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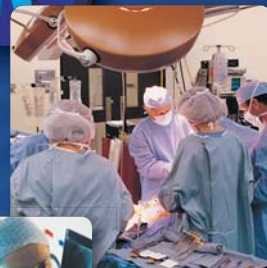
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Systematic Review and
Cost-Effectiveness Analysis of
Screening for Cervical Cancer Using
Liquid-Based Technology



Supporting Informed Decisions

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Canadian Agency for Drugs and Technologies in Health

**Systematic Review and Cost-Effectiveness
Analysis of Screening for Cervical Cancer
Using Liquid-Based Technology**

February 2008

We thank Suzanne Morphet for her assistance in creating this overview from a longer report authored by Krahn *et al.*

This overview is based on a technology report commissioned by CADTH: Krahn M, McLachlin M, 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

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Liquid-Based Techniques for Cervical Cancer Screening: Systematic Review and Cost-Effectiveness Analysis

Technology and Condition

Liquid-based cytology (with or without HPV testing) as an alternative to conventional cytology (CC) for cervical cancer screening of sexually active women who are 15 years of age or older.

Issue

Liquid-based cytology (LBC) is more expensive than CC. There is uncertainty about whether the use of this technology is justified.

Methods and Results

A systematic review and Bayesian meta-analysis, economic evaluation, and budget impact analysis were undertaken to compare CC, LBC, and LBC-based human papillomavirus (HPV) triage at one-, two-, and three-year screening intervals. Twenty studies of 68,114 participants suggested that LBC was 6% more sensitive and 4% less specific than CC, on average. An LBC-based HPV triage program could cost an additional \$6.35 per targeted individual. Compared to annual screening with CC, LBC with HPV triage every two years could reduce disease burden — 3,023 women screened would prevent one cancer-related death (a gain of 0.0002 QALYs) — and reduce costs (\$59 per person, discounted) while increasing colposcopy rates by 37.5%. The same screen annually leads to a larger reduction in disease burden (0.0007 QALYs) but increased average costs (\$23 per person, discounted) and colposcopy referrals by 63%.

Implications for Decision Making

- **LBC and CC perform similarly.** The clinical evidence suggests that LBC is similar to CC with respect to sensitivity and specificity. LBC is probably more sensitive and less specific, and may have a lower rate of unsatisfactory specimens.
- **LBC strategies can be cost-effective, but they increase colposcopy referrals.** Model projections suggest that LBC with HPV triage every two years can be cost-saving compared to an annual screening strategy with CC alone.
- **HPV triage is cost-effective.** Direct comparison of all screening and triage strategies show that annual screening with CC or LBC is always more costly and less effective than when paired with HPV triage. Adding HPV triage to annual CC can reduce colposcopy referrals by 5%. Compared to annual CC with HPV triage, LBC with HPV every two years will reduce disease burden further by 0.0004 QALYs, while increasing costs (\$52 per person, discounted) and colposcopy referrals by 72%.

This summary is based on a comprehensive health technology assessment available from CADTH's web site (www.cadth.ca): 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*.

1 Introduction

A decline in the incidence of cervical cancer since the 1950s has been attributed to Papanicolaou (Pap) smear screening programs for the early detection and treatment of precancerous and cancerous lesions.^{1,2} In 2007, it was estimated that 1,350 women will be diagnosed with cervical cancer, and approximately 390 will die from it.³

The Pap test is imperfect, with false-negatives due to errors in sampling, preparation, screening, and interpretation.⁴ In Ontario, for instance, 0.58% of Pap test samples are unsatisfactory and need to be repeated.^{5,6} In 2003, this resulted in 7,200 additional samples being taken out of approximately 1.2 million.

The recognition that human papillomavirus (HPV) infection is the necessary cause of cervical cancer brought new prevention paradigms in screening and immunization. Techniques are now available to detect precancerous and cancerous lesions. The aim of using liquid-based cytology (LBC) is to produce better results. Clinicians place samples in a liquid fixative rather than smearing them on a glass slide. Final samples are produced in the laboratory and are relatively free of obscurities.

The Canadian government has approved two commercially available LBC preparation systems: the ThinPrep Pap Test (CYTYC, Boxborough MA) and the SurePath Pap Test (Tripath Care Technologies, Burlington NC). The former uses a microprocessor-controlled filtration technique, while the latter uses a density gradient. Both result in uniformly fixed and distributed cells. Both require proprietary sampling tools, fixatives, and preparation devices, which increase the cost of testing compared with that of conventional cytology (CC).

The HPV test is used to detect HPV DNA in cervical cells. Two companies are marketing different versions of this test in Canada. One uses DNA hybridization, and the other uses polymerase chain reaction (PCR). The Hybrid Capture 2 (HC-2; Digene Corporation, Gaithersburg MD) uses the former to detect any of the 13 types of HPV that have been proven to cause virtually all cases of cervical cancer.⁷ It has been approved by the US Food and Drug Administration. Roche Diagnostics Canada markets the AMPLICOR HPV test, which amplifies DNA using PCR and nucleic acid hybridization to detect the 13 high-risk HPV genotypes in cervical cells. Studies show that both tests give comparable results, and both are suitable for routine use.⁸⁻¹⁰ In addition, the recently approved Linear Array HPV genotyping test (Roche Molecular Systems) is a PCR-based HPV detection kit that allows for multiple HPV typing of 37 genotypes.

HPV testing could be used in triage of borderline abnormalities, primary screening for selected age groups, and follow-up to the treatment of lesions.^{11,12} In triage, HPV testing differentiates between cervical samples that contain high-risk HPV and those that do not, saving approximately 50% of women from unnecessary colposcopy, without compromising sensitivity.^{13,14}

LBC for cervical cancer screening remains controversial. Ontario, and Newfoundland and Labrador have adopted it, while other provinces have considered it.^{5,15} A report from the Canadian Coordinating Office for Health Technology Assessment (now CADTH) suggested that LBC is more sensitive than CC and may be cost-effective at three-year intervals. It also suggested that the technology needs to be evaluated in a Canadian context.¹⁶ Australia, Switzerland, France, and Germany no longer reimburse for LBC, citing lack of evidence.^{17,18} In the US, some guidelines favour its adoption with HPV testing.¹⁹

2 Objectives

This report aims to assess the effectiveness and cost-effectiveness of LBC versus CC for cervical cancer screening in a population of sexually active women 15 years of age or older. To achieve these objectives, the report addresses four research questions.

- How effective and cost-effective is LBC compared with CC?
- What populations and population-based parameters influence the estimates of effectiveness or cost-effectiveness?
- How does HPV testing affect the cost-effectiveness of LBC-based screening?
- What is the budget impact of adopting LBC and HPV triage from the perspective of a provincial health-care payer?

3 Clinical Review

Methods

We conducted a systematic review to update the CCOHTA technology assessment by searching BIOSIS Previews, CANCERLIT, EMBASE, MEDLINE, and the Cochrane Library from November 2002 to June 2006, with no language restriction or exclusion of unpublished material. Earlier studies on LBC versus CC were deemed to have been included in the CCOHTA assessment.¹⁶ For HPV triage, we updated a systematic review by Arbyn *et al.*²⁰ Grey literature was found by searching the web sites of HTA agencies and abstracts from scientific meetings.

Selection criteria

Primary diagnostic studies, systematic reviews, or HTA reports evaluating LBC that is manually read compared to CC were included. Two reviewers independently screened citations and resolved differences by discussion. For HPV triage, we had three criteria: study participants presented with an index CC showing atypical squamous or atypical glandular cells of undetermined significance (ASCUS-AGUS); an HPV DNA test was performed; and participants underwent colposcopy followed by biopsies to verify the histological state of the abnormality.²⁰

Data abstraction strategy

One reviewer independently abstracted data while another verified it on a form created in MS Excel. We extracted diagnostic data from 2×2 tables (i.e., false- and true- positive and negative values) according to the cytological cut-off and disease status for each technique (ThinPrep, SurePath, or CC). For split-sample studies (where one sample was used for LBC and CC), we calculated the percentages of discordant data between the two techniques using low-grade squamous intraepithelial lesion and higher grade lesions (LSIL+) as the threshold. This approach was used in previous HTA reports.

For two-cohort studies (where one sample was examined using LBC or CC, but not both), we extracted the number of participants and percentage of cases of LSIL+ and high-grade squamous intraepithelial lesion and higher grade lesions (HSIL+). We extracted the percentages of inadequate or unsatisfactory specimens from all studies, if available.

Strategy for quality assessment

The quality of the reporting of included studies was assessed using a validated checklist designed to evaluate LBC and adopted from a systematic review.²¹ To be considered high quality, a split-sample study had to be read by cytologists who did not know the results from other cytologists, and discordant slides had to be verified. A two-cohort study was deemed to be high quality if it used a blind reference standard and verified all positive and at least some randomly chosen negative slides.

Data analysis

We used a summary receiver-operating characteristics curve model to concurrently estimate the relative sensitivity and specificity of LBC and CC, given their inverse relationship (test sensitivity increases as specificity decreases).²² The model was used to combine estimated pairs of true-positive and false-positive values from many studies. It provided the flexibility to incorporate in- and between-study variation in diagnostic threshold values and precancerous lesion severity.²³ Two reviewers analyzed the results using Markov chain Monte Carlo simulations in WinBugs²⁴ with guidance from a third reviewer.

We used a random-effects meta-analytic model to derive combined estimates for accuracy and classification outcomes, including sensitivity and specificity, discordant percentages from split-sample studies, and cytological classifications from two-cohort studies.

Results

Our literature search identified 108 unique studies on LBC, of which 20 directly compared LBC and CC, 49 reported on sensitivity or specificity, and 66 reported unsatisfactory samples. There were 47 split-sample studies by which to assess the discordance between LBC and CC, and 31 two-cohort studies reporting the cytological classification from both techniques.

The meta-analysis of data from the 20 head-to-head studies, with a total of 68,114 participants, showed no statistical difference in sensitivity or specificity between LBC and CC. On average, LBC was 6% more sensitive than CC (mean sensitivity 80.5% versus 74.0%) and 4% less specific (mean specificity 82.6% versus 86.8%) (Table 1). Across a range of test thresholds and cytology abnormalities, LBC has an 83% chance to be more sensitive and a 72% chance to be less specific than CC.

For HPV triage, we found 45 primary studies, two systematic reviews, five HTA reports, and 12 economic evaluations. Arbyn *et al.* updated their original systematic review twice. They consistently reported that triage with the Hybrid Capture-2 was more sensitive than repeat cytology at the ASCUS+ cut-off.^{11,12}

Table 1: Direct comparison between LBC and CC					
Study Characteristics	Number of Groups/Number of Participants	Sensitivity Median (Range)*	Sensitivity Estimate (95% CI)†	Specificity Median (Range)*	Specificity Estimate (95% CI)†
Main analysis					
liquid-based cytology	20/28,736	0.8111 (0.5259, 1.00)	0.8049 (0.7201, 0.8711)	0.7962 (0.1667, 1.00)	0.8260 (0.6939, 0.9085)
conventional cytology	20/39,377	0.6889 (0.5686, 0.9412)	0.7400 (0.6327, 0.8386)	0.8459 (0.3636, 1.00)	0.8675 (0.7421, 0.9454)
difference (LBC–CC)			0.0643 (–0.0650, 0.1879)		–0.0402 (–0.1986, 0.1057)
Sensitivity analysis					
High quality‡					
liquid-based cytology	6/6,898	0.795 (0.67, 1.00)	0.773 (0.662, 0.856)	0.855 (0.73, 0.98)	0.861 (0.541, 0.97)
conventional cytology	6/16,097	0.695 (0.64, 0.86)	0.694 (0.554, 0.91)	0.88 (0.75, 0.94)	0.90 (0.68, 0.99)
difference (LBC–CC)			0.077 (–0.172, 0.235)		–0.044 (–0.193, 0.4339)
Histology**					
liquid-based cytology	13/17,534	0.81 (0.53, 1.00)	0.802 (0.68, 0.88)	0.83 (0.46, 1.00)	0.8621 (0.73, 0.93)
conventional cytology	13/28,151	0.6878 (0.57, 0.90)	0.79 (0.65, 0.92)	0.87 (0.66, 1.00)	0.8584 (0.6881, 0.9571)
difference (LBC–CC)			0.0114 (–0.1657, 0.1644)		–0.0057 (–0.1884, 0.1729)
ThinPrep††					
liquid-based cytology	17/27,759	0.81 (0.53, 0.95)	0.809 (0.7521, 0.8576)	0.79 (0.1667, 1.00)	0.82 (0.631, 0.9162)
conventional cytology	17/28,547	0.69 (0.57, 0.94)	0.757 (0.661, 0.8541)	0.76 (0.31, 1.00)	0.858 (0.6881, 0.9553)
difference (LBC–CC)			0.051 (–0.061, 0.157)		–0.036 (–0.153, 0.244)

*Values are observed median and range of sensitivity and specificity. †Estimates taken from hierarchical regression model. ‡Includes Ferenczy, 1996; Sherman, 1998; Bergeron, 2001; Coste, 2003; Longatto-Filho, 2005; and Taylor, 2006. **Histology was reference standard used in these studies. ††These studies evaluated ThinPrep. Pooled estimates not generated for SurePath because of lack of data. CC=conventional cytology; CI=Bayesian credible intervals; LBC=liquid-based cytology.

Our updated systematic review confirmed this, with HPV testing being 7% more sensitive and having at least similar specificity to detect high-grade lesions defined as cervical intraepithelial neoplasia stage 2 (CIN2+). The combined estimate of sensitivity was 86%, and that of specificity 62% with the Hybrid Capture-2. For repeat cytology, the corresponding estimates were 79% and 58% respectively.

4 Economic Analyses

We identified economic evaluations in our main literature search.

Economic review

a) Methods

Studies were included if they evaluated the cost-effectiveness of replacing CC with LBC or HPV triage in a cervical cancer screening program. Studies were assessed for their local applicability (e.g., similar burden of disease and compliance rates). The cost per life-year gained and the cost per quality-adjusted life-year gained were abstracted in the year that they were reported and converted to 2006 Canadian dollars. The median cost per attained outcome was used as a summary statistic across studies.

b) Strategy for quality assessment

One reviewer used a validated tool for assessing the quality of reporting of cost-utility studies.^{25,26} Each study was rated on a scale of 1 to 7 (the higher the number, the better the quality).

c) Results

We found nine cost-effectiveness studies on LBC and CC, three of which also evaluated HPV triage. All but two were of high quality (ratings between 5.5 and 7). These studies evaluated LBC in prevention programs in the US, UK, and Alberta. All studies found that LBC was economically attractive at a median cost of \$17,000 per life-year gained for programs with screening intervals of three or more years. Two- and three-year screening intervals led to median costs per life-year gained of \$41,000 and \$186,000 respectively.

Seven studies in the US, UK, the Netherlands, France, and Italy assessed HPV triage exclusively. In quality, they rated between 4 and 6. HPV triage was found to be economically attractive at intervals of three or more years and a cost ranging from \$300 to \$61,800 per life-year gained. The results were inconsistent for intervals of less than 3 years, ranging from dominant (i.e., cost saving and improved predicted health outcomes) to a cost of \$206,000 per life-year gained.

Primary economic evaluation

a) Methods

We developed a Canadian cervical cancer model using TreeAge Pro 2007 software. The model simulated the progression of healthy cervical tissue that may be infected with HPV, to precancerous lesions, and to invasive cervical cancer. The model incorporates biological information, epidemiological data, and Canadian costs. The input data and data used in model calibration were derived from targeted literature searches. The transition probabilities were specified as ranges derived from cervical cancer models for HPV vaccines.^{27,28} The estimates were derived to ensure consistency between model output and Canadian data.²⁹

Costing data came from five Canadian studies and included consumable supplies, cytology tests, office visits, out-of-hospital diagnostic procedures, and professional fees. The unit costs for tests and related fees were extracted from the Ontario Ministry of Health Schedule of Benefit. The average costs of colposcopy and biopsy came from a Canadian study on resource use in four provinces.³⁰ The average costs of treatment came from a background paper on HPV immunization in BC,² two

economic evaluations on managing low-grade Pap abnormalities,^{31,32} and an Alberta study on LBC and HPV triage.¹⁵

In our model, individuals progress along the disease pathway while facing a risk of acquiring an infection with high- or low-risk HPV every six months, depending on age. Infection can clear spontaneously or persist. A diseased state can be detected based on symptoms or by using routine screening, and subsequently managed according to current practice guidelines. Given the long latency between infection and cancer, we used a lifetime horizon to capture the long-term outcomes.³³ Our perspective was that of a provincial ministry of health, which bears the cost of screening, diagnosis, and cancer treatment.

b) Results

According to our model, without screening, a woman’s lifetime risk of cervical cancer would be 2.87%. The incidence of cervical cancer was 42.22 per 100,000, and the incidence of mortality was 16.61 per 100,000 (Table 2). Annual CC screening reduced the lifetime risk to 0.67%, cancer incidence to 9.77 per 100,000, and mortality to 3.27 per 100,000. Increasing the interval of current screening with CC to every two years increased the cancer and mortality incidence by about 7%. Increasing the interval of current screening to every two years and using LBC kept the incidence of disease virtually unchanged at a lower average lifetime cost.

At three-year screening intervals, LBC resulted in higher average life-years and cost saving compared with CC, but the incidence of disease increased by approximately 11%.

Screening Option	Interval	Cost	Cancer Cases /10 ⁵	Deaths /10 ⁵	Colposcopy Rate/10 ⁵	Life-Years	QALY	Incremental Cost-Effectiveness Ratio
no screen	0	\$2,870	42.22	16.61	0	19.536034	17.787440	
efficiency ¹								
CC	2	\$1,091	10.46	3.50	881	19.556526	17.863407	least expensive
LBC	3	\$1,103	10.85	3.65	1,279	19.556226	17.863055	dominated
CC	3	\$1,108	11.79	3.98	746	19.555560	17.862301	dominated
LBC	2	\$1,108	9.65	3.22	1,525	19.557091	17.864019	\$30,939 per LY, \$28,572 per QALY
CC	1	\$1,147	9.77	3.27	1,033	19.557168	17.864076	extended dominated
LBC	1	\$1,188	9.08	3.03	1,801	19.557637	17.864557	\$146,617 per LY, \$148,797 per QALY

Projected cervical cancer cases and related mortality per 100,000. ICER incremental cost-effectiveness ratio calculated in each screening interval. ¹Screening options ordered by lowest to highest cost according to efficiency frontier graph. CC=conventional cytology; LBC=liquid-based cytology; LY=life-year; QALY=quality-adjusted life-year.

Our cost-effectiveness analysis was sensitive to seven parameters. From most to least influential, these were marginal sensitivity and marginal specificity of LBC; screening coverage; marginal cost of LBC; compliance rate to follow-up cytological abnormalities; cost of terminal care for a cervical cancer death; and cost of colposcopy. Table 3 examines the trade-off between sensitivity and specificity.

Table 3: Cost-effectiveness of LBC and quality of studies evaluating LBC accuracy	
LBC Versus CC Accuracy Estimates	Incremental Cost-Effectiveness Ratio of LBC versus CC in 2-Year Screening Programs
main analysis (20 study groups), sensitivity gain 6.43%; specificity loss 4.02%	\$30,939 per LYS
high quality studies (6 study groups), sensitivity gain 7.70%; specificity loss 4.40%	\$16,568 per LYS
histology standard (13 study groups), sensitivity gain 1.14%; specificity loss 0.57%	\$298,336 per LYS

CC=conventional cytology; LBC=liquid-based cytology; LYS=life-year saved.

We performed a probabilistic sensitivity analysis (PSA) to understand the effect of uncertainty when the parameters are combined. This was done by converting the incremental cost per life-year saved for each screening option at different levels of willingness to pay to an incremental net benefit. The results were presented in a cost-effectiveness acceptability curve.

Table 4: Long-term effectiveness and costs of all screening options							
Screening Options	Interva l	Cost (\$)	Cancer Cases/ 10⁵	Deaths/ 10⁵	Colposcopy Rate/10⁵	Life- Years	QALY
no screening	0	2,870	42.22	16.61	0	19.536034	17.787440
S1: CC	1	1,147	9.77	3.27	1,033	19.557168	17.864076
S3: CC+HPV triage 0	1	1,122	9.23	3.10	977	19.557432	17.864370
S4: CC+HPV triage 1	1	1,128	9.23	3.10	977	19.557432	17.864370
S2: LBC	1	1,188	9.08	3.03	1,801	19.557637	17.864557
S5: LBC+HPV triage	1	1,170	8.64	2.89	1,681	19.557872	17.864813
S6: CC	2	1,091	10.46	3.50	881	19.556526	17.863407
S8: CC+HPV triage 0	2	1,066	9.98	3.34	834	19.556778	17.863694
S9: CC+HPV triage 1	2	1,070	9.98	3.34	834	19.556778	17.863694
S7: LBC	2	1,108	9.65	3.22	1,525	19.557091	17.864019
S10: LBC+HPV triage	2	1,088	9.23	3.08	1,420	19.557314	17.864267
S11: CC	3	1,108	11.79	3.98	746	19.555560	17.862301
S13: CC+HPV triage 0	3	1,078	11.25	3.79	707	19.555858	17.862651
S14: CC+HPV triage 1	3	1,081	11.25	3.79	707	19.555858	17.862651
S12: LBC	3	1,103	10.85	3.65	1,279	19.556226	17.863055
S15: LBC+HPV triage	3	1,077	10.38	3.49	1,190	19.556491	17.863361

CC=conventional cytology; CC + HPV triage 0=screening option with sample for HPV triage collected concurrent with original Pap smear or self-sampling, without additional visit; CC + HPV triage 1 = screening option with 1 additional visit to collect cervical cells sample for HPV triage sample; HPV=human papillomavirus; ICER=incremental cost-effectiveness ratio; LBC=liquid-based cytology; LBC + HPV triage=liquid-based cytology with HPV triage; QALY=quality-adjusted life-year.

According to the PSA, LBC screening every two years was likeliest to produce the highest incremental net health benefits if the willingness to pay for one discounted life-year gained exceeded \$40,000. Below this threshold, CC screening every two years was the preferred option.

HPV triage was more effective than repeat cytology with CC or LBC for diagnosing abnormalities of undetermined significance at every screening interval. LBC and HPV triage were cost-effective every two years at approximately \$42,000 per life-year saved compared with HPV triage and CC. According to the PSA, LBC and HPV triage screening every two years was likeliest to produce the highest net health benefits if the willingness to pay for one discounted life-year gained exceeded \$50,000. Below this threshold, CC and HPV triage screening every two years was the preferred option.

5 Limitations

Our cost-effectiveness analysis was limited in three ways. First, screening every two or three years, as suggested by the model, may be unfeasible in opportunistic screening programs. Second, we measured health benefits mainly in the number of life-years saved, rather than as quality of life. The sensitivity analyses were conducted with quality-adjusted life-years. Third, our model did not account for the potential variations in values among many cohorts. Therefore, it may reflect real-life scenarios inaccurately, although the conclusion regarding the relative merits of screening options is most likely to be valid.

6 Health System Implications

We conducted a budget impact analysis using data from the Ontario pilot study for SurePath implementation (406,000 CC and 379,000 LBC tests),⁵ cytology classification data from British Columbia (539,000 tests),³⁴ and the estimated increase in colposcopy referrals derived from the current model for two-year screening with LBC only (approximately 48%) and LBC and HPV triage (approximately 38%), compared with current screening programs.

We projected that the additional annual cost to replace CC by LBC in cervical cancer programs would range from \$262,000 to \$14.6 million across provinces except Ontario, and Newfoundland and Labrador, which have adopted LBC. The corresponding additional annual cost to introduce LBC with HPV triage would range from \$255,000 to \$14.2 million, indicating that HPV triage could be cost-neutral. Our analysis suggested an average 12% increase in first-year budgets in anticipation of an increase in colposcopy services. This did not account for other factors such as human resources, training, workload, and waiting time.

The introduction of vaccines to prevent HPV infection may affect how future screening is done. Research will be needed to determine if programs should be modified because of a lower prevalence of precancerous lesions in the post-vaccination era.

7 Conclusions

The clinical evidence suggests no statistical differences in sensitivity and specificity between LBC and CC. LBC is estimated to be on average 6% more sensitive and 4% less specific than CC across a range of cytological thresholds. There is an 83% chance that LBC is more sensitive than CC and a 72% chance that it is less specific. On average, LBC classifies approximately 1% more cell abnormalities than CC at the low-grade threshold of LSIL+. At the high-grade threshold of HSIL+, LBC may classify fewer abnormalities than CC, but the difference is not statistically different. On average, LBC may have a lower rate of unsatisfactory specimens, but the estimated differences from individual studies varied.

HPV triage of ASCUS is more sensitive to detect cervical intraepithelial lesions than repeat cytology. HPV triage has a similar specificity compared to repeated cytology. Model projections suggest that, over a woman's lifetime, LBC is likely to improve health outcomes (e.g., cancer incidence and cancer death) and increases costs when compared with CC at the same screening interval. Model projections also suggest that, over a woman's lifetime, HPV triage reduces costs and improves health outcomes when paired with any cytologic screening strategy.

Direct comparison of all screening and triage strategies show that annual screening with CC or LBC is always more costly and less effective than when paired with HPV triage. HPV triage used with LBC screening at two-year intervals is preferred to CC with HPV triage at a willingness-to-pay threshold of \$50,000 per LY gained, and CC with HPV triage every two years is preferred to LBC with HPV triage at lower willingness-to-pay thresholds. In comparison with current practice, using liquid-based cytology with HPV triage at two-year screening intervals will reduce costs, with a similar or reduced burden of disease. Thus, the health economic evidence suggests that two-year screening strategies using HPV triage, with or without LBC, represents the best use of resources for cervical cancer screening. These results will require revision given the introduction of automated screening, HPV vaccination, and organized screening programs.

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