
	Siebers AG, Klinkhamer PJ, Grefte JM, Massuger LF, Vedder JE, Beijers-Broos A. Comparison of liquid-based cytology with conventional cytology for detection of cervical cancer precursors: A randomized controlled trial. JAMA 2009, 302(16):1757-1764

Trial	Reports
Strander 2007	Strander B, Andersson-Ellström A, Milsom I, Rådberg T, Ryd W. Liquid-based cytology versus conventional Papanicolaou smear in an organized screening program : a prospective randomized study. Cancer, 2007; 111(5):285-291
Maccallini 2008	Maccallini V, Angeloni C, Caraceni D, Fortunato C, Venditti MA, Gabriele G, Antonelli C, Lattanzi A, Puliti D, Ciatto S, Confortini M, Sani C, Zappa M. Comparison of the conventional cervical smear and liquid-based cytology: Results of a controlled, prospective study in the Abruzzo Region of Italy. Acta Cytologica, 2008; 52(5):568-574
Obwegeser 2001	Obwegeser JH, Brack S. Does liquid-based technology really improve detection of Cervical neoplasia? A Prospective, Randomized Trial Comparing g the ThinPrep Pap Test with the Conventional Pap Test, Including Follow-up of HSIL cases. Acta Cytologica, 2001; 45(5):709-714
RHINE-SAAR Study	Ikenberg H, Harlfinger W, Neis K, Konig J, Klug S. A Randomized Trial Comparing Conventional Cytology to Liquid-Based Cytology with Computer-Assistance: Results of the RHINE-SAAR Study. Journal of Cytopathology, 2011; 22(Suppl. 1):55-183
	Ikenberg H, Harlfinger W, Neis K, Jordan B, Konig J, Klug S. A Randomized Trial Comparing Conventional Cytology to Liquid-Based Cytology with Computer-Assistance: Results of the RHINE-SAAR Study EUROGIN 2011Congress, held in Lisbon, May 8–11, 2011
	Ikenberg H, Klug S, Jordan B, Spieth S, Harlfinger W, Neis K. Results of the Randomized German RHINE-SAAR Study: The ThinPrep Imaging System is Superior to Conventional Cytology. EUROGIN 2010 Congress, held in Monte Carlo, 17–20 February 2010
	Ikenberg H. Results of the RHINE-SAAR Study, a Randomized Trial Comparing Conventional Cytology with Thinlayer cytology and Computer-Assistance. 5th European Congress of the European Federation for Colposcopy and Cervical Pathology, 27–29 May 2010
	Ikenberg H, Klug S, Jordan B, Harlfinger W, Malter A, Brinkmann-Smetanay, Konig J, Neis K. Results of the RHIN-SAAR Study: A Randomized Trial Comparing Conventional Cytology to Thinlayer Cytology with the ThinPrep Imaging System. Acta cytologica V54 N3 (supplement) May–June 2010
Manual versus automated cytology	
MAVARIC Study	Kitchener HC, Blanks R, Dunn G, Gunn L, Desai M, Albrow R, Mather J, Rana D, Cubie H, Moore C, Legood R, Gray A, Moss S. Automation-assisted versus manual reading of cervical cytology (MAVARIC): A randomised controlled trial. Lancet Oncol 2011; 12:56-64
	Kitchener HC, Blanks R, Cubie H, Desai M, Dunn G, Legood R, Gray A, Sadique Z, Moss S. Automation-assisted versus manual reading of cervical cytology (MAVARIC): A randomised controlled trial. Health Technology Assessment 2011; Vol. 15: No. 3
Palmer 2012	Palmer TJ, Nicoll SM, McKean ME, Park AJ, Bishop D, Baker L, Imrie JEA. Prospective parallel randomized trial of the MultiCyte™ ThinPrep® imaging system: The Scottish experience. Cytopathology. 2012 May 22. doi: 10.1111/j.1365-2303.2012.00982.x. [Epub ahead of print]

Systematic reviews/meta-analyses

Citation details of the systematic reviews, five full publications and one abstract that were identified in the literature search, and one publication identified from the sponsor's database, are provided (Table 10). More recent and higher level evidence is available from the direct randomised trials identified in the literature search, and on this basis, these systematic reviews and meta-analyses were excluded from the submission.

Table 10 Meta-analyses and systematic reviews of cervical cancer screening methodologies

Author (year)	Citation	Type of study
Arbyn (2008)	Arbyn M, Bergeron C, Klinkhamer P, Martin-Hirsch P, Siebers AG, Bulten J. Liquid compared with conventional cervical cytology: A systematic review and meta-analysis. Obstetrics and Gynecology 2008, 111(1):167–77	Systematic review and meta-analysis
Canfell (2008)	Canfell K, Yoon JK, Clements M, Moa AM, Beral V. Normal endometrial cells in cervical cytology: Systematic review of prevalence and relation to significant endometrial pathology. Journal of Medical Screening 2008, 15(4):188–98	Systematic review and meta-analysis
Castle (2010)	Castle PE, Bulten J, Confortini M, Klinkhamer P, Pellegrini A, Siebers A, Ronco G, Arbyn M. Age-specific patterns of unsatisfactory results for conventional Pap smears and liquid-based cytology: Data from two randomised clinical trials. BJOG: An international Journal of Obstetrics and Gynaecology 2010, 117(9):1067–73	Meta-analysis
Fontaine (2012)	Fontaine D, Narine N, Naugler C. Unsatisfactory rates vary between cervical cytology samples prepared using ThinPrep and SurePath platforms: A review and meta-analysis. BMJ Open 2012 2(2)	Systematic review and meta-analysis
Klinkhammer (2003)	Klinkhammer P, Meerding W, Rosier P, Hanselaar A. Liquid-based cervical cytology. A review of the literature with Methods of Evidence-Based Medicine. Cancer (Cancer Cytopathology) 2003, 99(5):263–71	Systematic review
Li (2011, 2011a)	Li KM, Yin RT, Kang DY, Wu WW, Wen J. Diagnostic accuracy of liquid-based cytology versus conventional cytology for cervical neoplasia: A systematic review of randomized controlled trials. Chinese Journal of Evidence-Based Medicine 2011, 11(10):1133–9	Systematic review and meta-analysis Abstract only—Full publication not in English
	Li K. Diagnostic accuracy of liquid-based cytology versus conventional cytology for cervical neoplasia: A systematic review of randomized studies. International Journal of Gynecological Cancer 2011, 21(11):51	Abstract only

Fontaine 2012

A systematic review and meta-analysis was conducted by Fontaine 2012 to investigate the unsatisfactory rate of cervical cytology smears between "the two major liquid-based cytology (LBC) platforms, namely ThinPrep® (Hologic) and SurePath™ (Becton Dickinson)". The search retrieved all relevant English studies between January 1990 and August 2011. The authors included 42 studies in the quantitative analysis and 4 studies in the meta-analysis that presented data in the same population by the same laboratory for both cell enrichment and cell filtration LBC methodologies. No new RCTs were identified from the review of this paper.

The pooled unsatisfactory rate of the 1,120,418 cervical cytology smears reported in 14 different studies using cell enrichment LBC, was 0.3%. Using cell filtration LBC, 1,148,755 smears reported from 28 studies determined a pooled unsatisfactory rate of 1.3%. The observed power of these LBC studies was very low (0.087) therefore a meta-analysis was conducted of those studies evaluating the same patient population by the same laboratory. The meta-analysis demonstrated cell

enrichment LBC to have a significantly lower unsatisfactory rate compared with cell filtration LBC with a pooled relative risk of 0.44 (95% CI: 0.25 to 0.77).

Fontaine 2012 concluded that significantly fewer unsatisfactory smears were reported using cell enrichment LBC in comparison to cell filtration LBC. This systematic review and meta-analysis supports the results presented in this submission.

Li 2011

The full publication of Li 2011 is not available in English, but the Chinese language publication includes an English abstract, and a subsequent conference abstract was published in English. The study aimed to identify RCTs published before June 2010 to evaluate the diagnostic accuracy of LBC compared with conventional cytology (CC). Whilst the included studies could not be identified, a bibliographic search was conducted and no new RCTs were identified.

Contradictions between the two abstracts are evident. Based on selection criteria one of the abstracts details a total of five RCTs were included for analyses. The other states eight studies were included. Despite these differences both abstracts concluded that in the detection of high grade CIN, LBC was neither more specific nor sensitive than CC.

Castle 2010

Castle 2010 investigated the patterns of unsatisfactory results between LBC and CC by meta-analysing the results of two RCTs—the NTCC and NETHCON trials— which are included RCTs for this submission. The aim of the study was to understand the main determinates of unsatisfactory smears including cytologic method, age of participants and skill of the cytotechnician or pathologist reading and interpreting the slides.

Castle 2010 examined the percentage of unsatisfactory smears by five year age groups for both the NTCC and NETHCON trials. More unsatisfactory smears were reported in the NETHCON trial for CC (1.11%) compared to LBC (0.33%). A similar result was evident in the NTCC trial with 2.59% of LBC slides reported as unsatisfactory compared to 4.10% of the CC smears.

Castle 2010 concluded that LBC had lower rates of unsatisfactory smears in comparison to CC in all situations. Age was a minor factor contributing to the unsatisfactory rates. The NTCC and NETHCON trials are included RCTs in this submission, and as such lend to the same conclusion made in Section B.6, that lower unsatisfactory rates are associated with LBC.

Arbyn 2008

Arbyn 2008 conducted a systematic review of studies comparing LBC with CC published between 1991 and 2007. It was this review that contributed a substantial evidence base for the MSAC 2009

evaluation of LBC. Only those studies where tested subjects were submitted to gold standard verification with colposcopy and biopsies were included for meta-analysis. Eight studies met these entry criteria, only one of which—Ronco 2007—was an RCT, and is also an included study for this submission. It is noted that the reviewers identified the RCT published by Obwegeser 2001 but it was excluded due to insufficient completeness of verification of test positives (Arbyn 2008 p. 170).

The strict entry criteria of studies in the meta-analysis by Arbyn 2008 enabled the calculation and comparison of absolute sensitivity and specificity. The specificity for the detection of low-grade squamous intraepithelial lesions or higher (LSIL+) and high-grade squamous intraepithelial lesions or higher(HSIL+) abnormalities were the same for both LBC and CC. When applying a cut-off of atypical squamous cells of undetermined significance grade or higher (ASCUS+, which also included glandular abnormalities) the specificity of LBC was lower (65%) compared to CC (71%). The sensitivity varied more dramatically depending on the cut-off applied, however overall LBC was slightly (but not significantly) more sensitive than CC when detecting CIN 2+.

The results of the systematic review and meta-analysis conducted by Arbyn 2008 determined no significant differences in the specificity or sensitivity of detecting cervical intraepithelial neoplasia (CIN) lesions between LBC and CC. Results from this meta-analysis should be interpreted carefully as only one of the studies was conducted in a screening population.

Canfell 2008

Canfell 2008 compared the prevalence of normal endometrial cells and the proportion of which were associated with significant endometrial pathology in LBC versus CC. A systematic review was undertaken to identify literature published between 1970 and 2007. However the patient population of included studies was confined to postmenopausal women or women aged 40 years or older. No new RCTs were identified from this systematic review.

In this very limited and restrictive population, Canfell 2008 determined that a higher prevalence of normal endometrial cells was apparent using LBC methods compared to CC. However, it was determined fewer of these normal cells detected with LBC were likely to be associated with endometrial pathology.

Klinkhammer 2003

A systematic review of all available LBC (specifically, cell enrichment LBC and cell filtration LBC) literature between 1995 and 2000 was conducted by Klinkhammer 2003. After screening and a detailed review of 60 articles, 10 studies were included for meta-analysis. Conventional cytology was compared with LBC on the detection of ASCUS, LSIL and HSIL. The study was not designed to detect glandular lesions although the review recognised that some studies have indicated

increased sensitivity for glandular lesion detection using LBC (Ashfaq 1999; Schorge 2002). No new RCTs were identified from this systematic review.

True and false positives, as well as true and false negatives were extracted or calculated from the results of each study. The relative sensitivities and specificities were deduced. It could be concluded that cell enrichment LBC had lower sensitivity than CC in the detection of ASCUS+. However, no comment could be made on the detection rate of LSIL and HSIL in cell enrichment LBC due to conflicting results. Cell filtration LBC results indicated higher detection rate of ASCUS when compared to CC, with slightly lower sensitivity. These results should be interpreted with caution due to the varying methodologies used between included studies and application of varied reference standards.

Clinical trials

A comparative summary of characteristics of the included RCTs is provided (Table 11).

Table 11 Comparative summary of characteristics of the included direct randomised trials

Author, year, setting	Population, test comparisons	Study design	Outcomes	Authors conclusion
Cell enrichment versus conventional cytology				
Beerman 2009 Netherlands July 1997—June 2002	N=86,469 Cell enrichment LBC vs. CC	**Study design:** RCT **Reference standard:** NR	- Test yield - Unsatisfactory tests - Correlation for all cytology with histology results - Sensitivity and specificity - False negative and positive rates	The rate of unsatisfactory slides was significantly lower using liquid-based cytology (0.13% vs.0.89%, p<0.0001). The rate of ASCUS was significantly higher using liquid-based cytology (2.07% vs.0.87%, p<0.0001). The sensitivity for detection of a histological proven lesion is significantly higher in the liquid cohort compared to the conventional cohort (96.2% vs. 92.0%), with only a slight difference in specificity (97.8% vs. 98.2%).
RODEO Study Brazil May 2010–December 2010	N=12,048 Cell enrichment LBC vs. CC	**Study design:** RCT **Reference standard**: NR	- Test yield	Dichotomic analyses of LBC versus conventional smears have showed 5,872 (97,9%) and 5,981 (98,9%) negative cases; and 127 (2.1%) and 61 (1.0%) abnormal cases respectively (p=0.001). Data strongly support the superior performance of LBC to detect intraepithelial lesions.
Cell filtration versus conventional cytology				
NTCC trial (Ronco 2006a, b, 2007) Italy 2002–2003	N=45,174 Cell filtration LBC vs. CC	**Study design:** RCT conducted in two separate age groups (< 35 and 35–60) with varying procedures (HPV testing was conducted in the LBC arm only) **Reference standard:** ASCUS+ went for colposcopy; conventional group protocol was for LSIL+ to go for colposcopy but 7/9 centres referred for colposcopy based on ASCUS+ and 2/9centres sent ASCUS+ for repeat cytology and then if LSIL referred for colposcopy. Normal slides that were HPV positive could also be referred for colposcopy	- Test yield (including HPV) - Unsatisfactory test - 1 year follow-up test yield - Sensitivity and specificity - Positive predictive value	Liquid based cytology showed no statistically significant difference in sensitivity to conventional cytology for detection of cervical intraepithelial neoplasia of grade 2 or more. More positive results were found, however, leading to a lower positive predictive value. A large reduction in unsatisfactory smears was evident.

NETHCON Trial (Siebers 2008, 2009) Netherlands April 2003–July 2006	N=85,076 Cell filtration LBC vs. CC	**Study design:** RCT **Reference standard:** colposcopy: LSIL repeat cytology and colposcopy only if repeated abnormal, high grades colposcopy	- Test yield - Relative sensitivity - Positive predictive values	The study found no statistically significant difference in cytologic test positivity rates between liquid-based and conventional cytology. However, liquid- based cytology resulted in significantly fewer unsatisfactory tests. Liquid-based cytology does not perform better than conventional Pap tests in terms of relative sensitivity and PPV for detection of cervical cancer precursors.
Strander 2007 Sweden May 2002–Dec 2003	N=13,484 Cell filtration LBC vs. CC	**Study design:** RCT **Reference standard:** ASCUS and CIN 1 repeat smear or colposcopy after 4 months, CIN 2/3 for colposcopy	- Test yield - Correlation for all cytology with histology results - Inadequate tests	Liquid cytology produced a significantly higher yield of histologic high-grade lesions compared with conventional Pap smears.
Maccallini 2008 Italy 2001–2002	N=8,654 Cell filtration LBC vs. CC	**Study design:** RCT **Reference standard:** colposcopy ASCUS+ or higher	- Test yield - Frequency of inadequate reports - Referral rate to colposcopy - CIN2+ detection rate - Referral PPV for CIN 2+	LBC reduced the inadequacy rate and decreased reading and was at least as sensitive as and more specific than conventional cytology.
Obwegeser 2001 Switzerland July 1998–Sep 1998	N=1999 Cell filtration LBC vs. CC	**Study design:** RCT **Reference standard:** Not reported. Only histological follow up of HSIL was performed in this study	- Test yield - Unsatisfactory tests - Specimen adequacy (sensitivity and specificity)	No statistically significant differences in diagnostic categories. Specimen adequacy was superior with CC ($p<0.001$).
RHINE-SAAR Study Germany August 2007 –October 2008	N=21,081 Cell filtration LBC vs. CC	**Study design:** RCT **Reference standard:** NR	Relative sensitivity for histologically confirmed CIN 2+	LBC without and with thin prep imaging system compared to CC had a significantly higher sensitivity for the detection of CIN without deterioration of PPVs.
Manual verses automated				

MAVARIC Study (Kitchener 2011a, b) UK Mar 2006–Feb 2009	N=73,266 Cell filtration manual LBC vs. cell enrichment manual LBC vs. cell filtration automated and manual LBC vs. cell enrichment automated and manual LBC	**Study design:** RCT Manual only arm compared with manual reading paired with automated reading. Both cell enrichment and cell filtration methodologies evaluated. **Reference standard:** colposcopy—high grade abnormality and HPV positive cases referred	- Test yield - Sensitivity and specificity - Cost effectiveness of manual vs. automated reading to detect CIN 2+	Automation-assisted reading was 8% less sensitive than manual in the detection of CIN2+ and 5% less sensitive for CIN3+.
Palmer 2012 Scotland	N=169,917 Cell filtration manual LBC vs. cell filtration automated LBC	**Study design:** RCT **Reference standard:** referral to colposcopy for all cytology results classified as ASCUS+	- Test yield - Inadequate rates - Sensitivity, specificity and predictive value for final cytology report - Correlation between cytology and histology (CIN 2+ and CIN 3+ detection rates) - Productivity data	There was no evidence of a significant difference in the detection of CIN2 + or CIN3 + . Positive, abnormal and total predictive values (high-grade, low-grade and all abnormal cytology found to be CIN2 + , respectively) were similar in both arms. Productivity was significantly higher in the imager arm.

Abbreviations: CC, conventional cytology; CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus; LBC, liquid-based cytology; LSIL low-grade squamous intraepithelial lesion; NR, not reported; PPV, positive predictive value; RCT, randomised controlled trial

As recommended by the MSAC secretariat the format of the submission aligns with the template provided in the PBAC guidelines (Version 4.3 December 2008). Particular attention will be focused on the following study characteristics which potentially influence test validity estimation for cervical screening derived from the Standards for Reporting of Diagnostic Accuracy (Arbyn et al. 2008). The following study quality properties and population characteristics are checked and summarized in comprehensive tables:

- service properties (geographical area, type of health service, professional groups taking the smears);
- clinical setting (screening population, women examined for clinical indications, or mixed population);
- inclusion and exclusion criteria;
- age range;
- blinding of interpreters to results;
- applied quality system to assure reliability of the test and outcome result (selective or systematic rereading of cytologic and histologic samples by expert cytologists or cytopathologists);
- collection device used to sample cervical cells; and
- the level of experience of cytotechnologists in liquid-based cytology.

B.3 Assessment of the measures taken by investigators to minimise bias in the direct randomised trials

Various randomisation procedures were used across the trials. An uneven distribution of patients between the arms of the Beerman 2009, NETHCON , Strander 2007, RHINE-SAAR l and Palmer 2012 trials . Whether the differences were significant or whether statistical adjustments of results were conducted was reported in few trials.

For trials that reported information on the reference standards applied, colposcopy and/or biopsy was used as the reference standard. The NTCC and MAVARIC performed HPV triage on LBC samples only which went on to inform the application of the reference standard. The test

threshold at which the reference standard was uniformly applied was either ASCUS+ or HSIL+.

The outcome assessor, colposcopist and where relevant histologist, were not blinded to the index/screening test result. Although in four trials—NETHCON; Strander 2009, Maccallini 2008; MAVARIC—the outcome assessors were blinded to the cytology test type.

There were similarities between individual trials in the application of the reference standard and outcome assessed. Generally:

- Maccallini 2008; RHINE-SAAR; and Palmer 2012 referred all ASCUS+ for colposcopy ± histology.
- NETHCON and Strander 2009 referred all ASCUS and CIN 1+/LSIL for repeat smear or colposcopy and CIN 2+/HSIL for colposcopy ± histology.
- Obwegeser 2001 and the MAVARIC trial referred HSIL+ for colposcopy ± histology.

The NTCC trial was unique in the application of different reference standards between the arms of the trial. ASCUS+ in the LBC arm was referred for colposcopy± histology, whereas LSIL+ in the conventional arm was referred for colposcopy± histology.

Where reported the proportion of patients with histological follow up ranged from 0.6% to 1.53% and was balanced between the arms within each trial. Only 70% of the histological follow up data were reported for Obwegeser 2001.

Beerman 2009 and Strander 2007 were the only trials to report the histological follow up from all randomised patients by review of a national database and report true false negative rates.

A summary of measures undertaken to minimise bias in the direct randomised trials is provided in Table 12.

Concealment of randomisation varied widely between the included trials

Allocation in Beerman 2009 was based on clusters rather than individuals, with family practice as the unit of randomisation. This was done to prevent contamination by patient preference (selection bias) and for other practical reasons. The method was not successful in achieving an even distribution of patients between the interventions. The implications of this or a possible explanation were not provided, although varying attendance rates at the practices randomised could justify the difference.

Whilst the RODEO study abstracts outline that patients were randomised to either LBC or CC, the methods used for randomisation and the measures undertaken to minimise bias are not reported.

In the NETHCON trial, allocation was based on clusters with family practice as the unit of randomisation. This prevents contamination by patient preference (selection bias). The method was not successful in achieving an even distribution of patients between the interventions. By chance, six of the largest centres were all randomised to LBC with only one randomised to CC. Possible confounding due to these cluster effects were controlled for by multivariate logistic regression.

The RHINE-SAAR study, Maccallini 2008 and Strander 2007 used a weekly alternation method of randomisation, whereby each participating centre switched between LBC and CC every seven days. Randomisation for all three trials was unsuccessful in achieving a 1:1 ratio between interventions. Maccallini 2008 further demonstrated the faults in this method, whereby patients switched between the modality of sampling they were randomised to due to either patient refusal for the specified intervention or because a mistake was made by the smear taker. Uneven patient distribution in Strander 2007 was due to clinics forgetting to shift to the alternate method as well as distribution errors of LBC materials. These mistakes randomly occurred and were adjusted for in statistical analyses. An explanation for the uneven distribution of patients was not provided for the RHINE-SAAR study.

Obwegeser 2001 used sequentially labelled, sealed envelopes to randomise participants, as did the NTCC trials with the exception of two centres that used a computer to access the sequential numbering.

Due to the multiple interventions examined in the MAVARIC study, a complex concealment of randomisation was implemented. The first stage of randomisation required a sequence of random digits to evenly distribute the six combinations of the two technologies between each practice. Then within the laboratory, samples were randomised to either manual only or the paired arm using a prepared spread sheet. Initially randomisation was 1:1, but after a third of the samples had been obtained, at a slower than expected rate of accrual, the ratio was changed to 1:3 in favour of the paired arm to accelerate the accrual of samples for paired reading. Non-randomised methods were used to achieve these changes and any adjustment was not reported.

Palmer 2012 achieved randomisation by laboratory accession number whereby slide numbers 1 to 50 were processed using automated methods, slides 51 to 100 were manually read, and so on. An

uneven distribution in patients resulted due to one laboratory temporarily stopping imaging for technical reasons and some slides that failed imaging.

Blinding varied among the included trials

Study investigators—GPs, midwives and gynaecologists—who collected the index or screening cytology were trained on the varying collection methods to which either their patient or the practice were randomised. Experience levels of each investigator varied across all trials (discussed further in section B.4.3). Blinding of investigators who collected the samples to the cytology method was not possible for any of the studies due to the different sample preparation methods required for CC and LBC.

The trials were performed in a screening population in which index test results led to possible application of reference standard. Therefore, the index test results were interpreted without knowledge of the reference standard. Blinding outcome assessors (colposcopists and histologists) to the index test result and cytology method is possible but was not always the case. Blinding methods of outcome assessors are detailed in Table 12.

Blinding the outcome assessor to the result of the index test result or cytology method is not reported in the majority of trials. The blinding of outcome assessors is not reported in the two cell enrichment LBC trials—Beerman 2006 and the RODEO study.

The blinding of outcome assessors was not blinded to the result of the index test in all of the cell filtration LBC trials with the possible exception of the NETHCON trial. The NETHCON trial publication states that the primary outcome was based on the blinded review of histological follow-up, and whilst we know that histology is blinded to cytology method, it is unclear from the paper if assessors were also blinded to the cytology results. The outcome assessment in the NETHCON trial, Strander 2007, Maccallini 2008 and the MAVARIC study was performed with no knowledge of the cytology method.

Table 12 Summary of the measures undertaken to minimise bias

Trial ID	Concealment of randomisation	Blinding			
		Participants	Investigators	Outcome assessors	
				Cytology method	Result index test†
Cell enrichment versus conventional cytology					
Beerman 2009	A–randomisation by GP	NR	No	NR	NR[a]
Source: Beerman 2009, Materials and Methods p. 573					
RODEO study	NR	NR	No	NR	NR
Source: Longatto-Filho 2011; Fregnani 2012					
Cell filtration versus conventional cytology					
NTCC trial	C & D–2 centres using method D and all remaining centres using method C	No	No	NR	No[b]
Source: Ronco 2007 Methods p.2; Ronco 2006 Methods p.548					
NETHCON trial	A–randomised by family practice	NR	No	Yes	Possible[c]
Source: Siebers 2009 Methods pp.1758–60; Siebers 2008 Materials and methods p.1328					
Strander 2007	B–alternation of collection method every other week by centre	NR	No	Yes	No
Source: Strander 2007 Materials and methods pp. 286–7					
Maccallini 2008	B–alternation of collection method every other week by centre	NR	No	Yes	No
Source: Maccallini 2008 Material and methods p.570 and Results p.571					
Obwegeser 2001	C–sequential labelled envelopes	NR	No	NR	NR
Source: Obwegeser 2011 Materials and methods pp.710–2					
RHINE-SAAR study	B–alternation of collection method every other week by centre	NR	No	NR	NR
Source: Ikenberg 2010a, 2010b, 2010c, 2011a, 2011b					
Manual versus automated cytology					
MAVARIC	E–two stages: randomisation to technology and randomisation of manual only or paired arm	NR	No	Yes	NR
Source: Kitchener 2011 Methods pp. 57–8					
Palmer 2012	F–randomised by laboratory accession number	NR	No	NR[d]	NR[d]
Source: Palmer 2012. Methods pp.2–3					

Abbreviations: GP, general practitioner; NR, not reported

† Was the reference standard assessed without knowledge of the index or screening test results?

A=Cluster randomisation, B=All centres alternated method of cytology collection weekly between LBC and CC, C=sequentially labelled, sealed envelopes, D=computer access for sequential numbering E=Random sequence of digits to randomise GPs to cell enrichment or cell filtration LBC technologies, Followed by spread she location within laboratories for stage two randomisation to manual only or paired arm, F=randomised by laboratory accession number 1–50 imaged and 51–100 manually read

a Histology data obtained from national database of pathology and the paper does not report if the histology was performed with knowledge of the initial cytology report
b Whilst preliminary histology review was not blinded to cytology and HPV result, all histology reports identified as CIN+ underwent secondary independent histology blinded to the preliminary histology reading.
c The paper states the primary outcome is based on the blinded review of histological follow-up and whilst we know that histology is blinded to cytology method it is unclear from the paper if assessors were also blinded to the cytology results.
d. Data derived from information routinely entered onto the SCCRS database. Palmer 2012 does not report if the method of cytology or test results were blinded at any stage of screening.

To assess the validity and quality of the included trials, the reference standards applied and the appropriateness of these standards to the study design are presented (Table 13).

Reference standards

The application of a reference standard (referral for colposcopy ± biopsy) was not reported for Beerman 2009. The authors of the trial report that a distinguishing feature of the trial is that all cytological and histological outcomes are available for all women who participated which avoids the verification bias associated with the selective follow up of subjects (Beerman et al. 2009 p. 575). Beerman 2009 reports "The histological follow-up of all patients with a cytological classification of ASCUS or higher was retrieved from the PALGA database. To determine the true false negative rate of the screening results, we collected the data from all patients with a negative cytology (i.e. within normal limits), but with a histological proven cervical lesion (CIN 1 or higher)". This implies that patients with ASCUS+ outcome were sent for further follow up. Although this suggestion is speculative, it does align with a publication of the cervical cancer screening practices in Netherlands at the time of the Beerman trial which states that, "Borderline smears (ASCUS) must be repeated after 6 months"(vam Ballegooijen and Hermens 2000) . Nonetheless the histological outcome for all patients with the same follow up period of 510 days are provided and within trial comparison of the screening tests are valid. The RODEO study does not indicate the reference standards applied and reports cytological outcomes only.

The reference standard applied in the six cell filtration LBC RCTs varied. Both NETHCON and Strander 2007 applied the same reference standard whereby ASCUS and CIN 1 cases led to either colposcopy or a repeat smear. Strander reports that follow up was to occur at 4 months whereas timing of follow up in NETHCON is not reported. Those with CIN 2–3 results were referred to colposcopy and possible biopsy. The terminology used by Strander 2007 is different from all other trials whereby CIN, traditionally a histological classification scale, is used to describe cytological abnormalities (Table 4).

Maccallini 2008 and RHINE-SAAR implemented the same reference standard of referral for colposcopy for all cytology results of ASCUS+.

NTCC and Obwegeser 2001 each reported unique reference standards.

In the NTCC trial any participant in the LBC group with a cytology result of ASCUS+ were to be referred to colposcopy. The protocol for the conventional group was for LSIL+ cytology women were to go for colposcopy, but seven of the nine centres referred for colposcopy based on ASCUS+ and two of the nine centres sent ASCUS+ women for repeat cytology and subsequent LSIL results were referred for colposcopy.

Obwegeser 2001 reported follow up of all HSIL cases only. It is stated that follow-up of LSIL and ASCUS cases is in progress implying a reference standard of ASCUS+ was applied in the study. A specific search was performed to identify any publication regarding the follow up of ASCUS and LSIL cases. Although 62 citations were found that referred to the article there was no subsequent publication by either author (Attachment 2). A reference standard applied to HSIL cases only is available for results published to date.

Only HSIL and HPV positive cases were referred to colposcopy and possible histology in the MAVARIC study. Palmer 2012 referred all cytology results of ASCUS+ for colposcopy and possible histology.

Appropriateness of reference standards

For trials that reported information on the reference standards applied, colposcopy and/or biopsy as the reference standard. The NTCC and MAVARIC trial also included application of the reference standard to HPV test positive cases. The test threshold at which the reference standard was uniformly applied was either ASCUS+ or HSIL+ did vary between studies. In all studies, only abnormalities visible on colposcopy were biopsied; negative colposcopy was interpreted as absence of disease. This introduces performance bias in that the colposcopist decides if a lesion is present and then whether to biopsy the lesion. The visual assessment of the cervix in colposcopy, which was used to report outcomes, has a high inter-observer variability (Arbyn 2009). For this reason and others the validity of colposcopy and biopsy as a reference standard has been questioned (Davey 2006 p.129). But, even an imperfect reference standard, if applied without knowledge of the two tests being compared, will provide an unbiased reference comparison of the accuracy of the two tests (Ibid. 2006). That colposcopy and biopsy is the most widely used reference standard in clinical practice is reflected in the RCTs. The colposcopic examination in the NETHCON trial, Strander 2007, Maccallini 2008 and the MAVARIC studies were performed without knowledge of the cytology method.

It is noted that in the 2009 MSAC assessment report colposcopy with biopsy (threshold for positive histology CIN 2+/CIN 3+) was considered the most valid reference standard to

determine the true disease status of patients with a positive test (pLSIL, LSIL, pHSIL, HSIL or SCC). Clinical follow-up with repeat cytology at one year was considered the most valid reference standard MSAC 2009).

Table 13 Reference standards applied to the included trials

Trial ID	Reference standard	Appropriateness of the reference standard to the study design	Time period between index test and reference standard
Cell enrichment versus conventional cytology			
Beerman 2009	NR after cytological outcomes however histology for all ASCUS+ and normal outcomes reported[a]	N/A[a]	Within 18 months
Source: Beerman 2009			
RODEO Study	None[b]	N/A[b]	NR
Source: Longatto-Filho 2011; Fregnani 2012			
Cell filtration versus conventional cytology			
NTCC Trial	LBC group: ASCUS+ referred to colposcopy ± histology[c] Conventional group: LSIL+ referred to colposcopy ± histology[c] However 7/9 centres referred for colposcopy based on ASCUS+ and 2/9 centres sent ASCUS+ for repeat cytology and then if LSIL referred for colposcopy Normal/benign cytology referred to colposcopy if HPV positive on case by case basis ± histology[c]	Not appropriate - Patients received different reference standards depending on the index test results and type of test - Reference standard was applied to those patients with a normal/benign cytology result if HPV positive	Within 12 months
Source: Ronco 2006a; 2006b			
NETHCON Trial	ASCUS and CIN 1 repeat smear Repeat smear remains abnormal or initial smear CIN 2/3 for colposcopy± histology[d]	Not appropriate - Patients received different reference standards depending on the index test results - Reference standard was not applied to those patients with a normal/benign cytology result	Within 18 months
Source: Siebers 2008; 2009			
Strander 2007	ASCUS and CIN 1 repeat smear or colposcopy ± histology[e] CIN2/3 for colposcopy ± histology[e]	Appropriate All patients randomised were followed up using a national histological outcome database	Within 3 years
Source: Strander 2007			
Maccallini 2008	ASCUS+ referred to colposcopy ± histology[f]	Not appropriate - Reference standard was not applied to those patients with a normal/benign cytology result	Referred immediately to colposcopy
Source: Maccallini 2008			
Obwegeser 2001	HSIL+ referred to colposcopy± histology[g]	Not appropriate - Reference standard was not applied to those patients with a normal/benign cytology result	Within 12 to 15 months

Trial ID	Reference standard	Appropriateness of the reference standard to the study design	Time period between index test and reference standard
Source: Obwegeser 2001			
RHINE-SAAR Study	ASCUS+ referred to colposcopy± histology	Not appropriate - Reference standard was not applied to those patients with a normal/benign cytology result	NR
Source: Ikenberg 2010a,b,c; 2011a,b			
Manual versus automated cytology			
MAVARIC study	HSIL and HPV positive cases referred to colposcopy± histology[h]	Not appropriate - Reference standard was not applied to those patients with a normal/benign cytology result	3-12 months
Source: Kitchener 2011			
Palmer 2012	Low-grade cytological abnormalities or higher (ASCUS+) referred to colposcopy ± histology	Not appropriate - Reference standard was not applied to those patients with a normal/benign cytology result	NR
Source: Palmer 2012			

Abbreviations: NR, not reported; ASCUS, atypical cells of undetermined significance; ASCUS+, atypical cells of undetermined significance/atypical glandular cells or more severe; CI, confidence interval; HSIL, high-grade squamous intraepithelial lesion; HSIL+, high-grade squamous intraepithelial lesion or more severe; LSIL, low grade squamous intraepithelial lesion; LSIL+, low grade squamous intraepithelial lesion or more severe; CIN 1, cervical intraepithelial neoplasia grade one; CIN 2/3, cervical intraepithelial neoplasia grade two or three; HPV, Human papillomavirus; N/A, not available

a Beerman 2006 does not report the application of a reference however all patients randomised were followed up using a national histological outcome database. The authors report "The histological follow-up of all patients with a cytological classification of ASCUS or higher was retrieved from the PALGA database. To determine the true false negative rate of the screening results, we collected the data from all patients with a negative cytology (i.e. within normal limits), but with a histological proven cervical lesion (CIN 1 or higher)."(p.573)

b The RODEO study abstracts do not report the application of a reference standard therefore appropriateness of a reference standard applied cannot be determined.

c. Regarding the NTCC trial, histology was first reviewed locally and was not masked to cytology or HPV result. For women with CIN of any grade, all histological samples from the relevant time were reviewed by one or two independent pathologists who were not aware of the original histology results. If a pathologist did not agree with the original diagnosis regarding the presence of CIN 2+, samples were discussed by a group of nine pathologists (three in some instances) and a consensus diagnosis reached (Ronco 2006a p548.

d. Regarding the NETHCON trial, histology is taken from colposcopically abnormal areas. High-grade cytological abnormalities on initial or repeat test are immediately referred to a gynaecologist for colposcopy and further histological evaluation (Siebers 2008 p. 1759).

e. Strander 2006 reports that histopathology diagnoses were searched for in the Regional Database for Prevention of Cervical Cancer, which covers all 5 laboratories in the region, including, among other data, all histopathology related to cervical disease (biopsies, cones, and hysterectomy specimens). The highest grade of histopathologic diagnosis from the cervix uteri obtained after the index smear during the study period was used. Thus, histopathologic diagnoses were made as part of the clinical routine (p.287). Whilst the reference standard was not applied to those patients receiving a normal/benign cytology result, these patients were followed up in the database for any further cytology and histology results within a 1.5 year and again at 3 year 7months time period.

f. Maccallini 2008 reports cases from both study arms were referred to the same colposcopy clinics. Histologic reading was blinded to cytology sampling modality. Treatment was recommended to all women with CIN2+ (p. 570).

g. Obwegeser 2001 only reported the follow up of all HSIL cases. It is stated that follow-up of LSIL and ASCUS cases is in progress implying a reference standard of ASCUS+ referral to cytology may be applicable in the future. However for the current study results of a reference standard applied to HSIL cases only is available. All histology specimens were evaluated by pathologists independent of the cytology laboratory on conization or hysterectomy specimens, not on

biopsies (p. 712).
h. Within the MAVARIC trial women with high-grade cytology (moderate dyskaryosis or worse) underwent either a targeted biopsy with subsequent treatment for CIN 2+ or an immediate 'see and treat' loop excision (Kitchener 2011 p.21).

The flow of participants throughout the included RCTs, including patients lost to follow up and the proportion of women who had cytology and histology analysed, is presented in Table 14.

All studies randomised more than 1000 patients to each study intervention. However, the sample size was varied for all studies, with Beerman 2009, the NTCC trial, NETHCON trial, Palmer 2012, and the MAVARIC study considerably larger with more than 20,000 women randomised to each study arm.

Loss to follow-up

Percentages lost to follow up were generally not reported. Where reported, the rates were low (< 1.04%) and balanced within each trial, except for NTCC (cell filtration LBC 0.4% versus CC 0.17%). The difference was small and thought to be of little significance.

Cytology analysed

More than 95% of patients randomised participated in the trial. In Maccallini (2008), between randomisation and undertaking the cytology test 173 (4%) women randomised to the conventional arm changed to the alternate intervention, as did 136 (3.2%) women originally randomised to the LBC arm of the study.

For the remaining studies as no distinction was made, it is assumed that the number of participants randomised at study commencement was the same as those whose cytology was analysed.

Histology analysed

The number of participants with histological outcomes was presented in five trials (Beerman 2009; Strander 2007; Obwegeser 2001, NTCC; NETHCON). The proportion of patients with histology ranged from 0.6% to 1.53% and was balanced within each trial with the exception of the NTCC trial (cell filtration LBC 5.87% versus conventional cytology 1.53%). The difference was attributed to the different referral practices undertaken between the arms of the trial.

Beerman 2009 used the Dutch Network and National Database for Pathology (PALGA) which interconnects all Dutch Pathology and cytology departments. This enabled 99.2% correlation of all study participants in the conventional cytology arm and 99.1% correlation in the LBC group.

The results presented for Strander 2007 are the number of histology cases followed up at 1.5 years. Overall 95.8% of patients did not have any histology follow up across the normal, ASCUS, LSIL, HSIL categories. The proportion with no histology was evenly balanced between the cell filtration LBC arm and conventional cytology for each category, 97.5% vs. 97.7%, 57.7% vs. 43.3%, 49.3% vs. 51.8% and 0 vs. 2.2%, respectively (Strander 2007, Table 3). In the CC arm, the number of women with histology follow up at 1.5 years (75/8810, 0.85%) increased to 122/8810 (1.4%) at 3 years and 7 months. Similarly the histology reports increased in the LBC arm from 56/4676 (1.2%) at 1.5 years to 84/4676 (1.8%) at 3 years 7 months.

Beerman 2009 was the only study to follow up all randomised patients (including those with unsatisfactory cytology results) by review of any histology results in a national database. Strander 2007 followed up all patients for histological outcome but did not report those with an unsatisfactory cytology result. All other studies failed to review the histological outcomes for those participants who received normal/benign cytological results on their index screening test. It has been reported that in RCTs at least all positive tests should be verified, and given there should be no differences between the groups, there was no need for verification of a sample of negative results (Davey 2006, web appendix).

In the NETHCON trial ASCUS and CIN 1 cases led to either colposcopy or to a repeat smear. Those with a CIN2/3 result were referred to colposcopy and possible biopsy. Most cases (56.4%) were followed up cytologically. Histology was performed in 36.3% of the cases. Six cases had only colposcopy during follow-up, and 171 cases (6.9%) were lost to follow-up.

Obwegeser 2001 only analysed the histology for 70% of the HSIL cases.

Table 14 Flow of participants in the direct randomised trials

Trial ID intervention	Randomised N	Lost to follow-up n (%)	Discontinued n (%)	Cytology analysed n (%)	Histology analysed n (%)
Cell enrichment versus CC					
Beerman 2009					
CC	51154	398 (0.8) [g]	NR	51154 (100)	50756 (99.2) [f]
LBC	35315	319 (0.9) [g]	NR	35315 (100)	34996 (99.1) [f]
RODEO study					
CC	6047	NR	NR	6047 (100)	NR
LBC	6001	NR	NR	6001 (100)	NR
Source: Longatto-Filho 2011; Fregnani 2012					
Cell filtration versus CC					
NTCC Trial					
CC	22547	39 (0.17) [k]	NR	22056 (97.8)	344 (1.53) [L]
LBC	22760	93 (0.41) [k]	NR	22438 (98.6)	1337 (5.87) [L]
Source: Ronco 2007					
NETHCON Trial					
CC	40047	72 (0.18)	NR	38504 (96.4) [i]	418 (1.04) [j]
LBC	48941	97 (0.20)	NR	45818 (93.6) [i]	480 (0.98) [j]
Source: Siebers 2009					
Strander 2007					
CC	8810	NR	NR	8810 (100)	75 (0.85) [h]
LBC	4676	NR	NR	4674 (100)	56 (1.2) [h]
Maccallini 2008					
CC	4299	NR	NR	4336 (100)[a]	NR
LBC	4355	NR	NR	4318 (100)[a]	NR
Source: Maccallini 2008					
Obwegeser 2001					
CC	1002	1[b]	NR	1002 (100)	12[e] (0.6)
LBC	997	1[b]	NR	1999 (100)	11[d] (1.1)
RHINE-SAAR Study					
CC	9296 [c]	NR	NR	9296 (100)	NR
LBC	11331 [c]	NR	NR	11331 (100)	NR
Source: Ikenberg 2010a, 2010b, 2010c, 2011a, 2011b					
Manual versus automated cytology					
MAVARIC Study					
Manual	24,688	257 (1.04)	NR	24,309 (98.46)	NR

Trial ID intervention	Randomised N	Lost to follow-up n (%)	Discontinued n (%)	Cytology analysed n (%)	Histology analysed n (%)
Paired arm (Manual and Automated)	48,578	343 (0.71)	NR	46,489 (95.70)	NR
Source: Kitchener 2011					
Palmer 2012					
Manual	90,551	NR	NR	90,551 (100)	NR
Automated	79,366	NR	NR	79,366 (100)	NR
Source: Palmer 2012					

Abbreviations: CC, conventional cytology; LBC, liquid-based cytology; NR, not reported

a. Between randomisation and undergoing the test 173(4%) women randomised to the CC arm changed interventions as did 136 (3.2%) women originally randomised to the cell filtration arm.
b. One patient from each intervention with cytology of HSIL+ was lost to follow up. The number of patients with a cytology reading of less than HSIL+ was not reported in Obwegeser 2001
c. Reported n for patients included in analyses. Those included in the analyses are 97.8% of the initial recruitment. Whilst Ikenberg report the initial recruitment number of 21,081 it is not reported if 100% of these women were randomised and if so to what arm.
d. Of the 19 HSIL cytology cases histology was available for 12 women (63%)
e. Of the 16 cell filtration HSIL cytology cases, histology was available for 11 women (69%)
f. For Beerman 2009 the histology analysed represents the number of women who were followed up for histology results using the PALGA database.
g. Lost to follow up manually calculated and represents the difference in the number of women randomised and those followed up by histology
h. Representative of the number of women with histology follow-up performed at 1.5 years. Strander 2007 also presents the number of women with follow-up histology at 3years 7 months: 122 (1.38%) for the conventional arm and 84 (1.8%) for the LBC arm.
i. Representative of the number of cases included in the per protocol analysis
j. Of all the ASCUS+ cytology cases, 36.3% (480) LBC women had follow-up histology performed and 36.3% (418) of those in the conventional arm had histological follow-up.
k. The number of women who did not have a colposcopy carried out after referral
l. The number of women whose colposcopies were carried out after referral.

B.4 Characteristics of the direct randomised trials

All included trials represent a screening population and invited women generally between 23 and 65 years of age to participate. The mean age of participants ranged from 37 to 44 years of age.

The RODEO trial is unique in that it represents a different geographical location (remote areas of Brazil) and type of health service (recruitment through mobile units).

Cytobrush or spatulas were generally used to collect samples and the type of tool was identical between the arms within each trial except Obwegeser 2001 (who used a spatula for the collection of cells for conventional slides and cytobrush to collect cells for LBC).

For most trials the implementation of LBC was new and as such training was reportedly provided to collectors of the LBC specimen and cytology reviewers.

Regarding manual versus automated review, there was a variety of experience in the use of the different systems within the labs and training was provided accordingly.

B.4.1 Eligibility criteria

The eligibility criteria applied to the included RCTs are presented (Table 15).

Inclusion criteria

Whilst the RODEO Study failed to mention distinct inclusion criteria, all other trials generally restricted inclusion to women aged from 23 to 65 years. The RHINE-SAAR study also included women as young as 19 years; Obwegeser 2001 included women as young as 15 years and some over 70 years of age.

Clinical setting

All trials included a cervical screening population; Obwegeser 2001 also included patients who had previous abnormal Pap smear results. The RODEO trial recruited women in mobile units across remote areas of Brazil which represents a different geographical location and type of health service. Only the NTCC trial reported exclusion criteria explicitly stating that pregnant women, women who had undergone hysterectomy, those who had never had sexual intercourse or those who were recently treated for CIN (in the last 5 years) were not eligible for participation in the study.

Table 15 Eligibility criteria applied to the included trials

Trial ID	Inclusion criteria	Exclusion criteria
Cell enrichment versus CC		
Beerman 2009	Asymptomatic women aged 30–60 years. The women chosen were asymptomatic according to the entry criteria as assessed by the general practitioner according to a medical checklist. There was no pre-selection for age or demographic distribution of adherent patient population when selecting general practitioners for participation in the trial. Women participating in population based screening program	NR
Source: Beerman 2009 Materials and Methods p.573		
RODEO study	No eligibility criteria outlined. Included women who underwent gynaecological examination in prevention mobile units (MUs) which covered low-risk women in Brazilian remote rural areas or in the ambulatory of the Barretos Cancer Hospital which covered high-risk women for HPV related disease	NR
Source: Longatto-Filho 2011; Fregnani 2012		
Cell Filtration versus Conventional cytology		
NTCC Trial	Women aged 25–60 years. Included women who are routinely invited to cervical cancer screening centres every three years	Women who were pregnant, had undergone hysterectomy, had never had sexual intercourse or were recently treated for CIN (in the last 5 years) were not eligible
Source: Ronco 2007 Methods p.2		
NETHCON trial	Women aged 30–60 years. Included women who are routinely invited to cervical cancer screening program every five years by a family physician	NR
Source: Siebers 2009 Methods p.1758		
Strander 2007	Women aged 23 to 50 years are invited to undergo cervical screening every third year and at ages 55 and 60 years	NR
Source: Strander 2007 Materials and methods p.286		
Maccallini 2008	Women aged 26–64 years Included women who were invited for cervical cancer screening at one of 16 smear taking units across 2 existing and 1 new program in Italy	NR
Source: Maccallini 2008 Materials and methods p.569		
Obwegeser 2001	Age distribution 15– > 70 years Women visiting 15 gynaecologists in private practice for a pap smear were invited to participate. Patients with a previous abnormal Pap smear were included in the study	NR
Source: Obwegeser 2001Materials and methods p.710 and Figure 2 p.711		

Trial ID	Inclusion criteria	Exclusion criteria
RHINE-SAAR study	Women aged 19 years or older Included women attending routine cervical cancer screening at 20 office-based gynaecologists. Note: Authors quote that Germany does not have an organised cervical screening program but three year participation rates are equal that in Great Britain	NR
Source: Ikenberg 2010a,b,c; 2011 a,b		
Manual versus automated cytology		
MAVARIC	Women aged 25-64 years Included women attending screening within general practices, family planning clinics and colposcopy clinics. Fewer samples were obtained from women aged 45–64 years (21,231; 29·1%) than were obtained from women aged 25–44 years (47,987; 65·7%) because women aged 50–64 years are invited every 5 years for screening, whereas women aged 25–49 years are invited every 3 years. In real life, some women outside these age ranges are screened, and exclusion of these samples was felt to be inappropriate. There were 3619 (5·0%) slides from women outside the screening age range; 3103 from women aged less than 25 years and 606 from women aged 65 years or older	NR
Source: Kitchener 2011 Methods p.57 and Results p.60		
Palmer	Women aged 20–60 years Samples were all screening program LBC preparations	NR
Source: Palmer 2012 Methods p.2 and Discussion p.8		

Abbreviations: CC, conventional cytology; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; NR, not reported

B.4.2 Patient baseline characteristics

Patient baseline characteristics were not reported in the RODEO Study, the RHINE-SAAR Study, or Palmer 2012. The age of participants was reported in the remaining studies in addition to the mean Townsend deprivation scores in the MAVARIC study. These baseline characteristics are presented in Table 16.

Age

The mean age of participants between the trials was consistent and generally ranged between 37 and 44 years of age.

Only the NETHCON trial and Maccallini 2008 reported significant differences in age between interventions within a trial, although in both cases the difference in the average age was less than one year, and therefore unlikely to affect the overall results.

It was also noted that the difference between mean age reported by Strander 2007, 38.18 years in the CC arm and 41.67 in the LBC arm was greater than the NETHCON trial and Maccallini 2008; no statistical analyses are mentioned.

Table 16 Characteristics of participants in the direct randomised trials varying across randomised groups

Trial ID/baseline characteristic		
Cell enrichment LBC versus conventional cytology		
Beerman 2009	**CC** N=51,154	**Cell enrichment LBC** N=35,315
Mean age (years)	43.9	43.7
Source: Beerman 2009 Results p.574		
RODEO Study		
No baseline characteristics reported		
Source: Longatto-Filho 2011; Fregnani 2012		
Cell filtration LBC versus conventional cytology		
NTCC Trial	**CC** N=22,056	**Cell filtration LBC** N=22115
Age n(%)		
< 35 years	5673 (49.2)	5860 (50.8)
≥ 35 years	16,383 (50.2)	16,255 (49.8)
Source: Ronco 2006 Figure p.549		
NETHCON trial (Siebers 2008)	**CC** N=39,010	**Cell filtration LBC** N=46,066
Mean age (years ± SD)	44.1 (±9.2)†	43.8 (±9.2)†
Number of practices	124	122
Source: Siebers 2008 Table 1 p.1331		
Strander 2007	**CC** N=8810	**Cell filtration LBC** N=4674
Age (years)		
Median	39.28	42.13
Mean	38.18^	41.67^
Source: Strander 2007 Table 1 p.287		
Maccallini 2008	**CC** N=4299	**Cell filtration LBC** N=4355
Mean age (years)	36.9*	37.6*
Source: Maccallini 2008 Results p.571		
Obwegeser 2001	**CC** N=1002	**Cell filtration LBC** N=997
Age n[a]		
15–19 years	16	21
20–24 years	84	70
25–29 years	130	138
30–34 years	165	178

Trial ID/baseline characteristic		
40–44 years	94	86
45–49 years	68	58
50–54 years	64	64
55–59 years	44	40
60–64 years	28	44
65–69 years	20	26
> 70 years	22	14
Source: Obwegeser 2001 Figure 2 p.711		
RHINE-SAAR Study		
No baseline characteristics reported		
Source: Ikenberg 2010a,b,c; 2011a,b		
Manual versus automated		
MAVARIC	**Manual arm**	**Paired arm**
Mean age (years)	39	39
Mean Townsend deprivation score		
Cell filtration LBC	3.99	3.85
Cell enrichment LBC	3.84	3.64
Source: Kitchener 2011 Results p.60		
Palmer 2012		
No baseline characteristics reported		
Source: Palmer 2012		

Abbreviations: CC, conventional cytology; LBC, liquid-based cytology; SD, standard deviation

a Age distribution of patients calculated manually from the graph in Figure 2, Obwegeser 2001 p.711

† $P < 0.001$, using the Student t test

* The authors report that the slight difference in age (CCT 36.9 years, LBC 37.6 years) is, "statistically significant but is compatible with the adopted method of randomisation and is not likely to affect the overall results"(Maccallini 2008 p. 571)

^ The authors report that the, "distribution was uneven but random", and no statistical comparison was provided (Strander 2007 p. 287)

B.4.3 Interventions in the direct randomised trials

The methods of sample collection, slide preparation and the tools and equipment used varied between the included trials. Table 17 compares these interventions and the different protocols applied.

Sample collection and training

Generally midwives, GPs or gynaecologists collected samples for the trials; an exception was Obwegeser 2001 in which only gynaecologists collected the samples. Obwegeser 2001 describes a very different method of sample collection whereby mucus and debris of the cervix were removed with a cellulose swab before cervical cells were collected under colposcopic guidance. Colposcopic guidance was not reported in any other trial and is not possible in many countries. Whilst removing mucus and cellular debris may increase the specimen adequacy of slides, degenerated abnormal cells can be lost on the cellulose swab prior to cell collection (Obwegeser 2001). The collection methods used by Obwegeser 2001 may explain the uncharacteristic result of higher unsatisfactory rates in the LBC arm compared to CC (see section B.6). The NETHCON trials and Strander 2007 reported the provision of specific training for the collection of the LBC sample.

Collection tool

The collection tool used was not reported for all trials, but in those that did report the tool type, these were identical in both arms of each trial with the exception of Obwegeser 2001, wherein a Szalay spatula was used for the collection of cells for CC, with either a Rovers Cervix-Brush or an Orifice Oribrush to collect cells for LBC. The Strander 2007 protocol was for fornix and portio cells to be collected using a wooden spatula for the CC slide and a plastic spatula for LBC slides. Endocervical cells were to be collected using a cytobrush regardless of the intervention. Generally a cytobrush or spatula was used to collect samples.

Applied quality system

Most trials reported a quality system that assured reliability of the test and outcome result.

Technology and experience

Strander 2007 and Obwegeser 2001 used the ThinPrep2000 processor and the NETHCON trial used the ThinPrep3000 processor for LBC cells. The MAVARIC study used both the FocalPoint GS imaging system for review of SurePath slides and the ThinPrep imaging for ThinPrep slides. The ThinPrep Remote Imaging System, MultiCyte™ was used in Palmer 2012.

Most trials reported specific LBC training for cytotechnologists and cytologists; exceptions were the RODEO and NTCC trials, and Macallini 2008.

In the MAVARIC trials of automated versus manual review of slides was conducted in a single centre. The Palmer 2012 study encompassed six laboratories and used only one new technology. In the MAVARIC trial there was a variety of experience with manual and automated LBC, training was provided to a pool of cytoscreeners. There is no mention of feedback to screeners in the MAVARIC study after initial training. By contrast, review and reinforcement of training was carried out in the Palmer 2012 study when screening errors were identified by quality control review.

The diverse range of sampling methods, collection tools and processing technology may provide an explanation for some of the discrepancies identified in the results between the included trials (See section B.6).

Table 17 Interventions compared by the direct randomised trials

Trial ID	Intervention	Professional groups taking the smears	Collection tool/s	Technology used for slide preparation	Applied quality system	Experience with technology	Technology of imaging system
Cell enrichment versus conventional cytology							
Beerman 2009							
Conventional	Conventional Pap smear	Collected by GP. Method not outlined	Rovers Cervix-Brush	Slides prepared according to standard laboratory protocols and stained with Pap stain	All abnormal smears of ASCUS or higher were reviewed by experienced cytopathologists	NR	NR
LBC	SurePath	Collected by GP. Method not outlined	Rovers Cervix-Brush	Tip of the brush removed and completely immersed in a disposable collection vial from TriPath Imaging. Slides were then prepared according to manufacturer's guidelines		Slides prepared according to manufacturer's guidelines. Participating cytopathologists and cytotechnicians trained in interpretation of LBC prior to study start	NR
Source: Beerman 2009							
RODEO study							
Conventional	Conventional Pap smear	NR	NR	NR	NR	NR	Manual
LBC	SurePath	NR	NR	NR		Prior LBC experience by lab not mentioned	Manual
Source: Longatto-Filho 2011; Fregnani 2012							
Cell filtration versus conventional cytology							
NTCC Trial							

Trial ID	Intervention	Professional groups taking the smears	Collection tool/s	Technology used for slide preparation	Applied quality system	Experience with technology	Technology of imaging system
Conventional	Conventional Pap smear	NR	Plastic Ayre's spatula and cytobrush	A standard Pap smear was prepared	The same cytologists were assigned to liquid-based and conventional cytology. Abnormal slides were reviewed by a local supervisor or, by a panel of cytologists) before they reported the results to the women.	NR	NR
LBC	ThinPrep + HPV testing (Hybrid Capture 2, HC2)	NR	Plastic Ayre's spatula and cytobrush	Cells were placed in PreserveCyt Solution and prepared using the ThinPrep system		Prior LBC experience by lab not mentioned	NR
Source: Ronco 2006a,b; Ronco 2007							
NETHCON Trial							
Conventional	Conventional Pap smear	Collected by family physician or their assistant. Method not outlined	Rovers Cervix-Brush	Slides were prepared by spreading cells quickly on a glass slide and performing cell fixation within a few seconds	Abnormal slides with diagnosis HSIL were reviewed by a senior cytotechnologist and a trained pathologist as were slides with diagnosis ASCUS/AGUS/ LSIL.	NR	NR
LBC	ThinPrep	Collected by family physician or their assistant. Method not outlined. The practices that converted to liquid-based cytology received additional training, either by a regional course or by in-practice training by the manufacturer	Rovers Cervix-Brush	Samples were prepared by transferring the sampled cells from the brush to the transport solution by firmly rotating and pushing the brush against the vial wall 10 times. Samples were then processed using the ThinPrep3000 processor		At the start of the trial, one of the participating laboratories had experience with screening liquid-based slides for 1 year; the other laboratory did not have previous experience with liquid-based cytology. Before implementation of the liquid-based method in the laboratories, cytotechnologists and cytopathologists attended a 3-day training course, provided by the manufacturer. The course finished with a test, which was mandatory before starting to	NR

Trial ID	Intervention	Professional groups taking the smears	Collection tool/s	Technology used for slide preparation	Applied quality system	Experience with technology	Technology of imaging system
						screen liquid-based cytology slides. During the learning stage a minimum of 200 liquid-based slides, taken from the routine workload, were screened within a multiple screening protocol by two cytotechnologists until cytologic consensus was reached. After these 200 liquid-based slides, cytotechnologists had a final test, and when they passed they were allowed to screen liquid-based cytology independently. Technical operators received instruction for operating and maintenance of the ThinPrep 3000 Processor from Cytyc Corporation	
Source: Siebers 2008; Seibers 2009							
Strander 2007							
Conventional	Conventional Pap smear	Cells were taken from the fornix, portio and endocervix. Collection was performed by midwives	- Wooden spatula (Ayre) for collection of cells from fornix and portio - Cytobrush used for collection of endocervical cells	Slides were stained according to the Pap method	All LBC specimens were screened by 1 of 3 cytotechnicians with special training in LBC. This group also screened 73% of the conventional Pap smears in the study. All positive cytology in the remaining 27% of smears was reviewed by 1 or 2 of these cytotechnicians	CV smears were reviewed by 1 of 3 or 1 of 2 of the cytotechnicians who reviewed the LBC smears	NR
LBC	ThinPrep	Cells were taken from	- Plastic spatula	Specimens were placed		All LBC specimens were	NR

Trial ID	Intervention	Professional groups taking the smears	Collection tool/s	Technology used for slide preparation	Applied quality system	Experience with technology	Technology of imaging system
		the fornix, portio and endocervix. Collection was performed by midwives The midwives received special training in smear taking and also were trained in handling LBC samples	for fornix and portio - Cytobrush used for collection of endocervical cells	in a PreserveCyt solution and processed in the ThinPrep2000 machine. Slides were stained according to the Pap method		screened by 1 of 3 cytotechnicians with special training in LBC	
Source: Strander 2007							
Maccallini 2008							
Conventional	Conventional Pap smear	NR	NR	NR	NR	NR	NR
LBC	ThinPrep	NR	NR	PreserveCyt solution		Participating laboratories had no experience with LBC prior to the study. Intensive training to provide cytologists with information on the cytologic features unique to thin-layer preparation was provided to all cytologists as well as the main diagnostic criteria to be applied	NR
Source: Maccallini 2008							
Obwegeser 2001							
Conventional	Conventional Pap smear	Samples were collected by gynaecologists after mucus and debris had been removed from the cervical surface with a cellulose swab. Samples were then	Szalay Spatula	Slides were fixed immediately in a 96% alcohol solution and stained with the laboratory's routine Pap staining	NR	CV smears were evaluated by three other cytotechnologists with experience in reading CV smears	NR

Trial ID	Intervention	Professional groups taking the smears	Collection tool/s	Technology used for slide preparation	Applied quality system	Experience with technology	Technology of imaging system
		collected under colposcopic guidance. Cells were collected from the endocervical canal and cervical surface					
LBC	ThinPrep	Samples were collected by gynaecologists after mucus and debris had been removed from the cervical surface with a cellulose swab. Samples were then collected under colposcopic guidance	Rovers Cervix-Brush or Orifice Oribrush for endocervical cell collection combined with a plastic spatula for the cervical service	The collection device was rinsed immediately after use in a vial of PreservCyt Solution, and a slide was prepared using the ThinPrep 2000 processor according to the manufacturer's guidelines. Slides were stained with the laboratory's routine Pap staining		TP slides were evaluated by an experienced cytotechnologist who had successfully completed a training program offered by Cytyc and received primary training and certification	NR
Source: Obwegeser 2001							
RHINE-SAAR Study							
Conventional	Conventional Pap smear	NR	NR	NR	NR	Smear evaluation performed only by experienced cytotechnicians (> 2000 slides in each technique)	N/A
LBC	ThinPrep	NR	NR	NR		Smear evaluation performed only by experienced cytotechnicians (> 2000 slides in each technique)	ThinPrep Imaging System
Source: Ikenberg 2010a, 2010b, 2010c, 2011a, 2011b							

Trial ID	Intervention	Professional groups taking the smears	Collection tool/s	Technology used for slide preparation	Applied quality system	Experience with technology	Technology of imaging system
Manual versus automated							
MAVARIC Study							
Manual arm	SurePath +HPV testing low grade abnormalities using HC2	NR	NR	Manual screening was carried out according to laboratory protocols	After an initial read by the cytoscreener, whether automated or manual, a manual rapid review was done for every sample.	**M**anual screening performed in the routine lab workflow by auto-trained and non-auto-trained cytoscreeners. This created the potential for the same screener to read the slide both manually and on the automated system; however, owing to the large pool of cytoscreeners performing manual screening the chance of this happening was low. There is no mention of feedback to screeners after initial training	N/A
	ThinPrep + HPV testing low grade abnormalities using HC2	NR	NR	Manual screening performed according to lab protocols. Same stain used for both manual and automated readings so Imager stain was used on all ThinPrep slides			N/A
Paired arm	SurePath + HPV testing low grade abnormalities using HC2	NR	NR	In the paired arm the automated reading was undertaken first using the FocalPoint GS Imaging system, followed by the manual read		Staff with varying levels of LBC experience were selected to receive automated screening training. Both companies performed the training. Eight medical laboratory assistants were trained in the handling and maintenance of the imaging	FocalPoint GS Imaging System

Trial ID	Intervention	Professional groups taking the smears	Collection tool/s	Technology used for slide preparation	Applied quality system	Experience with technology	Technology of imaging system
						systems. Eight cytoscreeners and one chief biomedical scientist were trained in the use of the automated microscopes and cell morphology recognition. The laboratory trial co-ordinator and two cytopathologists were trained in the handling and maintenance of the imaging systems, the use of the automated microscopes and cell morphology recognition for both systems. There is no mention of feedback to screeners after initial training	
	ThinPrep + HPV testing low grade abnormalities using HC2	NR	NR	In the paired arm the automated reading was undertaken first using the ThinPrep Imaging system, followed by the manual read. The same stain was used for both manual and automated readings so an Imager stain was used on all ThinPrep slides			ThinPrep Imaging System
Source: Kitchener 2011							
Palmer 2012							
Manual	ThinPrep	NR	NR	All slides were stained	Quality control by rapid		N/A

Trial ID	Intervention	Professional groups taking the smears	Collection tool/s	Technology used for slide preparation	Applied quality system	Experience with technology	Technology of imaging system
				using the proprietary Hologic stain	review/ preview was continued throughout the study. Technical and interpretive external quality assurance (EQA) methods were modified to reflect the standardized stain required by the TIS. The participating laboratories also joined the Hologic technical EQA scheme.		
Automated	ThinPrep	NR	NR	All slides were stained using the proprietary Hologic stain		Training in the use of the ThinPrep Imaging System was delivered by Hologic personnel according to their standard protocols. Review and reinforcement of training was carried out when screening errors were identified by quality control	The Hologic ThinPrep Remote Imaging System– MultiCyte™
Source: Palmer 2012							

Abbreviations: CV, conventional; GP, general practitioner; GS, guided screening; HPV, human papillomavirus; LBC, liquid-based cytology; NR, not reported, N/A, not applicable; TP, ThinPrep

B.5 Outcome measures and analysis of the direct randomised trials

The detection rate of histological abnormalities was the primary outcome in most trials.

Varying cytological and histological classification systems and terminology were used across trials.

The category of outcomes required to address the research questions proposed in the DAP are health outcomes, diagnostic accuracy, change in management and patient outcomes.

Reductions in mortality, morbidity or incidence of cervical cancer provide the highest level of evidence of efficacy in screening.

Cytological test yield of ASCUS, LSIL or HSIL define the rate of investigation in a screening population, and thus have clinical, personal and financial importance. Cytological findings without a reference method are quite inaccurate, rather the essential objective of cervical screening programs are detecting and removing histologically confirmed high-grade lesions (CIN 2+).

Sensitivity and specificity traditionally represent diagnostic accuracy but in cervical screening trials patients with normal cytology are generally not followed up for outcome. Therefore positive predictive value for CIN 2+, preferably CIN 3+, will also be relied on for the assessment of diagnostic accuracy.

Because there are no head-to-head comparisons between cell enrichment LBC and cell filtration LBC an indirect comparison between the technologies was conducted.

B.5.1 Primary and secondary outcomes presented in the included trials

The outcome measures and statistical analyses reported for each RCT is presented in Table 18. The detection rate of histological abnormalities was the primary outcome in most trials, but the classification and categories of histological outcome reported varied. A comparison of different cytological and histological classification systems is therefore presented (Table 19).

Limited data were available for the RODEO cell enrichment LBC trial; data from two abstracts only were available. Similarly, RHINE-SAAR study data were available in abstract form only, with limited data reported. Essentially, detection of high grade or CIN 2+ lesions was all that was reported for these two trials.

For all other trials, test yield and unsatisfactory rates were reported as well as various other absolute and relative accuracy measures.

It is pertinent to note that the NTCC trial was conducted over two phases. The first phase presented cross-sectional sensitivity and specificity at the first screening examination, which is published separately for women aged 25 to 34 years (Ronco 2006a) and 35 to 60 years (Ronco 2006b). The main final endpoint of the study was long term rates of disease, reported for the two cohorts combined by Ronco 2007. The focus of the trial was to review the effect of using different criteria for referral to colposcopy (concerning the combined use of HPV and LBC and the cut-off used for HPV testing).

Table 18 Outcome measures and statistical analyses of the direct randomised trials

Trial ID	Definition of outcomes	Method of primary statistical analysis
Cell enrichment versus conventional cytology		
Beerman 2009	**Detection rate of histological abnormalities (CIN 1+)** Test yield Unsatisfactory rates Sensitivity Specificity False negative and positive rates	P values comparing histology and cytology were determined by the Cochran-Mantel-Haenszel test. False negative and false positive rates were compared using the 2-sided Fisher's exact test
Source:	Beerman 2009, Materials and methods pp.573–4	
RODEO Study	**Detection of HSIL lesions**	NR
Source:	Longatto-Filho 2011; Fregnani 2012	
Cell Filtration versus conventional cytology		
NTCC Trial	Test Yield Unsatisfactory rates/proportion of samples yielding unsatisfactory results Detection rate (endpoint of CIN 2+) Relative sensitivity(endpoint of CIN 2+) Positive predictive value (PPV)(endpoint of CIN 2+) Relative PPV (endpoint of CIN2+) Sensitivity and specificity available for LBC only Impact of screening on clinical management (Comparison of number of colposcopies and biopsies performed)	The cytology results, including unsatisfactory findings, were compared between the study groups. Uncorrected contingency $\chi 2$ analysis was applied for all comparisons between proportions, unless otherwise specified. We used unconditional logistic regression to calculate odds ratios for the association of different variables with persistent positive results from HPV tests repeated after 1 year. 95% CIs were calculated from Wald-type SEs. The sensitivities of the different combinations of cytology and HPV testing are also given as values relative to the conventional group, for all randomised eligible women (i.e. analysis was by intention to screen). PPV relative to conventional cytology was calculated only for women who actually received colposcopy. CIs were calculated with methods appropriate for ratios of independent proportions. Homogeneity in relative sensitivity and relative PPV between different groups was tested by the Breslow-Day test. SAS software version 8.2 was used for all analyses. All p values were two-sided. A study size of about 100,000 women was calculated from both recruitment phases, which would have a greater than 80% power to show a significant (two-sided test, 5% level) true reduction of 32% or more in the detection of CIN 2+ in the experimental group compared with the conventional group at the final round of screening (the main study endpoint)
Source:	Ronco 2006a pp.549–50	
NETHCON Trial	Test yield Unsatisfactory rates/proportion of samples yielding unsatisfactory results Proportion of CIN lesions detected in some cytological categories (ASCUS+) Positive predictive value (PPV)(endpoint of CIN 1+ and CIN 2+) Relative PPV (endpoint of CIN	Two data sets are presented for the NETHCON trial, the intention-to-treat set and the per protocol set. Only participants from randomised practices were included in the intention-to-treat analysis. The per-protocol analysis included only participants who received the test determined by randomisation. The authors report that results of the study using the different analysis sets are not significantly different. $\chi 2$ tests were used for comparison of proportions. Crude rate ratios (RRs) were computed as ratios of the DRs or the PPVs. Odds ratios (ORs) for finding a verified outcome in liquid-based cytology vs. conventional Pap test, adjusted for confounding factors, were computed by logistic regression. The following confounding factors were included

Trial ID	Definition of outcomes	Method of primary statistical analysis
	1+ and CIN 2+)	in multivariate analyses: age, urbanisation level, study site, and period. Period was defined as the first and second half of the study, using the median preparation date as a separator. ORs were converted into RRs using established methods. The ratios of the DR of verified cervical abnormalities in the LBC relative to the conventional Pap test group was assessed for the primary histological outcome of CIN grades 1+, 2+, and 3+ and carcinoma. The cluster design was taken into account for calculation of 95% CIs. Statistical testing was two-sided, and significance was defined at $P < 0.05$. Binomial exact 95% CIs were computed around proportions. Analyses were performed using Stata 10.0 statistical software (Stata-Corp LP, College Station, Texas)
Source:	Siebers 2007; Siebers 2009 p.1760	
Strander 2007	**Detection of HSIL in histopathology at 1.5 year and at 3 years 7 months follow-up** Test yield Inadequate rates	Multiple logistic regression modelling was used adjusting for age and the proportion of ThinPrep/conventional smears unevenly distributed between the screening clinics. The type of method was included as well as age and screening unit. Uncorrected differences in proportions between groups were calculated with the chi-square test using Stata software. P values were two-sided
Source:	Strander 2007, Statistical analysis p. 287 and Discussion p. 289	
Maccallini 2008	Test yield Frequency of inadequate reports Referral rate to colposcopy CIN 2+ detection rate Referral PPV for CIN 2+	Two separate analyses were performed according to intention to treat (comparing by screening arm) or intention to screen (comparing by actually performed sampling methods). As differences in results between intention to treat and intention to screen were quite limited and not statistically significant. Statistical analysis of observed differences was performed according to the actual test performed. CIs were calculated. All P values were two-sided
Source:	Maccallini 2008, Materials and methods p.570	
Obwegeser 2001	Test yield Unsatisfactory rates Specimen adequacy Detection of HSIL	The proportion of the two patient populations that were abnormal were compared using the two-sample test for binomial proportions
Source	Obwegeser 2001	
RHINE-SAAR Study	Detection of histologically confirmed CIN 2+ lesions	NR
Source:	Ikenberg 2010, Eurogin abstract	
Manual versus automated		
MAVARIC Study	**Sensitivity of automation-assisted reading relative to manual reading for the detection of underlying CIN 2+** Relative specificity Sensitivity of automation-assisted reading relative to manual reading for the detection of underlying CIN 3+ Sensitivity of the two automated technologies	Absolute sensitivity of manual reading or automated reading could not be calculated because the number of cases of CIN 2+ in samples negative according to both methods was unknown. However, an estimation of the ratio of the two sensitivities (the missing count cancels out) and an assessment of confidence intervals and statistical significance was possible. The ratio is the number of samples of CIN 2+ that were screen positive with automated screening divided by the number of samples of CIN 2+ that tested positive with manual screening. Similarly, relative specificity was calculated roughly as the ratio of the number of samples of CIN of grade 1 or less that were negative on automated reading, to the number that were negative on manual reading, on the assumption that the number of samples of CIN 2+ not detected by either screening method is zero

Trial ID	Definition of outcomes	Method of primary statistical analysis
	relative to manual screening and to each other Reliability of slides defined as needing no further review to exclude underlying CIN 2+	
Source:	Kitchener 2011, Procedures p.58; statistical analyses p.59	
Palmer 2012	Test yield Inadequate rates Sensitivity, specificity and predictive value for final cytology report Correlation between cytology and histology (CIN 2+ and CIN 3+ detection rates) Productivity data	95% CIs reported for the sum of all 6 laboratories was calculated using Wilson's method. P values are two-tailed Fisher's Exact tests except where stated otherwise. Sensitivity, specificity and false-negative rates using the final cytology report as the outcome, and PPV using histological biopsy as outcome are calculated according to National Health Service Cervical Screening Programme definitions from data collected automatically. PPV is the percentage of cases referred for high-grade cytological abnormalities (moderate dyskaryosis or worse) that are found on biopsy to have CIN 2 or CIN 2+; the abnormal predictive value is the percentage referred with borderline changes or mild dyskaryosis that have CIN 2+; and the total predictive value is the percentage of all women referred to colposcopy who have CIN 2+. Persistent inadequate LBC preparations were not included in the calculations
Source:	Palmer 2012 pp.3–4	

Abbreviations: ASCUS +, atypical squamous cells of undetermined significance; CI, confidence interval; CIN, cervical intraepithelial neoplasia; DR, detection rate; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LBC, liquid-based cytology; NR, not reported, PPV, positive predictive value; RR, rate ratio; SE, standard error

Note: items reported in **bold** represent specified primary outcomes

Minimum clinically important difference (MCID)

The RCTs tell us the relative accuracy of an experimental screening intervention compared to a reference standard, but they do not inform us about whether the differences in accuracy are clinically important, or the degree of clinical importance (in other words, the impact on patient outcomes). CIN 3 is the direct precursor of invasive cancer and therefore, reduced incidence of CIN 3+ is considered as an acceptable a proxy outcome of trials evaluating new preventive strategies (Arbyn 2009). CIN 1 is the histopathologic manifestation of a carcinogenic or non-carcinogenic HPV infection that rarely progresses on a per event basis to cancer. Its detection is not clinically useful, possibly leading to over-treatment, and should not be targeted by any screening test (Arbyn 2009). CIN 2, and especially CIN 3, indicate a considerable risk of developing cancer and should therefore not be missed by a screen test (Arbyn 2009).

Cytology and histology classification systems

Cytological and histological classification systems have changed over time as the natural history and pathogenesis of cervical cancer has become clearer (Wright 2006; Table 19). This is demonstrated in the varying terminology used throughout the included trials. Table 21 represents a comparison of various classification systems.

The Bethesda classification system, introduced in 1991, had several issues and was reviewed and modified in 2001. A comparison of the changes made is presented (Table 20). The three tier system for assessing the adequacy of a slide in the 1991 system was changed to just two in 2001, by removing the term 'Satisfactory but limited by…' This was due to confusion among clinicians resulting in a large number of early repeat smears (NHMRC Guidelines 2005, p.19). All possible low-grade and possible high-grade smears were combined into the one category of ASCUS using the 1991 system. This was corrected in the 2001 system by creating a separate field for possible high grade (ASC-H) results (NHMRC Guidelines 2005, p.19).

Table 21 lists the cytology and histology classification systems used in the included trials. The Bethesda 1991 system was the confirmed cytology classification method used in NTCC trial, and Maccallini 2008. Strander 2007 used the 2001 Bethesda system. Cytotechnologists in Beerman 2009 and the NETHCON trial classified slides using the CISOE-A/KOPAC-B systems before results were converted to the Bethesda system for reporting purposes. Bethesda terminology was also used in Obwegeser 2001 and the RHINE-SAAR and RODEO studies.

The MAVARIC study did not explicitly state use of a classification system, however Bethesda, two tier and NHSCP terminology were all used in the paper. Palmer 2012 used the NHSCSP for both cytology and histology classification. Almost all other trials used CIN classification for histology results, except for Obwegeser 2001, which also used the terms HSIL and LSIL in reporting.

It can be seen that the Australian modified Bethesda Classification terms, although not used in any of the trials, are compatible and can be converted between systems. Of importance is the clarification that the term atypical cells of undetermined significance (ASCUS) used in most trials corresponds to the Australian term of possible low-grade squamous intraepithelial lesion (pLSIL).

Table 19 Comparison of different cytological and histological classification systems

Papanicolaou	The Bethesda System 1991	The Bethesda System 2001	Australian modified Bethesda System	WHO	Two-tier	CIN	NHSCSP/BSCC	Modified CIN
Pap I	Within normal limits	Within normal limits	Within normal limits				Normal	
Pap II	ASCUS	ASCUS	pLSIL		Low grade		Borderline squamous and glandular changes without HPV	
Pap III	LSIL	LSIL	LSIL	Mild dysplasia		CIN I	Borderline with HPV and mild dyskaryosis	Low-grade CIN (CIN 1)
		ASC-H	pHSIL					
	HSIL	HSIL	HSIL	Moderate dysplasia	High grade	CIN II	Moderate dyskaryosis	High grade CIN (CIN 2, 3)
				Severe dysplasia		CIN III	Severe dyskaryosis	
Pap IV		AIS		Carcinoma in situ		CIN III		
Pap V	SCC	SCC	SCC	Micro-invasive/invasive carcinoma		Invasive carcinoma	Invasive carcinoma	Invasive cancer

Source: Wright 2006, Table 2 p.S25, Palmer 2012, Box 3 p.4, 2009 MSAC report Table 1 p.5, and https://openaccess.leidenuniv.nl/bitstream/handle/1887/4435/01.pdf?sequence=13 Chapter 1, Equivocal cytology; Table 1 p.12

Abbreviations: NHSCSP, National Health Service Cervical Screening Program; HPV, human papillomavirus; ASCUS, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cell cannot exclude high-grade squamous intraepithelial lesion; pLSIL, possible low-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; pHSIL, possible high-grade intraepithelial lesion HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma

Table 20 Changes made between the 1991 and 2011 Bethesda Classification Systems

The Bethesda System 1991	The Bethesda System 2001
Reporting of unsatisfactory smears	
Satisfactory for evaluation	Satisfactory for evaluation
Satisfactory but limited by…	
	Unsatisfactory for evaluation
Unsatisfactory for evaluation	
Reporting of atypical cells	
ASCUS	ASCUS
	ASC-H
Reporting of adenocarcinoma in situ	
AGUS	AGUS
	AIS

Source: NHMRC cervical cancer screening guidelines 2005, problems with TBS 1991 p.19
Abbreviations: ASCUS, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cell cannot exclude high-grade squamous intraepithelial lesion; AGUS, atypical glandular cell of undetermined significance; AIS, adenocarcinoma in situ

Table 21 Classification systems used in the included trials

Trial ID	Cytology classification system	Histology classification system
SurePath versus conventional cytology		
Beerman 2009	Cytotechnologists classified using the KOPAC-B which was then converted to the Bethesda system for reporting purposes*	No dysplasia, CIN 1/2/3, squamous carcinoma, adenocarcinoma
RODEO Study	Bethesda terminology used in reporting[a]	NR
ThinPrep versus conventional cytology		
NTCC Trial	Bethesda 1991 system[b]	CIN 1/2/3
NETHCON Trial	Cytotechnologists classified using CISOE-A which was then converted to the Bethesda system for reporting purposes*	CIN 1+ or low-grade SIL+ (which encompassed CIN 1–3 and carcinoma) CIN 2+ or HSIL+ (which encompassed CIN 2–3 and carcinoma)
Strander 2007	Bethesda 2001 criteria Yet discusses CIN terminology as defining cytological abnormalities for referral to colposcopy or repeat smear	Reported in table as benign/low-grade/high-grade Yet discusses CIN terminology elsewhere in text.
Maccallini 2008	Bethesda 1991 system	CIN[a]
Obwegeser 2001	Bethesda terminology used in reporting[a]	Not explicitly stated, CIN terminology used in one part and HSIL and LSIL used when referring to histology in other section of the paper
RHINE-SAAR Study	Bethesda terminology used in reporting[a]	CIN[a]

Manual versus automated		
MAVARIC Study	Two tier, Bethesda and NHSCP terminology all used. Doesn't explicitly state a classification system adhered to. (High grade, low grade, ASCUS and mild dyskaryosis all used.)	CIN[a]
Palmer 2012	NHSCSP	NHSCSP

Abbreviations: NHSCSP, National Health Service Cervical Screening program; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; CISOE-A, classification system composition (C), inflammation (I), squamous epithelium (S), other and endometrium (O), and endocervical columnar epithelium (E); KOPAC-B, dutch classification system kompositie (K), ontsteking (O), plaveisel epitheel (P), andere en endometrium afwijkingen (A), cylinder epitheel (C); NR, not reported, QC, quality control:
* In the CISOE-A system (also known as KOPAC-B in the Dutch language) cervical smears are examined and categorised by five different categories; composition (C), inflammation (I), squamous epithelium (S), other and endometrium (O) and endocervical columnar epithelium (E), with the (A) of the acronym indicating the adequacy of the smear. Both the Beerman and NETHCON trial report the conversion to the Bethesda system but do not report the correlation between categories of the different reporting systems

a Whilst the terminology is used in the paper, it does not explicitly state the classification system adhered to in the study protocol.

b The subcategories for ASCUS were not applied in the study

B.5.2 Outcomes presented in the submission

As agreed by the DoHA and the Protocol Advisory Subcommittee (PASC) of MSAC in their advice and final DAP (May 2012) the following outcomes are presented in the submission to address the review questions:

Health outcomes

- Overall survival
- Incidence of cervical cancer (including glandular abnormalities, CIN 3+ and adenocarcinoma in situ)
- Cervical cancer-specific mortality.

Diagnostic outcomes

Accuracy in terms of assessing squamous abnormalities and glandular abnormalities (HSIL, pLSIL, LSIL, CIN) measured as:

- Test yield
- Sensitivity and specificity
- Positive and negative predictive value (PPV and NPV)
- True positive: false positive

- Incremental rate of true positive
- Unsatisfactory rates
- Proportion of CIN lesions detected in each cytological category
- Proportion of samples yielding unsatisfactory results (Note: same outcome as "Unsatisfactory rates" required above and therefore not repeated).

Change in management

- Impact of screening on clinical management (e.g. further investigations, treatment avoided).

Patient outcomes

- Quality of life
- Patient preference
- Satisfaction, anxiety
- Patient compliance.

B.5.3 Health outcomes

Health outcomes required by the DAP will be reported where available from each RCT. However the accepted strategy for preventing and diagnosing cervical cancer in Australia and many countries worldwide is via an organised NCSP as dictated in the NHMRC 2005 Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities (MSAC September 2005 p.27). This is because cervical screening reduces illness and deaths from cervical cancer, achieved by review of cervical cytology collected via a Pap smear test (conventional cytology, CC). Although the DAP requires a comparative assessment of health outcomes, it is felt that, should health outcomes not be reported in the selected studies, a comparative assessment of diagnostic outcomes will be sufficient to determine whether cell enrichment LBC is equally safe and effective as conventional cytology .

B.5.4 Diagnostic outcomes

Diagnostic outcomes required by the DAP will be reported where available from each RCT.

Test yield only without a reference method is a quite an inaccurate measure of true disease status (Strander 2007). Classifications of ASCUS, LSIL or HSIL define the rate of investigation in a screening population, and thus have clinical, personal and financial importance. Based on this and in line with the DAP, the rates of cytological detection are presented. Given that the Australian

reference to pLSIL is equivalent to ASCUS (Table 19), diagnostic outcomes for ASCUS abnormalities are reported in lieu of pLSIL. As specified in the DAP the rates of unsatisfactory slides are presented as an outcome separate from test yield.

Several studies have demonstrated that even strict participation in regular screening does not provide full protection from cervical cancer, indicating a need for the improved detection of HSIL (Strander 2007). As mentioned, cytological findings without a reference method are quite inaccurate, rather the essential objective of cervical screening programs are detecting and removing histologically confirmed high-grade lesions (CIN 2+, Table 4). The proportion of CIN lesions detected in each cytological category will put the test yield for each cytological category reported into context against the reference standard applied. A qualitative review of the correlation will be performed unless trial publications report the statistical comparisons of the correlation between cell enrichment or cell filtration LBC and conventional cytology.

Test sensitivity is the ability of a test to correctly identify those with the disease (true positive rate), whereas test specificity is the ability of the test to correctly identify those without the disease (true negative). Both are prevalence independent as their values are intrinsic to the test and do not depend on the disease prevalence of the population. To calculate the sensitivity and specificity, the number of patients who have the condition or do not have the condition ascertained via histopathology, needs to be obtained. There needs to be verification of negative results and fully verified positive results. However, often in a research context (because of cost and/or ethical concerns), only women with positive screen tests and none or only a few with negative screen tests are verified and this situation results in verification bias yielding inflated sensitivity and underestimated specificity (Arbyn 2009). Furthermore outcome terms such as sensitivity are not interchangeable across trials. There is sensitivity calculated for trials with follow-up of all patients including test negatives and there is the calculation of relative detection and sensitivity rates which are quoted as being equivalent to the ratio of the absolute sensitivities (Ronco 2006a; Ronco 2006b).

It is therefore proposed that increased, similar or hardly reduced positive predictive value for CIN 3+ is the proposed outcome of trials, in lieu of mortality, morbidity and incidence of cancer, for evaluating cervical cancer screening technologies (Arbyn 2009). Positive predictive value (PPV) and negative predictive value (NPV) are not intrinsic to the test—they depend on disease prevalence (Altmen & Bland 1994). However outcomes are reported in a comparative sense based on a population randomised to each arm within a trial. The disease prevalence is the same in each arm of the trial; therefore, within trial comparisons of PPV and NPV are valid. Disease prevalence between trials is not known and unlikely to be constant across the trials therefore the results will not be pooled. Nonetheless if consistent conclusions are drawn irrespective of the prevalence then

it is reasonable to assume that the conclusions from the comparative PPV results are applicable to various geographic settings. The DAP also requires that PPV and NPV are reported.

Sensitivity and specificity and positive and negative predictive values will therefore be relied on for a comprehensive comparison of the accuracy of the different sampling modalities.

The DAP requires that the ratio of true positive to false positive tests be reported as well as the incremental rate of true positive results. However the application of the ratio of TP:FP and the incremental rate of TP is relevant to a paired-sample trial design rather than a RCT (Davey et al. 2006 web appendix, Chock et al. 1997). Nonetheless, the ratio of true positive to false positive tests will be reported as will the incremental rate of true positive results as required by the DAP. The results are presented in Appendix B.

B.5.5 Change in management and patient outcomes

Any change in clinical management, such as change in further investigations or treatments avoided as reported in RCT publications, will also be documented, as will any patient reported outcomes.

B.5.6 Definition of composite outcome and quality of life measures presented in the submission

There are no composite outcomes or quality of life measures presented in the RCTs.

B.5.7 Statistical analyses

Data extraction

The outcomes reported in each study are presented as per the publication. Where the publications reported percentages only, raw numbers were determined from the number of patients on which each test was performed. Where only raw numbers were reported, percentages or rates were calculated from the number of patients reported to have had the test.

Given the randomised design of all the studies, the same numbers of lesions are expected in each of the arms except for random variation and differences in the actual detection attributed to differences in sensitivity. Therefore, we compared cell enrichment liquid-based cytology (LBC) and cell filtration LBC with conventional cytology (CC) on a relative, rather than an absolute, scale. Where available relative comparisons provided within a publication were reported. If not reported, the odds ratio (OR) or relative risk (RR)were calculated using the Intervention Review function in Review Manager (RevMan) Version 5(Attachment 4).

True positive and false positive values are extracted from correlation between cytological and histological data presented in the 'Proportion of CIN lesions detected in each cytological category' outcome. The PPV was then calculated using the equation described in Table 22.

The ratio of true positive to false positive rates are presented where both results are divided by the false positive rate (i.e. true positive relative to false positive rate of 1) so that that the incremental or additional true positive findings detected by each screening method can be reported.

Table 22 Sensitivity, specificity, positive and negative predictive value equations

	Condition: Positive	**Condition: Negative**	
Test: Positive	True positive (TP)	False positive (FP)	PPV=TP / (TP + FP)
Test: Negative	False negative (FN)	True negative (TN)	NPV=TN / (FN + TN)
	Sensitivity=TP / (TP + FN)	Specificity=TN / (FP + TN)	

Abbreviations: FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; TP, true positive; TN, true negative

Where verification of negative results was reported the sensitivity, specificity were calculated using the equation presented above (Table 22). The PPV, ratio of true positive to false positive and incremental rate of true positive results and comparisons were performed manually and are presented in Attachment 4.

Direct meta-analyses

At least two studies using one technology are necessary for meta-analysis. Pooling between cell enrichment LBC and cell filtration LBC was not performed based on the research questions (Table 6) that require comparisons between the technologies or with conventional cytology (CC).

For each study the percentage of slides classified as unsatisfactory, normal, ASCUS, LSIL, and HSIL+ by cell enrichment or cell filtration LBC and cc are pooled as was performed in the systematic review by Davey 2006. HSIL+ was chosen as a category rather than HSIL because some studies presented only HSIL and cancer combined (HSIL+) and others as HSIL and cancer separately. Where statistics were presented separately (for example HSIL and squamous cell carcinoma, SCC) they were combined to give a HSIL+ classification. Most publications report the OR and/or P value for differences between LBC and CC for each classification. Where it was not reported, the OR was calculated. In addition, as was performed by Davey 2006, the percentage of slides in each category by CC was subtracted from the percentage classified in each category by LBC, to give a difference in percentage (risk difference, RD) for each cytological classification. The RD was calculated using the Intervention Review function in Review Manager (RevMan) Version 5.

Meta-analyses were carried out on summary information obtained from published papers for cell enrichment (SurePath) studies and cell filtration (ThinPrep) studies. Results are dichotomous and as such are presented as RD and OR with 95% confidence intervals (CI). Zero cells cause problems with computation of standard errors, so any category with zero results were substituted with 0.5, or by subtracting 0.5 (Egger, Smith and Altman: Chapter 15 Statistical methods for examining heterogeneity and combining the results from several studies in meta-analysis, Systematic reviews in Healthcare 2003). Analyses were conducted using the random-effects method as required by the PBAC guidelines (version 4.3 2008). These differences are depicted in forest plots. Results were considered to be of statistical significance if $P < 0.05$, or to show a statistical trend if $0.1 > P \geq 0.05$. Heterogeneity was measured using a Chi^2 test for heterogeneity and the I^2 statistic. A significance level of 0.1 rather than 0.05 was used because the Chi^2 test has low power to detect whether heterogeneity was due to chance alone. To investigate heterogeneity, the I^2 statistic, given by the formula $[(Q - df)/Q] \times 100\%$, where Q is the Chi^2 statistic and df is its degrees of freedom, was used (Higgins 2011). This measure describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). The I^2 statistic quantifies the inconsistency across trials and enables an assessment of the impact of the heterogeneity on the meta-analysis. A value greater than 50% may be considered to indicate substantial heterogeneity (Higgins 2011). However, thresholds can be misleading since the importance of the inconsistency depends on several factors; these will be discussed where relevant.

Indirect analyses

The indirect analysis of cell enrichment LBC compared with cell filtration LBC (via CC) was completed for the following test yield and accuracy outcomes:

- proportion of unsatisfactory slides
- sensitivity
- specificity.

The outcomes of interest are dichotomous; they were analysed using OR and associated 95% CI.

Methods of indirect analysis

The unsatisfactory rates and accuracy of cell enrichment (E) LBC and cell filtration (F) LBC were indirectly compared using conventional (C) cytology as common comparator, using the following the method developed by Bucher 1997. The steps are as follows:

1. The summary measures (OR) and their precision are calculated for each study.

2. The indirect effect of the two treatments of interest and the associated 95% bilateral confidence interval are then calculated using the formulas below (presented for OR).

   $\ln(OR)F \text{ vs. } E = \ln(OR)F \text{ vs. } C - \ln(OR)E \text{ vs. } C$

   $SE(\ln(OR)F \text{ vs. } E) = [Var(\ln(OR)F \text{ vs. } C) + Var(\ln(OR)E \text{ vs. } C)]1/2$

The 95% CI around the logarithm of the indirect effect was calculated as:

$$\ln(OR)F \text{ vs. } E \pm 1.96 * (\ln(OR)F \text{ vs. } E)$$

Due to their mathematical characteristics, it was necessary to perform the analysis of the ORs on the logarithmic scale and then back-transform (exponentiate) the results at the end. This methodology follows the PBAC guidelines on indirect comparisons. Indirect comparison calculations are located in Attachment 4 .

B.6 Systematic overview of the results of the direct randomised trials

No mortality data were reported in the included RCTs. Although some trials reported CIN 3+ incidence, the numbers of cervical cancers or CIN 3+ detected were too few to enable statistical comparison. Therefore, results from each trial were pooled. The pooled OR (OR 0.69, 95% CI 0.50 to -0.95) indicates that the odds of detecting CIN3+ with conventional cytology is 31% lower than with LBC The comparison of rates of unsatisfactory slides indicate:

- Cell enrichment LBC is associated with a significant reduction in the proportion of unsatisfactory slides compared with CC (OR 0.15, 95% CI 0.11 to -0.21).
- Pooled results for cell filtration LBC showed a significant reduction in the proportion of unsatisfactory slides compared with CC (OR 0.44, 95% CI 0.27 to -0.73).
- There were significantly fewer unsatisfactory slides associated with cell enrichment LBC compared with cell filtration LBC (indirect OR [95% CI] 0.3586 (0.19, 0.69), P=0.0022).

There was significant heterogeneity between the cell enrichment trials as well as the cell filtration trials therefore results were not pooled. Generally,

- The results for the two cell enrichment LBC trials consistently indicate significantly lower rates of normal and significantly higher rates of ASCUS outcomes.
- The direction of the point estimates for each cytological outcome is more variable with the six cell filtration LBC trials limiting the ability to make any conclusions other than the test yield results are variable with cell filtration LBC. Although there is significantly more LSIL detected with cell filtration LBC in half the trials

Both trials that reported sensitivity and specificity for CIN 1+ outcomes based on an ASCUS+ index test resulted in consistent conclusions. Both showed that LBC (cell enrichment or cell filtration) was associated with significantly increased sensitivity for CIN 1+ (an increase of 4%) and significantly reduced specificity (less than 1% reduction with cell enrichment LBC and a 3.5% reduction with cell filtration LBC). An indirect comparison showed that there was no statistically significant difference between cell enrichment LBC and cell filtration LBC in sensitivity or specificity (P=0.4712 and P=0.1033, respectively).

All trials, except the NTCC trial, showed no significant difference in positive predictive value (PPV) between LBC (cell enrichment or cell filtration) and CC. As the test positivity threshold improved from ASCUS+ to HSIL+, the PPV for the detection of CIN 1+, CIN 2+ and CIN 3+ increased for both test preparation methods.

Where reported, most trials reported no significant impact on clinical management associated with LBC compared with CC.

There were no patient reported outcomes.

In regard to the comparison of manual versus automated review, the results of the MAVARIC trial are confounded due to triage HPV testing. The results from the study by Palmer 2012 showed that image-assisted screening is at least as good as screening with conventional cytology and is significantly more specific than manual screening.

In terms of accuracy (sensitivity, specificity and PPV) cell enrichment LBC is deemed to be comparable to conventional cytology. The differences between cell enrichment LBC and conventional cytology are confined to differences in detection of pLSIL (more with cell enrichment LBC) and differences in rates of unsatisfactory smears (more with conventional cytology).

Cell enrichment LBC is comparable with cell filtration LBC in terms of accuracy and superior in terms of reduction in unsatisfactory slides.

B.6.1 Efficacy data

Outcomes

The results of the direct comparison of LBC (cell enrichment and cell filtration) to CC, and automated and manual review of cytology from the randomised trials are presented in this section. Pooled results are presented where possible.

The correlation between the DAP-required outcomes and the outcomes available for analysis reported by the RCTs are summarised (Table 23). No patient outcomes were available from the RCT evidence used for the submission.

This section presents the comparative evidence for cell enrichment LBC versus CC followed by cell filtration LBC versus CC for each outcome. Comparisons between automated and manual review of cytology from the RCTs is presented after review of the trial outcomes.

Table 23 Summary of outcomes presented from the direct comparison of LBC and CC

	Beerman 2009	RODEO study	NTCC trial	NETHCON trial	Strander 2007	Macallini 2008	Obwegeser 2001	Ikenberg 2011
Comparison	**SurePath vs. CC**	**SurePath vs. CC**	**ThinPrep vs. CC**	**ThinPrep vs. CC**	**ThinPrep vs. CC**	**ThinPrep vs. CC**	**ThinPrep vs. CC**	**ThinPrep vs. CC**
Health outcomes								
Overall survival	-	-	-	-	-	-	-	-
Cervical cancer incidence	✓	-	✓	✓	✓	-	✓	-
Cervical cancer incidence	-	-	-	-	-	-	-	-
Diagnostic outcomes								
Unsatisfactory rates	✓	-	✓	✓	✓	✓	✓	-
Test yield	✓	✓	✓	✓	✓	✓	✓	-
Proportion of CIN lesions	✓	-	✓	✓	✓	✓	✓	-
Sensitivity/specificity	✓	-	✓	-	✓	✓	-	✓
Positive and negative predictive value	✓	-	✓	✓		✓	-	✓
True positive: false positive and incremental rate of true positive	✓	-	✓	✓	✓	✓	-	-
Change in management								
Impact on change in management	-	-	✓	✓	✓	✓	-	-
Patient outcomes								
Quality of life	-	-	-	-	-	-	-	-
Patient preference	-	-	-	-	-	-	-	-
Satisfaction, anxiety	-	-	-	-	-	-	-	-
Patient compliance	-	-	-	-	-	-	-	-
Safety, adverse events	-	-	-	-	-	-	-	-

Abbreviations: CC, conventional cytology; CIN, cervical intraepithelial neoplasia; LBC, liquid-based cytology

B.6.2 Health outcomes

Overall survival

No data available.

Incidence of cervical cancer (including glandular abnormalities, CIN 3+ and adenocarcinoma in situ)

Where available, the incidence of cervical cancer reported from each trial is presented.

Cell enrichment LBC vs. CC

Beerman 2009 reported the proportion of patients with cytologically-detected squamous cell carcinoma (SCC). There were four patients in the conventional cytology (CC) arm with reported SCC; however, only three resulted in a histological finding of CIN 1+, with one either determined to be normal or had no histology available. There were two patients in the liquid-based cytology (LBC) arm both of whom resulted in a histological finding of CIN 1+. Although there was a minor difference in the occurrence rate of SCCs between the study groups, this was not statistically significant (P=0.2068).

Cell filtration LBC vs. CC

The percentages of ASCUS, LSIL, and HSIL cytology samples showing CIN 3+ histology was very similar between cell filtration LBC compared with CC in the NTCC trial. The proportion of patients with CIN 3+ detected in the 25 to 34 years age cohort was 14/6002 (0.23%) and 22/5808 (0.38%) for cell filtration LBC and CC, respectively. For the 35 to 60 years cohort, the proportions were 31/16706 (0.19%) and 31/16658 (0.19%), respectively.

In the NETHCON trial the percentages of ASCUS, LSIL, and HSIL cytology samples showing CIN 3+ histology was very similar between cell filtration LBC compared with CC, 236/39010 (0.6%) and 183/46066 (0.4%), respectively. Overall, any difference in the percentage of cytology samples showing CIN 3+ histology between the cell filtration LBC compared with CC were reportedly not statistically significant (Siebers 2009, Table 3).

As reported by Strander 2007, six women in the study were diagnosed with invasive cancers, all of which were SCCs. Of those six women, five underwent CC sampling, and one had cell filtration LBC. The cell filtration LBC sample was inadequate, no diagnosis was provided, and the follow-up cytology demonstrated HSIL. Four of the index conventional Pap smears showed HSIL, but the fifth test was diagnosed as within normal limits, and there was an interval of nearly three years from this smear to the cancer diagnosis. This cancer was identified in the second search for follow-up histological outcomes (mean follow-up, 3 years and 7 months), and the other five cancers were identified in the first search (mean follow-up, 1.5 years).

Detection of one carcinoma was reported in the trial by Obwegeser 2001 for the CC arm.

The numbers of cervical cancers or CIN 3+ detected was too low to be compared statistically. The results from each trial were therefore pooled in an attempt to increase the power to detect any difference between LBC and CC. The results of the meta-analysis are provided in a forest plot (Figure 3). It is evident that the results varied between trials and there was a moderate degree of heterogeneity (I^2=61%). The removal of the Ronco 2006a trial had the largest impact on the I^2 statistic, its removal reduced the heterogeneity to 26% (Figure 4). The pooled OR (OR 0.69, 95% CI 0.50 to -0.95) indicates that the odds of detecting CIN3+ with conventional cytology is 31% lower than with LBC.

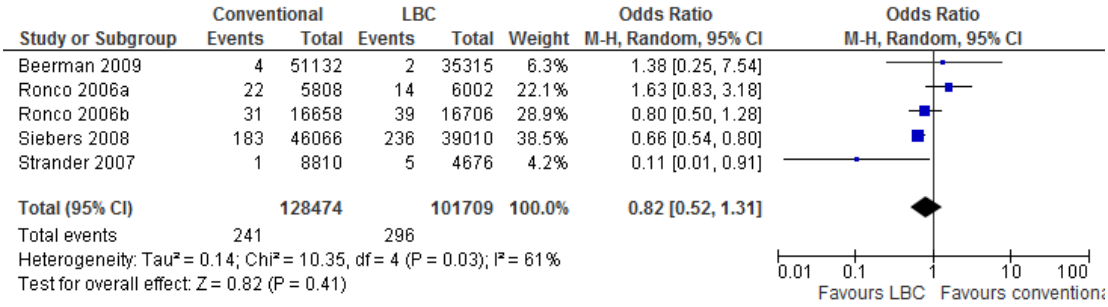

Figure 3 Forest plot: Proportion of cervical cancer (OR)
OR<1 indicates that LBC is better than CC

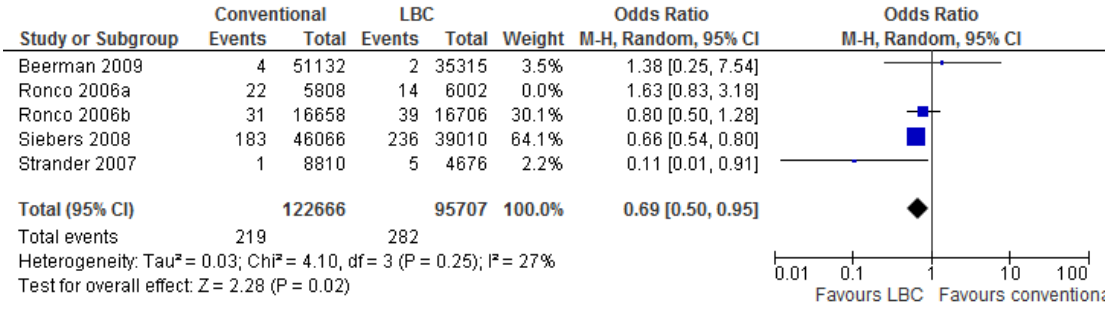

Figure 4 Forest plot: Proportion of cervical cancer (OR) with Ronco 2006a removed
OR<1 indicates that LBC is better than CC

Cervical cancer-specific mortality

No data available.

B.6.3 Diagnostic outcomes

Rates of unsatisfactory slides

Overall five of six trials showed a statistically significant reduction in the proportion of unsatisfactory slides reported for cell enrichment and cell filtration LBC compared with CC. The only trial that did not (Obwegeser 2001) implemented the unusual collection procedure that was not performed in any other study (refer to section B.4).

The results of the indirect comparison showed the odds of producing an unsatisfactory slide with cell enrichment LBC was 65 % lower compared with cell filtration LBC (indirect OR [95% CI] 0.3586 (0.19, 0.69), P=0.0022). The higher incidence of unsatisfactory slides seen with cell filtration LBC compared with cell enrichment LBC (0.3% versus 0.1%)is most likely a function of differences in the proprietary methodology for each platform (cell filtration LBC filter-based technology versus cell enrichment LBC density/sedimentation/enrichment process with 100% of the collected sample).

Cell enrichment LBC vs. CC

As reported by Beerman 2009, the percentage of unsatisfactory slides based on cell enrichment LBC was significantly fewer compared with CC screening (0.13% vs. 0.89%, OR 0.15, 95% CI 0.11 to 0.21, P ‹ 0.0001)(Table 24).

Table 24 Unsatisfactory rates—CC versus cell enrichment LBC: Beerman 2009

Trial	CC n/N(%)	LBC n/N(%)	Risk difference (95% CI)	Odds ratio (95% CI), P value
Beerman 2009	435/51,132 (0.89)	46/35,315 (0.13)	-0.01(-0.01,-0.01)	0.15 (0.11, 0.21), p < 0.0001
Source: Beerman 2009 p. 574				

Abbreviations: CC, conventional cytology; CI, confidence interval; LBC, liquid-based cytology
Risk difference and Odds Ratio manually calculated for the purposes of submission (Attachment 4);an OR <1 indicates performance of LBC is better than CC

Cell filtration LBC vs. CC

Across the entire NTCC trial, reported by Ronco 2007, the overall proportion of women with at least one unsatisfactory cytology result was significantly reduced with cell filtration LBC (2.57% vs. 4.11%, OR 0.62, 95% CI 0.55 to 0.68) (Table 25). The reduction was significantly larger for results considered unsatisfactory because of obscuring inflammation (OR 0.20, 95% CI 0.16 to 0.25) but not for other reasons (OR 1.09, 95% CI 0.95 to 1.24) (Table 25).

Table 25 Unsatisfactory rates—CC versus cell filtration LBC: Ronco 2007

Trial	CC n/N(%)	LBC n/N(%)	Risk difference (95% CI)	Odds ratio (95% CI)
Unsatisfactory cytology (any reason)	923/22,466 (4.11%)	583/22,708 (2.57%)	0.02 (0.01, 0.02)	0.62 [0.55, 0.68]
Unsatisfactory due to obscuring inflammation	483/22,466 (2.15%)	100/22,708 (0.44%)	0.02 (0.02, 0.02)	0.20 [0.16, 0.25]
Unsatisfactory for other reasons	440/22,466 (1.96%)	483/22,708 (2.13%)	-0.00 (-0.00,0.00)	1.09 [0.95, 1.24]
Source	Ronco 2007 Table 1			

Abbreviations: CI, confidence interval; CC, conventional cytology; LBC, liquid-based cytology
Odds Ratio and Risk difference manually calculated for the purposes of submission (Attachment 4); an OR <1 indicates performance of LBC is better than CC

In the NETHCON trial, reported by Siebers 2008, the unsatisfactory rate in the cell filtration LBC arm was significantly lower compared with CC screening (0.33% vs. 1.11%, OR 0.29, 95% CI 0.23 to 0.38).

Table 26 Unsatisfactory rates—CC versus cell filtration LBC, NETHCON trial: Siebers 2008

	CC N=39,010	LBC N=46,066	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
	n (%)	n (%)		
Unsatisfactory	434 (1.11)	153 (0.33)	0.30 (0.23, 0.38)	0.29 (0.22, 0.37)
Source: Siebers 2008 Table 2, Table 3				

Abbreviations: CI, confidence interval; CC, conventional cytology; LBC, liquid-based cytology; OR, odds ratio
An OR <1 indicates performance of LBC is better than CC

The number of inadequate smears reported by Strander 2007 was significantly lower with cell filtration LBC specimens compared to CC screening (0.3% vs. 0.7%, OR 0.47, 95% CI 0.27 to 0.82).

Table 27 Unsatisfactory rates—CC versus cell filtration LBC: Strander 2007

Trial	CC n[a]/N(%)	LBC n[a]/N(%)	Risk difference (95% CI)	Odds ratio (95% CI)
Inadequate smears	62/8810 (0.7)	14/4674 (0.3)	0.00 (0.00, 0.01)	0.47 (0.27, 0.82)
Source: Strander 2007 Table 2, p.287				

Abbreviations: CI, confidence interval; CC, conventional cytology; LBC, liquid-based cytology
a. manually back calculated from percentages presented in Strander 2007, Table 2. A rounding error is apparent within the percentage yield presented for Pap smear arm totalling 100.1% resulting in a back calculation total N of 8819, that is 0.001% off the reported N of 8810. For LBC calculations N determined as 4673 one less than the number reported in Table 1, 4674
An OR <1 indicates performance of LBC is better than CC

The number of inadequate smears reported by Maccallini 2008 was significantly lower with cell filtration LBC specimens compared to CC screening (1.3% vs. 4.3%, OR 0.29, 95% CI 0.22 to 0.40; Table 28). Most inadequacy reports at LBC were caused by the absence of endocervical cells (LBC=42/58, 72%), which was much less frequent among inadequacies at CC screening (CCT=7/178, 4%) (Maccallini 2008 p. 571).

Table 28 Unsatisfactory rates—CC versus cell filtration LBC: Maccallini 2008

Trial	CC n[a]/N(%)	LBC n[a]/N(%)	Risk difference (95% CI)	Odds ratio[b] (95% CI)
Inadequate smears	185/4299 (4.3)	57/4355 (1.3)	-0.03 (-0.04, -0.02)	0.29 (0.22, 0.40)
Source: Maccallini 2008 Table 1, Table 2, p.571				

a. n manually back calculated from percentages presented in Maccallini 2008, Table 2. N taken from Maccallini 2008, Table 1

b. Odds ratio presented is the crude value as the adjusted OR is not reported, an OR <1 indicates performance of LBC is better than CC

For assessment of adequacy, the Bethesda System 1991 (TBS 1991) criteria were used by Obwegeser 2001, but it was a visual estimate and cell counts were not performed. The TBS 1991 allowed the designation of slides as "'satisfactory but limited by (SBLB)…", or "unsatisfactory". A review of the specimen adequacy rates, according to SBLB or unsatisfactory, for various reasons is provided in Table 29.

There were significantly more unsatisfactory slides reported in the cell filtration LBC group (14, 1.4%) when compared with CC screening (0%). The unsatisfactory cell filtration LBC slides is primarily due to scant cellularity (14/14, 100%) but also obscuring blood (8/14, 57%).

The primary reason for SBLB slides in the cell filtration LBC group (55/997, 5.5%) compared with CC screening (25/1002, 2.5%) was "no endocervical cells" (30/55, 55% vs. 14/25, 56%) and "scant cellularity" (16/55, 29% vs. 3/25, 12%).

Table 29 Specimen adequacy (unsatisfactory and SBLB rates)[a]—CC versus cell filtration LBC: Obwegeser 2001

Trial	Conventional n/N(%)	LBC n/N(%)	Risk difference (95% CI)[c]	Odds ratio (95% CI)[c]
Total unsatisfactory	0/1002 (0)	14/997 (1.4)	-0.01 (-0.02,-0.01)	29.56 [1.76, 496.21]
Scant cellularity	0 (0)	14 (100)	NC	NC
Obscuring blood	0 (0)	8[b] (57)	NC	NC
Total SBLB	25/1002 (2.5)	55/997 (5.5)	-0.03(-0.05,-0.01)	2.28 [1.41, 3.69]
Scant cellularity	3 (12)	16 (29)	NC	NC
Obscuring blood	1 (4)	3 (5.5)	NC	NC
No endocervical cells	14 (56)	30 (55)	NC	NC
Obscuring inflammation	3 (12)	5 (9)	NC	NC
Cytolysis	4 (16)	1 (1.8)	NC	NC
Source: Obwegeser 2001, Table 2				

Abbreviations: LBC, liquid-based cytology; NC, not calculated; SBLB, significant but limited by; CI, confidence interval

a. For the assessment of adequacy The 1991 Bethesda System criteria were used, however a visual estimate was used and cell counts were not performed
b. 8 of the 14 unsatisfactory slides had both scant cellularity and obscuring blood
c. Risk Difference and Odds Ratio manually calculated for the purposes of submission(Attachment 4); an OR <1 indicates performance of LBC is better than CC

Meta-analysis

Figure 5 and Figure 6 provide the results of the meta-analysis of the proportion of unsatisfactory slides.

Cell enrichment LBC is associated with a significant reduction in the proportion of unsatisfactory slides compared with CC (OR 0.15, 95% CI 0.11 to -0.21).

The pooled results for cell filtration LBC showed a significant reduction in the proportion of unsatisfactory slides compared with CC (OR 0.44, 95% CI 0.27 to -0.73).

A $\chi 2$ test for heterogeneity among cell filtration studies included in the meta-analysis revealed an I^2 of 96% with P=< 0.00001, indicating significant heterogeneity among these studies. Based on a sensitivity analysis whereby one and then two studies were removed at a time, there were no key studies that were the major driver of the heterogeneity (refer to RevMan database in Attachment 4). Nonetheless virtually all trials show a significant reduction in the rate of unsatisfactory slides with cell filtration LBC. Factors associated with heterogeneity in other systematic reviews of unsatisfactory rates include year of publication and to a greater extent country (Fontaine 2012). Other factors that could contribute to heterogeneity are the classification system used and populations screened.

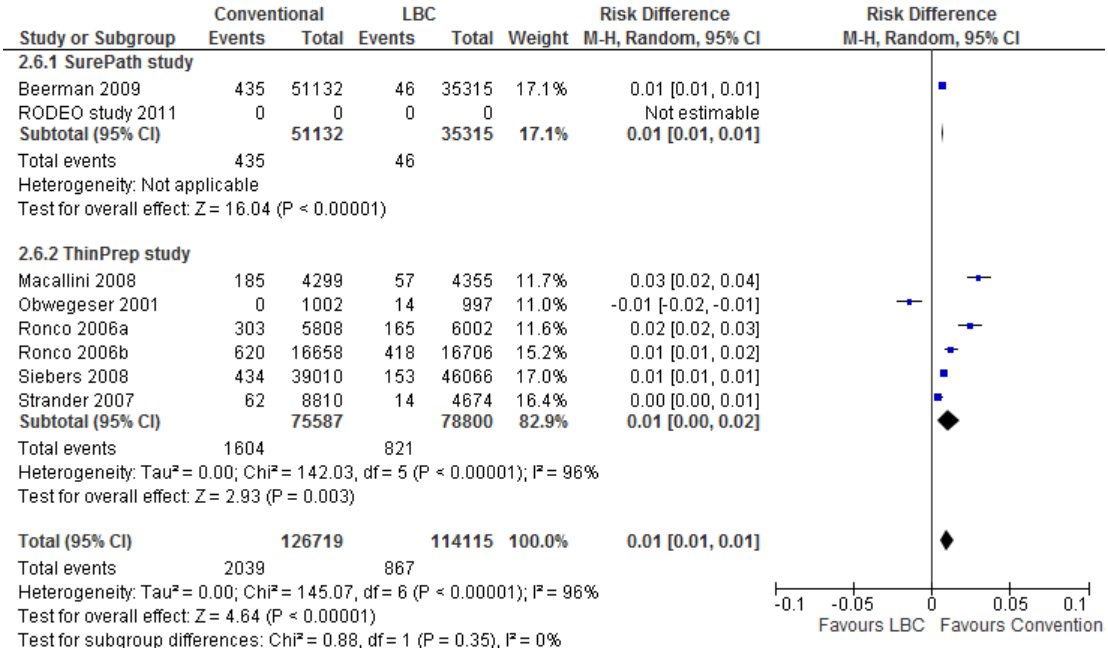

Figure 5 Forest plot: Proportion of unsatisfactory cytology (RD)

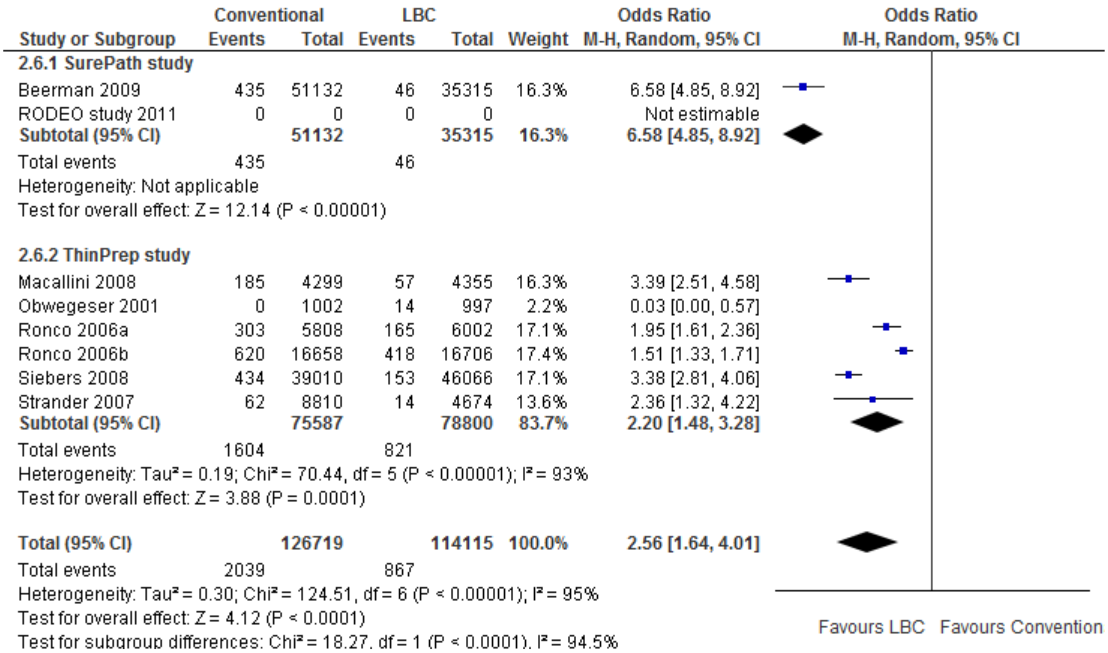

Figure 6 Forest plot: Proportion of unsatisfactory cytology (OR)
An OR <1 indicates performance of LBC is better than CC

To further explore the heterogeneity a review of the baseline proportion of unsatisfactory slides for the conventional cytology arm in each trial was performed according to year(s) and countries in which the study took place.

There was considerable variation in the proportion of unsatisfactory slides among jurisdictions, with Italy representing the highest rate of unsatisfactory slides (4.1% to 4.3%) and Switzerland showing no unsatisfactory slides (0%) (Table 30).

This is partially attributable to variations in adequacy criteria compared with The Bethesda System. In particular the Obwegeser study in Switzerland categorised cytological findings according to the TBS 1991 system which allowed the designation of slides as "satisfactory but limited by (SBLB)…", or "unsatisfactory". The results presented below represent unsatisfactory slides only (0/1002, 0.0%), when slides classified as SBLB are combined with unsatisfactory slides for the conventional cytology arm, the result is 2.5% (25/1002). Furthermore, Obwegeser 2001 details a very different method of sample collection as discussed above (section B.4) which likely reduced the number of unsatisfactory smears.

Table 30 Unsatisfactory cervical cytology smear rates with conventional cytology by year and location

Study author	Year	Total number of CC smears	Number of unsatisfactory smears	Percentage of unsatisfactory smears	Location of study
Beerman 2009	1997–2002	435	51132	0.9%	Holland
Ronco 2007	2002–2003	923	22466	4.1%	Italy
Strander 2007	2002–2003	62	8810	0.7%	Sweden
Siebers 2008	2003–2006	434	39010	1.11%	Netherlands
Maccallini 2008	2001–2002	185	4299	4.3%	Italy
Obwegeser 2001	1998	0	1002	0.0%	Switzerland

Abbreviations: CC, conventional cytology

The cell filtration LBC study by Strander 2007 has the closest baseline rate of unsatisfactory slides (0.7% in CC) compared with the cell enrichment LBC trial reported by Beerman 2009 (0.9% in CC) (Table 30). Given the results of the pooled analysis of cell filtration trials cannot be used due to heterogeneity and the similarity in the trial designs between Beerman 2009 and Strander 2007, only these two trials were included in the indirect comparison of cell enrichment LBC and cell filtration LBC in the proportion of unsatisfactory slides reported. Furthermore, because of the heterogeneity the indirect comparison is performed on a relative scale rather than an absolute. The validity of using one trial to represent cell filtration LBC is further justified based on the similarity

of results upon comparison of the pooled OR from the cell filtration trials (OR 0.44, 95% CI 0.27 to -0.73) and that for Strander 2007 (OR 0.42, 95% CI 0.24 to -0.76).

It is noted however that despite the inability to pool the results a review of the forest plots indicates that all trials, except Obwegeser 2001, irrespective of sample size and baseline rate of unsatisfactory slides demonstrates a significant reduction in unsatisfactory slides with LBC.

Indirect comparison

The results of the indirect comparison of the proportion of unsatisfactory slides with cell enrichment LBC and cell filtration LBC showed that there was a statistically significant difference between cell enrichment LBC and cell filtration LBC (indirect OR [95% CI] 0.3586 (0.19, 0.69), P=0.0022) (Table 31). The higher incidence of unsatisfactory slides seen with cell filtration LBC compared with cell enrichment LBC (0.3% versus 0.1%) is most likely a function of differences in the proprietary methodology for each platform (cell filtration LBC filter-based technology versus cell enrichment LBC density/sedimentation/enrichment process. Differences are also encountered when collecting the sample; cell filtration LBC requires the collector to rinse the collection device in the liquid media followed by disposal of the collection device. In contrast, the cell enrichment LBC collection device is placed in the media and sent to the laboratory for processing. This difference has been demonstrated to account for up to 37% loss of the cell filtration LBC sample in a study by Bigras 2003. These preparatory differences represent a significant technical difference (Fontaine 2012).

Table 31 Summary of results of the indirect comparison of cell enrichment LBC and cell filtration LBC proportion with unsatisfactory slides

	Trial of cell enrichment LBC			Trial of cell filtration LBC			Indirect estimate of effect OR [95% CI]
	Treatment effect OR (95% CI)	Cell enrichment LBC, %(n/N)	CC, %(n/N)	CC, %(n/N)	Cell filtration LBC, %(n/N)	Treatment effect OR (95% CI)	
Beerman	0.15 (0.11, 0.21)	0.1% (46/35315)	0.9% (435/51132)				0.3586 (0.19, 0.69), P=0.0022
Strander				0.7% (62/8810)	0.3% (14/4674)	0.42 (0.24, 0.76)	
Source	Beerman 2009 p. 574, Attachment 4			Strander 2007 Table 2, p.287, Attachment 4			

Abbreviations: CC, conventional cytology; CI, confidence interval; LBC, liquid-based cytology; OR, odds ratio
An indirect OR <1 indicates performance of cell enrichment LBC is better than cell filtration LBC

Test yield

A cytologic finding only, without a reference method is a quite an inaccurate measure of true disease status (Strander 2007). However, in line with the DAP required outcomes, the rates of cytological detection are presented first by individual study followed by a meta-analysis of data for

each cytological outcome. The rates of unsatisfactory slides reported for each arm of each study is not reported within the test yield outcome as it is reported as unsatisfactory slide outcome.

Cell enrichment LBC vs. CC

In Beerman 2009, the percentage of satisfactory specimens containing endocervical cells was higher in cell enrichment LBC compared to CC screening (89.01% vs. 86.17%, P < 0.0001; Table 32). Significantly more samples were classified as ASCUS with cell enrichment LBC than with CC (2.07% vs. 0.87%; P < 0.0001), while the percentages of LSIL and HSIL lesions and (either adeno-, or squamous cell) carcinoma were similar between the cohorts.

Table 32 Test yield comparison (by cytology)—CC versus cell enrichment LBC: Beerman 2009

	Conventional N=51,132	LBC N=35,315	P value[a]
	n (%)	n (%)	
Within normal limits	49856 (97.47)	34219 (96.9)	<0.0001
Abnormal (ASCUS or higher)	845 (1.65)	1052 (2.98)	<0.0001
-ASCUS	443 (0.87)	730 (2.07)	<0.0001
-LSIL	110 (0.22)	94 (0.27)	0.1284
-HSIL	288 (0.56)	226 (0.64)	0.1493
Squamous cell carcinoma	4 (0.008)	2 (0.006)	0.2068
Endocervical cells	44411 (86.17)	32328 (89.01)	<0.0001[b]
Source Beerman 2009 Table 2			

Abbreviations: AGUS, atypical glandular cells of undetermined significance; ASCUS, atypical cells of undetermined significance; CC, conventional cytology; HSIL, high-grade squamous intraepithelial lesion; LBC, liquid-based cytology; LSIL, low grade squamous intraepithelial lesion

a. P value was given by Cochran-Mantel-Haenszel test controlling for abnormal cytology (ASCUS, LSIL, HSIL)
b. P value determined using Chi^2 test

In the RODEO study, the percentage of normal or negative specimens was lower in the cell enrichment LBC cohort compared to CC screening (97.9% vs. 98.9%; Table 33). Significantly more samples were classified as ASCUS with cell enrichment LBC than with CC (0.7% vs. 0.1%; P < 0.01) as well as more LSIL (0.7% vs. 0.3%; P < 0.01), while the percentages of HSIL was not significantly different. The authors report that despite the two fold increase in the number of HSIL cases reported with LBC (0.4% vs. 0.2%; P=0.186) they did not reach significance due to sample size. It appears that the study therefore recruited 3799 more patients from the high risk cohort. Significantly more samples were classified as abnormal in the cell enrichment LBC cohort than in the CC cohort. (22.1% vs. 18.1%, P=0.003), driven by significantly more cases of LSIL (4.9% vs. 2.6%; P < 0.001) and HSIL (8.2% vs. 6.2%; P=0.017).

It was noted that the total number of cases calculated based on percentage of ASCUS, LSIL and HSIL reported did not equal the total number of abnormal cases reported, and the abstract reports that no invasive cancer was detected. It is uncertain whether the remaining abnormal cases might reflect glandular changes or otherwise, nonetheless there were a significantly increased number of abnormal cases reported in the cell enrichment LBC cohort driven by an increase in the percentage of ASCUS and LSIL compared to the CC cohort.

Table 33 Test yield comparison (by cytology)—CC versus LBC (cell enrichment): RODEO study (Longatto-Filho 2011; Fregnani 2012)

	CC N=6047	LBC N=6001	P value[b]
	n (%)	n (%)	
Normal	5981 (98.9)	5872 (97.9)	NR
Abnormal cases	61 (1.0)	127 (2.1)	0.001
ASCUS	6[a] (0.1)	42[a] (0.7)	<0.001
LSIL	18[a] (0.3)	42[a] (0.7)	<0.001
HSIL	12[a] (0.2)	24[a] (0.4)	0.186
Screening in high risk population			
	Conventional N=1755	LBC N=2044	
Abnormal	314 (18.1)	447(22.1)	0.003
LSIL	46 (2.6)	100 (4.9)	<0.001
HSIL	109 (6.2)	168 (8.2)	0.017
Source: Longatto-Filho 2011; Fregnani 2012			

Abbreviations: ASCUS, atypical cells of undetermined significance; CC, conventional cytology; CI, confidence interval; HSIL, high-grade squamous intraepithelial lesion; LBC, liquid-based cytology; LSIL, low grade squamous intraepithelial lesion; NR, not reported

a. n value back calculated from percentages presented in both Longatto-Filho 2011 and Fregnani 2011
b. Extracted from the publication

Cell filtration LBC vs. CC

Ronco 2006a and Ronco 2006b represent two cohorts from the same RCT, the New Technologies for Cervical Cancer screening (NTCC), 25 to 34 years of age and 35 to 60 years, respectively. The difference between the subgroups was the means with which cytology results were followed up to ascertain those with cervical neoplasia (discussed in section B.3). Another difference within the study was that the cell filtration LBC specimen underwent testing for HPV. Although slides were read without knowledge of the results for HPV testing there is an uneven bias introduced regarding follow-up practices for the LBC arm of the study.

Ronco 2007 presents analyses that did not consider the results of cytological and histological tests that were carried out because of a positive HPV test result in the presence of normal cytology.

These tests would not have been carried out if cytology alone was used. The authors report results for both cohorts (25 to 34 years and 35 to 60 years) combined which are presented below.

The proportion of women with ASCUS or AGUS, LSIL and HSIL+ was significantly increased with cell filtration LBC (Table 34). The increase in ASCUS or AGUS associated with cell filtration LBC was larger in women aged 25 to 34 years (relative frequency 1.92, 95% CI 1.56 to 2.36, P=0.0199) than in women aged 35 to 60 years (1.44, 95% CI 1.27 to 1.64).

Test findings for glandular lesions were only reported as a combined category of ASCUS-or AGUS, so glandular test results could not be separated from squamous findings.

Table 34 Test yield comparison (by cytology)—CC versus cell filtration LBC, NTCC trial age 24 to 60 years: Ronco 2007

	CC N=22,466	LBC N=22,708	Relative frequency (95% CI)[a]
	n (%)	n (%)	
ASCUS or AGUS	514 (2.29)	815 (3.59)	1.57(1.41 ,1.75)
ASCUS or AGUS (25 to 34 years)	*NR*	*NR*	*1.92 (1.56, 2.36) (P=0.0199)*
ASCUS or AGUS (35 to 60 years)	*NR*	*NR*	*1.44 (1.27, 1.64)*
-LSIL	283 (1.26)	527 (2.32)	1.84(1.60, 2.13)
-HSIL+	58 (0.26)	92 (0.41)	1.57(1.13, 2.18)
Source: Ronco 2007 Table 1, Table 2 p.3			

Abbreviations: AGUS, atypical glandular cells of undetermined significance; ASCUS, atypical cells of undetermined significance; CI, confidence interval; HSIL, high-grade squamous intraepithelial lesion; LSIL, low grade squamous intraepithelial lesion.

a. Ratio of percentages. LBC compared with conventional cytology

In the NETHCON trial reported by Siebers 2008, the number of practices in the trial was evenly distributed over the two study arms (122 in the LBC arm and 124 in the CC arm). However, the overall distribution of participants between the study arms was unbalanced, with more samples examined in the cell filtration LBC arm (n=49,222) than in the CC arm (n=40,562). This was mainly caused by an uneven distribution of LBC and CC slides at one site (57.7% LBC compared with 42.3% CC), due to allocation, by chance, of six large (n=1,000) practices to LBC compared with only one to the CC arm. To adjust for potentially confounding variables (age, site, urbanisation level, and experience with LBC) a logistic regression was used to compare study arms.

The proportion of slides that were classified as normal was not reported for the NETHCON trial. However, given that all slides would be classified to one of five categories (unsatisfactory, normal, ASCUS+AGUS, LSIL and HSIL+) the number was estimated by summing the proportions of

reported slides and subtracting from 100 (i.e. 100-[% unsatisfactory+% ASCUS+AGUS +% LSIL +%HSIL+]).

Based on the 95% confidence interval around the crude and adjusted OR, there was no significant difference between the proportions of slides in each cytological category between the study arms (Table 35).

Test findings for glandular lesions were only reported as a combined category of ASCUS-or AGUS, so glandular test results could not be separated from squamous findings.

Table 35 Test yield comparison (by cytology)—CC versus cell filtration LBC; NETHCON trial, Siebers 2008

	CC N=39,010	LBC N=46,066	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
	n (%)	n (%)		
Normal	37477 (96.07)[c]	44670 (96.96) [c]	NR	NR
ASCUS/atypical glandular cells	700 (1.81)	769 (1.67)	0.92 (0.77,1.10)	NR
LSIL	154 (0.40)	191 (0.42)	1.04 (0.82, 1.33)	NR
HSIL+	245 (0.64)	283 (0.62)	0.97 (0.77, 1.22)	0.96 (0.79, 1.18)
ASCUS+	1099 (2.85)	1243 (2.71)	0.95 (0.82, 1.10)	0.97 (0.88, 1.07)
LSIL+	399 (1.03)	474 (1.03)	1.00 (0.83, 1.20)	0.98 (0.84, 1.15)
Source: Siebers 2008 Table 2 and Table 3				

Abbreviations: ASCUS, atypical cells of undetermined significance; ASCUS+, atypical cells of undetermined significance/atypical glandular cells or more severe; CC, conventional cytology; CI, confidence interval; HSIL, high-grade squamous intraepithelial lesion; HSIL+, high-grade squamous intraepithelial lesion or more severe; LBC, liquid-based cytology; LSIL, low grade squamous intraepithelial lesion; LSIL+, low grade squamous intraepithelial lesion or more severe; NR, not reported; OR, odds ratio
An OR <1 indicates performance of LBC is better than CC

a. Per-Protocol Analysis: crude rates of cytologic test positivity and unsatisfactory samples of LBC compared with conventional method by category of cytologic abnormality and unsatisfactory tests and odds ratios of LBC compared with conventional cytology, taking the cluster design into account.
b. Per-Protocol Analysis: Adjusted odd ratios taking the intracluster coefficient into account. Adjusted for age, study site, urbanisation level and study period.
c. The number of normal slides was estimated as follows: 100-[% unsatisfactory+% ASCUS+AGUS +% LSIL +% HSIL+])

Strander 2007 reported on findings from 13,484 smears entered into their trial (8810 CC smears and 4674 cell filtration LBC samples). There was an uneven distribution of women to both methods for reasons discussed in section B.3. These aberrations occurred randomly.

There was no significant difference in the ASCUS rates between the cell filtration LBC group compared with the CC group (1.7% vs. 1.4%, adjusted OR 1.27, 95% CI 0.95 to 1.70) (Table 36). The number of LSIL was significantly higher with cell filtration LBC compared with CC (1.7% vs. 1.0%,

adjusted OR 1.99, 95% CI 1.44 to 2.76) as was the number of HSIL findings (0.8% vs. 0.5%, adjusted OR 1.07, 95% CI 1.07 to 2.66).

Table 36 Test yield comparison (by cytology)—CC versus cell filtration LBC: Strander 2007

	Conventional N=8810	LBC N=4674	Adjusted OR (95% CI)
	n[a] (%)	n[a] (%)	
Benign	8502 (96.5)	4464 (95.5)	0.74 (0.62, 0.90)
ASCUS	123 (1.4)	79 (1.7)	1.27 (0.95, 1.70)
LSIL	88 (1.0)	79 (1.7)	1.99 (1.44, 2.76)
HSIL	44 (0.5)	37 (0.8)	1.07 (1.07, 2.66)
Source: Strander 2007 Table 2			

Abbreviations: ASCUS, atypical cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LBC, liquid-based cytology; LSIL, low grade squamous intraepithelial lesion; OR, odds ratio; CI, confidence interval

a. n manually back calculated from percentages presented in Strander 2007, Table 2. A rounding error is apparent within the percentage yield presented for Pap smear arm totalling 100.1% resulting in a back calculation total N of 8819, that is 0.001% higher than the reported N of 8810. For LBC calculation N determined as 4673 one less than the number reported in Table 1, 4674.
An OR <1 indicates performance of LBC is better than CC

Maccallini 2008 did not report the proportion of slides that were classified as normal. However given that all slides would be classified to one of five categories (unsatisfactory, normal, ASCUS+AGUS, LSIL and HSIL+) the number was estimated by summing the proportions of reported slides and subtracting from 100 (i.e. 100-[% unsatisfactory+% ASCUS+AGUS +% LSIL +%HSIL+]). As reported by Maccallini 2008, there were significantly lower numbers of ASCUS+AGUS reported with cell filtration LBC compared with CC (2.5% vs. 3.7%, OR 0.67, 95% CI 0.52 to 0.86, P < 0.01; Table 37). This caused a higher referral rate with CC compared with cell filtration LBC (5.0% vs. 4.1%, P=0.04). A small, non-significant excess of LSIL and HSIL+ reports was observed in the cell filtration LBC arm compared with CC (0.9% vs. 0.8%, P=0.47 and 0.7% vs. 0.5%, P=0.37, respectively).

Test findings for glandular lesions were only reported as a combined category of ASCUS-or AGUS, so glandular test results could not be separated from squamous findings.

Table 37 Test yield comparison (by cytology)—CC versus cell filtration LBC: Maccallini 2008

	Conventional N=4299	LBC N=4355	P value
	n[a] (%)	n[a] (%)	
Normal	3899 (90.7)[b]	4120 (94.6)[b]	NR
ASCUS+AGUS	159 (3.7)	109 (2.5)	< 0.01
LSIL	34 (0.8)	39 (0.9)	0.47
HSIL +	21 (0.5)	30 (0.7)	0.37
Colposcopy recommended	215 (5.0)	179 (4.1)	0.04
Source: Maccallini 2008 Table 2			

Abbreviations: ASCUS+AGUS, atypical cells of undetermined significance and atypical glandular cells of undetermined significance; CI, confidence interval; HSIL+, high-grade squamous intraepithelial lesion or more severe; LBC, liquid-based cytology; LSIL, low grade squamous intraepithelial lesion; NR, not reported

a. n manually back calculated from percentages presented in Maccallini 2008, Table 2

b. the number of normal slides was estimated as follows: 100-[% unsatisfactory+% ASCUS+AGUS +% LSIL +%HSIL+])

Obwegeser 2001 reported that over 90% of slides in each group were found to be within normal limits; there were no significant differences between cell filtration LBC and CC. There was no significant difference between the cell filtration LBC group compared with CC for the cytologic diagnoses of ASCUS/AGUS, LSIL, HSIL, or carcinoma (Table 38).

Test findings for glandular lesions were only reported as a combined category of ASCUS-or AGUS, so glandular test results could not be separated from squamous findings.

Table 38 Test yield comparison (by cytology)—CC versus cell filtration LBC at both the laboratory of the investigator and the independent rescreen results: Obwegeser 2001

	Conventional N=1002	LBCN=997	P value[a]
	n (%)	n (%)	
Within normal limits	931 (92.9)	924 (92.7)	NS
ASCUS/AGUS	14 (1.4)	10 (1.0)	NS
LSIL	37 (3.7)	47 (4.7)	NS
HSIL	19 (1.8)	16 (1.6)	NS
Carcinoma	1 (0.1)	0 (0.0)	NS
LSIL+	57 (5.6)	63 (6.3)	NS
ASCUS/AGUS+	71 (7.0)	73 (7.3)	NS
Source: Obwegeser 2001, Table 1			

Abbreviations: ASCUS, atypical cells of undetermined significance; ASCUS+, atypical cells of undetermined significance/atypical glandular cells or more severe; CI, confidence interval; HSIL, high-grade squamous intraepithelial lesion; LBC, liquid-based cytology; LSIL, low grade squamous intraepithelial lesion; LSIL+, low grade squamous intraepithelial lesion or more severe; NS, not significant

a. P Value < 0.05 was used as the criterion for statistical significance by Obwegeser 2001.

Meta-analysis

The forest plots displaying the meta-analysis for RD and OR per cytological outcome is displayed in Figure 7 to Figure 14.

A χ^2 test for heterogeneity among cell enrichment and cell filtration studies included in the meta-analysis revealed an I^2 of › 50% for the majority of outcomes indicating significant heterogeneity among these studies. Based on a sensitivity analysis whereby one and then two studies and so on were removed at a time, there were no key studies that were consistently the major driver(s) of the heterogeneity (refer to Attachment 4).Therefore, a meta-analysis of the test yield results for the two for cell enrichment LBC and six for cell filtration LBC studies is not used to draw conclusions.

Some of the factors that likely contributed to heterogeneity are the uneven distribution of patients within trials, as well as the different collection tools and techniques and the classification system used in the trials (refer to section B.3, B.4 and B.5). It was also reported in section B.4 that for most trials the implementation of LBC was new and may theoretically result in better performance and therefore higher detection rates (Maccallini 2008). To further explore the heterogeneity, a review of the test yield outcome for each cytological category for the conventional cytology arm in each trial was performed (Table 39). There was considerable variation in the distribution of cytological outcomes for each classification in the conventional arms from the RCTs. An indirect comparison could not be performed for any test yield outcomes between cell enrichment LBC and cell filtration LBC due to the variability in test yield outcomes in the conventional cytology arm (common

reference) across trials. In this instance, unlike the rate of unsatisfactory outcomes, there were no cell filtration LBC trials with baseline rates of Normal, ASCUS (pLSIL), LSIL or HSIL outcomes that were comparable with either of the cell enrichment LBC trials.

Table 39 Test Yield with conventional cytology by study

Study author	Normal	ASCUS	LSIL	HSIL	Source
Beerman 2009	97.47%	0.87%	0.22%	0.56%	Table 32
RODEO trial	98.9%	0.1%	0.3%	0.2%	Table 33
Ronco 2007	NR	2.29%	1.26%	0.26%	Table 34
Siebers 2008	96.07%	1.81%	0.40%	0.64%	Table 35
Strander 2007	96.5%	1.4%	1.0%	0.5%	Table 36
Maccallini 2008	90.7%	3.7%	0.8%	0.5%	Table 37
Obwegeser 2001	92.9%	1.4%	3.7%	1.8%	Table 38

There are fewer trials on which to make the conclusion of comparative test yield outcomes between cell enrichment LBC and conventional cytology compared with the number of cell filtration LBC versus conventional cytology trials. Furthermore the baseline test yield results vary between trials as does the relative difference. It is important to recognise that the differences in test yield outcomes between LBC and conventional cytology are very small with 0.04 (4%) being the largest RD reported in an individual trial (Macallini 2008). Overall any conclusions regarding differences in test yield outcomes between the tests should be viewed with caution.

The results for the two cell enrichment LBC trials consistently indicate significantly lower rates of normal and significantly higher rates of ASCUS outcomes. Unlike the Beerman 2009 trial the RODEO trial reports a significant increase in LSIL detected with cell enrichment LBC versus conventional cytology. However the sample size for the RODEO trial is much smaller than the Beerman 2009 trial and it represents a different geographical location (remote areas of Brazil) and type of health service (recruitment through mobile units, refer to section B.4). This is the likely reason for the heterogeneity noted upon pooling the cell enrichment LBC trials and provides a rationale for using the test yield conclusions from the Beerman 2009 trial.

The direction of the point estimates for each cytological outcome is more variable with the six cell filtration LBC trials. There is more LSIL detected with cell filtration LBC compared with conventional cytology in half of the cell filtration trials however no conclusions regarding test yield outcomes can be made for cell filtration trials.

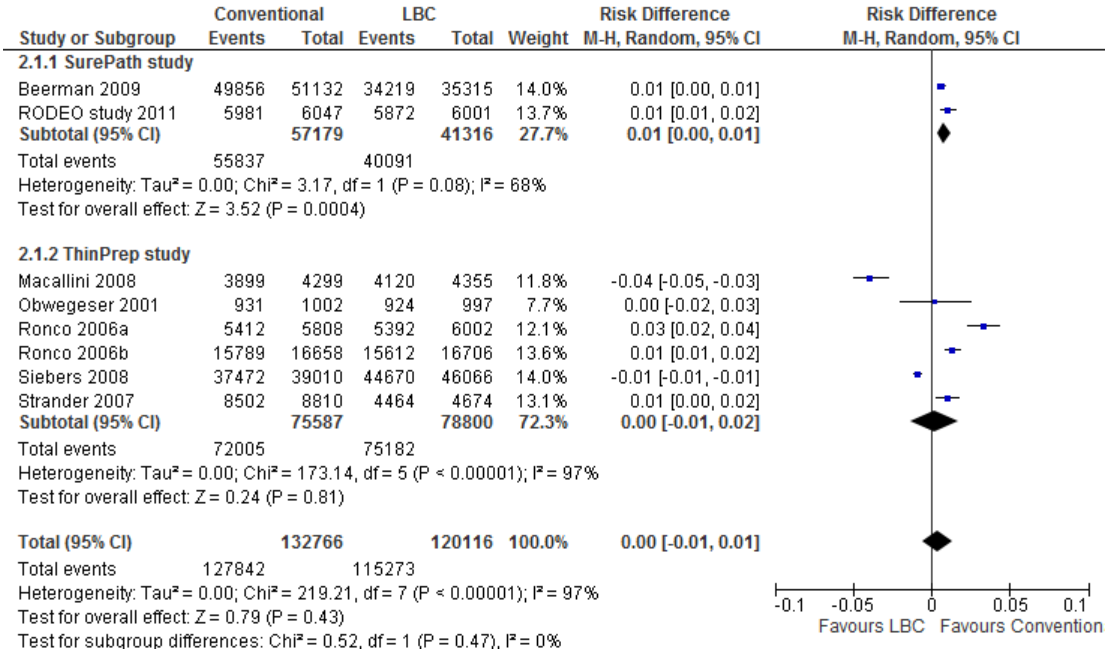

Figure 7 Forest plot: Proportion of normal cytology (RD)

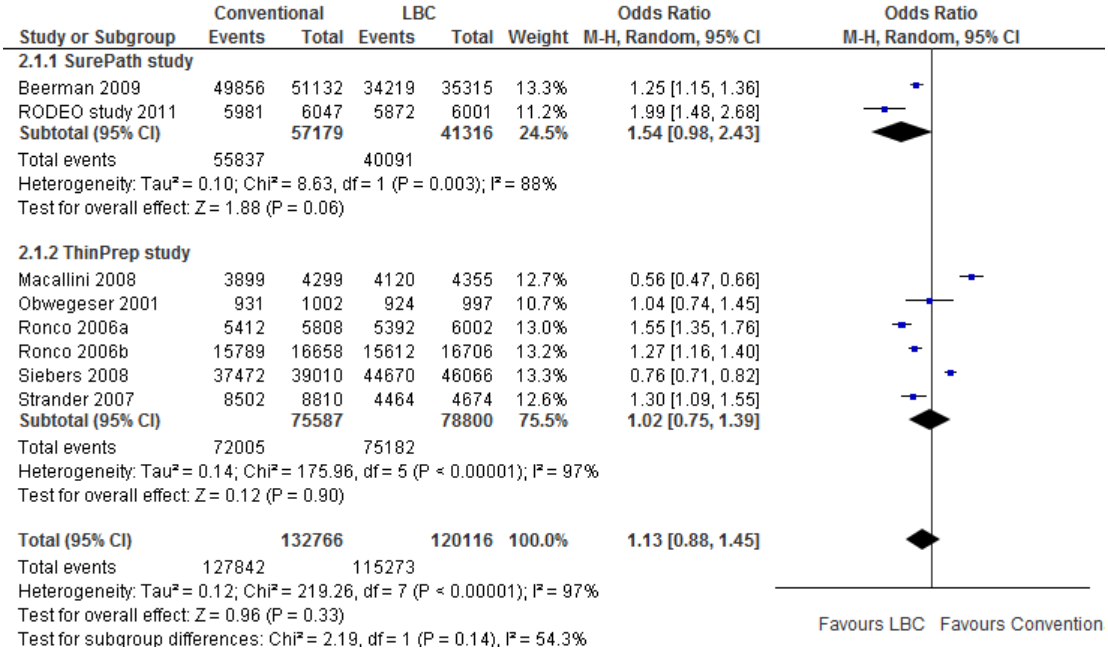

Figure 8 Forest plot: Proportion of normal cytology (OR)

An OR<1 indicates a greater proportion of findings with LBC compared with conventional cytology

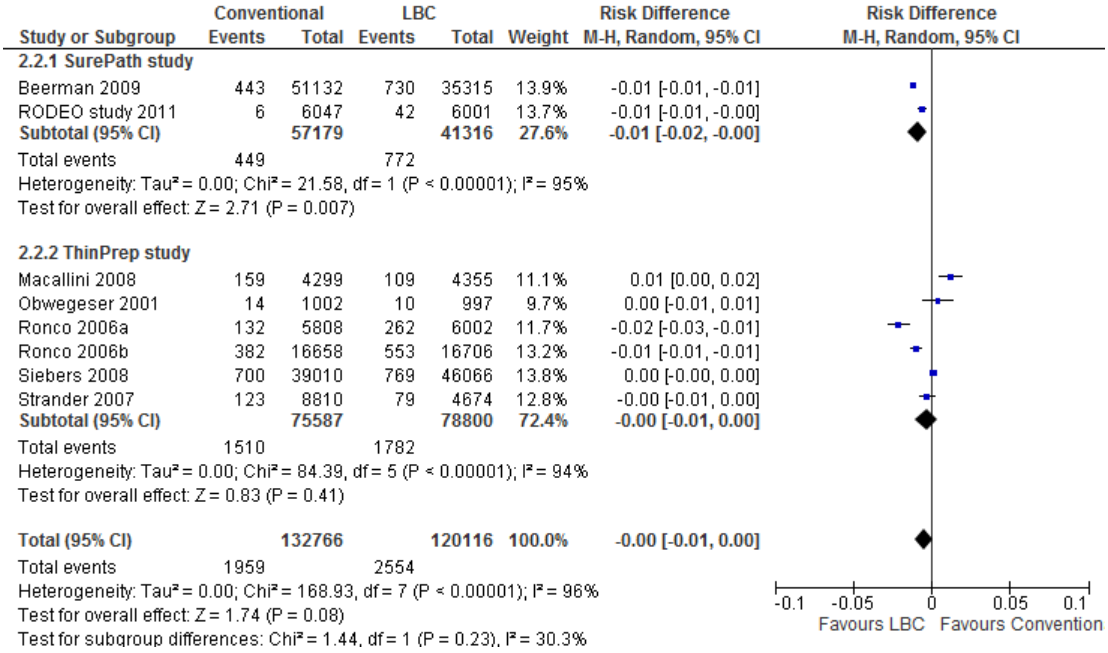

Figure 9 Forest plot: Proportion of ASCUS cytology (RD)

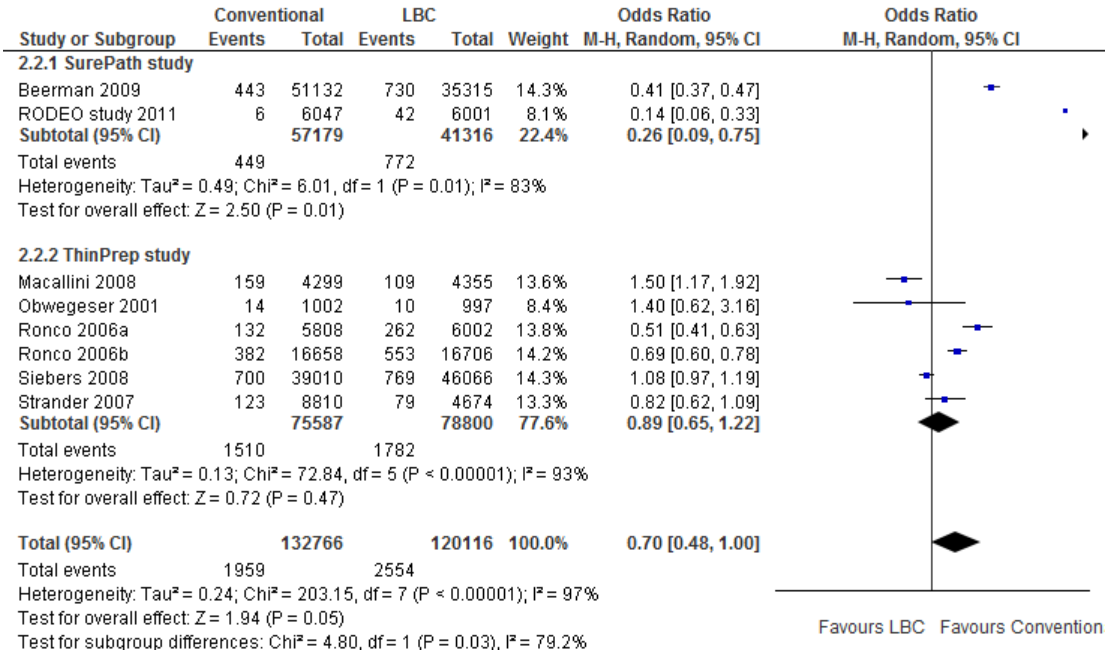

Figure 10 Forest plot: Proportion of ASCUS cytology (OR)

An OR<1 indicates a greater proportion of findings with LBC compared with conventional cytology

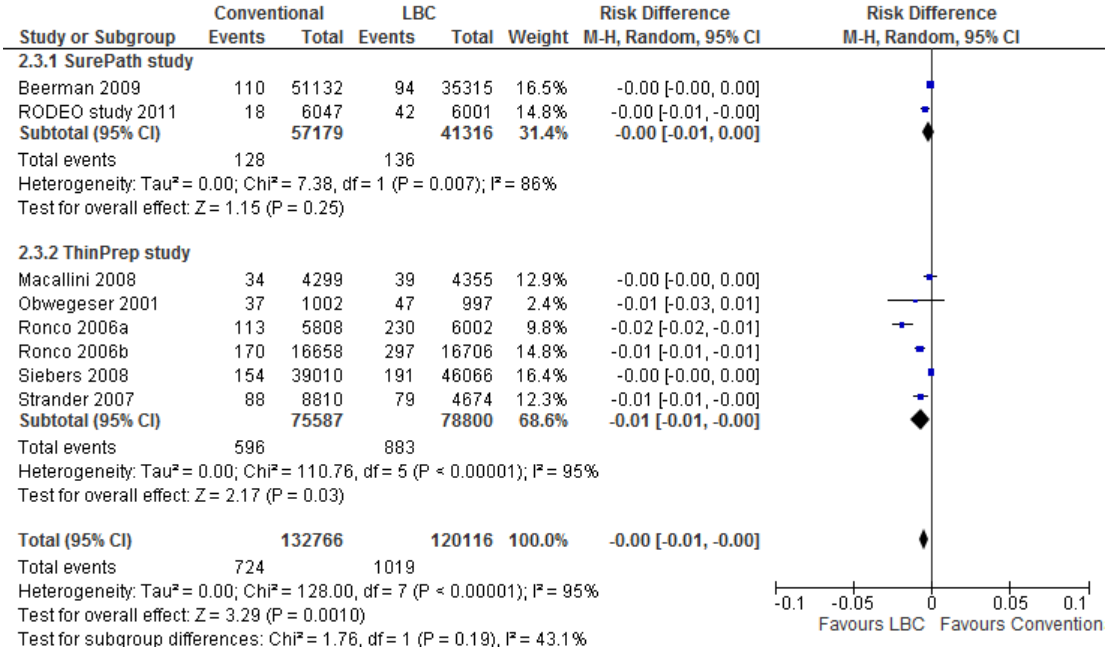

Figure 11 Forest plot: Proportion of LSIL cytology (RD)

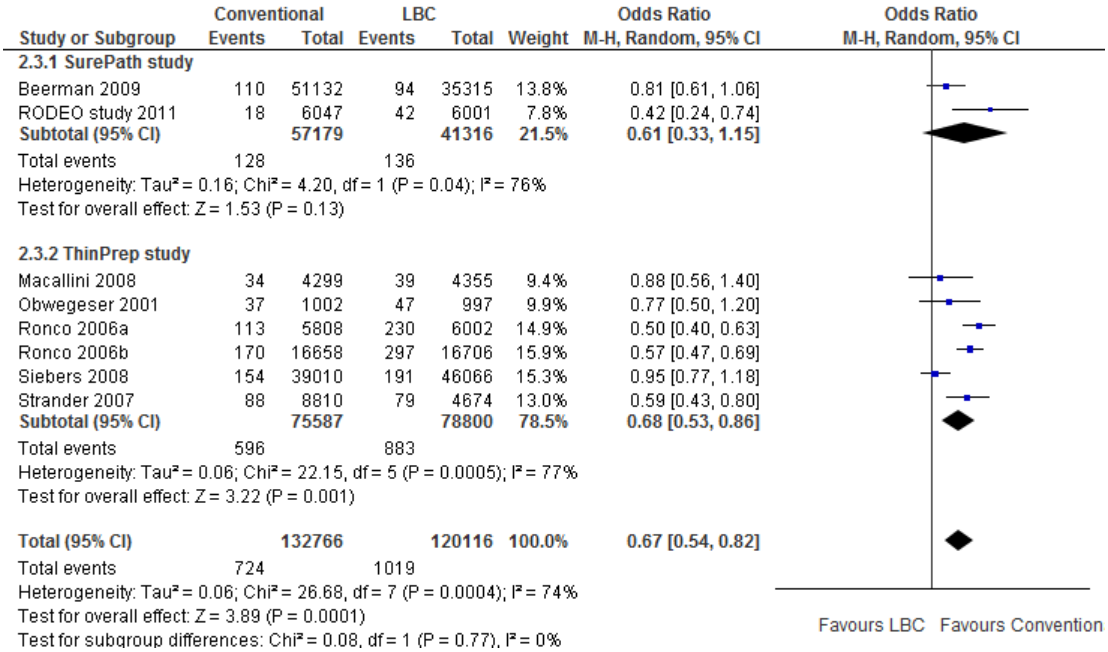

Figure 12 Forest plot: Proportion of LSIL cytology (OR)

An OR<1 indicates a greater proportion of findings with LBC compared with conventional cytology

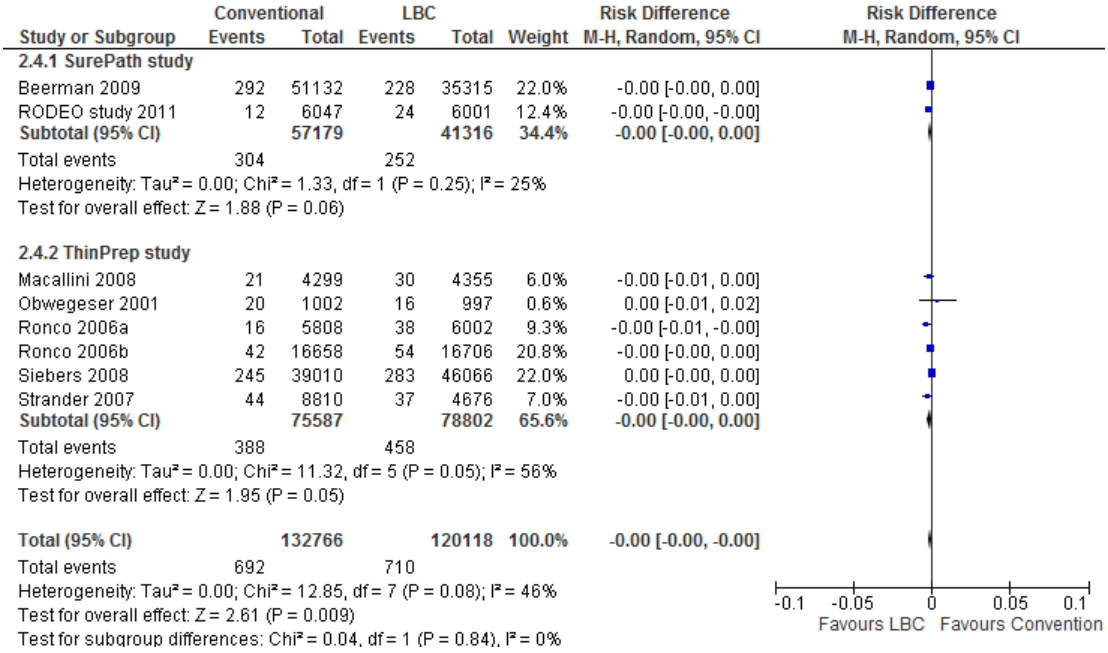

Figure 13 Forest plot: Proportion of HSIL cytology (RD)

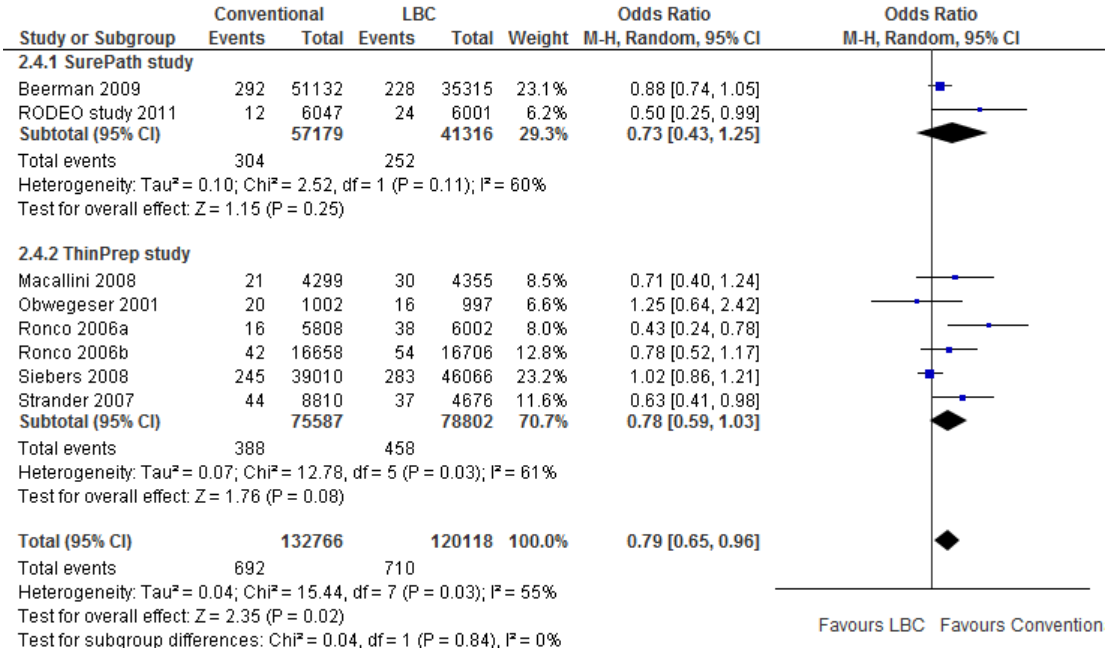

Figure 14 Forest plot: Proportion of HSIL cytology (OR)
An OR<1 indicates a greater proportion of findings with LBC compared with conventional cytology

Proportion of CIN lesions detected in each cytological category

The proportion of CIN lesions detected in each cytological category is provided below. A qualitative review of the correlation will be performed unless trial publications report the

statistical comparisons of the correlation between cell enrichment or cell filtration LBC and conventional cytology.

Cell enrichment LBC vs. CC

The histological follow-up of all patients with a cytological classification of ASCUS or higher was retrieved from a Dutch national database and reported by Beerman 2009.

The correlation between histological follow-up data, within the study period, and cytological classifications in the Beerman 2009 study is shown in Table 40. There was no significant difference in the percentages of ASCUS, LSIL, and HSIL cytology samples showing normal and CIN 1+ histology between the two cohorts ($P > 0.05$).

Table 40 Correlation between cytological and histological data—CC versus cell enrichment LBC: Beerman 2009

	Conventional cytology N=51,132			LBC N=35,315			P value
	Histology			Histology			
	Normal/none		CIN 1+	Normal/none		CIN 1+	
	N	n (%)		N	n (%)		
Unsatisfactory	435	432 (99.31)	3 (0.69)	46	46 (100)	0	1.0
Within normal limits	49,856	49,826 (99.94)	30[a](0.06)	34,219	34,207 (99.96)	12[b](0.04)	0.1183
Abnormal ASCUS	443	396 (89.39)	47 (10.61)	730	657 (90)	73 (10.0)	0.7384
-LSIL	110	57 (51.82)	53 (48.18)	94	50 (53.19)	44 (46.81)	0.8448
-HSIL	288	44 (15.28)	244 (84.72)	226	36 (15.93)	190 (84.07)	0.8398
Squamous cell carcinoma	4	1 (25.00)	3 (75.00)	2	0 (0.00)	2 (100.0)	1.0

Abbreviations: ASCUS, atypical cells of undetermined significance; CIN, cervical intraepithelial neoplasia; LSIL, low grade squamous intraepithelial lesion; HSIL+, high-grade squamous intraepithelial lesion or more severe

a. 21 of the 30 cases (70%) were CIN 2 or higher

b. 7 of the 12 cases (58%) were CIN 2 or higher

Cell filtration LBC vs. CC

The correlation between histological follow-up data, within the study period, and cytological classifications for women aged 25 to 34 years in the NTCC trial and women aged 35 to 60 years is shown in Table 41 and Table 42, respectively.

Overall, for the 25 to 34 years cohort the percentages of ASCUS, LSIL, and HSIL samples showing CIN 1 histology with cell filtration LBC are double that in the CC arm. The proportions of ASCUS, LSIL, and HSIL LBC cytology samples showing CIN 2 histology were also higher in the LBC arm than in the CC arm, twice as high, with the exception of HSIL-CIN2 findings. There are a similar number of ASCUS, LSIL, and HSIL LBC cytology samples showing CIN 3 histology compared with the CC arm (Table 41).

The correlation between cytological and histological findings for the 35 to 60 years cohort is similar to that seen for the younger women (25 to 34 years). The percentages of ASCUS, LSIL, and HSIL cytology samples showing CIN 1 and CIN 2 histology were higher in the cell filtration LBC arm but the same or lower for CIN 3 findings.

Table 41 Correlation between cytological and histological data—CC versus cell filtration LBC; NTCC trial, ages 25 to 34 years: Ronco 2006a

	Conventional N=5808					LBC N=6002[c]				
			Histology					Histology		
	No colposcopy, n(%)	No CIN[a], n(%)	CIN 1, n(%)	CIN 2, n(%)	CIN 3, n(%)	No colposcopy, n(%)	No CIN[a], n(%)	CIN 1, n(%)	CIN 2, n(%)	CIN 3, n(%)
Unsatisfactory	131[b] (2.3)	4[b] (0.1)	0	0	0	77 (1.3)	3 (0.05)	0	0	0
Normal or benign change	5410 (93.2)	2 (0.03)	0	0	0	5376 (89.6)	14 (0.2)	2 (0.03)	0	0
ASCUS or AGUS	40 (0.7)	70 (1.2)	17 (0.3)	1 (0.02)	4 (0.1)	18 (0.3)	195 (3.2)	37 (0.6)	5 (0.08)	7 (0.1)
LSIL	8 (0.1)	69 (1.2)	21 (0.4)	6 (0.1)	9 (0.2)	11 (0.2)	130 (2.2)	67 (1.1)	20 (0.3)	2 (0.03)
HSIL+	0 (0)	3 (0.05)	0	4 (0.07)	9 (0.2)	2 (0.03)	12 (0.2)	13 (0.2)	6 (0.1)	5 (0.1)
Source: Ronco 2006a Table 1										

Abbreviations: AGUS, atypical glandular cells of undetermined significance; ASCUS, atypical cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; LBC, liquid-based cytology; LSIL, low grade squamous intraepithelial lesion

Note: Percentages (%) calculated using for the purpose of this submission, using sample size obtained from Ronco 2006a, Table 1.

a. Includes women who had a colposcopy but not a biopsy, only colposcopies done as a result of baseline testing were included

b. Footnote to table 1 in the publication by Ronco 2006a from which the data were collected states that “15 women did not receive cytological analysis”. The Figure in the publication with the disposition of patients states that none of these women had colposcopy.

c. Footnote to table 1 in the publication by Ronco 2006a from which the data were collected states that “A total of 77 patients had no valid HPV test, 15 had no valid test (and no colposcopy) and were classified as “unsatisfactory”, 54 patients received test as per conventional group and 8 samples had insufficient material”. The figure in the publication with the disposition of patients’ states that 4 of these women had a colposcopy, 1 without referral however Table 1 indicates that only 3 had colposcopy

Table 42 Correlation between cytological and histological data—CC versus cell filtration LBC; NTCC trial, ages 35 to 60 years: Ronco 2006b

	Conventional N=16658					LBC N=16706[c]				
			Histology					Histology		
	No colposcopy, n(%)	No CIN[a], n(%)	CIN 1, n(%)	CIN 2, n(%)	CIN 3, n(%)	No colposcopy, n(%)	No CIN[a], n(%)	CIN 1, n(%)	CIN 2, n(%)	CIN 3, n(%)
Unsatisfactory cytology only	272 (1.63)[b]	3 (0.018)[b]	0	0	0	152 (0.91)	36 (0.22)	0	1 (0.006)	1 (0.006)
Normal or benign change	15785 (94.76)	3 (0.018)	1 (0.006)	0	0	14818 (88.7)	702 (4.2)	73 (0.44)	12 (0.07)	7 (0.04)
ASCUS or AGUS	130 (0.78)/27 (0.16)	213 (1.28)/211 (1.27)	30 (0.18)/30 (0.18)	4 (0.02)/3 (0.018)	5 (0.03)/4 (0.02)	34 (0.2)	466 (2.8)	39 (0.23)	0/8 (0.05)	6 (0.04)
LSIL	14 (0.08)	111 (0.67)	29 (0.17)	8 (0.05)	8 (0.05)	29 (0.17)	209 (1.25)	49 (0.29)	4 (0.023)	6 (0.04)
HSIL+	2 (0.012)	11 (0.07)	3 (0.018)	8 (0.05)	18 (0.11)	4 (0.024)	11 (0.07)	9 (0.05)	11 (0.07)	19 (0.11)
Source: Ronco 2006b Table 2										

Abbreviations: AGUS, atypical glandular cells of undetermined significance; ASCUS, atypical cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; LBC, liquid-based cytology; LSIL, low grade squamous intraepithelial lesion

Note: Percentages (%) calculated using for the purpose of this submission, using sample size obtained from Ronco 2006b, Table 2

a. Includes women who had a colposcopy but not histology

b. Footnote to table 2 in the publication by Ronco 2006b from which the data were collected states that "In 30 women, no test was performed. Women directly referred to colposcopy are shown in parentheses (under ASCUS/AGUS cytology)". A total of 275 slides had unsatisfactory cytology and all of these patients were referred for colposcopy and the results presented under ASCUS/AGUS cytology. IT is uncertain whether all of these unsatisfactory slides were repeated and resulted in a finding of ASCUS/AGUS.

c. Table 2 in the publication by Ronco 2006b indicates that 296 patients had "No valid HPV test". The footnote to Table 2 that "In 35 women, no test was performed; in 247, conventional samples were taken; and in 14, there was insufficient materials"

The correlation between the baseline cytological result and the verified outcome for cell filtration LBC and CC from the intention-to-treat analysis reported in the NETHCON trial by Siebers 2009 is provided in Table 43.

Overall, any differences in the percentage of ASCUS, LSIL, and HSIL cytology samples showing normal, CIN 1+, CIN 2+, CIN 3+ histology between the cell filtration LBC arms compared with CC were not statistically significant. Both the intention to treat and per protocol analyses demonstrated non-significant differences between the cell filtration LBC arm and CC (Siebers 2009 p.1762).

Table 43 Correlation between cytological and verified follow up outcome[a]—CC versus cell filtration LBC; NETHCON trial: Siebers 2009

	Conventional				LBC				P value
	Within normal limits, ATYPIA or ASCUS, n/N(%) [95% CI]	**CIN 1 or low-grade SIL, n/N(%) [95% CI]**	**CIN 2 or moderate dysplasia, n/N(%) [95% CI]**	**CIN 3+ or severe dysplasia, n/N(%) [95% CI]**	**Within normal limits, ATYPIA or ASCUS, n/N(%) [95% CI]**	**CIN 1 or low-grade SIL, n/N(%) [95% CI]**	**CIN 2 or moderate dysplasia, n/N (%) [95% CI]**	**CIN 3+ or severe dysplasia, n/N(%) [95% CI]**	
ASCUS or AGUS	563/640 (88.0) [82.2, 90.4]	38/640 (5.9) [4.2, 8.1]	18/640 (2.8) [1.7, 4.4]	21/640 (3.3) [2.0, 5.0]	613/696 (88.1) [84.4, 90.4]	35/696 (5.0) [3.5-6.9]	28/696 (4.0) [2.7, 5.8]	20/696 (2.9) [1.8, 4.4]	P=0.5[b]
LSIL	85/149 (57.1) [48.7, 65.1]	23/149 (15.4) [10.0, 22.3]	21/149 (14.1) [8.9, 20.7]	20/149 (13.4) [8.4, 20.0]	98/179 (54.8) [47.2, 62.2]	31/179 (17.3) [12.1-23.7]	16/179 (8.9) [5.2, 14.1]	34 (19.0) [13.5, 23.5]	P=0.42 [b]
HSIL+	30/238 (12.6) [8.7, 17.5]	14/238 (5.9) [3.2, 9.7]	52/238 (21.9) [16.8, 27.6]	142/238 (59.7) [53.1, 66.0]	21/269 (7.8) [5.0, 11.9]	15/269 (5.6) [3.2-9.2]	51/269 (19.0) [14.8, 24.7]	182/269 (67.7) [63.2, 74.7]	P=0.23 [b]
Source: Siebers 2009 Table 4									

Abbreviations: AGUS, atypical glandular cells of undetermined significance; ASCUS, atypical cells of undetermined significance; ATYPIA or ASCUS, atypical epithelium or atypical squamous cells of undetermined significance; CI, confidence interval; CIN, cervical intraepithelial neoplasia; HSIL+, high-grade squamous intraepithelial lesion or more severe; LSIL, low grade squamous intraepithelial lesion; SIL, squamous epithelial lesion

a. Follow up tests included cytological testing, colposcopy, or histology depending on the baseline cytological finding. Per-protocol analysis of correlation between the baseline cytological result and verified outcome (histology, colposcopy, or cytology). P value based on Chi² comparison. Correlations based on the intention to treat analysis were similar and likewise no significant difference seen between LBC and conventional Pap smear.

Table 44 shows the correlation between the baseline cytological result and the verified outcome diagnosis from a regional database by Strander 2007 at the initial follow up 8 months after the study was completed.

With LBC, ASCUS/AGUS resulted in 16.7% benign histopathological findings, 11.5% LSIL findings and 14.1% HSIL findings. For conventional Pap smears these figures were 18.3%; 20% and 18.3%, respectively.

With LBC, LSIL resulted in 12.3% benign histopathological findings, 17.8% LSIL findings and 20.5% HSIL findings. For conventional Pap smears these figures were 9.6%; 27.7% and 10.8%, respectively.

With LBC, HSIL resulted in 5.7% benign histopathological findings, 11.4% LSIL findings and 82.9% HSIL findings. For conventional Pap smears these figures were 4.4%; 0% and 93.3%, respectively.

The accuracy of HSIL cytology for predicting HSIL in histopathology appeared to be greater for cell filtration LBC; whereas LSIL cytology versus LSIL in histopathology appeared to be greater for CC; however, the numbers were rather small, and the difference was not statistically significant (P=0.17 and P=0.57, respectively, Table 44).

The numbers of specimens with glandular cell atypia and adenocarcinoma were too low to be compared statistically. One cell filtration LBC test identified AGUS in which the histology was benign, and another cell filtration LBC sample had a diagnosis of AIS in which histology demonstrated benign glandular change and HSIL. Two CC smears correctly diagnosed histopathologically confirmed AIS.

The search for histopathologic diagnoses was made on two occasions. The first search occurred 8 months after the study was closed. The mean follow up was 1.5 years (range from 9 months to 2 years and 5 months). The maximum time from smear to follow up histopathology was well within the period of one screening round. The second search in the regional database was made 2 years and 1 month later. The mean follow-up at that time was 3 years and 7 months (range from 2 years and 10 months to 4.5 years). According to Swedish national guidelines women are invited to be screened for cervical cancer every three years. The follow-up histological diagnoses reported after the second round could therefore be as a result of a second cytological screen although further details are not reported by Strander 2007. Table 45 reports the number of high-grade lesions (CIN 2 or 3, AIS, or cancer) on histopathology reported for LBC and conventional Pap smear after 1.5 years (18 months) and 3 years and 7 months (43 months).

Approximately 42% more high-grade lesions were identified by histopathology as a result of a screening test with cell filtration LBC (P=0.05) compared with CC. This difference was even more significant after adjusting for age and screening unit in the logistic regression model (Table 45). The crude difference was reduced to 30% when the follow-up was increased by 25 months, but the authors report this difference remained statistically significant in the regression model.

Table 44 Correlation between cytological and histological data—CC versus cell filtration LBC[a]: Strander 2007

	Conventional N=8810				LBC N=4674				P value
	No histology n(%)	Histology			No histology n(%)	Histology			
		Benign n(%)	Low grade[b], n(%)	High grade[b], n(%)		Benign n(%)	Low grade[b], n(%)	High grade[b], n(%)	
Benign	8297 (97.7)	194 (2.3)	4 (0)	1 (0)	4358 (97.5)	112 (2.5)	0 (0)	0 (0)	NR
ASCUS	52 (43.3)	22 (18.3)	24 (20)	22 (18.3)	45 (57.7)	13 (16.7)	9 (11.5)	11 (14.1)	NR
LSIL	43 (51.8)	8 (9.6)	23 (27.7)	9 (10.8)	36 (49.3)	9 (12.3)	13 (17.8)	15 (20.5)	NR
HSIL	1 (2.2)	2 (4.4)	0 (0)	42 (93.3)	0 (0)	2 (5.7)	4 (11.4)	29 (82.9)	NR
Source: Strander 2007, Table 3									

Abbreviations: ASCUS, atypical cells of undetermined significance or more severe; HSIL, high-grade squamous intraepithelial lesion; LSIL, low grade squamous intraepithelial lesion; NR, not reported

a. A total of 80 inadequate smears and 4 smears (2 ThinPrep and 2 Pap smears) that correctly identified glandular lesions were excluded

b. It is presumed that low grade histopathological findings are equivalent to cervical intraepithelial neoplasia 1 given High grade findings are reported to be equivalent to cervical intraepithelial neoplasia 2 or 3, adenocarcinoma in situ, or cancer (Strander 2007 Table 4)

Table 45 Detection rate of HSIL identified from cc versus cell filtration LBC on two follow up occasions: Strander 2007

	Conventional N=8810 n (%)	LBC N=4674 n (%)	Odds ratio adjusting for age (95% CI)	Odds ratio adjusting for age and screening unit (95% CI)	P value
Follow up at mean 1.5 years	75 (0.85)	56 (1.20)	1.71 (1.20, 2.43)	1.60 (1.12, 2.28)	0.05
Follow up at a mean 3 years 7 months	122 (1.38)	84 (1.80)	1.62 (1.22, 2.16)	1.51 (1.13, 2.01)	0.06
Source: Strander 2007 Table 4 p. 289					

Abbreviations: LBC, liquid-based cytology; 95% CI, 95% confidence interval

Maccallini 2008 did not report the histological diagnosis for all cytological categories: only the proportions of women in whom CIN 2+ was histologically confirmed in screen positive patients within one year of colposcopy were reported (Table 46).

The CIN 2+detection rate was not statistically different in either arms (CC=0.54%, cell filtration LBC=0.66%, P=0.45), despite the higher referral for colposcopy in the conventional arm. There is a discrepancy in the P value reported in the body of the text (P=0.28) compared with Table IV (P=0.45). The reason for the difference is uncertain; nonetheless, both indicate no significant difference.

Table 46 CIN 2+ detection rate: CC versus cell filtration LBC: Maccallini 2008

	Conventional N=4299, n[a] (%)	LBC N=4355, n[a] (%)	P value
Detection rate	23 (0.54)	29 (0.66)	0.45
Source: Maccallini 2008, Table 4 p.571			

a. n back calculated from percentages presented in Maccallini 2008, Table 4 p.571.

Follow-up of cytologic HSIL cases only were compared between cell filtration LBC and CC by Obwegeser 2001. Of the 19 cytologic diagnoses of HSIL in the CC arm, 12 (63%) of patients had histology available within 12 to 15 months of follow up. A similar proportion of histology data was available for the cell filtration LBC arm 11/16 (69%). Cytologic diagnoses of HSIL correlated with a histological HSIL in 91 % of the cell filtration LBC cases and 100% of the CC cases. The results of this Swiss trial will not be discussed further due to the insufficient completeness of verification of tests positive: less than 70% for HSIL cases and no verification data for abnormalities of lower severity. It is noted that the trial was also excluded from the systematic review performed by Arbyn 2008 for the same reasons.

Table 47 Correlation between cytological and histological data of HSIL cases—CC versus cell filtration LBC: Obwegeser 2001

	Conventional N=19[a], n(%)	LBC N=16 [a],n(%)
Histology available for HSIL cases	12/19[a] (63)	11/16 [a] (69)
Correlation of HSIL cytology cases with histology follow up		
HSIL	12/12[b] (100)	10/11[b] (91)
LSIL	0 (0)	0/11[b] (0)
No SIL	0 (0)	1/11[b] (9)
Source: Obwegeser 2001, Table 3		

Abbreviations: HSIL, high grade squamous intraepithelial lesion; LSIL, Low grade squamous intraepithelial lesion; SIL, squamous intraepithelial lesion

a. n=number of cytology HSIL cases
b. n=number of cytology HSIL cases whereby histology results are available

Sensitivity and specificity

Sensitivity and/or specificity were reported or could be calculated from four trials. Beerman 2009 and Strander 2007 checked for histological follow-up of all patients, including normal cytological outcomes, using national or regional database that captures the outcome of each cytological and/or histological investigation. Hence, the sensitivity and specificity reported for these trials are comparable.

In the NTCC and RHINE SAAR trials, only women with cytological positive cases (or HPV positive in the NTCC trial) were followed up via referral for colposcopy with subsequent biopsy taken on a case by case basis. Therefore, there was no means to understand the proportion of cytological negative/normal cases who were truly negative, or false negatives. The relative 'sensitivity' reported by the NTCC trial (Ronco 2007) and the RHINE SAAR trial (Ikenberg 2010 and 2011) are therefore reported after the sensitivity and specificity from the aforementioned trials.

Given the differences between the relative sensitivity reported in the NTCC trial and RHINE SAAR trial, and the sensitivity from the Strander 2007 trial the results from these cell filtration LBC trials were not meta-analysed.

Cell enrichment LBC vs. CC

In the Netherlands, the outcome of each cytological and/or histological investigation is submitted to the Dutch Network and National Database for Pathology (PALGA). As a result, all Dutch pathology and cytology departments are interconnected for 100% of cytology and histology specimens. This enabled Beerman 2009 to report a unique population-based study with nearly 100% correlation. The histological follow-up of all patients with a cytological classification of

ASCUS or higher was retrieved from the PALGA database. To determine the true false negative rate of the screening results, the study team collected the data from all patients with a negative cytology (i.e. within normal limits), but with a histological proven cervical lesion (CIN 1 or higher).

The contingency table with the correlation of index test (ASCUS+) and histological outcome (CIN 1+) was generated for the purposes of the submission from data reported by Beerman 2009. The correlation, calculated sensitivity, specificity, positive and negative predictive value for the cell enrichment LBC arm are presented in Table 48 and the CC arm in Table 49. The sensitivity and specificity (and corresponding 95% confidence intervals) were then formally calculated and compared (refer to Attachment 4) and are presented in Table 50.

A very small number of patients with a negative cytology (that is, within normal limits) were found to have unforeseen histology performed within the window of follow up. In the conventional arm, 30 patients (0.06%) with cytology results within normal limits had subsequent histology within 510 days showing CIN 1 or higher lesions. With cell enrichment LBC, 12 patients (0.04%) with normal cytology were identified with CIN 1, or higher lesions in histology. The false-negative rate relative to total CIN 1+ lesions for the cell enrichment LBC arm (12/319, 3.76%) was significantly lower than for the CC arm (30/377, 7.96%)(P=0.0247). (In both cohorts, the majority of these false negative lesions were CIN 2 or higher (21/ 30, 70%, with conventional cytology and 7/12, 58%, with cell enrichment LBC) (Beerman 2009 Table 2).

Table 48 Contingency table—cell enrichment LBC: Beerman 2009

		Reference standard (histology, threshold CIN 1+)		
		Positive	**Negative**	
Index test, ASCUS+[a] (cell enrichment LBC)	Positive	309	789 [a]	PPV=309/1098 =0.2814
	Negative	12 [b]	34,207	NPV=34207/34219 =0.9996
		Sensitivity: =309/321 =0.9626	Specificity: =34207/34996 =0.9775	

Abbreviations: ASCUS, atypical cells of undetermined significance or more severe; CIN, cervical intraepithelial neoplasia grade; NPV, negative predictive value; PPV, positive predictive value

a. The false positives (positive index test but negative reference standard) includes the histological outcomes for 46 unsatisfactory specimens

b. Just over half of the false negative findings (7/12, 58%) were CIN 2+ lesions

Table 49 Contingency table—CC: Beerman 2009

		Reference standard (histology, threshold CIN 1+)		
		Positive	**Negative**	
Index test, ASCUS+ [a] (Conventional Cytology)	Positive	347[a]	929 [a]	PPV=347/1276 =0.2719
	Negative	30[b]	49,826	NPV=49826/49856 =0.9994
		Sensitivity: =347/377 =0.9204	Specificity: =49826/50755 =0.9817	

Abbreviations: ASCUS, atypical cells of undetermined significance or more severe; CIN, cervical intraepithelial neoplasia grade; NPV, negative predictive value; PPV, positive predictive value

a. Includes the histological outcomes for 435 unsatisfactory specimens

b. The majority of these false negative findings (21/ 30, 70%) were CIN 2+ lesions

The sensitivity for detection of a histological proven lesion (CIN 1+) based on an ASCUS+ index test is significantly higher with cell enrichment LBC compared to conventional cytology (96.3% vs. 92.04%, OR 2.23, 95% CI 1.12 to 4.42, P=0.0244). The same was true for the detection of CIN 2+ lesions using LBC (97.19%; 95% CI 94.31–98.63 vs. 93.46%; 95% CI 90.21–95.68) (Beerman 2009 p.574).

The specificity for the detection of a histological proven lesion (CIN 1+) based on an ASCUS+ index test is significantly lower with cell enrichment LBC compared to conventional cytology (97.75% vs. 98.17%, OR 0.81, 95% CI 0.73 to 0.89, P < 0.0001).

It is noted that the absolute difference in increased sensitivity is in the order of 4% whereas the decrease in specificity is 0.5%.

Table 50 Sensitivity and specificity—CC versus cell enrichment LBC: Beerman 2009

	Sensitivity (95% CI)	Specificity (95% CI)
LBC (cell enrichment)	96.24 (93.54, 97.84)	97.75 (97.58, 97.90)
Conventional cytology	92.04 (88.87, 94.37)	98.17 (98.05, 98.28)
OR (95% CI), P value	2.23 (1.12, 4.42), P=0.0244	0.81 (0.73,0.89), P < 0.0001
Source	Beerman 2009 Table 3, Attachment 4	

Abbreviations: CI, confidence interval; LBC, liquid-based cytology; OR, odds ratio
Note: Include unsatisfactory specimens
An OR >1 indicates performance of LBC is better than CC

Cell filtration LBC vs. CC

Histopathology diagnoses were searched for by Strander 2007 in a Swedish Regional Database for Prevention of Cervical Cancer, which covered the laboratories involved in the trial, including, among other data, all histopathology related to cervical disease (biopsies, cones, and hysterectomy specimens). The database was searched for any histological outcomes for patients in the trial at 1.5 years after patients were screened and enabled the detection of any false negative cytological reports.

The contingency table with the correlation of index test (ASCUS+) and histological outcome (CIN 1+) was generated for the purposes of the submission from data reported by Strander 2007. The correlation, calculated sensitivity, specificity, positive and negative predictive value for the cell filtration LBC arm are presented in Table 51 and the conventional arm in Table 52. The sensitivity and specificity (and corresponding 95% confidence intervals) were then formally calculated and compared (refer to Attachment 4) and are presented in Table 53.

No patients with benign cytology using cell filtration LBC had subsequent histology showing low grade or higher lesions (Table 51). A very small number of patients with a negative cytology (i.e. benign) using conventional cytology were found to have unforeseen histology performed within the window of follow up (n=5, 0.06%) (Table 52).

Table 51 Contingency table—cell filtration LBC: Strander 2007

		Reference standard (histology, threshold CIN 1+)		
		Positive	**Negative**	
Index test, ASCUS+ (cell filtration LBC)	Positive	81	105 [a]	PPV=81/186 =0.4355
	Negative	0	4470[a]	NPV=4470/4470 =1
		Sensitivity: =81/81 =1.00	Specificity: =4470/4575 =0.9770	

a. Clinical management of atypical cytology and referral to colposcopy and treatment were performed as routine procedures within the screening program. ASCUS and CIN type 1 (CIN 1) led either to colposcopy after 4 months or to a repeat smear. Therefore "no histology" outcome was assumed to represent a benign or normal outcome for women with benign cytology and ASCUS+ given all women in the latter category would have undergone follow up procedures

Table 52 Contingency table—CC: Strander 2007

		Reference standard (histology, threshold CIN 1+)		
		Positive	**Negative**	
Index test, ASCUS+ (conventional cytology)	Positive	120	128 [a]	PPV=120/248 =0.4839
	Negative	5	8491 [a]	NPV=8491/8496 =0.9994
		Sensitivity: =120/125 =0.96	Specificity: =8491/8619 =0.9851	

a. Clinical management of atypical cytology and referral to colposcopy and treatment were performed as routine procedures within the screening program. ASCUS and CIN type 1 (CIN 1) led either to colposcopy after 4 months or to a repeat smear. Therefore "no histology" outcome was assumed to represent a benign or normal outcome for women with benign cytology and ASCUS+ given all women in the latter category would have undergone follow up procedures

The sensitivity for detection of a histological proven low grade lesion or worse (equivalent of CIN 1+) is higher with cell filtration LBC compared with CC (100% vs. 96%, OR 6.71 95% CI 0.36 to 124.47; P < 0.0001).

The specificity for the detection of a histological proven lesion (CIN 1+) based on an ASCUS+ index test is significantly lower with cell enrichment LBC compared to conventional cytology (82.32% vs. 85.84%, OR 0.64, 95% CI 0.49 to 0.83, P=0.0008).

Table 53 Sensitivity and specificity—CC versus cell filtration LBC: Strander 2007

	Sensitivity (95% CI)	Specificity (95% CI)
LBC (cell filtration)	100.00[a] (96,100)	82.32 (75, 88)
Conventional cytology	96.00 (91, 99)	85.84 (81, 90)
OR (95% CI), P value	6.71 (0.36 to 124.47), P < 0.0001	0.64 (0.49 to 0.83), P=0.0008
Source	Strander 2007, attachment 4	

Abbreviations: CI, confidence interval; LBC, liquid-based cytology; OR, odds ratio
An OR >1 indicates performance of LBC is better than CC
a. Zero cells cause problems with computation of standard errors so rather than using 81/81=1 in the calculation of the odds ratio (p/1-p) which would result in 1/0, 80.5 was substituted in the numerator according to standard practice (Egger, Smith and Altman 2003)

Relative sensitivity

Ronco 2007 presents analyses that did not consider the results of cytological and histological tests carried out because of a positive HPV test result in the presence of normal cytology. These tests would not have been performed if cytology alone was used. The authors report combined results for both 25 to 34 years and 35 to 60 years cohorts. The detection and relative sensitivity rates for the entire NTCC trial are reported in Table 54. The sensitivities of the different combinations of cytology are given as values relative to the conventional cytology group, for all randomised eligible women.

No significant increase was observed in sensitivity for CIN 1+ for cell filtration LBC compared with CC with either ASCUS or LSIL as cut-off points (Table 54).

There was a significant increase in sensitivity for CIN 2+ for cell filtration LBC compared with CC with ASCUS or LSIL as cut-off points (Table 54). There was a significant decrease in sensitivity for CIN3+ for cell filtration LBC compared with CC with either ASCUS or LSIL as cut-off points (Table 54).

Table 54 Relative sensitivity—CC versus cell filtration LBC; NTCC trial, age 24–60 years: Ronco 2007

	Histological CIN endpoint		
	CIN 1+, %(n)	**CIN 2+, %(n)**	**CIN 3+, %(n)**
Positive if cytology shows ASCUS or more			
Detection rate			
Conventional group	0.82 (184)	0.37 (84)	0.24 (53)
LBC group[a]	1.38 (313)	0.44 (99)	0.20 (45)
Relative sensitivity[b] (95% CI)	1.68 (1.40 to 2.02)	1.17 (0.87 to 1.56)	0.84 (0.56 to 1.25)
Positive if cytology shows LSIL or more			
Detection rate			
Conventional group	0.55 (123)	0.31 (70)	0.20 (44)
LBC group[a]	0.95 (211)	0.32 (73)	0.14 (32)
Relative sensitivity[b] (95% CI)	1.70 (1.36 to 2.12)	1.03 (0.74 to 1.43)	0.72 (0.46 to1.13)
Source: Ronco 2007 Table 3			

Abbreviations: ASCUS, Atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; CI, confidence interval

Note: For detection rate and relative sensitivity denominators are 22,466 women in conventional group and 22,708 in LBC group. For positive predictive values and relative positive predictive values denominators are women with positive cytology for atypical cells of undetermined significance who had had colposcopy: 661 in conventional group and 1337 in LBC group

a. Only CIN detected by cytology considered
b. Ratio of percentages. LBC compared with conventional cytology

The relative sensitivity for histologically confirmed CIN 2+ reported in the RHINE SAAR trial is presented in Table 55.

There was a significant increase in sensitivity for CIN 2+ for cell filtration LBC compared with CC read manually (relative sensitivity 2.74, 95% CI 1.66 to 4.53).

All cell filtration LBC slides were also investigated with the computer-assisted ThinPrep Imaging System (TIP). The relative sensitivity reported for histologically confirmed CIN 2+ for cell filtration LBC analysed using the ThinPrep Imaging System (TIS) compared to CC was significantly higher (3.17, 95% CI 1.9 to 5.19).

Table 55 Relative sensitivity for histologically confirmed CIN 2+ of CC versus cell filtration LBC (manual and automated analysis): RHINE-SAAR Study 2010–2011

	CC (n=9296) vs. LBC (n=11331)	CC (n=9296) vs. Computer-assisted ThinPrep Imaging System (n=11331)
Relative sensitivity (95% CI)	2.74 (1.66 to 4.53)	3.17 (1.9 to 5.19)
Source: Ikenberg 2011a,b and Ikenberg 2010b,c		

Abbreviations: CC, conventional cytology; CI, confidence interval; LBC, liquid-based cytology
Women who participated in the RHINE-SAAR trial reported by Ikenberg 2010 with cytological abnormalities ASCUS+ were invited for expert colposcopy, including biopsy if indicated

Summary of results

The two trials that reported sensitivity and specificity for CIN 1+ outcome based on an ASCUS+ index test resulted in consistent conclusions. Both showed that LBC (cell enrichment or cell filtration) was associated with significantly increased sensitivity for CIN 1+ and significantly reduced specificity. Of the two trials that reported relative sensitivity, the RHINE SAAR trial resulted in the same conclusion of increased sensitivity but for CIN 2+ (associated with an ASCUS+ index test). The results from the entire NTCC trial were variable showing no significant difference in relative sensitivity for CIN 1+ (based on an index test of ASCUS or LSIL) for cell filtration LBC compared with CC. There was however increased relative sensitivity for CIN 2+ (based on an index test of ASCUS or LSIL) for cell filtration LBC compared with CC. There was decreased relative sensitivity for CIN 3+ (based on an index test of ASCUS or LSIL) for cell filtration LBC compared with CC.

As stated by Davey 2006 the accuracy of tests is a trade-off between sensitivity and specificity. The absolute increase in sensitivity for CIN 1+ was 4% for both cell enrichment and cell filtration LBC. The absolute reduction in specificity was less than 1% with cell enrichment LBC and 3.5% with cell filtration LBC.

CIN 1 is the histopathologic manifestation of a carcinogenic or non-carcinogenic HPV infection that rarely progresses to cancer (Arbyn 2009). The Australian cervical screening guidelines take the conservative approach whereby the clinical investigation for a pLSIL outcome is follow up CC in 12 months (NHMRC 2005). Given the transient nature of much CIN1, Arbyn recommends that surrogate outcomes such as reduction of incidence of CIN 3+, increased detection rate of CIN 3+ or CIN 2+, or increased, similar or hardly reduced positive predictive provide more robust comparative assessment of the screening technology. CIN 3 in particular is the direct precursor of invasive cancer, and therefore a good proxy outcome of trials evaluating new technologies.

Although false positives are undesirable in a screening program, the follow up investigation in this circumstance does not expose patients to a high risk of adverse outcome.

Indirect comparison

Only two trials—Beerman 2009 and Strander 2007—reported the sensitivity and specificity for cell enrichment LBC versus CC and cell filtration LBC versus CC, respectively. Therefore the only indirect comparison possible between cell enrichment LBC and cell filtration LBC via CC as a common comparator is using these two trials. Both trials correlated an index test (ASCUS+) and histological outcome (CIN 1+) and both trials featured similar study designs.

Table 56 and Table 57 provide the results of the indirect comparison of sensitivity and specificity, respectively, for CIN 1+ between cell enrichment LBC and cell filtration LBC. The results showed that there was no statistically significant difference between cell enrichment LBC and cell filtration LBC in sensitivity or specificity (P=0.4712 and 0.1033, respectively).

Table 56 Summary of results of the indirect comparison of cell enrichment LBC and cell filtration LBC sensitivity for CIN 1+

	Trial of cell enrichment LBC			Trial of cell filtration LBC			Indirect estimate of effect OR [95% CI]
	Treatment effect OR (95% CI)	Cell enrichment LBC, %(n/N)	Conventional cytology, %(n/N)	Conventional cytology, %(n/N)	Cell filtration LBC, %(n/N)	Treatment effect OR (95% CI)	
Beerman	2.23 (1.12, 4.42)	96.3% (309/321)	92% (347/377)				0.3319 (0.0165, 6.6684), p=0.4712
Strander				96% (120/125)	99.4% (81/81)[a]	6.71 (0.36, 124.48)	
Source	Beerman 2009 p. 574, attachment 4			Strander 2007 Table 2, p.287, attachment 4			

Abbreviations: LBC, liquid-based cytology; OR, odds ratio; CI, confidence interval
Indirect OR < 1 indicates performance of cell filtration LBC is better than cell enrichment LBC
a. Zero cells cause problems with computation of standard errors so rather than using 81/81=1 in the OR calculation (p/1-p) which would result in 1/0, 80.5 was substituted in the numerator according to standard practice (Egger, Smith and Altman 2003)

Table 57 Summary of results of the indirect comparison of cell enrichment LBC and cell filtration LBC specificity for CIN 1+

	Trial of cell enrichment LBC			Trial of cell filtration LBC			Indirect estimate of effect OR [95% CI]
	Treatment effect OR (95% CI)	Cell enrichment LBC, %(n/N)	Conventional cytology, %(n/N)	Conventional cytology, %(n/N)	Cell filtration LBC, %(n/N)	Treatment effect OR (95% CI)	
Beerman	0.81 (0.73, 0.89)	97.7% (34207/34996)	98.2% (49826/50755)				1.2596 (0.9542, 1.6627), P=0.1033
Strander				98.5% (8491/8619)	97.7% (4470/4575)	0.64 (0.50, 0.83)	
Source	Beerman 2009p. 574, attachment 4			Strander 2007 Table 2, p.287, attachment 4			

Abbreviations: LBC, liquid-based cytology; OR, odds ratio; CI, confidence interval
Indirect OR < 1 indicates performance of cell filtration LBC is better than cell enrichment LBC

Positive and negative predictive value

Increased, similar or hardly reduced positive predictive value are a preferred method for evaluating cervical screening technology compared to a standard (section B.5).PPV is reported or calculated, for the purposes of the submission, for all but the RODEO cell enrichment LBC trial and the Obwegeser 2001 cell filtration trial. NPV is only reported for the two trials that checked for histological follow-up of all patients—Beerman 2009 and Strander 2007.

A comparison of the PPV percentage between trials and review of the within trial comparative outcomes between the trials is provided.

Cell enrichment LBC vs. CC

The PPV and NPV (based on ASCUS+ index test and CIN 1+ reference standard) were calculated using data reported by Beerman 2009 (Table 48, Table 49) and are presented in Table 58. There was no significant difference in PPV and NPV between cell enrichment LBC and CC (P=0.6067 and P=0.1138, respectively)

Table 58 Positive predictive value and negative predictive value for CIN 1+—CC versus cell enrichment LBC: Beerman 2009

Test threshold ASCUS+	Positive predictive value	Negative predictive value
LBC (cell enrichment)	28.14%	99.96%
Conventional cytology	27.19%	99.94%
OR (95% CI), P value	1.05 (0.88 to 1.26), P=0.6067	1.72 (0.88 to 3.35), P=0.1138
Source	Table 48, Table 49, attachment 4)	

Manually calculated for the purposes of the submission (Attachment 4)
OR > 1 indicates performance of LBC is better than CC

The PPV and relative PPV was calculated for each test threshold using data reported by Beerman 2009 (Table 40) and are presented in Table 59. The PPVs of cell enrichment LBC CC were comparable since the 95% confidence intervals around the PPV ratios never differed significantly from unity, irrespective of the cytological or verified outcome cut-off value.

The CIN 1+ PPVs for the ASCUS+, LSIL+, HSIL+ or SCC test thresholds within the trial were approximately 28%, 74%, 84% and 75 to 100%, respectively.

Table 59 Positive predictive value—CC versus cell enrichment LBC: Beerman 2009

	Conventional n/N(%)	LBC n/N(%)	Relative risk [95% CI]	P value
Test threshold	**Endpoint of CIN 1+ detection**			
ASCUS+	347/1277 (27.34)	309/1098 (28.14)	1.04 [0.91,1.18]	0.574
LSIL+	300/402 (74.63)	236/322 (73.29)	0.98 [0.9,1.07]	0.684
HSIL+	247/292 (84.59)	192/228 (84.21)	1 [0.92,1.07]	0.906
SCC	3/4 (75)	0/2 (0)	1.33 [0.76,2.35]	0.439
Source	Attachment 4			

Abbreviations: Abbreviations: ASCUS+, atypical squamous cells of undetermined significance of higher; LSIL, low grade squamous intraepithelial lesion; HSIL, high grade squamous intraepithelial lesion; SCC, squamous cell carcinoma; LBC, liquid-based cytology; CI, confidence interval; TP, true positive; FP false positive

RR < 1 indicates performance of CC is better than LBC

Cell filtration LBC vs. CC

Ronco 2007 reported the PPV and relative PPV for both age cohorts (25 to 34 years and 35 to 60 years) combined. It is limited to ACSUS+ and LSIL+ test thresholds based on CIN 1+, CIN 2+ and CIN 3+ histological outcomes (Table 60). Generally, based on an ASCUS+ test threshold, cell filtration LBC was associated with a significantly lower PPV compared with CC for CIN 1+, CIN 2+ and CIN 3+ histological outcomes. Based on an LSIL+ test threshold the PPV for CIN 1+ was the same for cell filtration LBC and conventional tests but significantly lower for cell filtration LBC with regard to CIN 2+ and CIN 3+ since the 95% confidence intervals around the PPV ratios never differed significantly from unity. However, only CIN detected by cytology was considered in the LBC arm.

The CIN 1+ PPVs for the ASCUS + and LSIL+ test thresholds within the trial were approximately 25% and 37%, respectively. The CIN 2+ and CIN 3+ PPVs for the ASCUS + and LSIL+ test thresholds were 7.4 to 12.7% and 12.7% to 22.1%, and 3.37% to 8.02% and 5.57% to 13.88%, respectively.

Table 60 Relative positive predictive value—CC versus cell filtration LBC; NTCC trial, age 24 to 60 years: Ronco 2007

	Histological CIN endpoint		
	CIN 1 or more, %(n)	CIN 2 or more, %(n)	CIN 3 or more, %(n)
Positive if cytology shows ASCUS or more			
Positive predictive value			
-Conventional group	27.84	12.7	8.02
-LBC group[a]	23.41	7.4	3.37
Relative positive predictive value[b] (95% CI)	0.84 (0.72 to 0.98)	0.58 (0.44 to 0.77)	0.42 (0.29 to 0.62)
Positive if cytology shows LSIL or more			
Positive predictive value			
-Conventional group	38.80	22.08	13.88
-LBC group[a]	36.76	12.72	5.57
Relative positive predictive value[b] (95% CI)	0.95 (0.80 to 1.13)	0.58 (0.43 to 0.78)	0.40 (0.26 to 0.62)
Source: Ronco 2007 Table 3			

Abbreviations: ASCUS, atypical squamous cells of undetermined significance; CI, confidence interval; CIN, cervical intraepithelial neoplasia; LBC, liquid-based cytology

Note: For detection rate and relative sensitivity denominators are 22 466 women in conventional group and 22 708 in LBC group. For positive predictive values and relative positive predictive values denominators are women with positive cytology for ASCUS who had had colposcopy: 661 in conventional group and 1337 in LBC group

a. Only CIN detected by cytology considered
b. Ratio of percentages. LBC compared with conventional cytology. A ratio < 1 indicates CC is better than LBC

The PPV and relative PPV was calculated for all test thresholds (ASCUS+, LSIL+ and HSIL+) and CIN 1 to CIN 3 outcomes using data reported in the NETHCON trial (Siebers 2009) (provided in Table 43). The outcomes calculated for the submission align with the few PPV outcomes reported in Table 5 of Siebers 2009.

The PPVs of cell filtration LBC and CC and their ratios for different levels of test positivity and outcome thresholds are presented in Table 61. The PPVs of cell filtration LBC and CC were comparable since the 95% confidence intervals around the PPV ratios never differed significantly from unity, this irrespective of the cytological or verified outcome cut-off value.

The CIN 1+ PPVs for the ASCUS +, LSIL+ and HSIL+ test thresholds within the trial were approximately 34%, 70% and 87%, respectively. The CIN 2+ and CIN 3+ PPVs for the ASCUS +, LSIL+ and HSIL+ test thresholds within the trial were approximately 27%, 61% and 82%, and 18%, 42% and 60%, respectively.

Table 61 Comparison of positive predictive value—CC versus cell filtration LBC; NETHCON: Siebers 2009

	Conventional n/N(%)	LBC n/N(%)	Relative risk [95% CI]	P value
Test threshold	**Endpoint of CIN 1+ detection**			
ASCUS+	349/1027 (33.98)	412/1144 (36.01)	1.06 [0.94,1.19]	0.322
LSIL+	272/387 (70.28)	329/448 (73.44)	1.04 [0.96,1.14]	0.312
HSIL+	208/238 (87.39)	248/269 (92.19)	1.05 [0.99,1.12]	0.073
	Endpoint of CIN 2+ detection			
ASCUS+	274/1027 (26.68)	331/1144 (28.93)	1.08 [0.95,1.24]	0.242
LSIL+	235/387 (60.72)	283/448 (63.17)	1.04 [0.93,1.16]	0.468
HSIL+	194/238 (81.51)	233/269 (86.62)	1.06 [0.98,1.15]	0.116
	Endpoint of CIN 3+ detection			
ASCUS+	183/1027 (17.82)	236/1144(20.63)	1.16 [0.97,1.38]	0.098
LSIL+	162/387 (41.86)	216/448(48.21)	1.15 [0.99,1.34]	0.066
HSIL+	142/238 (59.66)	182/269(67.66)	1.13 [0.99,1.3]	0.061
Source	Attachment 4			

Abbreviations: PPV, positive predictive value; CC, conventional cytology; LBC, liquid-based cytology; CI, confidence interval; CIN, cervical intraepithelial neoplasia; ASCUS+, atypical squamous cells undetermined significance grade or higher; LSIL+, low grade squamous intraepithelial lesion or higher; HSIL+, high grade squamous intraepithelial lesion or higher; TP, true positive; FP, false positive

RR < 1 indicates performance of CC is better than LBC

The PPV and NPV (based on ASCUS+ index test and CIN 1+ reference standard) were calculated using data reported by Strander 2007(Table 51 and Table 52) and are presented in Table 62. There was no significant difference in PPV and NPV between cell enrichment LBC and CC (P=0.3173 and P=0.2629, respectively).

Table 62 Positive predictive value and negative predictive value for CIN 1+—CC versus cell enrichment LBC: Strander 2007

Test threshold ASCUS+	Positive predictive value	Negative predictive value
LBC (cell enrichment)	43.55%	100%
Conventional cytology	48.39%	99.94%
OR (95% CI), P value	0.82(0.56 to 1.21), P=0.3173)	5.26 (0.29 to 96.37), P=0.2629
Source	Table 51, Table 52, Attachment 4	

Abbreviations: LBC, liquid-based cytology; OR, odds ratio; CI, confidence interval
Manually calculated for the purposes of the submission. (Attachment 4)
OR > 1 indicates performance of LBC is better than CC

The PPV and relative PPV were not reported for the trial by Strander 2007. To enable comparisons the PPV and relative PPV was calculated for each test threshold (ASCUS+, LSIL+ and HSIL+) using data reported in Strander 2007 (Table 44).

The PPVs of cell filtration LBC and CC and their ratios for different levels of test positivity and outcome thresholds are presented in Table 63. The PPVs of LBC and Pap smears were comparable since the 95% confidence intervals around the PPV ratios never differed significantly from unity, irrespective of the cytological or verified outcome cut-off value.

The CIN 1+ PPVs for the ASCUS+, LSIL+ and HSIL+ test thresholds within the trial were approximately 78%, 88% and 95%, respectively. The CIN 2+ PPVs for the ASCUS+, LSIL+ and HSIL+ test thresholds within the trial were approximately 48%, 61% and 95%, respectively.

Table 63 Comparison of positive predictive value—CC versus cell filtration LBC: Strander 2007

	Conventional n/N(%)	LBC n/N(%)	Relative risk [95% CI]	P value
Test threshold	**Endpoint of CIN 1+ detection**			
ASCUS+	120/248 (48.39)	81/186 (43.55)	0.9 [0.73,1.11]	0.317
LSIL+	74/128 (57.81)	61/108 (56.48)	0.98 [0.78,1.22]	0.837
HSIL+	42/45 (93.33)	33/35 (94.29)	1.01 [0.9,1.13]	0.861
	Endpoint of CIN 2+ detection			
ASCUS+	73/248 (29.44)	55/186 (29.57)	1 [0.75,1.35]	0.976
LSIL+	51/128 (39.84)	44/108 (40.74)	1.02 [0.75,1.4]	0.889
HSIL+	42/45 (93.33)	29/35 (82.86)	0.89 [0.75,1.05]	0.141
Source	Attachment 4			

Abbreviations: CC, conventional cytology; LBC, liquid-based cytology; CI, confidence interval; CIN, cervical intraepithelial neoplasia; ASCUS+ , atypical squamous cells undetermined significance, LSIL+, low grade squamous intraepithelial lesion or higher; HSIL+, high grade squamous intraepithelial lesion or higher TP, true positive; FP, false positive
RR < 1 indicates performance of CC is better than LBC

Maccallini 2008 reported only the proportion of women in whom CIN 2+ was histologically confirmed in screen positive (ASCUS+) patients within one year of colposcopy. The publication reports the percentage PPV only and indicates the data represents "PPV for CIN 2+ at referral" (Maccallini 2008, Table 4). It is uncertain what referral PPV means given all ASCUS+ patients were referred for colposcopy. In the overall series PPV was slightly, not significantly higher with cell filtration LBC arm compared with CC (P=0.20) (Table 64). There were three centres (Atri, Lanciano, Avezzano-Sulmona) involved in the trial. When reviewed by centre there was a

significant difference in PPV in favour of cell filtration LBC for the Avezzano-Sulmona centres (37.3% vs. 19.2%, p<0.05) (Maccallini 2008 p. 571).

The CIN 2+ PPV for the ASCUS+ test threshold within the trial was 12% to 17%.

Table 64 Positive predictive value for CIN 2+—CC versus cell filtration LBC: Maccallini 2008

	Conventional (N=4299) n/N(%)	LBC (N=4355) n/N(%)	P value
Test threshold	Endpoint of CIN 2+ detection		
ASCUS+	NR/NR (12.2)	NR/NR (17.1)	0.20
Source: Maccallini 2008, Table 4 p.571			

Abbreviations: CIN, cervical intraepithelial neoplasia; LBC, liquid-based cytology; ASCUS+, atypical squamous cells of undetermined significance grade or higher; NR, not reported

The RHINE-SAAR trial (Ikenberg 2011) reported the detection of histologically confirmed CIN 2+ lesions for screen positive patients (ASCUS+). Scant data were reported and data were presented in abstract form only. However, the authors report that PPV for cell filtration LBC and CC for CIN 2+ was 48% and 38%, respectively (Table 65). The PPV for LBC analysed using the TIS and CC for CIN 2+was 44% and 38%.

The CIN 2+ PPV for the ASCUS+ test threshold within the trial was 38% to 48%.

Table 65 Positive predictive value for histologically confirmed CIN 2+ of CC versus cell filtration LBC (manual and automated analysis): RHINE-SAAR study 2010–2011

	Conventional (N=9293) n/N(%)	LBC (N=11331) n/N(%)	LBC (ThinPrep Imaging System) n/N(%)
Test threshold	Endpoint of CIN 2+ detection		
ASCUS+	NR/NR (38)	NR/ NR (48)	NR/NR (44)
Source: Ikenberg 2011b			

Abbreviations: CIN, cervical intraepithelial neoplasia; LBC, liquid-based cytology; ASCUS+, atypical squamous cells undetermined significance or higher; NR, not reported

Summary of results

It was reported that the colposcopic examination and histologic reading of the biopsy was blinded to the cytology sampling modality in three trials—NETHCON (Siebers 2008), Strander 2007 and Maccallini 2008. Blinding to the sampling modality was not reported for the remaining trials. The reference standard applied in Beerman 2009 is unknown.

It should be noted that comparisons based on histologic follow-up of cytologic reports of ASCUS (pLSIL) and LSIL are subject to bias because of the selective nature of the subset biopsied. By comparison, the accepted procedure for cytologic reports of HSIL, as occurs in Australian guidelines, is referral for biopsy and is less prone to selectivity bias. Any differences in the PPV at various test thresholds across the three alternative histological reference standard may in part be due to differences in terminology and classification between trials.

It should also be noted that only CIN detected by cytology were considered in the LBC arm of the NTCC trial. Results from this trial are therefore viewed with caution .

Overall, for reference outcome CIN 1+ the PPV percentage for test threshold ASCUS+ and LSIL+ varied among the four trials (Beerman 2009, NTCC, NETHCON and Strander 2007), ranging from 23% to 48% and 36% to 74%, respectively. However all trials, except NTCC, showed no significant difference between LBC (cell enrichment or cell filtration) and CC. All trials except the NTCC trial reported the PPV percentage for test threshold HSIL+. The PPV percentage was generally similar between the trials (84%to 94% PPV) and none demonstrated any significant difference between LBC (cell enrichment or cell filtration) and CC.

Overall for reference outcome CIN 2+ the PPV percentage for test threshold ASCUS+ and LSIL+ was only available for six cell filtration LBC trials. The PPV percentage varied between the trials, ranging from 7% to 48% and 12% to 63%, respectively. However all trials, except NTCC, showed no significant difference between cell filtration LBC and conventional cytology. PPV percentage for test threshold HSIL+ was generally similar between the three trials for which data were available (81% to 100% PPV) and all trials showed no significant difference between cell filtration LBC and CC.

Only two trials—NTCC and the NETHCON trial—reported the reference outcome for CIN 3+, again the PPV percentage for test threshold ASCUS+ and LSIL+ varied between the trials, ranging from 3.37% to 20.63% and 13.88% to 48.21%, respectively. The NTCC trial found significantly reduced PPV for CIN 3+ based on test threshold ASCUS+ and LSIL+ but this was not the case in the NETHCON trial. The correlation between the reference outcome CIN 3+ and the HSIL+ test threshold was reported in the NETHCON trial only. The PPV percentage ranged from 59% to 67% with no significant difference calculated between cell filtration LBC and CC.

All trials, with the exception of the NTCC trial, showed no significant difference in PPV between LBC (cell enrichment or cell filtration) and CC. As the test positivity threshold improved from ASCUS+ to HSIL+ the PPV for the detection of CIN 1+, CIN 2+ and CIN 3+ increased for both test preparation methods.

B.6.4 Impact of screening on clinical management

The impact of screening on clinical management was documented in four cell filtration LBC trials only. Overall, three trials reported no significant differences in clinical management between cell filtration LBC and CC. Maccallini 2008 reported that significantly more patients were referred for colposcopy after CC compared with cell filtration LBC although the rates of CIN 2+ detection were no different between the arms.

Ronco 2007, reporting the NTCC trial, quantifies the number of colposcopies and biopsies performed for each arm of the trial. Referrals were also based on HPV testing results which were only performed in the LBC arm. Among women attending for colposcopy, the mean number of colposcopies and mean number of biopsies in the CC arm were 1.33 (standard deviation [SD] 0.53) and 0.76 (SD 0.90) and in the cell filtration LBC arm were 1.33 (SD 0.52) and 0.74 (SD 0.94). Colposcopists were not blinded to type of cytology, but the number of biopsies per woman undergoing colposcopy was similar in both arms. Histology was independently reviewed, with reviewers blinded to trial arm and cytology result. Again, a similar proportion of women underwent a biopsy in the two arms.

Siebers 2009, reporting the NETHCON trial, reported the proportion of women who underwent repeat cytology due to an ASCUS or LSIL cytological abnormality in the initial screen. Across both arms of the trial approximately 71% of women were followed up cytologically and six women had only colposcopy (P=0.343). For those with HSIL cytological abnormality, histology was performed across both arms of the trial in over 90% of the cases (P=0.145).

Strander 2007 reported that there were no significant differences in the proportion of smears that were followed with histopathology (P=0.71).

In Maccallini 2008, ASCUS+AGUS reports were more frequent with CC as compared to cell filtration LBC, and this caused a higher referral rate for colposcopy in the CC arm (5.0% vs. 4.1%, P=0.04).The CIN 2+detection rate was not statistically different in both arms (CC=0.54%, cell filtration LBC=0.66%, P=0.45), despite the higher referral for colposcopy in the CC arm.

B.6.5 Secondary comparison automated versus manual reading of slides

No studies were identified that assessed the impact of LBC with manual or automated slide reading on the incidence of invasive cervical cancer or consequent mortality rates compared to

conventional cytology. The evidence that is available is the relative accuracy of manual or automated LBC for detecting precancerous cervical lesions.

Kitchener 2011

The Manual Assessment Versus Automated Reading in Cytology (MAVARIC) trial compared the accuracy of the two techniques for the detection of underlying disease. Women aged 25–64 years undergoing routine screening or who had been referred for conventional Pap smear or colposcopy following a recent cervical abnormality in Manchester, UK, were randomly assigned (1:2) to receive either manual reading only or paired reading (automation assisted reading and manual reading), between 1 March 2006, and 28 February 2009. In the paired arm, two automated systems were used—the ThinPrep Imaging System and the FocalPoint GS Imaging System.

General practices and community clinics were randomised to either ThinPrep or to SurePath (for the FocalPoint system) LBC with block randomisation stratified by deprivation index.

Samples were then individually randomised to manual reading only or paired reading only at a single laboratory. Laboratory staff members were unaware of the allocation of each slide and concealment was maintained until the end of the reporting process.

Manual screening (in both arms) was done according to routine laboratory protocols. In the paired arm, automated reading was undertaken first, followed by the manual read.

High grade cytological abnormality prompted referral to colposcopy, **and low-grade abnormalities (borderline/ASCUS and mild dyskaryosis/LSIL) were triaged by human papillomavirus (HPV) testing, with HPV-positive cases referred to colposcopy**. Women with negative cytology and those with HPV-negative low-grade abnormalities were returned to routine recall. The reference standard was histopathology obtained at colposcopy from either a colposcopically directed punch biopsy or loop excision. Abnormalities were examined by specialist gynaecological pathologists who were blinded to the arm of the study.

The primary outcome was sensitivity of automation-assisted reading relative to manual reading for the detection of underlying CIN grade 2 or worse (CIN 2+) in the paired arm.

Results

There were 73,266 LBC samples obtained from women undergoing primary cervical screening; 24,688 allocated to the manual-only arm and 48,578 to the paired-reading arm. Most of the samples (82.5%) were derived from routine cervical screening, 10.6% were repeat samples

requested following a low-grade cytological abnormality and 6.2% were taken at a colposcopy clinic where there had not been a prior study sample from that woman (Table 66).

Table 66 Source of the randomised samples

	Cell Enrichment (SurePath)		Cell Filtration (ThinPrep)		Total (%)
	Manual	Paired	Manual	Paired	
Routine[a]	9765	19331	10207	20799	60102 (82.5)
Other/colposcopic clinic[b]	988	1576	657	1320	4541 (6.2)
Other[c]	1363	2327	1440	2556	7686 (10.6)
Missing	79	170	67	192	508 (0.7)
Total	12195	23404	12371	24867	72837(100.0)

a Defined as: routine call, routine recall, previous inadequate, opportunistic.
b Defined as: previous biopsy/treatment, annual tests.
c Defined as: clinically indicated, previously abnormal, other.
Source: Kitchener 2011a Table 14

Comparisons between results in the manual-only arm and those from the manual reading in the paired arm were restricted to routine screening samples as there were a larger proportion of non-routine samples in the manual-only arm.

All results were reported using the British Society for Clinical Cytology (BSCC) 1986 classification. A comparison between the BSCC 1986 classification and the Bethesda system 2001 is provided (Table 67).

Table 67 Cytology classification: Kitchener 2011a

BSCC 1986	Bethesda System 2001
Negative	Negative for intraepithelial lesion or malignancy
Inadequate	Unsatisfactory for evaluation
Borderline nuclear change (include koilocytosis)	ASCUS/Atypical endocervical/endometrial/glandular cells: NOS or favour neoplastic
Mild dyskaryosis	LSIL
Moderate dyskaryosis	HSIL
Severe dyskaryosis	HSIL
Severe dyskaryosis query invasive	Squamous cell carcinoma
Query glandular neoplasia	Endocervical carcinoma in situ, adenocarcinoma, endocervical, endometrial, extra-uterine, NOS

Abbreviations: HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NOS, not otherwise specified
Source: Kitchener 2011a Table 6

Data received from the cytology laboratory consisted of the manual reading results, the automated reading results and the final management result. The final management result was the result that determined clinical management (routine recall, triage by HPV test or direct colposcopy referral).

Comparison of manual results (manual arm) versus manual results (paired arm)

The actual management results were almost identical between the arms, with slightly fewer mild and moderate dyskaryosis and slightly more borderline in the paired arm (Table 68). The comparison of final manual results (FMRs) between the arms is important in indicating whether the manual reading in the paired arm was similar to 'real-life' manual reading in the manual-only arm which serves as a control. For routine samples, the rates of abnormality are very similar. The non-negative rates of cytology (as a percentage of all adequate samples) are 5.48% (2046/37,369) in the paired arm and 5.52% (1021/18,507) in the manual-only arm.

Table 68 Test yield comparison (by cytology)—Automated review versus manual review (SurePath and ThinPrep): Kitchener 2011a

	Paired sample				Manual only
	Final automated review		Final manual review		Final manual review
	BD FocalPoint GS Imaging system of SP smears	ThinPrep Imaging System of TP smears	BD FocalPoint GS Imaging system of SP smears	ThinPrep Imaging System of TP smears	TP and SP smears
Inadequate	397(1.70)	482(1.94)	626(2.67)	740(2.98)	639(2.60)
Negative	21,791(93.11)	22,980(92.41)	21,176(90.48)	22,471(90.36)	22,118(90.04)
Borderline/mild	917(3.92)	1122(4.5)	1277(5.5)	1364(5.49)	1476(6.01)
Moderate	118(0.50)	120(0.48)	130(0.56)	122(0.49)	158(0.64)
Severe	181(0.77)	163(0.66)	195(0.83)	170(0.68)	175(0.72)
Total	23,404(100)	24,867(100)	23,404(100)	24,867(100)	24,566(100)

Abbreviations: BD, Becker Dickenson; GS, guided system; SP, SurePath; TP, ThinPrep
Source: Kitchener 2011a Table 18 and Table 19

Comparison between manual readings in manual-only arm

Upon reviewing the association between manual result 1 (MR1) and final management result there was discordance in 5.1% of cases, half of which were due to borderline/negative mismatches; most were borderline MR1s downgraded to negative in checking (Table 69).

Table 69 Manual review concordance—First manual result versus final manual result (SurePath and ThinPrep smears): Kitchener 2011a

	Management result 1								
Final manual result	Inadequate	Negative	Borderline	Mild	Moderate	Severe	Glan Neo	Q invasive	Total
Inadequate	**564**	52	20	2	1				639
Negative	18	**21,528**	542	23	3	3		1	22,118
Borderline	2	72	**623**	89	13	4	2	3	808
Mild		18	201	**413**	33	3			668
Moderate		4	18	47	**80**	9			158
Severe		4	12	7	32	**105**	1		161
Glan Neo						2	**1**	1	4
Q invasive		2	3			3		**2**	10
Total	584	21680	1419	581	162	129	4	7	24,566

Abbreviations Glan neo, query glandular neoplasia; Q, query

a. MR1 (manual result) results are the result of the first manual read providing this was not by a trainee.

b. Final manual result is defined as the last manual result before any automated result is taken into account

c. Concordant results 23,316 (94.9%); discordant results 1250 (5.1%)

Source: Kitchener 2011a Table 21

When the final automated results and final manual results were compared (Table 70) there was a discordant rate of 3.8% (1850/48,271), of which half (931/1850) represented abnormal final manual results reported as negative on final automated result. This outweighs the discordant results where there were abnormal results on final automated result were reported as negative on final manual result (294/1850). This indicates a potential for greater relative sensitivity by manual than by automated reading.

Table 70 Manual review versus automated review concordance—Final manual result versus final auto result (SurePath and ThinPrep smears): Kitchener 2011a

	Final automated result						
Final manual result	Inadequate	Negative	Borderline/mild HPV positive	Borderline/mild HPV negative	Borderline/mild HPV not known	Moderate+	Total
Inadequate	**810**	556					1366
Negative	69	**43,284**	125	101	56	12	43,647
Borderline/mild HPV positive		317	**900**				1217
Borderline/mild HPV negative		350		**334**			684
Borderline/mild HPV not known		217			**523**		740
Moderate+		47				**570**	617
Total	879	44,771	1025	435	579	582	48,271

Abbreviations: HPV, human papilloma virus
Final manual result is defined as the last manual result before any automated result is taken into account.
Final auto result is defined as the last automated result.
Concordant results 46,421 (96.2%); discordant results 1850 (3.8%).
Source: Kitchener 2011a Table 22

Primary outcome

The primary outcome is the relative sensitivity of screening by automated or manually read cytology to detect CIN 3+ and CIN 2+. For the purposes of investigating sensitivity and specificity, the cytology results were translated into positive and negative outcomes for final manual result and final auto result.

Definition of result positive is a final auto result of borderline or worse, and the woman referred to colposcopy (i.e. if borderline/mild the **HPV result is positive**). Final negative is any negative result or where the final auto result was borderline/mild, but the **HPV result was negative**. Where the cytology result was borderline or mild, but the HPV status is not known, then it is assumed to be final auto result positive if the subject was sent for colposcopy. Samples where the women were referred to colposcopy, but no result has been obtained (either due to non-attendance or inadequate result) have been excluded. Samples where either the final auto result or the final manual result was inadequate have also been excluded.

The TBS 2001 equivalent cytological classifications of borderline and mild are ASCUS and LSIL. Results from both of these categories are captured as final auto/manual review positive and negative depending on whether the subsequent HPV test of the sample was positive or negative. **Therefore, borderline and mild results are captured in both positive and negative final manual/auto review reports distinguished only by colposcopy referral due to HPV result.** In

the Australian environment the current course of action is to repeat cytology for any ASCUS or LSIL findings. The protocol in the MAVARIC trial is therefore not representative of local processes or any other practice where HPV triage testing is not implemented. The sensitivity and specificity reported from MAVARIC reflect not just the manual versus auto review but concurrent HPV testing also.

There is a slight difference between the proportion of borderline and mild cytological results in the automated review of SP and TP slides and the manual review of SP and TP slides in the paired arm (n=917 (3.92%) and n=1122 (4.5%) versus n=1277 (5.5%) and 1364 (5.49%), respectively). HPV testing of this population meant that 46% (1334/2923) patients were referred for colposcopy due to positive HPV testing with a borderline/mild cytology outcome whereas only 10% (321/2923) of patients were referred for colposcopy despite a negative or unknown HPV test (Kitchener 2011a Table 31). Therefore there was almost five times the number of referrals for colposcopy for patients with LSIL cytological findings due to HPV testing that would otherwise have been the case had HPV testing not been performed. The distribution of HPV findings between SP and TP is not reported. Therefore the impact of the imbalance of LSIL findings between the technologies read via automated review is difficult to interpret. It is possible that one technology read via automated review is more sensitive for the detection of HPV related cytological changes.

The congruence of final auto result and final manual result reported in Table 70 subcategorises borderline/mild cytological outcomes according to HPV results but does not provide congruence for borderline and mild cytological outcomes separately. This is important because the rates of detection of CIN 2+ between borderline and mild cytological outcomes differ (14.2% versus 23.1%, Table 71).

Overall there is an uneven distribution of borderline/mild cytological outcomes between auto and manual review, the distribution of borderline and mild cytological outcomes within each group is unknown but the rates of CIN 2+ detection differ between HPV positive borderline and mild cytological outcomes. It is not known whether this may have impacted the relative sensitivity and specificity between final auto result and final manual result.

It is important to note that the majority of HPV positive borderline and mild cytological outcomes results in no abnormality detected, 35.6% and 30.2%, respectively. For borderline cytological outcomes, 26.2% of patients had no pre-cancerous abnormalities detected on colposcopically -directed biopsy. This most likely represents the natural history of acute HPV infections which spontaneously clear 8 to 14 months post infection (NHMRC guidelines p.12).

It is noted that most CIN 2+ in the MAVARIC study were found as a result of testing low-grade abnormalities found on manual screening for high-risk HPV. However, the TOMBOLA study into the management of low-grade abnormalities showed that there were fewer CIN 2+ cases in the arm followed with cytology than in the immediate colposcopy arm. This was presumed to be as a result of regression of CIN 2 in the cytology arm, as the rate of CIN 3 was similar in both arms, and raises questions about whether CIN 2 should be considered a high grade lesion (TOMBOLA group 2009). Castle 2009 discussed the behaviour of CIN 2 presenting as low-grade cytology, and suggested that HPV16-related CIN 2 is different from non-HPV16 disease. The latter is more likely to regress spontaneously, and so the reduced detection of low grade cytology harbouring high-grade histology may not be as important as it seems at first sight.

Table 71 Correlation cytology management and colposcopy outcome—LBC (SurePath and ThinPrep): Kitchener 2011a

	Cytology/HPV management result				
			Histology		
Colposcopy outcome	Colposcopy NAD n(%)	HPV only(%)	CIN 1, n(%)	CIN 2, n (%)	CIN 3+ n (%)
Negative	34 (4.4)	45 (7.9)	14 (4.0)	10 (3.3)	3 (0.7)
Inadequate	11 (1.4)	1 (0.2)	0 (0)	0 (0)	0 (0)
Borderline HPV positive	277 (35.6)	149 (26.2)	68 (19.2)	43 (14.2)	37 (9.2)
Borderline HPV negative	11 (1.4)	1 (0.2)	3 (0.8)	0 (0)	1 (0.2)
Borderline HPV not known	83 (10.7)	44 (7.7)	16 (4.5)	8 (2.6)	1 (0.2)
Mild HPV positive	235 (30.2)	166 (29.2)	130 (36.7)	70 (23.1)	34 (8.4)
Mild HPV negative	1 (0.1)	2 (0.4)	0 (0)	2 (0.7)	0 (0)
Mild HPV not known	93 (12.0)	101 (17.8)	68 (19.2)	29 (9.6)	11 (2.7)
Moderate	14 (1.8)	43 (7.6)	38 (10.7)	82 (27.1)	72 (17.8)
Severe	13 (1.7)	15 (2.6)	14 (4.0)	57 (18.8)	220 (54.5)
Q Inv	0 (0)	1 (0.2)	0 (0)	2 (0.7)	10 (2.5)
Q glan	5 (0.6)	0 (0)	3 (0.8)	0 (0)	15 (3.7)
Total	777 (100)	568 (100)	354 (100)	303 (100)	404 (100)

Abbreviations: CIN 3, squamous cell carcinoma; CIN 2, High-grade pre-cancerous squamous or glandular cell changes on colposcopically directed biopsy; CIN 1, low-grade pre-cancerous squamous cell changes on colposcopically directed biopsy; HPV only, No pre-cancerous abnormalities detected on colposcopically directed biopsy; NAD, no abnormalities seen during colposcopic examination; Q Glan, query glandular neoplasia; Q Inv, query invasive.
Source: Kitchener 2011a Table 43

Finally the colposcopy referral rates differ between the two LBC types. A comparison between the proportion of women referred for colposcopy broken down by arm and LBC type, as a result of HSIL cytology and HPV triage of low-grade abnormalities according to LBC type was reported (Kitchener 2011a p. 53). Between the two LBC systems, 3.7% (1025/27,897) were referred

following BD SurePath and 4.3% following ThinPrep cytology (1267/29,666) (P < 0.001). The reason for this difference is not clear but may reflect a difference in sensitivity for the detection of HPV related cytological changes of SP over TP.

Nonetheless the final conclusion reported from the MAVARIC trial are that Automation-assisted reading was 8% less sensitive than manual reading (relative sensitivity 0.92, 95% CI 0·89 to 0·95), which was equivalent to an absolute reduction in sensitivity of 6·3%, assuming the sensitivity of manual reading to be 79%. Specificity of auto-assisted reading, relative to manual reading, increased by 0.6% (1.006, 95% CI: 1.005 to 1.007). It is noted that a small proportion of CIN2+ cases missed with automated reading were due to human error. That is, the instrumentation detected the abnormal cells in the fields of view presented to the screeners. There is no mention of feedback to screeners in the MAVARIC study after initial training. Lack of feedback and ongoing learning opportunities for screeners may have contributed to the false negative rate persisting throughout the study as well as the reduced sensitivity of automated reading for CIN 2+ compared with manual screening.

Palmer 2012

In 2003 all 12 Scottish laboratories converted to LBC. The HPV immunisation program against HPV types 16 and 18 commenced in Scotland in 2008 for 13-year-old girls, with a catch up program for 17- to 18-year-olds. This was expected to reduce the incidence of HPV related cervical cancer and HSIL detected cervical screening. Evidence suggested that the implementation of image-directed screening can assist the detection of abnormalities with a low prevalence. Hence Palmer 2012 aimed to assess the feasibility of introducing computer assisted screening of ThinPrep cervical samples with the Hologic ThinPrep Remote Imaging system-Multicyte.

The study was a parallel group randomised trial, comparing manual screening with image-guided (Dual Review) screening. Samples were screened at two clusters of three laboratories, cluster 1 was more rural and cluster 2 more urban. Cases were allocated in a strict accession number order to achieve even distribution between arms.

The screeners had a range of experience and screening speeds. Training in the use of the ThinPrep Imaging System (TIS) was delivered by Hologic personnel according to their standard protocols and was completed by October 2008. The trial consisted of 169,917 samples, randomly allocated in each laboratory by accession number, 1–50 imaged and 51–100 manually screened. Samples were all screening program LBC preparations and there were no exclusions. Heavily bloodstained samples were included in both study arms and glacial acetic acid (GAA) washes were performed according to laboratory protocols. Quality control by rapid review/preview was continued throughout the study. Review and reinforcement of training was carried out throughout the

study. One laboratory (number 2) used rapid preview and all the others used rapid review (Table 1).

The hypothesis tested by statistical analysis was that image-assisted screening would be both qualitatively and quantitatively better than manual ThinPrep screening. The 95% confidence intervals are reported only for the sum of all six (not for individual) laboratories, and are calculated using Wilson's method. P values are two-tailed Fisher's Exact Tests except where stated otherwise.

Sensitivity, specificity and false-negative rates using the final cytology report as the outcome, and positive predictive value (PPV) using histological biopsy as outcome are calculated. Table 72 compares the reporting terminology used in the trial (according to National Health Service Cervical Screening Program) with the Bethesda system.

Table 72 Cytology classification: Palmer 2012

SNHSCSP	Two-tier	Bethesda System 2001
Borderline squamous and glandular changes without HPV	Low-grade	ASC-US/ASC-H/AGC
Borderline with HPV and mild dyskaryosis		LSIL
Moderate dyskaryosis	High-grade	HSIL
Severe dyskaryosis		Cancer
Severe dyskaryosis query invasive query glandular neoplasia		 AGC favour neoplasia AIS, adenocarcinoma

Abbreviations: AGC, atypical glandular cells, AIS, adenocarcinoma in situ, ASC-US, atypical squamous cells undetermined significance; ASC-H, ASC cannot exclude high grade squamous intraepithelial lesion (HSIL); HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion; SNHSCSP, Scottish National Health Service Cervical Screening Program

The formulae used for statistical analysis based on the final cytology report are provided in Table 73.

Table 73 Formulae used for statistical analysis for accuracy by final cytology report: Palmer 2012

	Final cytology report		
Primary screen	Negative/inadequate	Low-grade (borderline/mild)	High-grade (moderate or worse)
Negative/inadequate	a	b	c
Low-grade (borderline/mild)	d	e	f
High-grade (moderate or worse)	g	h	i

For data presented in Table 76: Sensitivity=(e+f+h+i)/(e+f+h+i)+(b+c).

Specificity=a/(a+d+g).

Predictive value=(e+f+h+i)/(e+f+h+i)+(d+g).

For data presented in Table 77: Sensitivity=i/(i+c).

Specificity=a/(a + g).

Predictive value=i/(h + i).

For data presented in Table 78: Sensitivity=i/i+(c + f).

Specificity=(a + b + d + e)/(a + b + d + e)+(g + h).

Predictive value=i/i+(g + h).

The formulae used for statistical analysis based on histology results are provided in Table 74.

Table 74 Formulae used for statistical analysis for accuracy by histology report: Palmer 2012

	Histology result			
Cytology result	Negative	HPV only	CIN 1	CIN 2, CIN 3, invasive cancer CGIN/adenocarcinoma in situ
Low-grade cytology (borderline/mild)	a	–	–	b
High-grade cytology (moderate or worse)	c	–	–	d

Abbreviations: CIN, cervical intraepithelial neoplasia; CGIN, cervical glandular intraepithelial neoplasia

For data presented in Table 79 and Table 80: Positive predictive value (PPV)=d/(c + d).

Abnormal predictive value (APV)=b/(a + b).

Total predictive value (TPV)=b+d/(a + b + c + d).

Results

A total of 169,917 LBC preparations—79,366 in the imager and 90,551 in the manual arm—were used for qualitative analysis. The reporting profiles of the laboratories as a whole are set out in Table 75. Crude odds ratio was calculated using RevMan for the purpose of this submission, using n values derived from the percentages presented in Palmer 2012 (Table 2) and N from the values presented in Palmer 2012 (Table 1).

There was a significant reduction in inadequate smear reports and in negative smear reports, and a significant increase in low-grade cytology reports in the imager arm. There was no significant difference in the reporting rate of HSIL cytology between the arms

Table 75 Test yield comparison (by cytology)—LBC manual versus LBC automated (ThinPrep): Palmer 2012

	LBC Manual N=90551		LBC automated N=79366		P value[b]	Crude OR[c] [95% CI]	Adjusted OR (95% CI)
	n[a] (%)	95% CI	n[a] (%)	95% CI			
Inadequate	2445 (2.7)	2.6–2.8	1508 (1.9)	1.8–2.0	0.0001	1.43 [1.34, 1.53]	NR
Negative	82492 (91.1)	90.9–91.3	71906 (90.6)	90.4–90.8	0.0003	1.06 [1.03, 1.10]	NR
LSIL	6791 (7.5)	7.4–7.7	6349 (8.0)	7.8–8.2	0.0008	0.93 [0.90, 0.97]	NR
HSIL	1268 (1.4)	1.3–1.5	1190 (1.5)	1.4–1.5	0.43	0.93 [0.86, 1.01]	NR
Source: Palmer 2012 Table 2							

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; NR, not reported

a. n manually back calculated from percentages presented in Palmer 2012, Table 2. A rounding error is apparent within the percentage yield presented for LBC automated arm totalling 100.1% resulting in a back calculation total N of 79445, that is 0.001% higher than the reported N of 79366.

b. P values calculated using two-tailed Fisher's Exact Tests

Primary screening was significantly more specific using the imager and an abnormal primary screen was significantly more likely to be reported as abnormal as a manual screen. This was true for all abnormalities and for HSIL cytology.

The sensitivity for any abnormality and for HSILs was not significantly different between the arms (Table 76, Table 77, and Table 78).

Table 76 Comparison of sensitivity, specificity and predictive value for any grade of abnormality—LBC manual versus LBC auto (ThinPrep): Palmer 2012

	LBC manual N=90551	LBC automated N=79366	P value[a]
Sensitivity, % (95% CI)	94.3 (93.8–94.8)	94.6 (94.0–95.1)	0.437
Specificity,% (95% CI)	94.9 (94.7–95.0)	95.6 (95.4–95.7)	<0.0001
Predictive value,% (95% CI)	63.8 (62.9–64.6)	68.6 (66.7–69.5)	<0.0001
Source: Palmer 2012, Table 3			

Abbreviations: LBC, liquid-based cytology; CI, confidence interval

a. P values calculated using two-tailed Fisher's Exact Test

Table 77 Comparison of sensitivity, specificity and predictive value for a report of high grade dyskaryosis[a]—LBC manual versus LBC auto (ThinPrep): Palmer 2012*.

	LBC manual N=90551	LBC automated N=79366	P value[b]
Sensitivity,% (95% CI)	95.9 (94.8–97.2)	97.2 (96.1–98.3)	0.141
Specificity,% (95% CI)	99.9 (99.9–100)	100 (99.9–100)	0.008
Predictive value,% (95% CI)	95.1 (93.8–96.4)	97.4 (96.4–98.4)	0.0095
Source: Palmer 2012, Table 4			

Abbreviations: LBC, liquid-based cytology; CI, confidence interval
*Note: False negatives are those found at interval quality control

a. Dyskaryosis is the NHSCSP terminology which correlates to High grade under the two-tier classification or HSIL+ under The Bethesda System (Source: Palmer 2012 Box 3, p.4)
b. P values calculated using two-tailed Fisher's Exact Test

Table 78 Comparison of sensitivity, specificity and predictive value for a report of high grade dyskaryosis[a]—LBC manual versus LBC auto (ThinPrep): Palmer 2012*.

	LBC manual N=90551	LBC automated N=79366	P value[b]
Sensitivity, % (95% CI)	81.7 (79.5–83.8)	79.9 (77.6–82.3)	0.152 (2-tail P=0.296)
Specificity, % (95% CI)	99.6 (99.5–99.6)	99.6 (99.6–99.7)	0.041(2-tail P=0.079)
Predictive value,% (95% CI)	73.0 (70.6–75.3)	76.0 (73.5–78.4)	0.045(2-tail P=0.086)
Source: Palmer 2012, Table 5			

Abbreviations: LBC, liquid-based cytology; CI, confidence interval
*Note: False negative LBC preparations are those found by rapid quality control and those with a primary screener report of low grade

a. Dyskaryosis is the NHSCSP terminology which correlates to High grade under the two-tier classification or HSIL+ under The Bethesda System (Source: Palmer 2012 Box 3, p.4)
b. P values calculated using one-tailed Fisher's Exact Tests and two tailed P value presented in parentheses for transparency

The ability of cytology to predict CIN 2+ and CIN 3+ histology is given in Table 79 and Table 80. There is no significant difference between the two arms when examining the positive, abnormal or TPVs. The significantly greater detection by the imager of low-grade cytology was not associated with a reduction in Abnormal Predictive Value.

Table 79 Abnormal, positive and total predictive values of cytology for a final histology of CIN 2+ for the whole study: Palmer 2012

	Cytological diagnosis for CIN 2+ on histology		
	LBC manual	**LBC automated**	**P value**
Abnormal predictive value[a],% (95% CI)	28.0 (26.0–30.0)	28.4 (25.9–31.0)	0.807
Positive predictive value[b],% (95% CI)	78.5 (76.7–80.3)	80.7 (78.5–82.9)	0.140
Total predictive value[c],% (95% CI)	51.8 (50.3–53.4)	52.8 (50.8–54.7)	0.478
Source: Palmer 2012, Table 6			

a. APV is the percentage referred with borderline changes or mild dyskaryosis that have CIN2+

b. PPV is the percentage of cases referred for high-grade cytological abnormalities (moderate dyskaryosis or worse) that are found on biopsy to have cervical intraepithelial neoplasia grade 2 or worse (CIN2+)

c. TPV is the percentage of all women referred to colposcopy who have CIN 2+

Table 80 Abnormal, positive and total predictive values of cytology for a final histology of CIN 3+ for the whole study: Palmer 2012

	Cytological diagnosis for CIN3+ on histology		
	LBC Manual	LBC Automated	P value
Abnormal predictive value[a],% (95% CI)	8.1 (7.0–9.4)	6.6 (5.3–8.1)	0.126
Positive predictive value[b],% (95% CI)	50.8 (48.6–53.0)	52.3 (49.5–55.1)	0.404
Total predictive value[c],% (95% CI)	28.8 (27.4–30.2)	28.5 (26.8–30.3)	0.823
Source: Palmer 2012, Table 7			

a. APV is the percentage referred with borderline changes or mild dyskaryosis that have CIN 2+

b. PPV is the percentage of cases referred for high-grade cytological abnormalities (moderate dyskaryosis or worse) that are found on biopsy to have cervical intraepithelial neoplasia grade 2 or worse (CIN 2+)

c. TPV is the percentage of all women referred to colposcopy who have CIN 2+

The results show that image-assisted screening is at least as good as conventional screening in detecting HSIL on cytology. The imager arm showed significantly increased reporting of low-grade cytology. The maintained APV indicates that an imager report of low-grade cytology has the same significance as with manual screening and therefore suggests that there may be increased detection of CIN 2+ as a result of increased numbers of cases reported as low-grade cytology. In addition, TIS is significantly more specific than manual screening. Automated slide review in Palmer 2012 averaged 17 slides per hour, a statistically significant increase of 70% compared to manual review.

B.7 Extended assessment of comparative harms

Collection of cervical cells is regarded as safe (MSAC 2009 p.25). A recent systematic review of screening for cervical cancer to assist the US Preventive Services Task Force in updating its recommendations on cervical cancer screening specifically quoted that they, "were unable to

identify any studies or data that identified direct harms resulting from collecting the cervical sample for LBC" (Vesco 2011 p.36).

B.8 Interpretation of the clinical evidence

The present review relies on high quality RCT evidence about the relative differences between LBC and conventional cytology to detect precancerous cervical lesions to draw conclusions about its relative accuracy.

Overall an assessment of the study characteristics that could potentially influence test validity, found the following trials demonstrated notable characteristics that differed from all other RCTs:

- The Beerman 2009 trial did not described the reference standards applied within the trial, nor the threshold of application
- The RODEO trial is unique in that it represents a different geographical location (remote areas of Brazil) and type of health service (recruitment through mobile units).
- The NTCC trial was unique in the application of different reference standards between the arms of the trial.
- The NTCC and MAVARIC performed HPV triage on LBC samples only which went on to inform the application of the reference standard.
- Obwegeser 2001 used different tools between the arms within the trial (a spatula for the collection of cells for conventional slides and cytobrush to collect cells for LBC).

The results of the NTCC, MAVARIC and Obwegeser 2001 trials are viewed with caution due to the imbalance of confounding factors between arms. However for the remaining trials, compared to conventional cytology, cell enrichment liquid-based cytology results in:

- fewer unsatisfactory tests (furthermore, cell enrichment LBC is associated with a lower rate of unsatisfactory tests than cell filtration) and
- significantly less normal outcomes and more ASCUS (+AGUS).

Upon application of the reference standard, compared to conventional cytology, cell enrichment liquid-based cytology:

- demonstrates a significantly greater sensitivity to detect CIN 1+ at a test threshold of ASCUS (pLSIL)

- demonstrates a significantly reduced specificity to detect CIN 1+ at a test threshold of ASCUS (pLSIL)
- is not significantly different in the PPV for CIN 2+ or CIN 3+ at a test threshold of ASCUS+ (pLSIL), LSIL+ or HSIL+.

These conclusions are similar to those reached in MSAC's second review of LBC in 2009 (MSAC 2009).

Compared to conventional cytology, cell filtration liquid-based cytology results in:

- fewer unsatisfactory tests and,
- similar to increased rates of LSIL (although trials are heterogenous with the baseline test yield results varying between trials as well the relative difference).

Upon application of the reference standard, compared to conventional cytology, cell filtration liquid-based cytology:

- demonstrates a significantly greater sensitivity to detect CIN 1+ at a test threshold of ASCUS (pLSIL) (96.3% vs. 92.0%, P=0.0244; an absolute increase of 4.3%)
- demonstrates a significantly reduced specificity to detect CIN 1+ at a test threshold of ASCUS (pLSIL) (97.7% vs. 98.2%, P < 0.0001, an absolute decrease of 0.5%).
- is not significantly different in the PPV for CIN 2+ or CIN 3+ at a test threshold of ASCUS+ (pLSIL), LSIL+ or HSIL+.

CIN 1 is the histopathologic manifestation of a carcinogenic or non-carcinogenic HPV infection that rarely progresses to cancer (Arbyn 2009). The Australian cervical screening guidelines take the conservative approach whereby the clinical investigation for a pLSIL outcome is follow up CC in 12 months (NHMRC 2005). Given the transient nature of much CIN1, Arbyn recommends that surrogate outcomes such as reduction of incidence of CIN 3+, increased detection rate of CIN 3+ or CIN 2+, or increased, similar or hardly reduced positive predictive provide more robust comparative assessment of the screening technology. CIN 3 in particular is the direct precursor of invasive cancer, and therefore a good proxy outcome of trials evaluating new technologies.

Although false positives are undesirable in a screening program, the follow up investigation in this circumstance does not expose patients to a high risk of adverse outcome.

These conclusions are similar to those reached in MSAC's second review of LBC in 2009 (MSAC 2009).

Importantly given the level of evidence and the number of trials now available it was possible to pool the numbers of cervical cancers or CIN 3+ detected thereby increasing the power to detect any difference between LBC and CC. The pooled OR (OR 0.69, 95% CI 0.50 to ~0.95) indicates that the odds of detecting CIN3+ with conventional cytology is 31% lower than with LBC.

In regard to the comparison of manual versus automated review, the results of the MAVARIC trial are confounded due to triage HPV testing, the results of which dictated the application of the reference standard. The results from the study by Palmer 2012 showed that image-assisted screening is at least as good as screening with conventional cytology and is significantly more specific than manual screening. Palmer and MAVARIC both note that productivity increased significantly with imager assisted reading. conclusions reached in the Palmer 2012 trial are similar to those reached in MSAC's review of automated review of LBC in 2009 (MSAC 2009).

The evidence base used to reach the conclusions above are summarised in Table 81 with respect to important features of the evidence outlined in Section B.8 of the PBAC Guidelines.

Table 81 Summary of the evidence base supporting the therapeutic claims

Comparison	Therapeutic claim	The level and quality of the evidence	Statistical precision and size of the effect	Consistency of the results over the trials presented
Cell enrichment LBC vs. conventional cytology	Cell enrichment LBC results in fewer unsatisfactory tests	Single head-to-head RCT of over 80,000 slides (Beerman 2009)	% of tests (n/N) LBC: 0.1% (46/35315) CC: 0.9% (435/51132) OR (95% CI): 0.15 (0.11, 0.21) (Table 24)	Not applicable (only one trial with evidence). Although unsatisfactory tests consistently lower with LBC (of either method compared with conventional cytology)
	Cell enrichment demonstrates a ***significantly greater sensitivity*** to detect CIN 1+ at a test threshold of ASCUS (pLSIL)		Sensitivity [95% CI] LBC: 96.24% [93.54, 97.84] CC: 92.04% [88.87, 94.37] P=0.0244 (Table 50)	Not applicable for evidence from a single trial
	Cell enrichment demonstrates a ***significantly reduced specificity*** to detect CIN 1+ at a test threshold of ASCUS (pLSIL)		Specificity (n/N) [95% CI] LBC: 97.75% [97.58, 97.90] CC: 98.17% [98.05, 98.28] P < 0.0001 (Table 50)	Not applicable for evidence from a single trial
	Higher detection of ASCUS (pLSIL)		Test yield comparison LBC: 2.07% (730/35,315) CC: 0.87% (443/51132) P<0.0001 (Table 32)	Consistent increase in ASCUS reported in RODEO trial
	No difference in the detection of LSIL		Test yield comparison LBC: 0.27% (94/35,315) CC: 0.22% (110/51132) P=0.13 (Table 32)	RODEO trial reported LBC= 0.7%(42/6001) CC=0.3%(18/6047) P<0.001(Table 33)*
	No difference in the detection of HSIL		Test yield comparison LBC: 0.64% (226/35,315) CC: 0.56% (288/51132) P=0.15 (Table 32)	Consistent with no difference reported in RODEO trial

Comparison	Therapeutic claim	The level and quality of the evidence	Statistical precision and size of the effect	Consistency of the results over the trials presented
Cell enrichment LBC vs. conventional cytology	No difference in PPV at various test thresholds	Single head-to-head RCT of over 80,000 slides (Beerman 2009)	Comparative PPV RR (95% CI) ASCUS+:1.04[0.91,1.18] LSIL+:0.98[0.9,1.07] HSIL+: 1[0.92,1.07] SCC: 1.33[0.76,2.35] (RR <1 indicates performance of CC is better than LBC)	Not applicable for evidence from a single trial
Cell enrichment LBC vs. cell filtration LBC	Cell enrichment LBC results in less unsatisfactory tests	Indirect comparison via conventional cytology with a single RCT of each LBC method compared with CC (Beerman and Strander for cell enrichment and cell filtration respectively)	Indirect estimate of effect OR (95% CI) 0.3586 (0.19, 0.69), p=0.0022 (Table 31)	Not applicable
	No difference in the detection of CIN 1+		Sensitivity: Indirect OR (95%): 0.3319 (0.0165, 6.6684), p=0.47 Specificity: Indirect OR (95%): 1.2596 (0.9542, 1.6627), p=0.10 (An OR >1 indicates performance of cell enrichment LBC is better than cell filtration LBC)	As above

* The sample size in the RODEO trial is much smaller than the Beerman 2009 trial and the trial represents a different geographical location (remote areas of Brazil) and type of health service (recruitment through mobile units). As such the results are seen to be less comparable with Beerman 2009 and viewed with caution.

Form of economic evaluation

The differences between cell enrichment LBC and conventional cytology are confined to differences in detection of pLSIL (more with cell enrichment LBC) and differences in rates of unsatisfactory smears (more with conventional cytology). The NCSP guidelines provide almost identical guidance with respect to the follow-up of pLSIL and unsatisfactory smears. That is, repeat the test within a year (as soon as possible in the case of unsatisfactory smears). As such, a cost-minimisation analysis which incorporates the costs of following up these repeat tests (whether for pLSIL or unsatisfactory tests) should be sufficient to determine the cost-effectiveness of SurePath relative to conventional cytology. All other costs relating to the follow-up of higher grade abnormalities will be the same because the detection of higher grade abnormalities between SurePath and conventional cytology is the same.

C. Translating the clinical evaluation to the listing requested for inclusion in the economic evaluation

Section C is provided to show that the conclusion of non-inferiority and the cost-minimisation approach is valid after issues of applicability are addressed.

The reference standards applied in the majority of trials are not applicable to the Australian context. For those that are representative of Australian practice the timing of repeat cytology is not known nor the outcome of the repeat test. Furthermore the participant baseline characteristics and test yield outcomes are not representative of the Australian population. Nonetheless across varying reference standards, patient characteristics and test yield outcomes the same conclusions that cell enrichment LBC demonstrates non-inferior accuracy compared with cell filtration LBC and conventional cytology are made.

Superior performance in decreasing the rates of unsatisfactory slides with cell enrichment LBC is evident across the trials. Differences between LBC and conventional cytology test yield outcomes are variable across trials and could be a reflection of LBC being new to the trial centres. However a conservative position has been taken in assuming increased rates of ASCUS outcomes with cell enrichment LBC in the cost minimisation calculations. Weighted proportions of unsatisfactory slides and low grade abnormalities (ASCUS +LSIL) across all LBC trials are utilised in the cost-minimisation calculations in section D.

The lower unsatisfactory outcomes associated with cell enrichment LBC are expected to outweigh the higher rate of ASCUS outcomes compared with conventional cytology. However the outcomes of repeat testing in both situations, performed at 3 months and 12 months, respectively, are not known. Despite the high likelihood that unsatisfactory slides harbour cervical abnormalities (OR 2.78,95% CI: 2.31 to 3.35) the follow up testing after repeat unsatisfactory or ASCUS is conservatively assumed to be the same in the cost-minimisation calculations in section D and E.

Despite potential anxiety associated with higher rates of ASCUS outcomes with cell enrichment LBC. Equally, unsatisfactory results also impose burden and anxiety on women. The fact that 18% of women are currently paying out of pocket for LBC suggest that the benefits of lower unsatisfactory results outweigh the costs of potential anxiety due to abnormal findings. This could be due to the fact that despite experiencing this anxiety, women would prefer to know

about their risk of cervical cancer.

A learning curve provides a reasonable explanation for the increase in the proportion of ASCUS outcomes reported with cell enrichment LBC that would be expected to diminish over time.

The trial evidence did not distinguish cervical glandular abnormalities. Retrospective evidence provides data to support the increased detection of glandular abnormalities with cell enrichment LBC. Technical differences between cell enrichment LBC and cell filtration LBC provide a plausible rationale supporting this claim.

Section B.8 of this submission concluded that cell enrichment LBC/LBC is non-inferior to and/or no worse than conventional Pap smears on a range of endpoints. This conservative conclusion was made on the basis of consistent evidence from a number of head-to-head randomised controlled trials (RCTs).

The therapeutic conclusion of non-inferiority is conservative because cell enrichment LBC/LBC produces fewer unsatisfactory slides than conventional Pap smears. This is explained by the fundamental differences in the collection and processing technology between the methods discussed in Section A and discussed further below.

The conclusion of non-inferiority means "the difference between the service and the appropriate comparator can be reduced to a comparison of costs" (MSAC Application 1157: DAP, Table 3 p.14).

With identical outcomes and treatment pathways, an economic model of the impact of cell enrichment LBC relative to conventional Pap smears is not necessary. The economic evaluation is based directly on the comparative clinical evaluation presented in Section B of this application. The economic evaluation is a cost-minimisation analysis to be presented in the following section (Section D) followed by cost-effectiveness which is also provided to meet the requirements of the final DAP.

Section C is provided to show that the conclusion of non-inferiority and the cost-minimisation approach is valid after issues of applicability, extrapolation and transformation have been considered.

C.1.1 Applicability of reference standards

According to the Australian Cervical Screening Guidelines, women with ASCUS+ (pLSIL) or LSIL should be recommended for repeat screening in 12 and 24 months, not colposcopy (NHMRC 2005, Appendix A). Referral for colposcopy in Australia would occur based on HSIL+ or repeat LSIL outcome at 12 months.

The two cell enrichment LBC RCTs do not report sufficient information on the reference standards used to understand the applicability to Australia. Only two cell filtration LBC trials reported the application of the same reference standards as Australia—NETHCON (N=85,076) and Strander 2007 (N=13,484), however the timing of the repeat screen is not specified in the NETHCON trial and in Strander the repeat was to occur within 4 months, much sooner than required in Australia.

The NETHCON trial showed no significant difference in the proportion of each cytological category (including ASCUS and LSIL) between cell filtration LBC and conventional cytology (Table 35). A review of the follow up information on test positives in the NETHCON trial indicated that 71.4% and 71.1% ASCUS and LSIL findings with conventional cytology and cell filtration LBC, respectively, remained the same with repeat cytology although the timing of the follow-up test is unknown (Siebers et al. 2009, Table 2).

Strander 2007 detected significantly more LSIL and HSIL with cell filtration LBC compared with conventional cytology. Approximately 50% of the patients with an LSIL finding did not go on to have any histology but it is not known what the repeat smear detected (Strander et al. 2007, Table 3).

The proportion of persistent low grade abnormalities (ASCUS and/or LSIL) in the Strander 2007 trial is unknown. In the NETHCON trial 71% of ASCUS and LSIL persisted at an unknown timepoint. It is therefore uncertain what the result of the repeat smear will detect and generally trial outcomes reported reflect more invasive assessment (such as colposcopy) sooner than would occur in Australia.

C.1.2 Applicability of the trial population

The clinical setting for the trials included in this submission reflects a cervical screening population. Therefore, overall the study participants are representative of the cervical cancer screening population in Australia. To verify the applicability of the trial population to Australia the baseline characteristics from the conventional cytology arm of the trials is compared with the

characteristics reported in the AIHW *Cervical screening in Australia 2009–2010 report* (AIHW 2012) (Table 82).

The age of the trial participants appears to be slightly lower than the majority of women participating in the Australian cervical screening program in 2009–2010.

The distribution of cytological outcomes in the conventional arms from the RCTs indicate that more slides were found to be normal and a lower proportion found to have any abnormalities compared with women participating in the Australian cervical screening program in 2009–2010.

Generally the proportion of histology that was found to contain a low or high grade abnormality was lower in the conventional cytology arm of the LBC trial by Strander 2007 compared with women participating in the Australian cervical screening program in 2009–2010.

The PPV was difficult to compare, given that reported by the AIHW (2012) report captures three categories. However, it appears that the approximate average PPV for CIN1-3 based on the test threshold HSIL was similar to or slightly higher than that reported for cervical screening carried out in Australia between 2009 and 2010.

Table 82 Comparison of RCT baseline characteristics with women participating in the Australian cervical screening program in 2009–2010

Characteristic	Australian characteristics	Trial characteristics
Age	Target age group is women aged 20–69 years 95.9% of women are 20–69 years, participation is highest (~63%) in women aged 45–54 years	Generally included participants aged 20–65 years Average age of trials' participants ranged from 37–44 years
Source	AIHW 2012 Table 1.2	Table 15 and Table 16
Cytology Yield Unsatisfactory Negative Low-grade abnormalities[a] High-grade abnormalities	 2.1% 92.6% 3.9% 1.4%	 0–4.3% 95.3%–97.7% 1.01%–2.79%[b] 0.53%–0.51%
Source	AIHW 2012 Summary Table Latest data 2010 reported only	Table 30 and Table 39
Histology Yield Low-grade abnormalities[c] High-grade abnormalities[c]	 17.2% 25.9%	Strander 2007r[d] 14.5% 21.0%
Source	AIHW 2012 Summary Table Latest data 2010 reported only	Table 44
Correlation PPV[e] for HSIL	71.2%	%PPV for HSIL test threshold CIN 1+ 84%–94% CIN 2+ 81%–100% CIN 3+59%–67%
Source	AIHW 2012 Summary Table Latest data 2010 reported only	Section B.6.

Abbreviations: AIHW, Australian Institute of Health and Welfare; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; PPV, positive predictive value

a. Low grade abnormalities represent ASCUS (pLSIL) and LSIL as reported in AIHW 2012 Table 3.10. High grade abnormalities represent pHSIL+ as reported in AIHW 2012 Table 3.10. Low grade reports in the CC arms of the trials were much lower than observed in Australian practice. Although low-grade cytology reports are very common in Australia the rates are declining (a decrease from 5.5% in 2005 to 3.9% in 2010)(AIHW 2012 p.31). In part, this is because screening is started at a young age (18–20 years), but also reflects the short two-yearly rescreening interval that results in greater detection of transient abnormalities)(NHMRC 2005 p.31 and AIHW 2012 figure 3.3 p. 32).

b. The pooled result for ASCUS from the cell enrichment trial was combined with the pooled result for LSIL (0.79% +0.22%). Likewise the pooled result for ASCUS from the cell filtration trials was combined with the pooled result for LSIL (2.0%+0.79%).

c. Histology outcomes reported as Low grade abnormalities do not represent CIN, High grade abnormalities represented CIN not otherwise specified (NOS). CIN 2 and CIN 3 AIHW 2012 Table 4.1

d. The histology outcomes reported in AIHW2012 reflect the proportion of all histology that is low grade or high grade. All RCTs included in the submission except Strander 2007 report reference standard outcomes from colposcopy and histology combined. This means that it is not possible to determine the proportion of histology that is low grade or high grade because it is not possible to determine the total number of patients who have histology only. Strander 2007 does report the histological outcomes for all cytology and is therefore used to represent the trial evidence in the submission.

e. PPV is the positive predictive value, calculated as the proportion of cytology results of possible or definite high-grade that were confirmed on histology to be a high-grade abnormality (CIN NOS, CIN 2 or CIN 3) or cervical cancer

Overall there are differences between the trial populations and the women participating in cervical screening in Australia in 2010. There are also differences in the test yield outcomes. Weighted results on an absolutes scale across trials are therefore applied in the cost-minimisation analysis in section D.

C.1.3 Applicability of unsatisfactory rates from the trials

Lower rates of unsatisfactory results with cell enrichment

The results presented in Section B demonstrate that both cell enrichment LBC and cell filtration LBC are consistently associated with lower rates of unsatisfactory cytology results compared with conventional cytology, despite variations in baseline rates of unsatisfactory slides. Furthermore, the results of the indirect comparison showed the odds of producing an unsatisfactory slide with cell enrichment LBC is 65 % lower compared with cell filtration LBC (indirect OR [95% CI] 0.3586 (0.19, 0.69); P=0.0022).

Fontaine 2012 performed a systematic review and meta-analysis of 42 studies of varying trial design to compare the unsatisfactory rates between the main platforms of LBC—cell enrichment and cell filtration. The overall pooled unsatisfactory rate of 14 cell enrichment studies was 0.3% compared to 1.3% determined from 28 cell filtration LBC studies. Meta-analysis of four studies that presented data in the same population by the same laboratory for the different LBC methodologies, demonstrated cell enrichment LBC to have a significantly lower rate of unsatisfactory smears compared with cell filtration LBC with a pooled relative risk of 0.44 (95% CI: 0.25 to 0.77). The results from Fontaine 2012 support the conclusions made from the indirect analysis of this submission.

Possible explanation for the difference in unsatisfactory rates

A conventional Pap smear involves the collection of cells from the uterine cervix using a small cytobrush/broom or spatula which is then smeared onto a glass slide. LBC uses a different method for collecting and preparing cervical cells for cytological examination. The BD SurePath™ cell enrichment LBC is a proprietary, sample collection, preservation, transport and slide preparation system that consists of the BD SurePath™ sample collection vial containing proprietary preservative solution and sample collection. Cells are collected using a brush, broom or spatula in the same way as they are collected for a conventional Pap test, but the head of the brush or spatula is detached into a vial of preservative fluid to produce a cell suspension which is sent to the laboratory where a large number of slides are prepared together using standardised protocols. Conversely, conventional cytology slides are prepared at the point of collection which

inevitably introduces wide variability as to the quality of the specimen. Another benefit of cell enrichment LBC is that 100% of the sampled material is captured. The more material collected and the better the standardisation of in the quality of the specimen collected, the greater the chance of both achieving a satisfactory sample for review and finding any abnormal cells.

An explanation for the significant difference between the LBC technologies is the varied collection and preparatory processes involved (Fontaine 2012). Cell enrichment uses a density-sedimentation process to collect viable cells for slide preparation. Cell filtration uses a filtration-based technology which may not separate obscuring elements such as blood and inflammatory cells as effectively as the sedimentation method, which may lead to an increase in unsatisfactory results. Additionally, the cell enrichment methodology requires the entire collection brush to be immersed in a liquid medium that is then sent to the laboratory for processing. In comparison, the cell filtration process requires the brush to be rinsed in a liquid medium before being disposed (Fontaine 2012). Bigras (2003) demonstrated that 37% of cellular material is lost when the collecting device is discarded as is the case with cell filtration LBC.

Unsatisfactory results associated with cervical abnormalities

The Bethesda System includes the cytology classification term 'unsatisfactory' to define those slides unreliable for the detection of cervical epithelial abnormalities (Randsell 1997). Several studies confirm that those slides classified as unsatisfactory are representative of missed opportunities for screening and are more often associated with a cervical abnormality (Fontaine 2012; Bentz 2002; Ransdell 1997; Nygard 2004).

Two studies reprocessed specimens initially classified as unsatisfactory and found that 6.4% (Bentz 2002) and 7.58% (Islam 2004) contained epithelial abnormalities (inclusive of ASCUS and squamous cell carcinoma). A longitudinal study conducted by Ransdell 1997 reported that 16% of initially unsatisfactory Pap smear samples were found to be from patients with squamous intraepithelial lesions or malignancy when follow-up samples were analysed. A study based on seven years of follow-up data at the Cancer Registry of Norway (CRN) demonstrated the risk of unsatisfactory smears masking HSIL findings. Nygard 2004 reported the unadjusted OR of being diagnosed with CIN 2 or CIN 3 after an unsatisfactory smear was 2.78 (95% CI: 2.31 to 3.35) compared with women with a normal index Pap smear, and 3.99 (95% CI: 2.17 to 7.35) of being diagnosed with invasive cervical carcinoma.

It is essential not to underestimate the significance of unsatisfactory Pap results, as this may result in missed opportunities to diagnose significant disease and prevent cervical carcinoma. Furthermore there is a chance that many women will not return for repeat smears. It is for this reason that women in remote areas of Queensland have had access to LBC since 2006 as

documented in the Queensland Health Policy and Protocol for use of ThinPrep. Women with an unsatisfactory result who do not return for a repeat smear are at a higher risk of an adverse health outcome.

Cost of unsatisfactory smear management

The Australian NHMRC guidelines state that unsatisfactory results require a repeat smear within 6 to 12 weeks (NHMRC 2005). Patient inconvenience and healthcare costs are associated with repeat cytology. Greater additional costs would therefore be associated with those cytology methods resulting in higher unsatisfactory rates for cell filtration and conventional cytology compared to cell enrichment LBC (Bentz 2002 and Nygard 2004).

The use of cell enrichment processing reduces this risk and will also be associated with lower costs due to the reduction of numbers of women required to undergo repeat cytology after an unsatisfactory smear.

Application of LBC in practice

Although this submission uses trial based data to demonstrate the implementation effects of LBC on low grade abnormalities, there are examples of the routine experiences of LBC when it has been applied in practice in populations similar to Australia. For example New Zealand has a National Cervical Screening Programme 'NZ NCSP' which undergoes independent monitoring against key targets reported on a six monthly basis. The latest published Independent Monitoring Report covers the six month period ended December 2010 (NCSP Monitoring report Number 34, http://www.nsu.govt.nz/health-professionals/1063.aspx).

During the period January 2008 through December 2010 the NZ NCSP moved from being predominantly a conventional Pap test based program to being virtually entirely (99.8%) LBC test based. A published split of Pap test numbers between LBC and conventional is not available prior to the second half of 2008. During the second half of 2008 34.9% of samples were LBC, 64.1% conventional, and 0.1% were a combination, whereas by the second half of 2010 the proportion of LBC was 99.8%.

In the 2008 to 2010 period the number of laboratories processing cytology specimens reduced from nine to eight. The laboratories process one LBC technology type only and hence the published individual laboratory data relate to the particular LBC technology in use. Seven of the eight laboratories processing LBC at 31 December 2010 were using either FocalPoint or ThinPrep Imager screening automation.

The NZ NCSP sets laboratory cytology reporting targets and investigates variations from these targets. In the 3 year period of conversion from conventional Pap testing to LBC unsatisfactory

rates have shown significant reduction and generally the rates of abnormalities detected has remained stable or decreased (Figure 15 and Figure 16). This may reflect a learning curve with LBC.

In particular during the second half of 2010 there were four laboratories reporting unsatisfactory rates of less than the minimum target of 1% all of which laboratories were using SurePath; Aotea Pathology Ltd (0.2%), Canterbury Health Laboratories (0.2%), Pathlab (0.2%) and Southern Community Labs (0.5%). In the July to December 2010 period the overall unsatisfactory rate in New Zealand was 0.72% with 0.33% for SurePath and 1.20% for ThinPrep processing laboratories respectively.

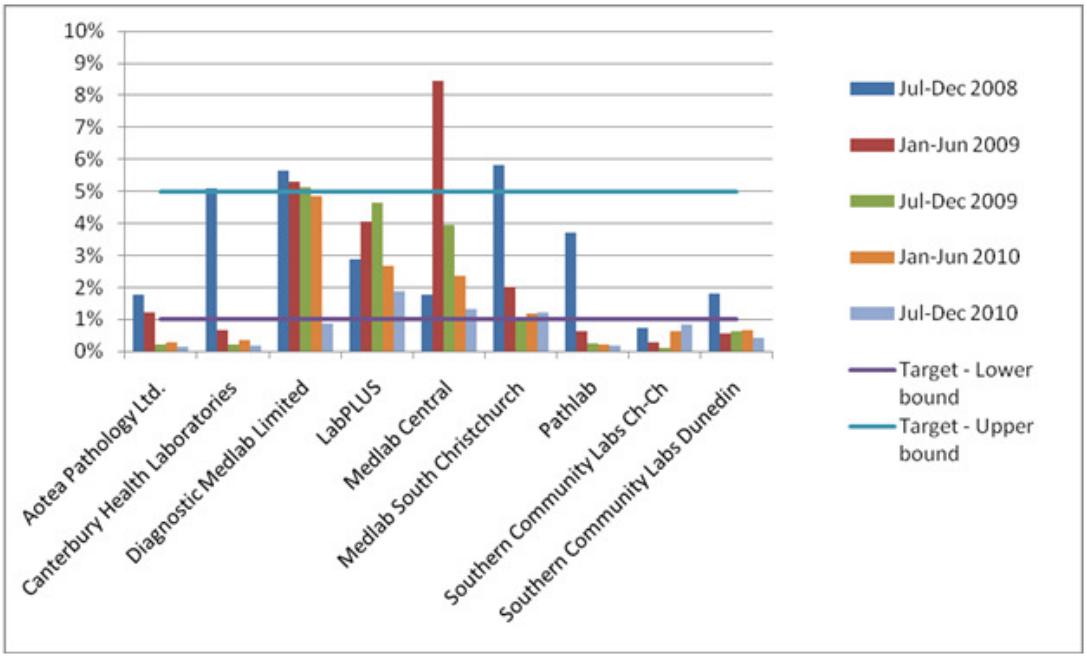

Figure 15 Trends in the proportion of LBC samples reported as unsatisfactory, by laboratory
(Source:NCSP Monitoring report Number 34 Figure 49 p.125)

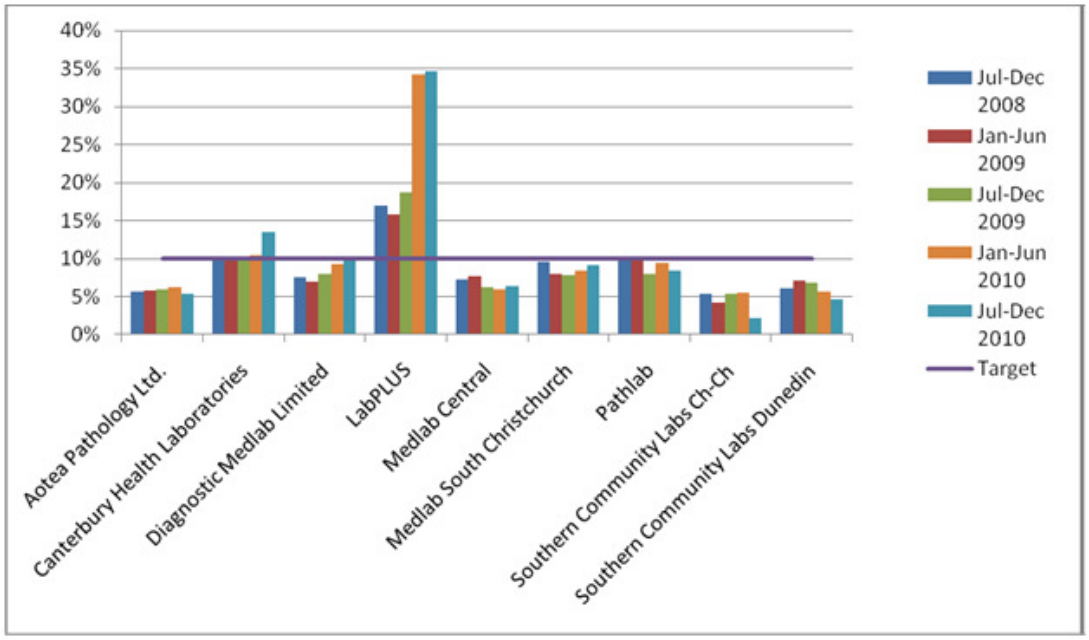

Figure 16 Trends in the proportion of satisfactory cytology samples reported as abnormal, by laboratory
(Source:NCSP Monitoring report Number 34 Figure 51p.126)
Note: a higher proportion of the samples received by LabPLUS are from colposcopy clinics compared to other laboratories)

The following comment from the July to December 2010 NZ NCSP Monitoring report (p39) recognises the difference recorded in unsatisfactory rates between LBC technologies.

"…Use of different LBC test technologies by different laboratories may be a factor in the variation in rates of unsatisfactory cytology (it is believed that all laboratories with unsatisfactory rates below 1% for LBC use SurePath), as well as reprocessing protocols of unsatisfactory samples and determination of adequacy by imager assisted screening. The target for unsatisfactory LBC samples will be reviewed as more evidence becomes available."(p.39).

The significant decrease in unsatisfactory slides associated with cell enrichment LBC are incorporated in the cost minimisation analysis. However the proportions of unsatisfactory slides in the conventional cytology arm of the Beerman 2009 study (0.9%) is much lower than that reported in Australia (2.1%) which introduces a degree of uncertainty if these differences are applied in the economic evaluation. The fact that unsatisfactory rates are so much higher in Australian practice compared to rates observed for conventional cytology in the Beerman trial suggests that the Beerman trial is likely to underestimate the benefit of LBC with cell enrichment in reducing unsatisfactory rates. As such, the proportion of unsatisfactory slides across all LBC trials is utilised in the cost-minimisation analysis.

C.1.4 Applicability of test yield rates from the trials

The increase in ASCUS outcomes associated with cell enrichment LBC are further explored in section D.

The significant increase in ASCUS outcomes associated with cell enrichment LBC are incorporated in the cost minimisation analysis. However the proportions of low grade outcomes (ASCUS +LSIL) in the conventional cytology arm of the Beerman 2009 study (0.87% +0.22%=1.09%) and the RODEO study (0.1%+0.3%=0.4%) is much lower than that reported in Australia (3.9%) which introduces a degree of uncertainty if these differences are applied in an economic evaluation. That is to say, it is difficult to conclude that there will be more low grade findings using LBC with cell enrichment over CC in Australian clinical practice on the basis of evidence where the rates of low grade findings with CC are much lower than that currently being observed in Australia.

The fact that detection of low grade abnormalities in Australian practice are much lower compared to rates observed for conventional cytology in the Beerman trial suggests that the Beerman trial is likely to overstate the difference between LBC with cell enrichment and CC. As

such, the cost-minimisation analysis which uses the rates of low grade abnormalities across all the trials is likely to be biased against LBC with cell enrichment.

Despite the fact that no patient outcomes are reported in section B.6, the 2009 MSAC assessment report noted "the negative psychological effects of receiving an abnormal cytology test, including anxiety, fears of cancer, infertility, depression, difficulties with sexual relationships and self-blame (Herzog & Wright 2007; Rogstad 2002). A study of 3731 women aged 20–59 years who participated in the Trial of Management of Borderline and Other Low-Grade Abnormal smears (TOMBOLA) observed that 23% of women with low-grade cytological abnormalities scored at levels that indicated probable clinically significant anxiety on the Hospital Anxiety and Depression Scale (Gray 2006). The authors reported that these findings were similar to earlier findings among women with high-grade cytological abnormalities."

Given cell enrichment LBC results in a higher rate of ASCUS+ findings it is reasonable to conclude that more women would suffer a degree of anxiety.

Still cytological classifications are a continuum, and a change in the percentage of slides in one category must change the percentage in at least one other category. Consequently the lower unsatisfactory rates associated with cell enrichment LBC (OR 0.15, 95%CI 0.11 to 0.21, Table 31) are in turn reflective of a higher number of ASCUS abnormalities detected with cell enrichment LBC (OR 2.42, 95%CI 2.14 to 2.72, Attachment 4). To illustrate the point more clearly, the OR associated with the reduction of ASCUS with conventional cytology is 0.41 (95% CI 0.37 to 0.47, Figure 10). Therefore there are lower odds of getting an unsatisfactory outcome with cell enrichment LBC (OR 0.15) than not getting an ASCUS outcome with conventional cytology (OR 0.41). It is important to note that the baseline rates of unsatisfactory slides and ASCUS outcomes in the conventional cytology arm of the Beerman 2009 trial are similar (0.9% and 0.8%, respectively, Table 30 and Table 39).

Raab 2002 reported on the willingness of women to pay to decrease their risk of dying from cervical cancer if LBC was used in place of conventional cytology. The mean amount they were willing to pay was $237. Furthermore Wordsworth 2006 demonstrated, via a discrete choice experiment, that women had a significant positive preference for reductions in recall rates and waiting time for results. Bearing in mind that unsatisfactory results may represent significant cervical disease these findings may outweigh any anxiety associated with an initial ASCUS outcome. Overall the preferences illustrated above are evident in Australia with approximately 18% of women paying an average of $45 in out-of-pocket expenses for LBC.

C.1.5 Applicability of higher sensitivity and lower specificity in LBC

Often in a research context only women with positive screen tests and none or only a few with negative screen tests are verified and this situation results in verification bias yielding inflated sensitivity and underestimated specificity (Arbyn 2009). It is therefore proposed that increased, similar or hardly reduced positive predictive value for CIN 3+ is the proposed outcome of trials for evaluating cervical cancer screening technologies (Arbyn 2009).

There were only two trials that reported sensitivity and specificity and the outcome was CIN 1+. The outcome was based on an ASCUS+ (pLSIL) index test and resulted in consistent conclusions between the trials. Both showed that LBC (cell enrichment or cell filtration) was associated with significantly increased sensitivity for CIN 1+ and significantly reduced specificity. As stated by Davey 2006, the accuracy of tests is a trade-off between sensitivity and specificity. Thus, even if LBC does improve sensitivity (true positive rate) for high grade abnormalities, it could simultaneously increase the number of low grade abnormalities (false positives), which are less likely to represent serious disease but might trigger clinical investigation. In Australia the clinical investigation based on a pLSIL or LSIL outcome is follow-up conventional cytology in 12 months (NHMRC 2005). Although false positives are undesirable in a screening program, the follow-up investigation does not place patients at high risk of adverse outcomes. Nonetheless, the follow-up tests and psychological concern associated is acknowledged. But CIN 1 is the histopathologic manifestation of a carcinogenic or non-carcinogenic HPV infection that rarely progresses on a per event basis to cancer. Its detection is not clinically useful, possibly leading to over-treatment, and should not be targeted by any screening test (Arbyn 2009).

With the exception of the NTCC trial, all trials consistently showed no significant difference in PPV between LBC (cell enrichment or cell filtration) and conventional cytology. As the test positivity threshold improved from ASCUS+ to HSIL+, the PPV for the detection of CIN 1+, CIN 2+ and CIN 3+ increased for both test preparation methods.

C.1.6 Circumstances of use – the learning curve

Studies have demonstrated a temporary increase in ASCUS rates in the first six months after conversion from conventional Pap to LBC (Colgan 2004; Nance 2006). This phenomenon is attributed to the learning curve in the interpretation of LBC.

Most of the trials that provided the evidence for this submission reflect a situation where LBC was implemented when the trial commenced. This is evident as most publications report that training was provided to the collectors of the LBC sample as well as the reviewer (cytotechnologist) of the LBC sample (Table 17). The trials therefore represent a situation whereby collection sites and labs are commencing the learning curve.

Beerman 2006 comments that "follow-up tissue correlation data confirmed that several HSIL cases had been classified as ASCUS, and that HSIL rates normalized after the initial 6 month training period" (p. 575).

Maccallini 2008 reports "Introducing a new procedure such as LBC implies training of sample takers and laboratory staff. In particular cytologists need to be trained in interpreting new slide preparations. In evaluating the present results the limited experience with LBC of our laboratories should be taken into account and, theoretically, better performances could be expected in the future with longer experience. This is a common problem with new technology. Part of the variance observed in published results may be due to different levels of training of operators in LBC. "(p. 572).

This learning curve phenomenon is also reported to occur when implementing automated review of cytology. The MAVARIC trial reported that automated review was less sensitivity than manual reading with equivalent specificity for the detection of CIN 2+. However, the Palmer study (2012) reported that automated review showed significantly better specificity compared with manual review and equivalent sensitivity for CIN 2+.

In the MAVARIC study automated versus manual review was conducted in a single centre. Palmer 2012 encompassed six laboratories and used only one new technology. There is no mention of feedback to screeners in the MAVARIC study after initial training. Lack of feedback and ongoing learning opportunities for screeners may have contributed to the false negative rate persisting throughout the study as well as the reduced sensitivity of automated reading for CIN 2+ compared with manual screening. By contrast, review and reinforcement of training was carried out in the Palmer 2012 study when screening errors were identified by quality control review. Moreover, it is noted that most cases of CIN 2+ in the MAVARIC study were found as a result of testing low-grade abnormalities found on manual screening for high-risk HPV (detected via HPV testing).

C.1.7 Circumstances of use – Glandular abnormalities

Although glandular abnormalities remain less common, the decline in incidence and mortality rates from invasive squamous cell carcinoma (SCC) has seen an increase in the incidence of

glandular cervical lesions. These trends highlight the need to accurately distinguish between squamous and glandular abnormalities (Blomfield 2008, Thiryayi 2010). The evidence based provided in this submission does not report sufficient information on the proportion of glandular abnormalities detected. Furthermore, the low incidence of glandular lesions means that large studies are needed to provide statistically relevant comparisons.

Several studies have however shown that conventional cytology is not as effective in detecting glandular abnormalities compared with LBC (Hoda 2012). Belsley 2008 performed a retrospective review of pathology files from a tertiary care hospital in the US for patients with diagnoses of endocervical adenocarcinoma in situ (AIS) or invasive endocervical adenocarcinoma (IEA) over five years. A total of 45 specimens were identified and the authors compared the morphology of glandular lesions and showed LBC to be at least as sensitive as and more specific than conventional cytology for detecting endocervical glandular lesions. Burnley 2010 prospectively followed six laboratories in the UK after conversion to cell enrichment LBC and compared glandular abnormalities (from 217,979 LBC samples) with historical data from 246,775 conventional smears. The authors demonstrated significant differences between conventional cytology and LBC samples for the total number of both glandular results (P=0.001, 95% CI: 0.00033 to 0.000088) and endocervical glandular results (P=0.001, 95% CI: 0.00028 to 0.000074). Furthermore, a retrospective audit of 165,000 patients in the UK that compared the two different platforms of LBC found that the overall detection rate of glandular neoplasia using cell filtration was 0.031% and 0.052% for cell enrichment. The difference between these proportions was found to be statistically significant (P=0.014) (Thiryayi 2010).

The differences in cell collection and slide preparation between LBC and conventional cytology methods offers a technically plausible reason as to why glandular findings are more easily visualised with LBC, and in particular, cell enrichment processing. The cellular presentation of glandular abnormalities in cell enrichment LBC includes single dyskaryotic cells, large groups of more than 20 cells showing crowding and overlapping and short pseudo-stratified strips, with fanning out of bulging nuclei. These features are documented less frequently in cell filtration and conventional cytology (Thiryayi 2010). The difference in cellular presentation could be explained by the ease of dense tissue fragments to settle using the sedimentation processing of cell enrichment compared with the vigorous processing of cell filtration whereby larger fragments may be prevented from reaching the filter (Hoda 2012; Belsley 2008). Other justifications include the use of varying fixatives between methods and glandular irregularities being miscategorised as squamous abnormalities or even being missed at screening (Belsley 2008; Thiryayi 2010).

The fixation and processing methods used when preparing LBC smears stand to reasonably account for the higher detection of glandular abnormalities compared with conventional cytology.

C.1.8 Extrapolation issues

There are no extrapolation issues to address for the base case cost-minimisation analysis. The technical report of the cost-effectiveness model describes the methods used to extrapolate the effects of introducing LBC with cell enrichment to the NCSP over a life-time model (Attachment 6).

C.1.9 Transformation issues

There are no transformation issues to address. As for extrapolation issues, please see Attachment 6 for the methods used to transform the diagnostic accuracy results presented in Section B to cost per life year and cost per quality adjusted life year (QALY) gained ratios.

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D. Economic evaluation for the main indication

The proposed MBS fee for cell enrichment LBC is the same as the current MBS fee for conventional cytology and is detailed in Section D.1. This section will demonstrate that "the proposed fee is sustainable and is not shifting out of pocket costs to the patient" (1157 Final DAP May 2012, p20). Nevertheless, "*women's total out-of-pocket costs (will be) a part of the economic evaluation*" as requested by the Department (Survey Responses to Application 1157 Response 2: Departmental Response).

The requested MBS fee amount represents a cost-minimising fee for cell enrichment LBC compared with conventional cytology. This reflects the clinical evidence demonstrating that cell enrichment LBC is at least as accurate and safe as conventional cytology (Section B).

It is acknowledged that the cost-minimisation analysis proposed in Section D.2 is contrary to the final DAP which states: "Model is to be a cost effectiveness model based on the 2009 LBC model". It is argued in Section D.2 that that a cost-effectiveness model is not necessary because the differences between cell enrichment LBC and conventional in terms of accuracy are confined to differences in detection of pLSIL (more with cell enrichment LBC) and differences in rates of unsatisfactory smears (more with conventional cytology). The NCSP guidelines provide almost identical guidance with respect to the follow-up of pLSIL and unsatisfactory smears. That is, repeat the test in 12 months (within 6 to 12 weeks in the case of unsatisfactory smears). As such, a cost-minimisation analysis which incorporates the costs of following up these repeat tests (whether for pLSIL or unsatisfactory cytology) should be sufficient to determine the cost-effectiveness of cell enrichment LBC relative to conventional cytology. All other costs relating to the follow-up of higher grade abnormalities will be the same because the detection of higher grade abnormalities is the same between cell enrichment LBC and conventional cytology.

Nevertheless, a cost-effectiveness model is provided as an Attachment to this submission (Attachment 6). Unfortunately, the cost-effectiveness model in Attachment 6 could not be based on the 2009 LBC Model so a separate cost-effectiveness model (using similar methodologies and data as the 2009 LBC Model) was constructed. As confirmed in the letter dated 23 August 2012 from Mr Shane Porter (Assistant Secretary Medical Benefits Division) "*the 2009 Economic Model is not available*" and it is acknowledged that "*Becton Dickinson will need to develop a model that will differ from the 2009 LBC model*". A brief critique of the 2009 LBC Model and an overview of the new model used (and as described in Attachment 6) is provided in Section D.3.

D.1 Commercial-in-confidence

Section D.1

The content of pages 168 to 179 inclusive is commercial-in-confidence and has been redacted.

D.2 Cost minimisation analysis

The clinical evidence presented in Section B demonstrated that the effectiveness and safety of cell enrichment LBC is at least as good as that of conventional cytology technique. This conclusion is applicable to cell enrichment LBC regardless whether it is performed using manual or automated review.

The requested MBS fee represents a cost-minimising fee for cell enrichment LBC compared with conventional cytology. This reflects the clinical evidence demonstrating that cell enrichment LBC is at least as accurate as and safe as the conventional test (Section B). From a cost-effectiveness point of view, this cost-minimising does not account for the savings possible due to lower rates of unsatisfactory smears with cell enrichment LBC relative to conventional cytology. Equally, it does not necessarily account for potentially higher rates of follow-up of possible low-grade findings with cell enrichment LBC. Therefore the cost-minimisation analysis includes the follow-up of repeat tests and for additional follow-up with low-grade abnormalities. It is important to note that the cost of following up high grade abnormalities is not included in the cost-minimisation analysis because there is no difference in the rate of detection of these abnormalities and any associated costs would cancel each other out.

NCSP guidelines on follow-up of possible low-grade abnormalities (pLSIL, ASCUS) are to repeat the test at 12 months and then again at 24 months (if the 12 month result was normal). The test at 24 months would occur for a normal result at the index smear so the additional cost of a pLSIL or ASCUS finding is a single additional test. In the rare circumstance that this single additional test did find a persistent, definite low-grade abnormality then this is actually a finding that has patient relevance and could potentially reduce the incidence of cervical cancer. In any case, the accuracy of LBC versus conventional cytology for detecting definite low grade abnormalities is the same, meaning any costs associated with the follow-up of repeated low-grade abnormalities will be the same across the two methods.

As such, the additional cost attributable to a potential higher rate of pLSIL/ASCUS findings with LBC is the cost of a single repeat test. The cost-minimisation analysis is presented in Table 83. Table 83 shows that the total cost of the index/primary/routine test along with follow-up costs of low grade abnormalities and unsatisfactory tests results in a cost saving with cell enrichment LBC of $0.29 per woman presenting for a routine test.

The Department response to this application (1157) requested that "*women's total out-of-pocket costs (be) a part of the economic evaluation*" (Survey Responses to Application 1157 Response 2: Departmental Response). The evidence presented in the previous section demonstrated that the

proposed MBS fee for LBC is sustainable and will not lead to out-of-pocket costs. Conversely, 18% of women are routinely paying $45 out of pocket for LBC test in current practice. These costs are included in the cost-minimisation analysis in Table 83.

From an MBS perspective there is cost saving with cell enrichment LBC of $0.29 per woman presenting for a routine test. From the patient perspective there is a cost saving of $8.10 per woman presenting for a routine test. From a societal perspective the cost saving is $8.39.

The cost-minimisation analysis uses rates of low grade abnormalities and rates of unsatisfactory tests from the randomised controlled clinical trial evidence base. This approach is conservative (biased against LBC with cell enrichment) because:

- It includes data from LBC with cell filtration which has higher rates of unsatisfactory results than LBC with cell enrichment
- The rate of low grade abnormalities with CC in these trials (2.98%) is lower than that observed in Australian clinical practice (approximately 4%). As such, it is difficult to conclude that there will be an increase in an already high rate of low grades attributable to LBC with cell enrichment.

Table 83 Cost-minimisation analysis comparing cell enrichment LBC with conventional cytology

Row	Parameter	Cell enrichment LBC	Conventional cytology	Difference	References and notes
A	Cost of primary screen	$68.42	$68.42	$0.00	Weighted average costs of MBS items 3, 23, 36, 44, 52, 53, 54, 57, 104, 105 for the cost of the consultation ($40.57) plus $19.60 (MBS Item 73053) for the pathology plus the cost of the patient episode initiation ($8.25. MBS item 73922) This is the same methodology as used in MSAC 1122. Weightings and unit costs have been updated. See the attachment 5 for more detail
B	Rate of unsatisfactory smears	1.13%	2.12%	-0.99%	Meta-analysed weighted proportions of absolute unsatisfactory slides across all LBC trials is utilised. See the attachment 5 for the calculations. Unsatisfactory findings require an additional follow-up test at 3 months. If this is normal then patients return to routine screening. However, it is more likely to be abnormal than a routine screen and as such further investigations are made. However, these further investigations are not included in the cost-minimisation analysis and this is biased against LBC with cell enrichment because it has lower rates of unsatisfactory results.
C	Expected cost of repeating unsatisfactory tests	$0.78	$1.45	-$0.68	A × B Cost of the repeat test is the same as for the primary test
D	Rate of (p)LSIL	3.55%	2.98%	0.57%	Weighted proportions of absolute low grade abnormalities across all LBC trials is utilised See the attachment 5 for the calculation.
E	Cost of follow-up per (p)LSIL finding	$68.42	$68.42	$0.00	A (p)LSIL findings require an additional follow-up test at 12 months. If this is normal then patients return to routine screening. If it is abnormal then further investigations are made. However, these further investigations will be the same in both arms because the only differences between cell enrichment LBC and CC are in initial LSIL, not in persistent LSIL
F	Expected cost of LSIL follow-up	$2.43	$2.04	$0.39	D × E
G	Total cost (MBS perspective)	$71.63	$71.91	-$0.29	A + C + F

Row	Parameter	Cell enrichment LBC	Conventional cytology	Difference	References and notes
H	Women paying out of pocket for LBC tests	–	18%	-18%	See **Error! Reference source not found.**
I	Out-of-pocket costs per LBC test	–	$45.00	$45.00	BD market estimates
J	Total patient out-of-pocket costs	–	$8.10	-$8.10	H × I
K	Total societal (MBS + patient) costs	$71.63	$80.01	-$8.39	G + J

It is acknowledged that the cost-minimisation analysis proposed in Table 83 is contrary to the final DAP which states: "Model is to be a cost effectiveness model based on the 2009 LBC model". It is argued in Section D.2 that that a cost-effectiveness model is not necessary because the differences between cell enrichment LBC and conventional in terms of accuracy are confined to differences in detection of pLSIL (more with cell enrichment LBC) and differences in rates of unsatisfactory smears (more with conventional cytology). The NCSP guidelines provide almost identical guidance with respect to the follow-up of pLSIL and unsatisfactory smears. That is, repeat the test at 12 months (within 6 to 12 weeks in the case of unsatisfactory smears). As such, a cost-minimisation analysis which incorporates the costs of following up these repeat tests (whether for pLSIL or unsatisfactory tests) should be sufficient to determine the cost-effectiveness of cell enrichment LBC relative to conventional cytology. All other costs relating to the follow-up of higher grade abnormalities will be the same because the detection of higher grade abnormalities between cell enrichment LBC and conventional cytology is the same.

D.3 Cost-effectiveness analysis

D.3.1 Cost-effectiveness using the 2009 model

In order to specifically acknowledge the DAP's request, a cost-effectiveness model is provided as an Attachment to this submission (Attachment 6). Unfortunately, the cost-effectiveness model in Attachment 6 could not be based on the 2009 model so a separate cost-effectiveness model (using similar methodologies as the 2009 LBC Model) was constructed.

As described, BD received a letter dated 23 August 2012 from Mr Shane Porter (Assistant Secretary Medical Benefits Division) confirming that "*the 2009 Economic Model is not available*" and it is acknowledged that "*Becton Dickinson will need to develop a model that will differ from the 2009 LBC model*".

Even if the 2009 LBC Model could be reproduced it is not necessarily the best evidence base upon which to make a reliable assessment of the cost-effectiveness of cell enrichment LBC. As such, a short critique of 2009 model is provided. Building models of this nature is complex combining a range of disparate data sources from different settings into a single summary measure of cost-effectiveness. This critique shows that a detailed economic model of the entire natural history of cervical cancer and cervical cancer screening is not necessary for the decision that is being made. Given that any differences between the tests (LBC and conventional cytology) are confined to rates of unsatisfactory smears and the detection of low grade abnormalities the assessment of

costs and cost-effectiveness can be limited to this scope. This is the cost-minimisation analysis in Section D.2.

Based on the MSAC review in 2009 and the evidence presented in this submission it is proposed that the cost-minimisation analysis in Section D.2 is more appropriate, transparent and reliable than a detailed economic model. The base case results of the model from 2009 themselves (Figure 17) support this view. The results show that the incremental cost-effectiveness ratios (which were important drivers of the decision not to include LBC on the MBS in 2009) were based on an incremental cost of less than $20 per woman over her lifetime with an additional life expectancy of 82 minutes.

Strategy	Discounted lifetime costs (5% discount rate[a])	Discounted life years [b] (5% discount rate[a])	Incremental discounted life years (min) [b] compared with current practice	ICER vs current practice ($ / LYS)	ICER vs next most cost-effective strategy ($ / LYS)
Current practice (CC)	$418.68	18.87175	–	–	–
Manual LBC ($2.40 incremental cost)	$438.34	18.87190	0.000156 (82)	$126 315	$126 315
Automated LBC	$515.44	18.87224	0.000497 (261)	$194 835	$226 100
Manual LBC ($10.90 incremental cost)	$478.74	18.87190	0.000156 (82)	$385 982	Dominated [c]

[a] Discounted at 5% starting from age 18 years [b] Discounted Life Years (or minutes) from age 18 [c] Strategy is said to be dominated as it is more expensive than a strategy with equal or greater effectiveness, in this case Manual LBC at the lower incremental cost

Figure 17 Predicted costs, effects, and incremental cost-effectiveness ratios, by cytology test technology

Source: Table 52 of the MSAC 2009 Assessment Report

With such small differences between the tests in terms of both costs and outcomes it is important to understand what is driving these results and whether or not they are reliable. With such small difference the results would need to be close to 100% reliable because a small change in either costs or outcome could result in a dramatic change in the incremental cost-effectiveness ratio (ICER). The MSAC Assessment Report makes the following observation with respect to the driver of the differences in outcomes:

> "We expect that relative differences between the matrices for conventional cytology, LBC and automated LBC will drive differences in outcomes". (p.154)

In other words, differences in the detection of low grade abnormalities are used as surrogate end-points for differences in the detection of high grade abnormalities and to differences in outcomes. The evidence for this transformation of surrogates is weak as evidenced in Table 19.

The differences between the matrices in the 1122 Assessment report are lower specificity but better sensitivity with LBC compared to conventional cytology. The lower specificity drives the

incremental cost of LBC versus conventional cytology and the better sensitivity drives the incremental outcomes with LBC over conventional cytology. Even in sensitivity analysis of the 2009 model where the MBS fees for LBC was set to the same as conventional cytology there was an incremental cost due to increased follow-up with LBC (the incremental cost per life year gained was less than $50,000; see Figure 14 of the 1122 Assessment report). This means that the 2009 model had two key drivers:

1. the cost of repeat follow-up tests due to the extra detection of low grade abnormalities with LBC

2. the additional life years gained as a result of detecting these abnormalities earlier with LBC.

When the ICER is driven by an incremental benefit which can be measured in minutes and an incremental cost of less than $1 per woman per year of life the calibrations would need to be almost perfect to provide reliable cost-effectiveness results. Unfortunately, the calibration of the 2009 model showed that it performed poorly on these two important drivers of the ICERs. The figures below are reproduced from the MSAC 1122 Assessment Report.

Figure 18 indicates that the 2009 model did not predict cancer mortality very well. The model underestimated risk of cervical cancer mortality by age 84 (lifetime risk) by more than half (that is the incidence of cervical cancer mortality in the model was less than half the incidence observed in Australia). This will have the impact of dramatically underestimating the benefit of additional detection with LBC. Given the model outcomes are based exclusively on cancer mortality (life years gained) and the model is so sensitive to small changes in cancer mortality this lack of calibration is likely to be highly biased against LBC.

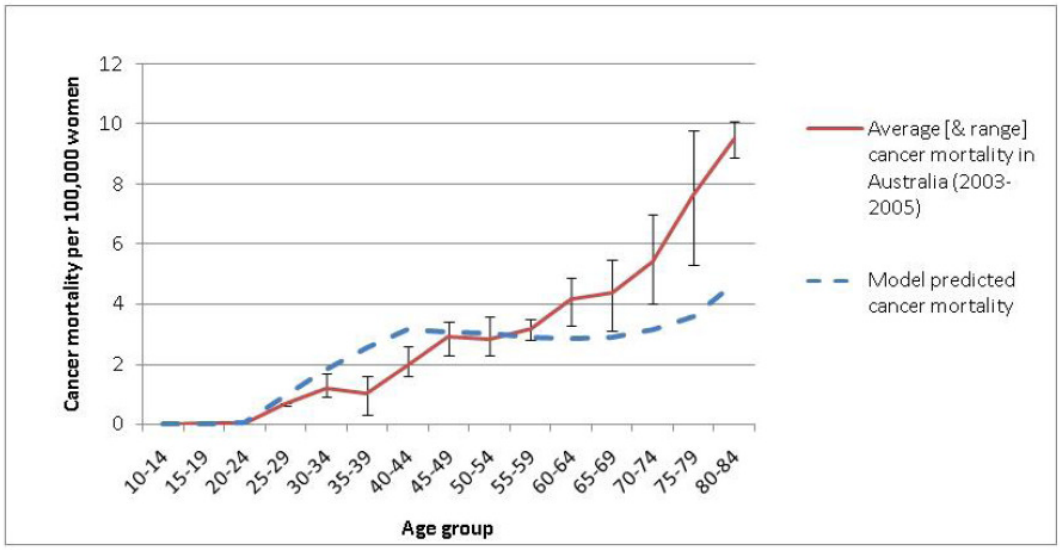

Figure 18 Predicted age-specific mortality in Australia, compared with cancer registry data from 2003–2005

Source: Figure 10 of the 2009 MSAC Assessment report

Another calibration which performed poorly was the proportion of low grade abnormalities detected (Figure 12 of the MSAC 2009 report, reproduced below). The model appears to underestimate the number of low grade abnormalities using conventional cytology by nearly half. This will have an impact on the incremental cost of LBC (which was less than $20 in the base case). This misspecification of low grade abnormalities could change the incremental cost to only $10 (ICER of approximately $63,000) or to $5 (ICER of approximately $31,000).

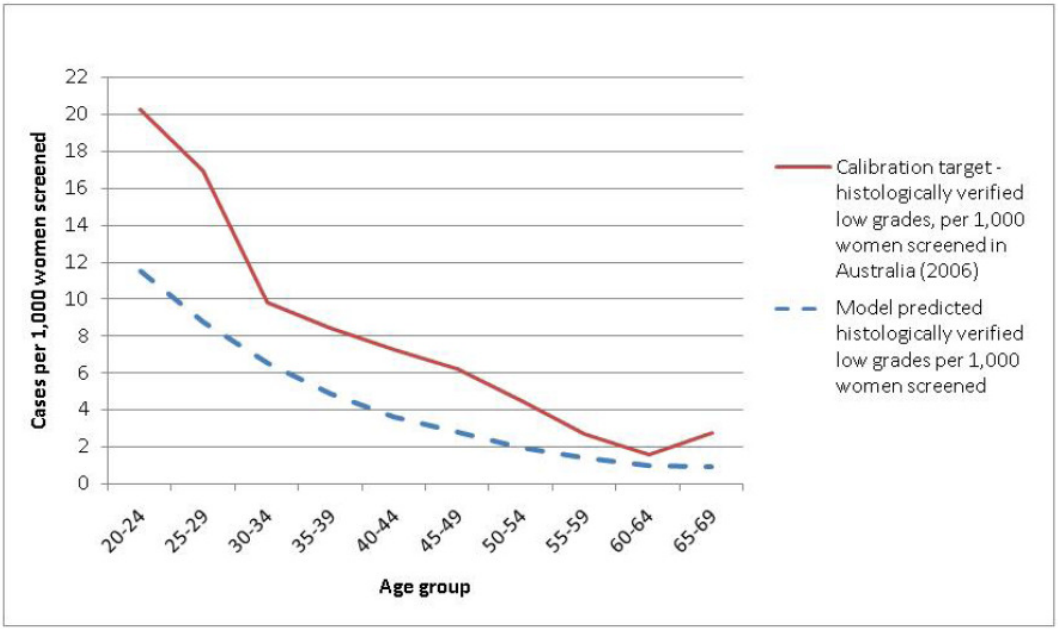

Figure 19 Predicted age-specific rate of histologically confirmed low grades detected compared with registry data (2006)

Source: Figure 12 of the 2009 MSAC Assessment report

In the scenario where the costs of the screening tests themselves are identical (as is the case in this submission) any cost differences and any outcome differences are driven by the resources associated with additional follow-up of abnormalities according to the NCSP Guidelines. As such, the cost-effectiveness results of any such economic model would actually reflect the cost-effectiveness of the screening guidelines themselves as opposed to the cost effectiveness of LBC relative to conventional cytology.

In 2009, MSAC concluded that LBC was safe, at least as effective, but "not cost effective at the price requested". The cost-minimisation analysis provided in this submission provides a sound and reliable basis to support MBS funding of cell enrichment LBC.

D.3.2 Cost-effectiveness model for this submission

The cost-effectiveness model for this submission is a supplementary analysis and is provided in full in Attachment 6. The results of the model are largely the same as the results of the cost-minimisation analysis, that is, LBC with cell enrichment provides almost identical health outcomes (a difference of 0.0000429 QALYs or 0.000218 life years in favour of cell enrichment LBC) but at a lower overall cost ($3.55 per patient). Table 84 presents a summary of the cost-effectiveness results calculated in the economic model.

Table 84 Results of the economic model, cell enrichment LBC versus conventional cytology

Pap test technique	Expected costs	Expected QALYs	Expected life years
Cell enrichment LBC	$451.87	19.159957	19.162980
CC	$455.43	19.159915	19.162958
Difference	-$3.55	0.0000429	0.0000218
Incremental cost-effectiveness ratios		Cell enrichment LBC is dominant	Cell enrichment LBC is dominant

The exceedingly small differences in outcomes (11.5 minutes in life expectancy) and costs ($3.55 over a woman's life time) and costs reinforce the conclusion that the cost-minimisation analysis presented in Section D.2 provides a sound basis for decision making. Any cost-effectiveness ratios that are calculated from such small incremental values are likely to be highly variable.

The incremental costs and life years estimated in this model are slightly lower than the difference predicted in the 2009 MSAC LBC model. The smaller incremental gain in life years with LBC in this model compared to the 2009 model can be attributed to the conservative assumption used in this model that there is no additional detection of CIN2+ disease with LBC compared to CC. incremental QALYs -effectiveness ratios. The smaller incremental cost in this model can be attributed to the lower MBS fee requested.

Pages 189 to 193 contain commercial-in-confidence information which has been redacted.

E. Estimated extent of use and financial implications

Becton Dickinson expects that the listing of cell enrichment LBC for routine screening for the prevention of cervical cancer will be cost saving to the MBS. This reflects the reduction in the number of unsatisfactory smears offered by cell enrichment LBC. Furthermore, the practice of split sampling (Pap smear test using conventional as well as LBC techniques) will be substantially reduced (or eliminated), thereby producing cost savings in out-of-pocket payments (currently affecting 18% of all women receiving MBS funded cytology tests).

The National Cervical Cancer Screening Program is currently under review in a process known as 'The Renewal'. The recommendations of The Renewal regarding screening technologies and or the screening interval are likely to have a significant impact on Pap test numbers regardless of type of Pap test i.e. conventional or LBC. The Renewal recommendations and timing for implementation are currently unknown, however. There is no proposed change in screening pathways by which the total number of Pap tests would increase. There is potential for a significant reduction in number of total Pap tests due to: amended age recommendations for commencement and cessation of screening tests; an increase in the recommended screening interval from 2 to 3 years; the introduction of an element of HPV testing within the screening pathways.

The suggested impacts presented below assume no change to the National Cervical Screening Guidelines. These comments are presented to illustrate the potential impact of MBS listing of cell enrichment LBC under current conditions whilst recognising that DoHA decision making will ultimately determine the extent of use and hence financial impact.

As set out in Section A, conventional Pap smear tests are currently available on the MBS. The proposed listing will offer an alternative to the conventional test, and these tests are not complementary to each other under the proposed listing. This means that given the cost-minimising benefit amount requested for cell enrichment LBC in this submission, any use of cell enrichment LBC on the MBS will be accompanied by substitution effect away from the use of conventional cytology existing listing, thereby generating cost savings to the MBS and thus offsetting the costs of cell enrichment LBC.

Given this, a market share approach is considered to be more appropriate than an epidemiological approach, whereby the available MBS statistics for conventional cytology tests are used to inform the likely extent of cell enrichment LBC use on the MBS.

Consideration is paid to difference in the re-test rate between cell enrichment LBC and conventional cytology test due to unsatisfactory smears and the follow up of low grade abnormalities. When compared with conventional cytology, cell enrichment LBC has been shown to reduce unsatisfactory smear collection, thereby reducing the need for re-tests and as a result offering cost savings to the MBS. cell enrichment LBC is shown to have a higher sensitivity for possible low-grade squamous intraepithelial lesions (pLSIL) when compared with conventional cytology. This means that a greater proportion of women tested with cell enrichment LBC require a follow-up test. The costs associated with these follow-up tests are also considered in this analysis.

Section E.1 describes data sources that are selected to inform the current analysis. Section E.2 estimates the likely extent of use for cell enrichment LBC and conventional cytology over the next five years. The projected use of conventional Pap smears for routine screening is determined on the basis of available historical utilisation data (see Section E.2.1 and Section E.2.2). The likely rate of uptake for cell enrichment LBC is then applied to the projected use of conventional cytology. Again, this assumes that the use of cell enrichment LBC on the MBS will be attributable to substitution away from conventional tests and its listing will not result in expansion of the overall usage volume of cytology tests for screening purpose on the MBS. Potential impacts of follow-up tests arising from unsatisfactory test and pLSIL positive result are also examined and their implications on the overall usage are estimated (see Section E.2.3). Section E.2.4 will then quantify the financial implications associated with the expected usage. Section E.3 determines the level of cost savings associated with the substitution effects with conventional cytology tests (to cell enrichment LBC). Finally, the net financial implications of the proposed cell enrichment LBC listing are determined in Section E.5. Electronic spread sheets with calculations contained in section E are provided in Attachment 7.

E.1 Justification of the selection of sources of data

A market share approach is taken to estimate the likely extent of cell enrichment LBC use for routine screening for the prevention of cervical cancer. Table 85 details MBS-listed conventional Pap tests for cervical cancer screening.

Table 85 Conventional Pap smear cytology tests currently available on the MBS

Category 6– Pathology Services (Cytology)
MBS 73053 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 (a) for the detection of precancerous or cancerous changes in women with no symptoms, signs or recent history suggestive of cervical neoplasia, or (b) if a further specimen is taken due to an unsatisfactory smear taken for the purposes of paragraph (a); or (c) if there is inadequate information provided to use item 73055; (See para P16.11 of explanatory notes to this Category) Fee: $19.60 Benefit: 75%=$14.70 85%=$16.70
MBS 73055 Cytology of a smear from cervix, not associated with item 73053, 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 test (a) for the management of previously detected abnormalities including precancerous or cancerous conditions; or (b) for the investigation of women with symptoms, signs or recent history suggestive of cervical neoplasia; (see para 16.11 of explanatory notes to this Category) (See para P16.11 of explanatory notes to this Category) Fee: $19.60 Benefit: 75%=$14.70 85%=$16.70

The item descriptors for 73053 and 73055 suggest that these listings would broadly account for four indications (Please note that item 73057 is applicable for smears of the vagina but is not included in this analysis because the frequency of repeat tests cannot be disaggregated using MBS item statistics. Item 73057 represents a small proportion (less than 2%) of the total MBS services rendered):

- Initial screening test
- Re-test due to previous unsatisfactory smear
- Follow-up test due to previous positive screening test
- Other follow-up investigative activities.

The first two indications are captured within Item 73053. The item descriptor suggests that Item 73053 is used for an initial test and also for re-tests due to unsatisfactory smear from previous test occasion.

The number of initial screening tests (i.e. the first indication) is unlikely to be affected due to the listing of cell enrichment LBC. However, the evidence presented in Section B suggests that the listing of cell enrichment LBC would reduce the number of unsatisfactory smear and thus reduces the needs for re-tests due to this reason (i.e. the second indication) when compared with

conventional cytology. The proposed listing would potentially increase the number of follow-up tests (i.e. the third indication) because of its higher sensitivity for pLSIL when compared with conventional test, while leaving the use under the fourth indication largely unaffected. These factors are considered in Section E.2.2.

E.1.1 MBS statistics for conventional cytology

The best available evidence is used to conduct the estimation. The Medicare MBS Item Statistics is a well-accepted source of MBS service utilisation data. Utilisation data are extracted for conventional cytology tests currently available for cervical cancer screening (as shown in Table 85). Historical usage over the past two decades is presented in Figure 25. It is shown that the use of Item 73053 has been around 1.4 to 1.5 million with a recent increase in 2011/2012, while the use of Item 73055 has been around 200,000 to 300,000 with a slightly declining trend in recent years. Table 86 presents usage data over the recent five years.

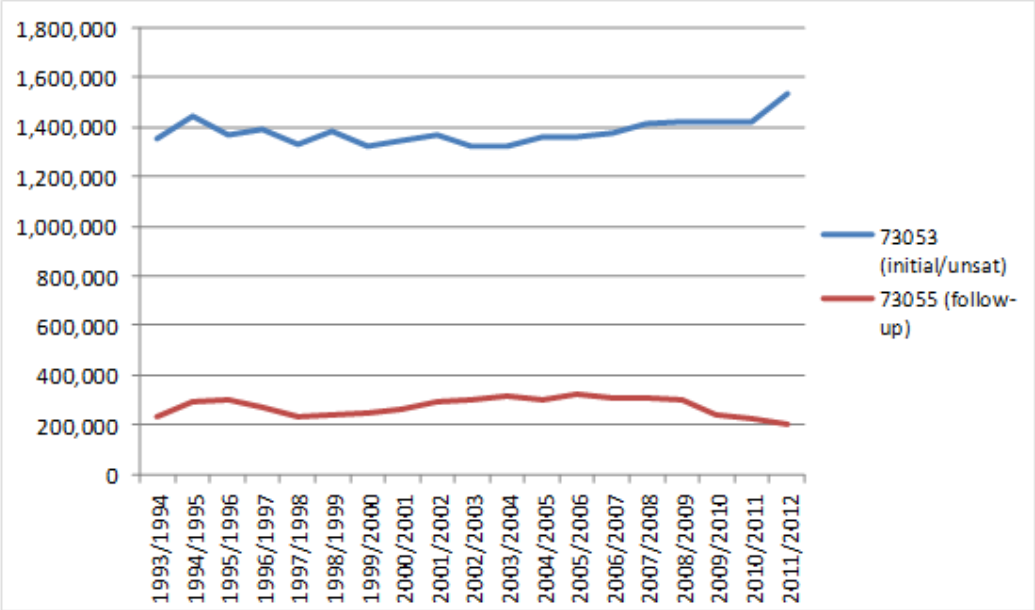

Figure 25 Historical use of conventional cytology tests for cervical cancer screening

Source: MBS Item Statistics Reports (financial year data are presented).
Abbreviations: unsat, unsatisfactory results

Table 86 MBS services for conventional cytology of a smear from cervix in 2008–2012

Year	2008	2009	2010	2011	2012
73053	1,409,404	1,419,216	1,421,936	1,423,872	1,535,752
73055	304,773	298,255	243,171	225,815	203,470
Total	1,714,177	1,717,471	1,665,107	1,649,687	1,739,222

Source: MBS Item Statistics Reports (financial year data are presented; financial year 2007–2008 for year 2008 and so on)

The use of conventional cytology over the next five years to 2017 is estimated based on these data. This is shown in Section E.2.1.

E.1.2 Rate of unsatisfactory smear and pLSIL result

The item descriptors for 73053 and 73055 suggest that the MBS statistics for these items would broadly account for four indications, as noted.

The service usage associated with initial screening tests and follow-up activities unrelated to the routine screening practice (the first and fourth indications enlisted in Section E.1) are unlikely to be affected due to the proposed listing of cell enrichment LBC. However, the listing of cell enrichment LBC would reduce the number of unsatisfactory smears and therefore the need for re-tests for this reason when compared with conventional cytology. The proposed listing would potentially increase the number of follow-up tests because of its higher sensitivity for pLISL when compared with conventional test.

Comparison of rates of unsatisfactory smear and pLSIL result between conventional cytology and cell enrichment LBC is presented in Table 87.

Table 87 Rates of unsatisfactory smear and pLSIL result, conventional cytology vs. cell enrichment LBC

Test	Cell enrichment LBC	Conventional	Difference
Unsatisfactory smear	1.13%	2.12%	-0.99%
Positive based on pLSIL	3.55%	2.98%	0.57%

Source: Section D.2 (Table 83)

The findings for the conventional cytology arm enable the available MBS statistics for Item 73053 and 73055 to be disaggregated into four different indications captured by these MBS items. The unsatisfactory smear rate (2.12%) is applied to the usage projection for Item 73053 to derive the number of services due to unsatisfactory smear with conventional cytology test. The remaining service number thus represents the total number of initial screening tests. The rate of positive

results with conventional cytology (1.13%) is applied to the total number of initial screening test, as derived above from Item 73053, in order to determine the number of screening-related follow-up tests within the total service numbers for Item 73055. The remaining service number for Item 73055 would then mean that they are for follow-up investigations that are unrelated to the routine screening.

E.2 Estimation of use and costs of the proposed listing

E.2.1 Historical and projected use of conventional cytology

The service numbers associated with conventional cytology tests in 2012–2017 are estimated under a scenario where there is no cell enrichment LBC becoming available on the MBS during this period.

Figure 25 presented the use of conventional cytology tests in 1994–2012. Projection of the service numbers for these items is based on a linear trend using the data from year 1993, as shown in Figure 26. For Item 73053, the average annual increase in its usage was 4512 and this is assumed to be applicable over the next five years. For 73055, this was -96, and again this was assumed to be applicable over the next five years.

These trend-based projections do not account for a recent increase and decline in the use of 73053 and 73055, respectively. An alternative analysis where the previous 5-year data is used is presented in Section E.5 as a sensitivity analysis. It is however unclear whether these recent observations reflect the fundamental (lasting) changes to the utilisation of these MBS items.

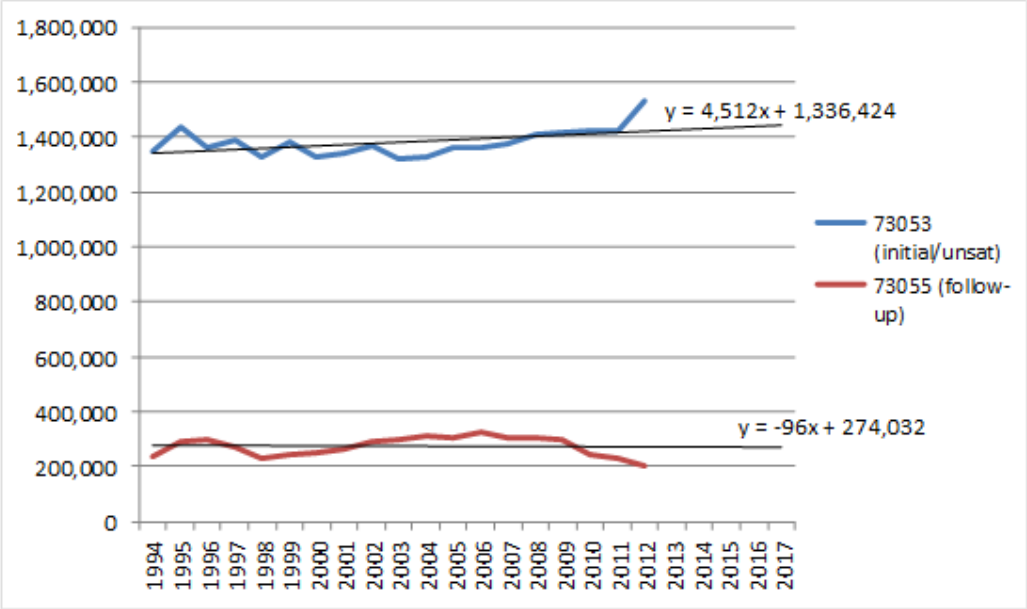

Figure 26 Projected use of Items 73053 and 73055 to 2017

The estimated extent of conventional cytology test each year in 2012–2017 is presented in Table 88. These estimates are derived using equations; service number for 73053=4,512 x Year + 1,336,424 and service number for 73055=-96 x Year + 274,032 (see Figure 26).

Table 88 Projected MBS service numbers for conventional cytology in 2013–2017

Year	Current (2012)[a]	2013	2014	2015	2016	2017
73053	1,422,152	1,426,664	1,431,176	1,435,688	1,440,200	1,444,712
73055	272,208	272,112	272,016	271,920	271,824	271,728
Total	1,694,360	1,698,776	1,703,192	1,707,608	1,712,024	1,716,440

a Derived numbers from the equations (see Figure 26).

As noted, a total of four indications are captured by these two MBS items. Disaggregation by each indication is performed in Section E.2.2.

E.2.2 Projected use of conventional cytology test by indication

It has been described that Items 73053 and 73055 account for four indications:

- Initial screening test
- Re-test due to previous unsatisfactory smear

- Follow-up test due to previous positive screening test
- Other follow-up investigative activities.

The first two indications are captured within Item 73053 together, while Item 73055 accounts for the third and fourth indications.

First, the projected use of 73053 is disaggregated into the two indications, as shown in Table 89. Table 87 described that 2.12% of conventional cytology tests return an unsatisfactory result due to inadequate smear collection. If a 100% follow-up is assumed (i.e. all unsatisfactory smears will be re-tested), the number of re-tests due to unsatisfactory smears in 2013, for example, can be estimated as 29,672 (that is, 1,426,664–(1,426,664/1.012)). This would then mean that the number of initial screening tests for that year is 1,396,992 (that is 1,426,664–29,672).

Table 89 Projected use of Item 73053 for initial screening tests and for re-tests due to previous unsatisfactory smear

Year	2013	2014	2015	2016	2017
73053—total	1,426,664	1,431,176	1,435,688	1,440,200	1,444,712
% due to re-test for unsatisfactory smear	2.12%	2.12%	2.12%	2.12%	2.12%
Services due to unsatisfactory smear	29,672	29,766	29,860	29,954	30,048
Services due to initial screening test	1,396,992	1,401,410	1,405,828	1,410,246	1,414,664

By the same token, the total usage of Item 73055 can be disaggregated into its use due to screening-related follow-up tests and its use due to other follow-up investigative activities, as shown in Table 90. Table 87 described that 2.98% of conventional cytology tests return a pLSIL positive result, thereby prompting a follow-up test.

If a 100% follow-up is assumed (i.e. all pLSIL results will receive a follow-up test), the number of screening-related follow-up tests in 2013, for example, can be estimated as 41,671 (that is, 1,396,992x 0.0298). This would then mean that the number of initial screening tests for that year is 230,441 (that is 272,112–41,671).

Table 90 Projected use of Item 73055 for screening-related follow-up tests and for other follow-up investigation

Year	2013	2014	2015	2016	2017
Services due to initial screening test (see Table 89)	1,396,992	1,401,410	1,405,828	1,410,246	1,414,664
% due to pLSIL follow-up	2.98%	2.98%	2.98%	2.98%	2.98%
Services due to pLSIL follow-up	41,671	41,803	41,934	42,066	42,198
73055—total	272,112	272,016	271,920	271,824	271,728
Services due to other follow-up investigation	230,441	230,213	229,986	229,758	229,530

Source: Table 88 and Table 89

E.2.3 Estimated extent of cell enrichment LBC use on the MBS

As noted, the use of cell enrichment LBC for routine screening for cervical cancer on the MBS would be attributable to substitutions away from conventional cytology tests currently available on the MBS.

For the purpose of this analysis, a full uptake is assumed from Year 1. This means that all screening tests will be conducted using cell enrichment LBC over the estimation period. This is presented in Table 91.

In practice, should cell enrichment LBC be added to the listing, the transition from conventional cytology to cell enrichment LBC would be gradual and the assumption of full uptake would represent a conservative approach from the perspective of the MBS (thereby overestimating the true extent of cell enrichment LBC usage on the MBS).

While presenting a set of conservative estimates, the cost-minimising benefit amount requested for cell enrichment LBC in this submission means that any substitution to cell enrichment LBC would be cost saving or at worst cost neutral to the MBS regardless of assumptions about its uptake.

Table 91 Estimated use of cell enrichment LBC as screening tests–initial screening tests and re-tests due to previous unsatisfactory smear

Year	Year 1 (2013)	Year 2	Year 3	Year 4	Year 5
Use of cell enrichment LBC for initial screening					
73053 services due to initial screening test (see Table 89)	1,396,992	1,401,410	1,405,828	1,410,246	1,414,664
Uptake of cell enrichment LBC	100%	100%	100%	100%	100%
Cell enrichment LBC for initial screening	1,396,992	1,401,410	1,405,828	1,410,246	1,414,664
Use of cell enrichment LBC for re-tests due to unsatisfactory smear					
Initial screening tests using cell enrichment LBC	1,396,992	1,401,410	1,405,828	1,410,246	1,414,664
% of unsatisfactory tests with cell enrichment LBC	1.13%	1.13%	1.13%	1.13%	1.13%
cell enrichment LBC for re-tests due to unsatisfactory smear	15,835	15,885	15,935	15,985	16,035
Total—initial screening tests and re-tests due to previous unsatisfactory smear	1,412,827	1,417,295	1,421,763	1,426,231	1,430,699

Note: Estimates relate to a 12-month period. Pro rata adjustments may be required to interpret these results.

The available evidence suggests that 1.13% of cell enrichment LBC tests return an unsatisfactory result due to an inadequate smear collection. As shown in Table 87, this compares favourably with conventional cytology (vs. 2.12%). It can be thus estimated that approximately 16,000 re-tests would be required with cell enrichment LBC each year due to previous unsatisfactory smears, as shown in Table 91.

In total, it is estimated that approximately 1.41–1.43 million cell enrichment LBC tests will be performed each year in Year 1 to Year 5 of the listing for these two indications. Again, these estimates reflect the conservative assumption of full-up take to be achieved by cell enrichment LBC.

In addition to its use for initial screening tests and re-tests due to a previous unsatisfactory smear (currently performed using conventional cytology under Item 73053; see Table 89), cell enrichment LBC will be used for follow-up tests due to a positive screening test result (i.e. pLSIL) as well as other follow-up investigations (currently performed using conventional cytology under Item 73055; see Table 90).

Table 90 estimated that a total of approximately 23,000 conventional cytology tests are administered each year as a follow-up investigation for potential cervical cancer cases that are **identified outside of the screening program**. The current analysis assumes that the listing of cell enrichment LBC would not affect the extent of cervical cytology test usage under this

indication and, again based on the full uptake assumption, all conventional cytology services will be replaced by cell enrichment LBC should it be added to the listing. This is shown in Table 92.

On the other hand, the number of follow-ups following a positive screening test result would slightly increase with cell enrichment LBC because of its higher sensitivity for pLSIL. This has been discussed in Section E.1.2. At a positive result rate of 3.55% (see Table 87), around 50,000 cell enrichment LBC tests are estimated to be administered each year following a positive test result with the initial screening test using cell enrichment LBC.

Table 92 Estimated use of cell enrichment LBC as follow-up tests–follow-up due to a positive screening test and other follow-up investigations

Year	Year 1 (2013)	Year 2	Year 3	Year 4	Year 5
Cell enrichment LBC for other follow-up investigations					
73055 services due to other follow-up investigations (see Table 90)	230,441	230,213	229,986	229,758	229,530
Uptake of cell enrichment LBC	100%	100%	100%	100%	100%
Cell enrichment LBC for other follow-up investigations	230,441	230,213	229,986	229,758	229,530
Cell enrichment LBC for follow-up due to a positive screening test					
Initial screening tests using cell enrichment LBC (see Table 91)	1,396,992	1,401,410	1,405,828	1,410,246	1,414,664
% of positive tests (pLSIL) with cell enrichment LBC	3.55%	3.55%	3.55%	3.55%	3.55%
Cell enrichment LBC for follow-up due to a positive screening test	49,657	49,814	49,971	50,128	50,285
Total—follow-up due to a positive screening test and other follow-up investigations	280,098	280,027	279,956	279,885	279,815

Note: Estimates relate to a 12-month period. Pro rata adjustments may be required to interpret these results.

Approximately 1.69–1.71 million of cell enrichment LBC tests are estimated to be administered each year should it be added to the MBS. Financial implications associated with these usage estimates are derived in the following section.

Table 93 Estimated use of cell enrichment LBC: Total

Year	Year 1 (2013)	Year 2	Year 3	Year 4	Year 5
Services due to initial screening test	1,396,992	1,401,410	1,405,828	1,410,246	1,414,664
Services due to unsatisfactory smear	15,835	15,885	15,935	15,985	16,035
Services due to follow-up tests after a positive result	49,657	49,814	49,971	50,128	50,285
Services due to other follow-up investigations	230,441	230,213	229,986	229,758	229,530
Total	1,692,924	1,697,322	1,701,719	1,706,117	1,710,514

These estimates are conservative from the perspective of the MBS (i.e. slight overestimation) because of the assumption of full uptake. A scenario where this assumption is relaxed to a 50% uptake (i.e. half of screening tests will be conducted using cell enrichment LBC) is presented in Table 94.

Table 94 Estimated use of cell enrichment LBC: 50% uptake scenario

Year	Year 1 (2013)	Year 2	Year 3	Year 4	Year 5
Services due to initial screening test	698,496	700,705	702,914	705,123	707,332
Services due to unsatisfactory smear	7,917	7,943	7,968	7,993	8,018
Services due to follow-up tests after a positive result	24,828	24,907	24,985	25,064	25,142
Services due to other follow-up investigations	115,221	115,107	114,993	114,879	114,765
Total	846,462	848,661	850,860	853,058	855,257

E.2.4 Estimated costs of cell enrichment LBC on the MBS

It has been estimate that approximately 1.69–1.71 million cell enrichment LBC tests are expected to be administered should it be added to the MBS.

Table 95 presents the estimated extent of financial implications associated with the usage estimations above. Again, these cost estimates reflect a full uptake assumption, thereby offering a conservative estimate from the perspective of the MBS.

The costs of cell enrichment LBC will be offset by substitution effects away from conventional cytology services that are currently funded on the MBS. Cost offsets associated with these substitution effects are determined in Section E.3.

Table 95 Estimated use of cell enrichment LBC: 100% uptake scenario

Year	Year 1 (2013)	Year 2	Year 3	Year 4	Year 5
Services due to initial screening test					
Services	1,396,992	1,401,410	1,405,828	1,410,246	1,414,664
Total MBS costs (at $19.60 per test)	$27,381,035	$27,467,630	$27,554,226	$27,640,822	$27,727,418
Total benefits (at 85% benefit)	$23,329,759	$23,403,542	$23,477,326	$23,551,109	$23,624,892
Services due to unsatisfactory smear					
Services	15,835	15,885	15,935	15,985	16,035
Total MBS costs (at $19.60 per test)	$310,366	$311,347	$312,329	$313,310	$314,292
Total benefits (at 85% benefit)	$264,444	$265,281	$266,117	$266,953	$267,790
Services due to follow-up tests after a positive result					
Services	49,657	49,814	49,971	50,128	50,285
Total MBS costs (at $19.60 per test)	$973,268	$976,346	$979,424	$982,503	$985,581
Total benefits (at 85% benefit)	$829,264	$831,887	$834,510	$837,132	$839,755
Services due to other follow-up investigations					
Services	230,441	230,213	229,986	229,758	229,530
Total MBS costs (at $19.60 per test)	$4,516,646	$4,512,182	$4,507,717	$4,503,252	$4,498,788
Total benefits (at 85% benefit)	$3,848,367	$3,844,563	$3,840,759	$3,836,955	$3,833,151
Total					
Services	1,692,924	1,697,322	1,701,719	1,706,117	1,710,514
Total MBS costs (at $19.60 per test)	$33,181,315	$33,267,506	$33,353,697	$33,439,887	$33,526,078
Total benefits (at 85% benefit)	$28,271,835	$28,345,273	$28,418,711	$28,492,149	$28,565,587

A scenario where the assumption of full uptake is relaxed to a 50% uptake (i.e. half of screening tests will be conducted using cell enrichment LBC) is presented in Table 96.

Table 96 Estimated use of cell enrichment LBC: 50% uptake scenario

Year	Year 1 (2013)	Year 2	Year 3	Year 4	Year 5
Services due to initial screening test					
Services	698,496	700,705	702,914	705,123	707,332
Total MBS costs (at $19.60 per test)	$13,690,517	$13,733,815	$13,777,113	$13,820,411	$13,863,709
Total benefits (at 85% benefit)	$11,664,880	$11,701,771	$11,738,663	$11,775,554	$11,812,446
Services due to unsatisfactory smear					
Services	7,917	7,943	7,968	7,993	8,018
Total MBS costs (at $19.60 per test)	$155,183	$155,674	$156,164	$156,655	$157,146
Total benefits (at 85% benefit)	$132,222	$132,640	$133,058	$133,477	$133,895
Services due to follow-up tests after a positive result					
Services	24,828	24,907	24,985	25,064	25,142
Total MBS costs (at $19.60 per test)	$486,634	$488,173	$489,712	$491,251	$492,790
Total benefits (at 85% benefit)	$414,632	$415,943	$417,255	$418,566	$419,877
Services due to other follow-up investigations					
Services	115,221	115,107	114,993	114,879	114,765
Total MBS costs (at $19.60 per test)	$2,258,323	$2,256,091	$2,253,858	$2,251,626	$2,249,394
Total benefits (at 85% benefit)	$1,924,183	$1,922,281	$1,920,379	$1,918,477	$1,916,575
Total					
Services	846,462	848,661	850,860	853,058	855,257
Total MBS costs (at $19.60 per test)	$16,590,657	$16,633,753	$16,676,848	$16,719,944	$16,763,039
Total benefits (at 85% benefit)	$14,135,917	$14,172,636	$14,209,355	$14,246,074	$14,282,794

E.3 Estimation of changes in use and cost of conventional cytology

The cell enrichment LBC usage on the MBS will be a result of substitution from conventional cytology tests that are currently available on the MBS. This has been discussed in Section E.1.

The current analysis made a conservative assumption where all conventional cytology services will be replaced by cell enrichment LBC should it be added to the MBS. The cost savings to the MBS arising from this submission effect are presented in Table 97.

These estimates also represent the MBS costs of conventional cytology without the listing of cell enrichment LBC, given the full uptake assumption made previously.

It is clearly shown that any costs associated with cell enrichment LBC, shown in Table 95, are offset by the expected cost offsets arising from a reduction in the use of conventional cytology (i.e. substitution effects). Net financial costs to the MBS are presented in Section E.4.

Table 97 Estimated cost savings arising from substitution away from conventional cytology tests to cell enrichment LBC: 100% uptake scenario

Year	Year 1 (2013)	Year 2	Year 3	Year 4	Year 5
Conventional cytology services due to initial screening test					
Services	1,396,992	1,401,410	1,405,828	1,410,246	1,414,664
Total MBS costs (at $19.60 per test)	$27,381,035	$27,467,630	$27,554,226	$27,640,822	$27,727,418
Total benefits (at 85% benefit)	$23,329,759	$23,403,542	$23,477,326	$23,551,109	$23,624,892
Conventional cytology services due to unsatisfactory smear					
Services	29,672	29,766	29,860	29,954	30,048
Total MBS costs (at $19.60 per test)	$581,580	$583,419	$585,258	$587,098	$588,937
Total benefits (at 85% benefit)	$495,530	$497,097	$498,664	$500,231	$501,798
Conventional cytology services due to follow-up tests after a positive result					
Services	41,671	41,803	41,934	42,066	42,198
Total MBS costs (at $19.60 per test)	$816,749	$819,332	$821,915	$824,498	$827,081
Total benefits (at 85% benefit)	$695,903	$698,104	$700,305	$702,506	$704,707
Conventional cytology services due to other follow-up investigations					
Services	230,441	230,213	229,986	229,758	229,530
Total MBS costs (at $19.60 per test)	$4,516,646	$4,512,182	$4,507,717	$4,503,252	$4,498,788
Total benefits (at 85% benefit)	$3,848,367	$3,844,563	$3,840,759	$3,836,955	$3,833,151
Total–conventional cytology					
Services	1,698,776	1,703,192	1,707,608	1,712,024	1,716,440
Total MBS costs (at $19.60 per test)	$33,296,010	$33,382,563	$33,469,117	$33,555,670	$33,642,224
Total benefits (at 85% benefit)	$28,369,559	$28,443,306	$28,517,054	$28,590,801	$28,664,548

E.4 Net financial implications to the MBS

Table 98 presents the estimated net financial implications to the MBS of adding cell enrichment LBC. It is estimated that the net financial implications to the MBS would be a saving of approximately $115,000 each year.

When the 50% uptake assumption is applied, as expected, the net costs to the MBS are also roughly halved, as shown in Table 99.

It is shown that cost savings offered cell enrichment LBC are due to the lower rate of unsatisfactory smear given by cell enrichment LBC, offsetting the additional follow-up costs (reflecting its higher sensitivity for pLSIL than conventional cytology).

Table 98 Estimated net financial implications of adding cell enrichment LBC to the MBS: 100% uptake scenario

Year	Year 1 (2013)	Year 2	Year 3	Year 4	Year 5
Services due to initial screening test					
Total benefits (at 100% benefit)	$0	$0	$0	$0	$0
Total benefits (at 85% benefit)	$0	$0	$0	$0	$0
Services due to unsatisfactory smear					
Total benefits (at 100% benefit)	-$271,214	-$272,072	-$272,930	-$273,787	-$274,645
Total benefits (at 85% benefit)	-$231,085	-$231,816	-$232,547	-$233,278	-$234,009
Services due to follow-up tests after a positive result					
Total benefits (at 100% benefit)	$156,519	$157,014	$157,509	$158,004	$158,499
Total benefits (at 85% benefit)	$133,361	$133,783	$134,204	$134,626	$135,048
Services due to other follow-up investigations					
Total benefits (at 100% benefit)	$0	$0	$0	$0	$0
Total benefits (at 85% benefit)	$0	$0	$0	$0	$0
Overall					
Total benefits (at 100% benefit)	-$114,695	-$115,058	-$115,420	-$115,783	-$116,146
Total benefits (at 85% benefit)	-$97,725	-$98,034	-$98,343	-$98,652	-$98,961

A scenario where the assumption of full uptake is relaxed to a 50% uptake (i.e. half of screening tests will be conducted using cell enrichment LBC) is presented in Table 99.

Table 99 Estimated net financial implications of adding cell enrichment LBC to the MBS: 50% uptake scenario

Year	Year 1 (2013)	Year 2	Year 3	Year 4	Year 5
Services due to initial screening test					
Total benefits (at 100% benefit)	$0	$0	$0	$0	$0
Total benefits (at 85% benefit)	$0	$0	$0	$0	$0
Services due to unsatisfactory smear					
Total benefits (at 100% benefit)	-$135,607	-$136,036	-$136,465	-$136,894	-$137,323
Total benefits (at 85% benefit)	-$115,543	-$115,908	-$116,274	-$116,639	-$117,004
Services due to follow-up tests after a positive result					
Total benefits (at 100% benefit)	$78,260	$78,507	$78,755	$79,002	$79,250
Total benefits (at 85% benefit)	$66,680	$66,891	$67,102	$67,313	$67,524
Services due to other follow-up investigations					
Total benefits (at 100% benefit)	$0	$0	$0	$0	$0
Total benefits (at 85% benefit)	$0	$0	$0	$0	$0
Overall					
Total benefits (at 100% benefit)	-$57,347	-$57,529	-$57,710	-$57,892	-$58,073
Total benefits (at 85% benefit)	-$48,862	-$49,017	-$49,171	-$49,326	-$49,480

Savings in terms of patients' out-of-pocket expenses

It has been discussed that up to 18% of smears are currently collected as a split sample (conventional as well as LBC). In these cases, the cost of conventional cytology is met by the MBS, while the cost of LBC is paid for by the patient. Referring practitioners and laboratories currently charge over $45 for LBC tests.

The proposed listing of cell enrichment LBC will thus generate substantial savings to the total financial burden associated with Pap smear cytology tests that is currently privately born by women themselves. Table 100 estimates that these savings would be up to $13.9 million a year.

Table 100 Out-of-pocket costs due to the use of LBC in split sample collection

Year	Year 1 (2013)	Year 2	Year 3	Year 4	Year 5
Total conventional cytology without cell enrichment LBC listing	1,698,776	1,703,192	1,707,608	1,712,024	1,716,440
% with split sample	18%	18%	18%	18%	18%
Number of split samples	305,780	306,575	307,369	308,164	308,959
Cost per LBC test	$45.00	$45.00	$45.00	$45.00	$45.00
Total costs of LBC (privately paid)	$13,760,086	$13,795,855	$13,831,625	$13,867,394	$13,903,164

E.5 Estimated financial implications for government health budgets

Section D considered, in addition to the cost of cytology testing, cost of consultation (at the time of smear collection. Each consultation is estimated to cost $40.57, which reflects the weighted average cost of MBS items 3, 23, 36, 44, 52, 53, 54, 57, 104, 105 (see Section D).

Table 101 shows that reflecting a reduction in the overall number of smear tests with cell enrichment LBC when compared with conventional cytology (see Section E.2.3), the proposed listing would provide cost savings in terms of reduced consultation requirement.

Table 101 Financial implications of consultation requirements: Comparison between conventional cytology and cell enrichment LBC

Year	Year 1 (2013)	Year 2	Year 3	Year 4	Year 5
Without cell enrichment LBC					
Total number of conventional cytology (without cell enrichment LBC)	1,698,776	1,703,192	1,707,608	1,712,024	1,716,440
Cost per consultation	$40.57	$40.57	$40.57	$40.57	$40.57
Total consultation costs with conventional cytology	$68,919,342	$69,098,499	$69,277,657	$69,456,814	$69,635,971
With cell enrichment LBC					
Total number of cell enrichment LBC	1,692,924	1,697,322	1,701,719	1,706,117	1,710,514
Cost per consultation	$40.57	$40.57	$40.57	$40.57	$40.57
Total consultation costs with cell enrichment LBC	$68,681,936	$68,860,342	$69,038,748	$69,217,155	$69,395,561
Cost difference	-$237,407	-$238,157	-$238,908	-$239,659	-$240,410

E.6 Identification, estimation and reduction of uncertainty

As demonstrated in Section E.4, the proposed listing of cell enrichment LBC can be achieved with negligible additional costs to the MBS.

These estimates are derived using a market share approach whereby a proportion of conventional cytology tests (projected amounts) are replaced by cell enrichment LBC should it be added to the MBS. The current analysis conservatively assumed that all conventional tests are related by cell enrichment LBC. Alternative scenario was also explored where the full uptake assumption is relaxed to 50%.

As discussed in Section E.2.1, the projection of conventional cytology use is based on the longitudinal MBS utilisation data for these relevant MBS items (over two decades). These projections do not account for a recent hike and decline observed with the use of Items 73053 and 73055, respectively. An alternative analysis where the previous five-year data only are used for the projection process is presented.

It should be noted that it is unclear whether these recent observations reflect the fundamental (lasting) changes to the utilisation of these MBS items. **Again, the cost-minimising benefit amount requested for cell enrichment LBC in this submission means that any substitution to cell enrichment LBC would be cost neutral to the MBS regardless of assumptions made in determining the future conventional cytology use without the listing of cell enrichment LBC.**

Projection of the service numbers for these items is based on a linear trend using the data from year 1993, as shown in Figure 27.

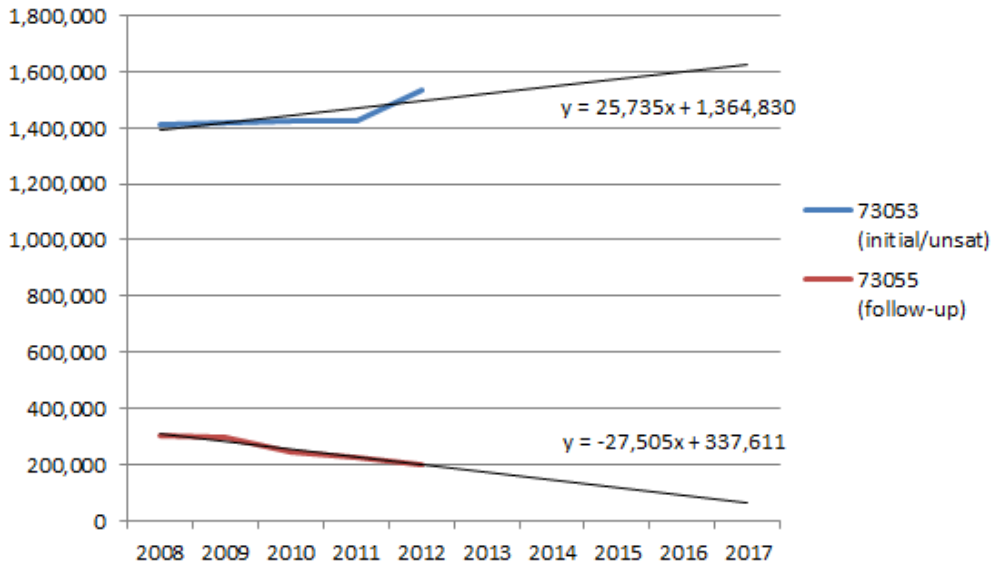

Figure 27 Projected use of Items 73053 and 73055 to 2017: Five-year data approach (sensitivity analysis)

The estimated extent of conventional cytology test each year in 2012–2017 is presented in Table 102. For Item 73053, the average annual increase in its usage was 25,735 (vs. 4512 in the base case) and this is assumed to be applicable over the next five years. For 73055, this was -27,505 (vs. -96 in the base case), and again this was assumed to be applicable over the next five years. Differences

from the base case coefficients reflect a recent hike and decline in the use of 73053 and 73055, respectively (see Figure 27).

Table 102 Projected MBS service numbers for conventional cytology tests in 2012–2013: Five-year data approach (sensitivity analysis)

Year	Current (2012)[a]	2013	2014	2015	2016	2017
73053	1,493,505	1,519,240	1,544,975	1,570,710	1,596,445	1,622,180
73055	200,086	172,581	145,076	117,571	90,066	62,561
Total	1,693,591	1,691,821	1,690,051	1,688,281	1,686,511	1,684,741

[a] Derived numbers from the equations (see Figure 27).

Table 103 presents the estimated net financial implications to the MBS of adding cell enrichment LBC under this alternative projection assumption. These estimates are based on the full uptake assumption. When the 50% uptake assumption is applied, the net costs to the MBS are again roughly halved, as shown in Table 104.

Under this alternative projection assumption, the net costs to the MBS were shown to be slightly more than the level demonstrated in the base case. This reflects the greater number of conventional cytology tests projected to be administered under this analysis (thereby increasing the number of follow-up tests associated with positive test results given by cell enrichment LBC).

Table 103 Estimated net financial implications of adding cell enrichment LBC to the MBS: 100% uptake scenario (sensitivity analysis)

Year	Year 1 (2013)	Year 2	Year 3	Year 4	Year 5
Services due to initial screening test					
Total benefits (at 100% benefit)	$0	$0	$0	$0	$0
Total benefits (at 85% benefit)	$0	$0	$0	$0	$0
Services due to unsatisfactory smear					
Total benefits (at 100% benefit)	-$288,813	-$293,705	-$298,598	-$303,490	-$308,382
Total benefits (at 85% benefit)	-$246,081	-$250,249	-$254,417	-$258,586	-$262,754
Services due to follow-up tests after a positive result					
Total benefits (at 100% benefit)	$166,676	$169,499	$172,323	$175,146	$177,969
Total benefits (at 85% benefit)	$142,015	$144,420	$146,826	$149,232	$151,637
Services due to other follow-up investigations					
Total benefits (at 100% benefit)	$0	$0	$0	$0	$0
Total benefits (at 85% benefit)	$0	$0	$0	$0	$0
Overall					
Total benefits (at 100% benefit)	-$122,137	-$124,206	-$126,275	-$128,344	-$130,413
Total benefits (at 85% benefit)	-$104,066	-$105,829	-$107,592	-$109,354	-$111,117

Table 104 Estimated net financial implications of adding cell enrichment LBC to the MBS: 50% uptake scenario (sensitivity analysis)

Year	Year 1 (2013)	Year 2	Year 3	Year 4	Year 5
Services due to initial screening test					
Total benefits (at 100% benefit)	$0	$0	$0	$0	$0
Total benefits (at 85% benefit)	$0	$0	$0	$0	$0
Services due to unsatisfactory smear					
Total benefits (at 100% benefit)	-$144,407	-$146,853	-$149,299	-$151,745	-$154,191
Total benefits (at 85% benefit)	-$123,040	-$125,125	-$127,209	-$129,293	-$131,377
Services due to follow-up tests after a positive result					
Total benefits (at 100% benefit)	$83,338	$84,750	$86,161	$87,573	$88,985
Total benefits (at 85% benefit)	$71,007	$72,210	$73,413	$74,616	$75,819
Services due to other follow-up investigations					
Total benefits (at 100% benefit)	$0	$0	$0	$0	$0
Total benefits (at 85% benefit)	$0	$0	$0	$0	$0
Overall					
Total benefits (at 100% benefit)	-$61,069	-$62,103	-$63,138	-$64,172	-$65,207
Total benefits (at 85% benefit)	-$52,033	-$52,914	-$53,796	-$54,677	-$55,559

List of References

Altmen DG and Bland JM. Diagnostic tests 2: predictive values. BMJ 1994;309:102

Arbyn M, Sasieni P, Meijer CJ, Clavel C, Koliopoulos G, Dillner J. Clinical applications of HPV testing: a summary of meta-analyses. Vaccine 2006; 24(S3):78–89.

Arbyn M, Bergeron C, Klinhammer P, Martin0Hirsch P, Siebers AG, Bulten J. Liquid Compared With Conventional Cervical Cytology: A Systematic Review and Meta-analysis. Obstetrics and gynecology 2008: 111(1):167-177

Arbyn M, Ronco G, Cuzick J, Wentzensen N, Castle PE. How to evaluate emerging technologies in cervical cancer screening? Int J Cancer. 2009 December 1; 125(11): 2489–2496.

Australian Institute of Health and Welfare 2012. Cervical screening in Australia 2009–2010. Cancer series 67. Cat. no. CAN 63. Canberra: AIHW.

AIHW 2007. ACIM (Australian Cancer Incidence and Mortality) Books. Canberra: Australian Institute of Health and Welfare. http://www.aihw.gov.au/cancer/

Ashfaq R, Gibbons D, Vela C, Saborrian MH, Iliya F. ThinPrep Pap test. Accuracy for glandular disease. Acta Cytol 1999; 43:81-85.

Beerman H, van Dorst EB, Kuenen-Boumeester V, Hogendoorn PC. Superior performance of liquid-based versus conventional cytology in a population-based cervical cancer screening program. Gynecol Oncol. 2009 Mar;112(3):572-6.

Belsley NA, Tambouret RH, Misdraji J, Muzikansky A, Russell DK, Wilbur DC. Cytologic Features of Endocervical Glandular Lesions: Comparison of SurePath, ThinPrep, and Conventional Smear Specimen Preparations. Diagn. Cytopathol. 2008; 36:232–237.

Bentz JS, Rowe LR, Gopez EV, Marshall CJ. The unsatisfactory ThinPrep Pap Test. Missed opportunity for disease detection. Am J Clin Pathol 2002;117:457-463.

Bigras G, Rieder MA, Lambercy JM, . Keeping collecting device in liquid medium is mandatory to ensure optimized liquid-based cervical cytologic sampling. J Low Genit Tract Dis 2003;7:168e74.

Biscotti C, Dawson A, Dziura B, Galup L, Darragh T, Rahemtulla A, and Wills-Frank L. Assisted primary screening using the authomated ThinPrep imaging system. Am J Clin Pathol 2005;123:281-287.

Blomfield P, Saville M. Outstanding problems – glandular lesions. Cancer Forum Produced by the Cancer Council Australia July 2008; 32(2):81-84

Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Lijmer JG, Moher D, Rennie D. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. BMJ 2003;326:41–4.

Bucher HC, Gyatt GH, Griffith LE, Walter SD. The results of Direct and Indirect Treatment Comparisons in Meta-Analysis of Randomised Controlled Trials. J Clin Epidemiol 1997; 50(6):683-691.

Canfell K, Kang YJ, Clements M, Myat Moa A, Beral V. Normal endometrial cells in cervical cytology: systematic review of prevalence and relation to significant endometrial pathology J Med Screen 2008; 15:188–198.

Castle PE, Stoler MH, Solomon D, Schiffman M. The relationship of community biopsy-diagnosed cervical intraepithelial neoplasia grade 2 to the quality control pathology-reviewed diagnoses: an ALTS report, Am.J.Clin.Pathol. 2007; 127(5):805–815.

Castle PE, Schiffman M, Wheeler CM, Solomon D. Evidence for Frequent Regression of Cervical Intraepithelial Neoplasia-Grade 2. Obstet Gynecol 2009;113:18–25.

Colgan TJ, McLachlin CM, Cotterchio M, . Results of the implementation of liquid-based cytology — surepath in the Ontario screening program. Cancer Cytopathol 2004;102:362–7.

Confortini M, Bergeron C, Desai M, Negri G, Dalla Palma P, Montanari G, Pellegrini A, Ronco G; New Technologies for Cervical Cancer Screening Study Cytology Group. Accuracy of liquid-based cytology: comparison of the results obtained within a randomized controlled trial (the New Technologies for Cervical Cancer Screening Study) and an external group of experts. Cancer Cytopathology, 2010; 118(4):203-208.

Dalla Palma P, Giorgi Rossi P, Collina G, Buccoliero AM, Ghiringhello B, Lestani M, Onnis G, Aldovini D, Galanti G, Casadei G, Aldi M, Gomes V, Giubilato P, Ronco G; NTCC Pathology Group. 2008 The risk of false-positive histology according to the reason for colposcopy referral in cervical cancer screening: a blind revision of all histologic lesions found in the NTCC trial. Am J Clin Pathol, 2008; 129(1):75-80.

DAP 1157: Final Decision Analytical Protocol (DAP) to guide the assessment of cell enrichment liquid-based cytology in routine screening for the prevention of cervical cancer. May 2012

Davey E, Barratt A, Irwig L, Chan SF, Macaskill P, Mannes P, Saville AM. Effect of study design and quality on unsatisfactory rates, cytology classifications, and accuracy in liquid-based versus conventional cervical cytology: a systematic review. Lancet 2006; 367: 122–32

Davey E. Effect of study design and quality on unsatisfactory rates, cytology classifications, and accuracy in liquid-based versus conventional cervical cytology: a systematic review. The Lancet, Published online January 14, 2006: Webappendix

Davey E, Irwig L, Macaskill P, Chan SF, D'Assuncao J, Richards A, . Cervical cytology reading times: a comparison between ThinPrep imager and conventional methods, Diagn Cytopathol. 2007 Sep;35(9):550-4.

DoHA 2006. Performance measures for Australian Laboratories reporting cervical cytology. Publications production unit, Australian Government Department of Health and Ageing.

DoHA . Australian Government Department of Health and Ageing. National Cervical Screening Program.
http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/cervical-about#overview

Egger M, Smith GD, Altman DG. Systematic Reviews in Health Care: Meta-analysis in context. Second Edition. BMJ publishing, London; 2003.

Ellis, Renshaw and Dudding Individual estimated sensitivity and workload for manual screening of SP gynaecologic cytology. Diagnostic Cytopathology 2010

Farnsworth, A. Liquid-based cytology: an Australian experience. Cytopathology 2003, 14, 48–52

Fontaine D, Narine N, Naugler C. Unsatisfactory rates vary between cervical cytology samples prepared using ThinPrep and SurePath platforms: a review and meta-analysis. BMJ Open 2012; 2:e000847. doi:10.1136/bmjopen-2012-000847

Fregnani JH, Scapulatempo C, Haikel RL, Mauad EC, Campacci N, Longatto-Filho A. Liquid-based cytology improves detection of cervical intraepithelial lesion in Low and High-risk women for HPV related diseases. Abstract presented at the Global Academic Program (GAP), 14-16 May 2012, Oslo, Norway.

Giorgi-Rossi P, Segnan N, Zappa M, Naldoni C, Zorzi M, Confortini M, Merito M, Cuzick J, Ronco G; NTCC Working Group. The impact of new technologies in cervical cancer screening:

results of the recruitment phase of a large randomised controlled trial from a public health perspective. Int J Cancer, 2007; 121(12):2729-2734.

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.2 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hoda RS, Loukeris K, Abdul-Karim FW. Gynecologic Cytology on Conventional and Liquid-Based Preparations: A Comprehensive Review of Similarities and Differences. Diagnostic Cytopathology 2012, 00:000-000 DOI 10.1002/dc.

Chapter One: Equivocal cytology Table 1 p.12 (Date accessed: 26.08.12) https://openaccess.leidenuniv.nl/bitstream/handle/1887/4435/01.pdf?sequence=13 Chapter 1, Equivocal cytology;

Ikenberg H, Harlfinger W, Neis K, Jordan B, Konig J, Klug S. A Randomized Trial Comparing Conventional Cytology to Liquid-Based Cytology with Computer-Assistance: Results of the RHINE-SAAR Study EUROGIN 2011Congress, held in Lisbon, May 8 - 11, 2011.

Ikenberg H, Harlfinger W, Neis K, Konig J, Klug S. A Randomized Trial Comparing Conventional Cytology to Liquid-Based Cytology with Computer-Assistance: Results of the RHINE-SAAR Study. Journal of Cytopathology, 2011; 22(Suppl. 1):55-183.

Ikenberg H, Klug S, Jordan B, Harlfinger W, Malter A, Brinkmann-Smetanay, Konig J, Neis K. Results of the RHIN-SAAR Study: A Randomized Trial Comparing Conventional Cytology to Thinlayer Cytology with the ThinPrep Imaging System. Acta cytologica V54 N3 (supplement) May-June 2010

Ikenberg H, Klug S, Jordan B, Spieth S, Harlfinger W, Neis K. Results of the Randomized German RHINE-SAAR Study: The ThinPrep Imaging System is Superior to Conventional Cytology. EUROGIN 2010 Congress, held in Monte Carlo, from February 17 to February 20, 2010.

Ikenberg H. Results of the RHINE-SAAR Study, a Randomized Trial Comparing Conventional Cytology with Thinlayer cytology and Computer-Assistance. 5th European Congress of the European Federation for Colposcopy and Cervical Pathology, 27-29 May 2010

Islam S, West AM, Saboorian MH, Ashfaq R. Reprocessing unsatisfactory ThinPrep Papanicolaou test specimens increases sample adequacy and detection of significant cervicovaginal lesions. Cancer Cyopathol 2004;102(2):67-73.

Kitchener HC, Blanks R, Cubie H, Desai M, Dunn G, Legood R, Gray A, Sadique Z, Moss S. Automation-assisted versus manual reading of cervical cytology (MAVARIC): A randomised controlled trial. Health Technology Assessment 2011; Vol. 15: No. 3

Kitchener HC, Blanks R, Dunn G, Gunn L, Desai M, Albrow R, Mather J, Rana DN, Cubie H, Moore C, Legood R, Gray A and Moss S. Automation-assisted versus manual cytology (MAVARIC): a randomised controlled trial. Lancet Oncol 2011; 12:56-64

Klinkhammer PJ, Meerding WJ, Rosier PF, Hanselaar AG. Liquid based Cervical Cytology. A Review of the Literature with Methods of Evidence-based Medicine. Cancer (Cancer Cytopathology) 2003; 99(5):263-271.

Krahn M, McLachlin M, Pham B, Rosen B, Sander B, Grootendorst P, Tomlinson G, John-Baptiste A, Frikemerid M, Hong Chen M, Woo G, Anonychuk A, Carcone S, Witteman H, Chen W, Liu K, Sampson M, Tricco A. Liquid-based techniques for cervical cancer screening: systematic review and cost-effectiveness analysis [Technology report number 103]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2008.

Li Ke-min1, Yin Ru-tie1, Kang De-yin, Wu Wei-wei, Wen Jin. Diagnostic Accuracy of Liquid-Based Cytology versus Conventional Cytology for Cervical Neoplasia: A Systematic Review of Randomized Controlled Trials. Chinese Journal of Evidence-Based Medicine 2011; 11(10): 1133-1139

Li K. Diagnostic accuracy of liquid-based cytology versus conventional cytology for cervical cancer neoplasia: a systematic review of randomised studies. Abstracts presented at the International Gynecologic Cancer Society Regional Meeting on Gynecologic Cancers. International Journal of Gynecological Cancer · Volume 21, Number S2, May 2011 page 51.

Longatti-Filho A, Fregnani JH, Scapulatempo C, Haikel R, Carloni AC, Souza NC, Campacci N, Mauad. Surepath liquid-based cytology improved the detection of high grade lesions in remote rural areas. Preliminary results of RODEO study. Abstract presented at the 17th International Meeting of the European Society of Gynaecological Oncology. International Journal of Gynecological Cancer, 2011; 21Suppl 3

Maccallini V, Angeloni C, Caraceni D, Fortunato C, Venditti MA, Gabriele G, Antonelli C, Lattanzi A, Puliti D, Ciatto S, Confortini M, Sani C, Zappa M. Comparison of the conventional cervical smear and liquid-based cytology: Results of a controlled, prospective study in the Abruzzo Region of Italy. Acta Cytologica, 2008; 52(5):568-574

Medical Services Advisory Committee 2002. Liquid Based cytology for cervical screening. MSAC reference 12a. Assessment report. August 2002.

Medical Services Advisory Committee 2009. Automation-assisted and liquid-based cytology for cervical cancer screening. MSAC application 1122 Assessment report. September 2009.

Melnikow J, Kulasingam S, Slee C, Helms J, Kuppermann M, Birch S, McGahan C, Coldman A, Chan B, Sawaya G. Surveillance After Treatment for Cervical Intraepithelial Neoplasia. Outcomes, Costs, and Cost-Effectiveness. Obstet Gynecol. 2010 Nov; 116(5):1158-70.

Nance KV. Evolution of Pap testing at a community hospital — a ten year experience. Diagnostic Cytopathol 2006;35:148–53.

NHMRC. Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities. Approved by the Australian Government National Health and Medical research Council on 9 June 2005.

National Institute for Clinical Excellence (NICE) 2003, Guidance on the use of liquid-based cytology for cervical screening. Technology Appraisal 69.London, UK: National Institute for Clinical Excellence, NHS.

National Cancer Screening Service. Guidelines for Quality Assurance in Cervical Screening. Cervical Check, the National Cervical Screening Program, Ireland, 2008 (Date accessed: 26.08.12) http://www.cancerscreening.ie/publications/QA_final_web_version.pdf.

New Zealand National Cervical Screening Programme. Monitoring Report Number 34, 1 July -31 Demcember 2010. NZ: National Screening Unit (Date accessed 08.10.12) http://www.nsu.govt.nz/health-professionals/1063.aspx

Nygard JF, Sauer T, Nygard M, Skare GB, Thoresen S. CIN 2/3 and cervical cancer in an organised screening programme after an unsatisfactory or a normal Pap smear: a seven-year prospective study of the Norwegian population-based screening programme. J Med Screen 2004, 11:70–76.

Obwegeser JH, Brack S. Does liquid-based technology really improve detection of Cervical neoplasia? A Prospective, Randomized Trial Comparing g the ThinPrep Pap Test with the Conventional Pap Test, Including Follow-up of HSIL cases. Acta Cytologica, 2001; 45(5):709-714.

Palmer TJ, Nicoll SM, McKean ME, Park AJ, Bishop D, Baker L, Imrie JEA. Prospective parallel randomized trial of the MultiCyte(trademark) ThinPrep(registered trademark) imaging system:

The Scottish experience. Cytopathology. 2012 May 22. doi: 10.1111/j.1365-2303.2012.00982.x. [Epub ahead of print]

Payne N, Chilcott J, McGoogan E. Liquid-based cytology in cervical screening: a rapid and systematic review. Health Technology Assessment 2000; 4(18): i-73

PBAC guidelines V4.3 2008: Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3) Australian Government Department of Health and Ageing, December 2008.

Peto J, Gilham C, Fletcher O, Matthews FE. The cervical cancer epidemic that screening has prevented in the UK. Lancet 2004; 364(9430):249–256.

Raab SS, Grzybicki DM, Hart AR, Kiely S, Andrew-JaJa C, Scioscia E Jr. Willingness to pay for new Papanicolaou test technologies. American Journal of Clinical Pathology 2002; 117(4):524-533.

Ransdell JS, Davey DD, Zaleski S. Clinicopathologic correlation of the unsatisfactory Papanicolaou smear. Cancer Cytopathol 1997;81:139-143.

Ronco G, Vineis C, Montanari G, Orlassino R, Parisio F, Arnaud S, . Impact of the AutoPap (currently FocalPoint) primary screening system location guide use on interpretation time and diagnosis. Cancer Cytopathol 2003;99:83–8.

Ronco G, Cuzick J, Pierotti P, Cariaggi MP, Dalla Palma P, Naldoni C, Ghiringhello B, Giorgi-Rossi P, Minucci D, Parisio F, Pojer A, Schiboni ML, Sintoni C, Zorzi M, Segnan N, Confortini M. Accuracy of liquid-based versus conventional cytology: overall results of new technologies for cervical cancer screening: randomised controlled trial. BMJ, 2007; 335(7609):28. Epub May 21 2007.

Ronco G, Giorgi-Rossi P, Carozzi F, Dalla Palma P, Del Mistro A, De Marco L, De Lillo M, Naldoni C, Pierotti P, Rizzolo R, Segnan N, Schincaglia P, Zorzi M, Confortini M, Cuzick J; New Technologies for Cervical Cancer screening Working Group. Human papillomavirus testing and liquid-based cytology in primary screening of women younger than 35 years: results at recruitment for a randomised controlled trial. Lancet Oncol, 2006; 7(7):547-555.

Ronco G, Segnan N, Giorgi-Rossi P, Zappa M, Casadei GP, Carozzi F, Dalla Palma P, Del Mistro A, Folicaldi S, Gillio-Tos A, Nardo G, Naldoni C, Schincaglia P, Zorzi M, Confortini M, Cuzick J; New Technologies for Cervical Cancer Working Group. Human papillomavirus testing and liquid-based cytology: results at recruitment from the new technologies for cervical cancer randomized controlled trial. J Natl Cancer Inst, 2006; 98(11):765-774.

Schiffman M, Solomon D. Findings to date from the ASCUS-LSIL Triage Study (ALTS). Arch Pathol Lab Med. 2003 Aug;127(8):946-9.

Schorge JO, Hossein Saboorian M, Hynan L, Ashfaq R. ThinPrep detection of cervical and endometrial adenocarcinoma: a retrospective cohort study. Cancer 2002; 96:338-343.

Siebers AG, Klinkhamer PJ, Arbyn M, Raifu AO, Massuger LF, Bulten J. Cytologic Detection of Cervical Abnormalities Using Liquid-Based Compared With Conventional Cytology: A Randomized Controlled Trial. Obstetrics & Gynecology, 2008; 112(6):1327-1334

Siebers AG, Klinkhamer PJ, Grefte JM, Massuger LF, Vedder JE, Beijers-Broos A. Comparison of liquid-based cytology with conventional cytology for detection of cervical cancer precursors: A randomized controlled trial. JAMA 2009, 302(16):1757-1764

Strander B, Andersson-Ellström A, Milsom I, Rådberg T, Ryd W. Liquid-based cytology versus conventional Papanicolaou smear in an organized screening program : a prospective randomized study. Cancer, 2007; 111(5):285-291.

Sweeney BJ, Haq Z, Happel JF, Weinstein B, Schneider D. Comparison of the effectiveness of two liquid-based Papanicolaou systems in the handling of adverse limiting factors, such as excessive blood. Cancer. 2006 Feb 25;108(1):27-31.

TOMBOLA Group. Cytological surveillance compared with immediate referral for colposcopy in management of women with low grade cervical abnormalities: multicentre randomised controlled trial. BMJ 2009;339

Van Ballegooijen.M., and Hermens. R., Cervical cancer screening in The Netherlands. European Journal of Cancer 2000; 36:2244-2246

Vesco KK, Whitlock EP, Eder M, Lin J, Burda BU, Senger CA, Holmes RS, Fu R, Zuber S. Screening for Cervical Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 86. AHRQ Publication No. 11-05156-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; May 2011.

Wordsworth S, Ryan M, Skåtun D, Waugh N. Women's preferences for cervical cancer screening: a study using a discrete choice experiment. International Journal of Technology Assessment in Health Care. 2006; 22(3):344–350.

Wright TC. Pathology of HPV infection at the cytologic and histologic levels: Basis for a 2-tiered morphologic classification system. International Journal of Gynecology and Obstetrics 2006, 94(Supplement 1):S22-S31.

Zhang J, Yu KF. What's the Relative Risk? A method of correcting the Odds Ratio in Cohort Studies of Common Outcomes. JAMA 1998; 280:1690-1691

Appendix A

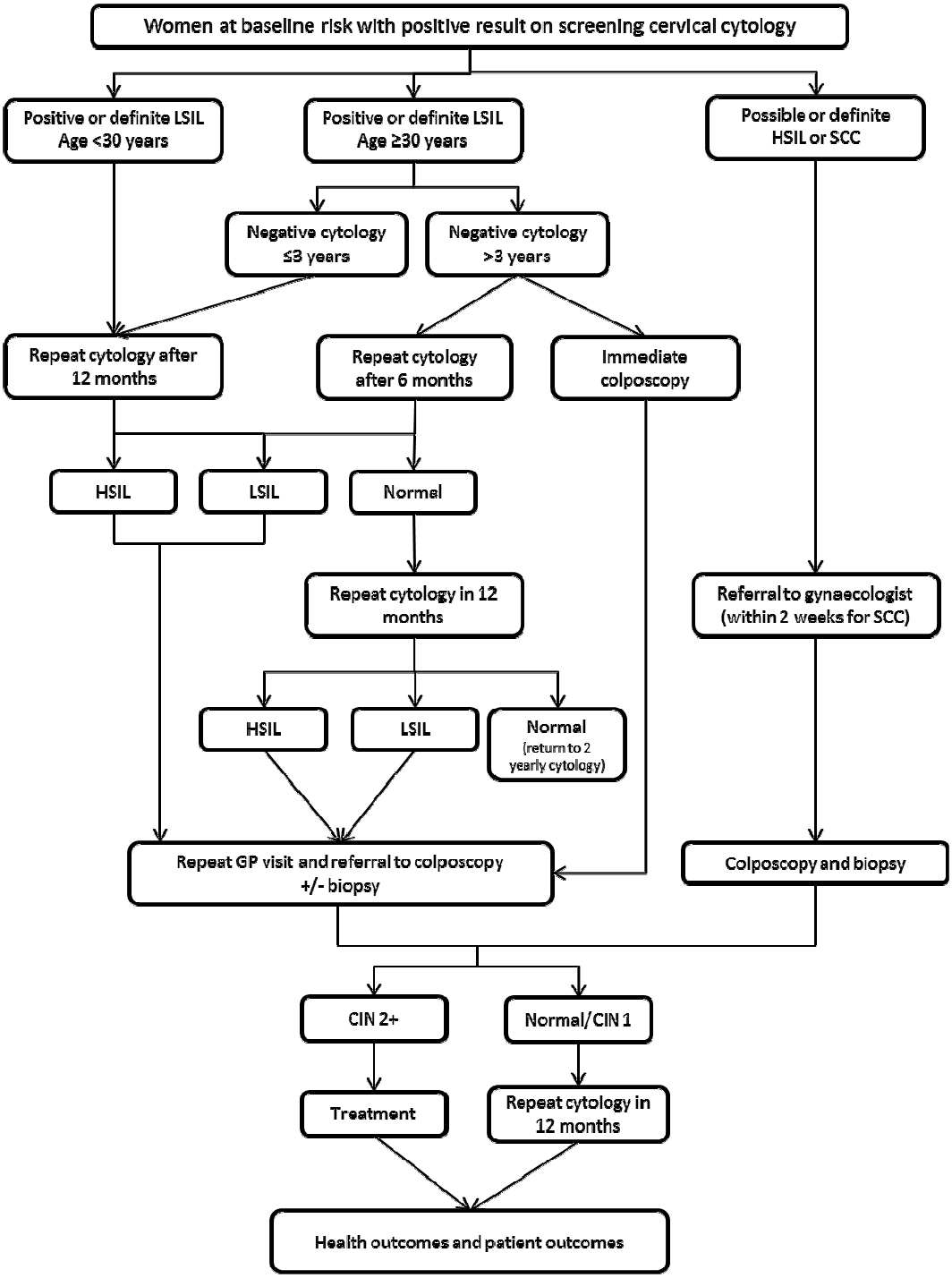

Figure 28 Management of participants testing positive in screening program (based on NHMRC 2005, Final DAP May 2012 Appendix A)

Appendix B

True positive: false positive and Incremental rate of true positive

The ratio of true positive to false positive tests and incremental rate of true positive results have been calculated for the purposes of the submission, as required by the DAP, and are presented below.

Cell enrichment LBC vs. CC

Generally there was similar to lower rate of true positive results for CIN 1+ across all test thresholds with cell enrichment LBC compared with CC in the Beerman trial (Table 105). The incremental rate of true positives for cell enrichment LBC compared with CC was less than one in all cases except for the SCC test threshold which resulted in three more CIN 1+ cases detected with CC.

Table 105 True positive: false positive; for histology CIN 1+ CC versus cell enrichment LBC: Beerman 2009

	Conventional			LBC			Incremental rate true positive
Test threshold	TP	FP	TP:FP	TP	FP	TP:FP	
ASCUS+	347	930	0.37:1	309	789	0.39:1	0.018517
LSIL+	300	102	2.94:1	236	86	2.74:1	-0.19699
HSIL+	247	45	5.49:1	192	36	5.33:1	-0.15556
SCC	3	1	3:1	2	0	0.42:1	-3
Source	Attachment 4						

Abbreviations: FP, false positive; SCC, squamous cell carcinoma; TP true positive
Only false negative and false positive rates reported by Beerman 2009. True positive rates manually calculated for the purposes of submission (Attachment 4)

Cell filtration LBC vs. CC

Generally there was a lower rate of true positive results for all reference standards across all test thresholds with cell filtration LBC compared to CC in the NTCC trial (25 to 34 years cohort, Table 106). The incremental rate of true positives for cell filtration LBC compared with CC was less than one in all cases except for the HSIL+ test threshold which resulted in one to four more histological abnormalities detected with CC.

Table 106 True positive: false positive; for histology CIN 1+, CIN 2+ and CIN 3+ CC versus cell filtration LBC -NTCC trial: Age 25 to 34 years: Ronco 2006b

	Conventional			LBC			Incremental rate true positive
	TP	FP	TP:FP	TP	FP	TP:FP	
Test threshold	**CIN 1+**						
ASCUS+	71	142a	0.5:1	162	337a	0.48:1	-0.01929
LSIL+	49	72a	0.68:1	113	142a	0.8:1	0.115219
HSIL+	13	3a	4.33:1	24	12a	2:1	-2.33333
	CIN 2+						
ASCUS+	33	180a	0.18:1	45	454a	0.1:1	-0.08421
LSIL+	28	93a	0.3:1	33	222a	0.15:1	-0.15243
HSIL+	13	3a	4.33:1	11	25a	0.44:1	-3.89333
	CIN 3+						
ASCUS+	22	191a	0.12:1	14	485a	0.03:1	-0.08632
LSIL+	18	103a	0.17:1	7	248a	0.03:1	-0.14653
HSIL+	9	7a	1.29:1	5	31a	0.16:1	-1.12442
Source	Attachment 4						

a. Does not include those patients who did not have a colposcopy as the reason that no colposcopy was performed is not explained. It is possible that the patient was lost to follow up and therefore inclusion in the FP category would be inappropriate

Generally there was a lower rate of true positive results for all reference standards across all test thresholds with cell filtration LBC compared to CC in the NTCC trial (35 to 60 years cohort, Table 107). The incremental rate of true positives for cell filtration LBC compared with CC was less than 1 in all cases.

Table 107 True positive: false positive; for histology CIN 1+, CIN 2+ and CIN 3+ CC versus cell filtration LBC: NTCC trial: Age 35 to 60 years: Ronco 2006b

	Conventional			LBC			Incremental rate true positive
	TP	FP	TP:FP	TP	FP	TP:FP	
Test threshold	**CIN 1+**						
ASCUS+	113	335a	0.34:1	143	686a	0.21:1	-0.12886
LSIL+	74	122a	0.61:1	98	220a	0.45:1	-0.1611
HSIL+	29	11a	2.64:1	39	11a	3.55:1	0.909091
	CIN 2+						
ASCUS+	51	397a	0.13:1	46	783a	0.06:1	-0.06972
LSIL+	42	154a	0.27:1	40	278a	0.14:1	-0.12884
HSIL+	26	14a	1.86:1	30	20a	1.5:1	-0.35714
	CIN 3+						
ASCUS+	31	417a	0.07:1	31	798a	0.04:1	-0.03549
LSIL+	26	170a	0.15:1	25	293a	0.09:1	-0.06762
HSIL+	18	22a	0.82:1	19	31a	0.61:1	-0.20528
Source	Attachment 4						

a. Does not include those patients who did not have a colposcopy as the reason that no colposcopy was performed is not explained. It is possible that the patient was lost to follow up and therefore inclusion in the FP category would be inappropriate.\

Generally there was a higher rate of true4 positive results for all reference standards across all test thresholds with cell filtration LBC compared to CC in the NETHCON trial (Table 108). The incremental rate of true positives for cell filtration LBC compared with CC was less than 1 in all cases except for the LSIL+ and HSIL+ test threshold which resulted in almost two and five more histological abnormalities detected with cell filtration LBC.

Table 108 True positive: false positive; for histology CIN 1+, CIN 2+ and CIN 3+: CC versus cell filtration LBC: NETHCON: Siebers 2009

	Conventional			LBC			Incremental rate true positive
	TP	FP	TP:FP	TP	FP	TP:FP	
Test threshold	**CIN 1+**						
ASCUS+	349	678	0.51:1	412	732	0.56:1	0.048092
LSIL+	272	115	2.37:1	329	119	2.76:1	0.399488
HSIL+	208	30	6.93:1	248	21	11.81:1	4.87619
	CIN 2+						
ASCUS+	274	753	0.36:1	331	813	0.41:1	0.043256
LSIL+	235	152	1.55:1	283	165	1.72:1	0.169099
HSIL+	194	44	4.41:1	233	36	6.47:1	2.063131
	CIN 3+						
ASCUS+	183	844	0.22:1	236	908	0.26:1	0.043087
LSIL+	162	225	0.72:1	216	232	0.93:1	0.211034
HSIL+	142	96	1.48:1	182	87	2.09:1	0.612787
Source	Attachment 4						

Generally the comparative true positive results varied for all reference standards across all test thresholds with cell filtration LBC compared to CC in the Strander trial (Table 109). The incremental rate of true positives for cell filtration LBC compared with CC was less than 1 in all cases except for the HSIL+ test threshold. At this test threshold there was almost three more CIN 1+histological abnormalities detected with cell filtration LBC compared to CC but nine less CIN 2+histological abnormalities detected with cell filtration LBC compared to CC.

Table 109 True positive: false positive; for histology low grade histology (CIN 1+and CIN 2+) CC versus cell filtration LBC: Strander 2007

	Conventional			LBC			Incremental rate true positive
	TP	FP	TP:FP	TP	FP	TP:FP	
Test threshold	**CIN 1+**						
ASCUS+	120	128	0.94:1	81	105	0.77:1	-0.16607
LSIL+	74	54	1.37:1	61	47	1.3:1	-0.0725
HSIL+	42	3	14:1	33	2	16.5:1	2.5
	CIN 2+						
ASCUS+	73	175	0.42:1	55	131	0.42:1	0.002704
LSIL+	51	77	0.66:1	44	64	0.69:1	0.025162
HSIL+	42	3	14:1	29	6	4.83:1	-9.16667
Source	Attachment 4						

a. Does not include those patients who did not have histology as the reason that no histology was performed is not explained. It is possible that the patient was lost to follow up and therefore inclusion in the FP category would be inappropriate

Generally there was a lower rate of true positive results for the CIN 2+ reference standard across all test thresholds with cell filtration LBC compared to CC in the Maccallini trial (Table 110). The incremental rate of true positives for cell filtration LBC compared with CC was less than 1 in all cases except for the HSIL+ test threshold which resulted in 16 more histological abnormalities detected with CC.

Table 110 True positive: false positive; for histology (CIN 2+): CC versus cell filtration LBC: Maccallini 2008

	Conventional			LBC			Incremental rate true positive
	TP	FP	TP:FP	TP	FP	TP:FP	
Test threshold	**CIN 2+**						
ASCUS+	73	79	0.92:1	55	50	1.1:1	0.175949
LSIL+	51	33	1.55:1	44	28	1.57:1	0.025974
HSIL+	42	2	21:1	29	6	4.83:1	-16.1667
Source	Attachment 4						