Liquid-Based Cytology: Evaluation of Effectiveness, Cost-Effectiveness, and Application to Present Practice

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Key Words
Liquid-based cytology (LBC), conventional Papanicolaou smear, human papillomavirus (HPV) testing, cervical cancer, cervical intraepithelial neoplasia grade 2 or 3 (CIN 2,3)

Abstract
This article reviews the data available as of 2004 on the effectiveness and cost-effectiveness of cervical screening with the two available cytologic methods, the conventional Papanicolaou (Pap; CP) smear and liquid-based cytology (LBC), and discusses the application of LBC to current practice. The majority of LBC studies are on the ThinPrep Pap Test (Cytyc, Boxborough, MA) and the remainder are on SurePath (TriPath, Burlington, NC), which was previously known as AutoCyte Prep. LBC identified more low-grade squamous intraepithelial lesion (LSIL) Pap test results compared with paired conventional cytology in 17 of 21 ThinPrep and 9 of 12 SurePath "split-sample" studies considered to fulfill the criteria for inclusion in the British NHS Health Technology Assessment (HTA) evaluation of cervical cytology. In four of the six recent ThinPrep and one of two SurePath split-sample studies, more high-grade squamous intraepithelial lesion-positive (HSIL+) results were identified by LBC than by CP. All 15 "direct-to-vial studies" meeting HTA criteria reported more LSIL+ results for LBC compared with CP, and all eight of the direct-to-vial studies reporting HSIL+ results separately showed increased detection of high-grade cytology interpretations. Fifteen studies met the criteria for evaluating sensitivity and specificity. Aggregate sensitivity for the CP was 71.5% and for LBC was 80.1%. Indirect comparisons of the two LBC methods did not detect a difference in sensitivity, and a meta-analysis of the six studies comparing specificity between CP and LBC found no difference. Other capabilities of LBC are improved specimen adequacy and the ability to do ancillary testing out of the liquid-based vial. In cost-effectiveness analyses based on models of disease natural history and/or the clinical effectiveness of each screening modality, screening with CP was always dominated by screening with LBC. Primary cervical screening guidelines issued by the American Cancer Society in 2002 recommend repeating the cytology biannually if liquid-based and annually if conventional. The gain in sensitivity, apparent cost-effectiveness, and advantage of having a representative specimen for ancillary testing, support the use of LBC. (JNCCN 2004;2:597–611)

Cervical cancer screening with the Papanicolaou (Pap) smear is one of the few interventions to have received an "A" recommendation from the U.S. Preventive Services Task Force, despite never having been tested in a randomized trial to prove effectiveness. The impact of this test can be seen in the nearly universal association of a "Pap test" with the "annual exam" among women in the United States. Unfortunately, in countries without cervical cancer screening, cervical cancer rates continue to rank first or second among all cancers in women. In contrast, countries with widespread availability of cervical cytologic screening have shown an approximately 75% reduction in the incidence and mortality of cervical cancer. In the United States, the incidence of cervical cancer decreased from second among all cancers in women before 1950 to tenth by 2002, with mortality falling from second to thirteenth.

Although incidence and mortality gains had begun to level off in the early 1990s, recent trends for both have shown further gains. Cervical cancer screening is successful because it most commonly detects cervical cell changes before they attain the capacity for invasion. With appropriate treatment of cervical precancer identified by screening, the 5-year survival rate is nearly 100%. Even when invasion has occurred, cervical cancers detected at an early stage (1A) have a 5-year survival rate of approximately 92%.

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Submitted August 4, 2004; accepted for publication September 22, 2004.
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Immense effort is being made to continue the decline in cervical cancer incidence and mortality, as evidenced by the Healthy People 2010 target for reduction in cervical cancer deaths over the next 6 years from nearly 3.0 to 2.0 per 100,000 women. Much of the effort is directed toward increasing screening rates within the population, for approximately 50% of the cervical cancers diagnosed in the U.S. are in women who have never been screened, and an additional 10% occur in women who have not been screened within the past 5 years.

Despite this success, a number of problems with the conventional Pap smear fostered research in new methods of preparing cytology slides. This review examines the data available as of 2004 on the clinical utility and cost-effectiveness of cervical screening with the two available cytologic methods, the conventional Pap smear and liquid-based cytology (LBC), and discusses the application of LBC to current practice.

**Conventional Pap Test**

Observations by George Papanicolaou in 1923 that vaginal cells of women with cervical cancer were different from vaginal cells from women without cancer initiated the study of cervical cytology and led, 20 years later, to publication of *Diagnosis of Uterine Cancer by the Vaginal Smear*. This lifelong pursuit established a simple test, known as the Papanicolaou or Pap smear, as the most successful cancer preventative test in widespread use to date. However, success of the Pap smear in cervical cancer screening generated expectations that the test was perfect. By 1987, reports of women being diagnosed with cervical cancer despite earlier screening and of poor quality work in the cytopathology laboratories led to intense public scrutiny, new government regulation of laboratories (the Clinical Laboratory Improvement Amendment; CLIA 88), and dramatic changes in cytologic terminology, known as the Bethesda System (TBS).

Until recently, test sensitivity was significantly overestimated despite increasing awareness that the Pap smear is not perfect. The 1995 meta-analysis of Pap sensitivity and specificity by Fahey et al. and the subsequent 1999 Agency for Health Care Policy Research (AHCPR) evaluation of the best 85 studies on Pap performance helped end this misperception by establishing Pap smear sensitivity for all grades of cervical intraepithelial neoplasia (CIN) to be between 51% and 66%. Partly because high-grade lesions (CIN II or III) are typically larger, the sensitivity of the Pap for these lesions is generally higher, but it rarely exceeds 70% to 80%.

Despite the poor sensitivity reported for individual conventional Pap (CP) screenings, their use has resulted in the dramatic reduction in cervical cancer incidence and mortality discussed previously. This success is secondary to the long precursor phase of cervical cancer, which provides significant leeway for the subsequent detection and treatment of missed CIN II or III before invasion. The Pap smear has worked because it has been inexpensive and traditionally repeated often to adjust for the relatively high false-negative rate. However, clinicians and patients must understand that false-negative Pap tests cannot be entirely eliminated and occur even in optimized screening programs.

In addition to poor sensitivity, CP has a number of limiting factors. The manual procedure of applying the cells to the glass slide is impossible to standardize; cells are distributed unevenly over the surface of the slide; thick overlapping areas that obscure visualization of individual cells are common; diagnostic cells can be obscured by mucus, blood, or inflammatory cells; the thickness of the cell layers requires constant focusing up and down by the cytologist to visualize the majority of cells; and cell air drying because of delay in fixation or inadequate penetration of the fixative can distort cells, making them uninterpretable.

**Liquid-Based Cytology**

In the early 1980s, work began on improving cytology preparations by distributing cell collections in a liquid-based preservative before placing them on the slide. Much of the original impetus for this research came from the early attempts to develop automated computer image analysis systems for the evaluation of Pap smears. A number of problems with computer image analysis of CP, such as inadequate visualization of cells because of cell overlap and obscuring by mucus, blood, and other debris, greatly complicated the development of image algorithms. Liquid-based preparations were soon shown to overcome most of these problems, facilitating the single-cell analysis favored by automated systems. These innovations, along with improved sampling devices, revolutionized
cervical cytologic screening that had essentially remained unchanged since the introduction of the Pap smear nearly 50 years previously.16,17

In 1996, ThinPrep (CYTYC, Boxborough, MA) became the first liquid-based cytology (LBC) to receive Food and Drug Administration (FDA) approval, followed 3 years later by AutoCyte Prep, now called SurePath (TriPath, Burlington, NC). Although LBC has been available for less than a decade, researchers estimate that approximately 80% of Pap tests now performed in the United States are LBC.

This dramatic acceptance is secondary to a number of theoretical advantages LBC has over CP, including capturing more of the exfoliated cells from the collection device,18 random and presumably more representative transfer of exfoliated cells to the slide,19 and improved microscopic visualization attributable to reduced overlapping, obscuring blood, and inflammation.15,19 Improved slide preparation of LBC is entirely responsible for these advantages and represents a very important achievement in cervical cancer prevention, because errors in slide preparation are responsible for up to two thirds of the Pap smear false negative rate.20 Liquid-based cytology also provides residual cells for testing for human papillomavirus (HPV), chlamydia, and gonorrhea.

Differences in Cell Collection and Specimen Preparation for Commercially Available LBC
The ThinPrep system disperses cells collected in a fluid preservative medium (PreservCyt; CYTYC) that provides long-term preservation of diagnostic cells while lysing red blood cells.19 The cells are subsequently transferred to a glass slide in the laboratory in a semi-automated system that captures them in a disposable filter before the application of a positive pressure that deposits an appropriate cell density on the slide.19

The preparation of the SurePath system is significantly different from that of ThinPrep in several ways.21 The SurePath Prep uses a cervical brush that breaks off in the fluid collection vial, thereby transferring all of the collected cells to the vial. The liquid-based medium is ethanol-based, which maintains cell morphology and nuclear features as customarily experienced on conventional Pap smears.21 Additionally, the cellular material is not separated through a filter, but instead is separated by a density gradient step that is said to maintain diagnostic cells, endocervical cells, and background features.22 The cell circle applied to the slide is approximately 50% the size of the cell circle deposited in the ThinPrep process but without sacrificing cell count.21,22 ThinPrep and AutoCyte Prep specimens have been examined independently, from the same specimens, with a high degree of concordance between the two techniques.21,24

Comparison of Liquid-Based Cytology With Conventional Smears
No randomized trials that use invasive cancer or mortality as outcome measures have evaluated either conventional Pap smears or LBC.24 Only a small number of the studies performed to date compare the sensitivity and specificity of CP with LBC using the gold standard histology endpoint. Most comparisons are split-sample studies comparing cytologic results from the same sample or direct-to-vial studies that compare CP to LBC either within a laboratory contemporaneously or to historical controls.24 Despite these shortcomings, thorough review of the entire body of literature on conventional Pap tests,14 and more recently on liquid-based Pap tests,24 has provided a reasonable basis for comparison of these two modalities.

The AHCPR released its Evidence-Based Report on Cervical Cytology in early 1999.14 This report continues to be the most comprehensive analysis available to date of cervical screening with conventional cytology, but it did not compare LBC with CP because not enough data were available on LBC at the time of the analysis. However, this large meta-analysis did provide estimation of the levels of improved sensitivity required of new cervical screening technologies to impact various clinical parameters; such as cervical cancer incidence and mortality, rates of hysterectomy and other morbidity, and other quality-of-life indicators.14 The AHCPR conclusion that the conventional Pap detects 51% of CIN is consistent with the International Agency for Research on Cancer (IARC) analysis showing that cervical cancer rates are explained by what is known about the natural history of HPV and sensitivity of cervical screening between 37% and 60%. Reducing this false negative rate by 60% or more by increasing the sensitivity of screening to 75% to 80% should improve clinical outcomes significantly. The AHCPR report
projected improvement in outcomes with improved sensitivities at various levels and at different screening intervals (Table 1).

The ideal study to evaluate the relative capability of LBC to achieve this goal could only be obtained in a randomized control trial (RTC) comparing women screened with the CP with women screened with LBC. In the absence of such data, less than perfect comparisons between CP and LBC in sensitivity, specificity, and in specimen adequacy have been derived from a review of three primary study designs: split-sample, two-cohort or "direct-to-vial," and sensitivity-specificity studies.

**CP Versus LBP: Study Designs**

**Split-Sample Studies**

Initial studies on LBC were split-sample studies. In split-sample studies, a conventional Pap smear is obtained using a variety of collection devices and the remaining cells on the sampling device are placed in the vial for the preparation of the LBC slide. This allows direct comparison of a conventional Pap smear and a liquid-based Pap taken from the same cervical sampling. However, split-sample studies are not the ideal study to compare sensitivity and specificity between these two techniques because of the disadvantage for the LBC sample of being the second specimen obtained. Additionally, most split-sample studies did not have a histologic outcome and, therefore, true sensitivity and specificity for the methods cannot be ascertained.\(^{24,25}\) Despite this disadvantage, LBC identified more low-grade squamous intraepithelial lesion and greater (LSIL\(^+\)) Pap test results compared with paired conventional cytology in 17 of 21 ThinPrep and 9 of 12 SurePath split-sample studies considered to fulfill the criteria for inclusion in the British NHS Health Technology Assessment (HTA) evaluation of cervical cytology (Tables 2 and 3).\(^{24,26-7}\) A number of these studies also evaluated the detection rates for high-grade squamous intraepithelial lesions. In four of the six recent ThinPrep and in one of two SurePath split-sample studies, more HSIL\(^+\) were identified by LBC than by CP.\(^{24}\)

**Direct-to-Vial Studies**

To more accurately assess the characteristics of LBC, many of the studies after 1997 compared historic or concurrent data on the conventional Pap smear with data on LBC derived from direct-to-vial studies in which the entire sample on the collection device is placed in the vial. Hence, these studies are called "direct-to-vial" or "two-cohort" studies. Whereas split-sample studies compared detection rates for LSIL or HSIL\(^+\) obtained from the same specimen, direct-to-vial studies assumed that if the samples come from women in the same underlying population, with similar rates of CIN and cervical cancer, then any difference in detection rates of LSIL\(^+\) and HSIL\(^+\) will be a proxy measure of increased sensitivity.\(^{24}\) All 15 direct-to-vial studies meeting the HTA criteria reported more LSIL\(^+\) results for LBC than for CP, and all 8 of the direct-to-vial studies reporting HSIL\(^+\) results separately showed an increased detection of high-grade cytology interpretations (Table 4).\(^{24,29-32}\) The odds ratios for the 8 studies evaluating both LSIL\(^+\) and HSIL\(^+\) findings combined were 2.15 (95% confidence interval [CI] = 2.05–2.26) for LSIL and 2.26 (95% CI = 2.06–2.47) for HSIL.\(^{24,33}\)

**Sensitivity and Specificity Studies**

Determining the true sensitivity of cervical cytology, whether for CP or LBC, has been hampered by

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**Table 1  Predicted Deaths, Cervical Cancer Cases, and Hysterectomies in 100,000 Women**

<table>
<thead>
<tr>
<th></th>
<th>Conventional Pap Smear</th>
<th>Increased Sensitivity to 80%</th>
<th>Change</th>
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<tbody>
<tr>
<td><strong>Every 3 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>116</td>
<td>50</td>
<td>−57%</td>
</tr>
<tr>
<td>Cancer Cases</td>
<td>506</td>
<td>246</td>
<td>−51%</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>179</td>
<td>101</td>
<td>−44%</td>
</tr>
<tr>
<td><strong>Every 2 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>65</td>
<td>25</td>
<td>−62%</td>
</tr>
<tr>
<td>Cancer Cases</td>
<td>305</td>
<td>132</td>
<td>−51%</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>179</td>
<td>101</td>
<td>−44%</td>
</tr>
<tr>
<td><strong>Every year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>21</td>
<td>6</td>
<td>−71%</td>
</tr>
<tr>
<td>Cancer Cases</td>
<td>109</td>
<td>33</td>
<td>−70%</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>47</td>
<td>16</td>
<td>−66%</td>
</tr>
</tbody>
</table>

The cohort ranged in age from 15 to 85 and was screened at 1, 2, and 3 year intervals with either the conventional Pap smear or with any new modality that increases the sensitivity for CIN II or III to 80%.

the lack of reproducibility of cytologic interpretations, bias in the review process, bias in case selection, selection and correction of the gold standard, and the value of surrogate markers. Because determining true sensitivity and specificity requires colposcopy and biopsy of large numbers of women with negative cytology as well as those with positive, studies evaluating sensitivity and specificity have used alternative methods to derive these statistics. The two alternative methods identified are those using a proxy gold standard of final cytologic interpretations derived by blinded consensus diagnosis, and colposcopy and biopsy of women referred for the evaluation of abnormal Pap tests. Of 15 papers evaluating sensitivity and specificity considered to fulfill the criteria for inclusion in the HTA, only 5 were from “ordinary” and 10 from “high-risk” colposcopy referral populations. Of the 15 studies, 11 were on ThinPrep and 4 on the SurePath method. Despite these sources of variation, a review of the literature on the sensitivity of various Pap techniques showed relatively consistent determinations. Sensitivity for the detection of CIN II or III at the threshold of atypical squamous cells of undetermined significance (ASC-US) or greater ranged from 50% to 75% for CP. Aggregate sensitivity for CP was 71.5% and for LBC was 80.1%, a 12% overall improvement in sensitivity for the liquid-based method. Indirect comparisons of the two LBC methods did not detect a difference in sensitivity.

Sensitivity has been shown to be higher for LBC than for CP in two meta-analyses, but specificity was reported to be possibly less. However, a 2003 meta-analysis evaluating 17 studies comparing

<table>
<thead>
<tr>
<th>Study</th>
<th>No. samples/women</th>
<th>CP &gt; LBC LSIL⁺ (HSIL⁺)(%)</th>
<th>LBC &gt; CP LSIL⁺ (HSIL⁺)(%)</th>
<th>Both LSIL⁺ (HSIL⁺)(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hutchinson et al. 1991</td>
<td>433</td>
<td>0.45</td>
<td>1.13</td>
<td>18.7</td>
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<tr>
<td>Hutchinson et al. 1992</td>
<td>2,655</td>
<td>0.68</td>
<td>2.64</td>
<td>12.3</td>
</tr>
<tr>
<td>Awen et al. 1994</td>
<td>1,000</td>
<td>0.0</td>
<td>0.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Wilbur et al. 1994</td>
<td>3,218</td>
<td>0.8</td>
<td>3.1</td>
<td>17.0</td>
</tr>
<tr>
<td>Laverty et al. 1995</td>
<td>1,872</td>
<td>2.4</td>
<td>3.3</td>
<td>7.5</td>
</tr>
<tr>
<td>Aponte-Cipriani et al. 1995</td>
<td>665</td>
<td>0.5</td>
<td>0.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Sheets et al. 1995</td>
<td>782</td>
<td>1.5</td>
<td>3.3</td>
<td>29.4</td>
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<tr>
<td>Bur et al. 1995</td>
<td>128</td>
<td>1.6</td>
<td>1.6</td>
<td>19.5</td>
</tr>
<tr>
<td>Tezuka et al. 1996</td>
<td>215</td>
<td>2.3</td>
<td>0.0</td>
<td>54.4</td>
</tr>
<tr>
<td>Ferency et al. 1996</td>
<td>364</td>
<td>7.7</td>
<td>8.8</td>
<td>33.5</td>
</tr>
<tr>
<td>Wilbur et al. 1996</td>
<td>259</td>
<td>3.1</td>
<td>1.9</td>
<td>13.5</td>
</tr>
<tr>
<td>Lee et al. 1997</td>
<td>6,747</td>
<td>1.9</td>
<td>3.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Roberts et al. 1997</td>
<td>35,560</td>
<td>0.3</td>
<td>0.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Corkill et al. 1998</td>
<td>1,583</td>
<td>0.8</td>
<td>3.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Hutchinson et al. 1999</td>
<td>8636</td>
<td>2.5</td>
<td>2.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Wang et al. 1999</td>
<td>990</td>
<td>0.1(0)</td>
<td>1.7(1.1)</td>
<td>3.6(3.2)</td>
</tr>
<tr>
<td>Monsonego et al. 2001</td>
<td>5428</td>
<td>0.4(0.1)</td>
<td>1.1(0.2)</td>
<td>1.4(0.4)</td>
</tr>
<tr>
<td>Park et al. 2001</td>
<td>478</td>
<td>2.9(1.4)</td>
<td>1.0(0.6)</td>
<td>18.2(13.7)</td>
</tr>
<tr>
<td>Biscotti et al. 2002</td>
<td>400</td>
<td>1.0(0.8)</td>
<td>3.0(0.3)</td>
<td>8.8(4.0)</td>
</tr>
<tr>
<td>Luthra et al. 2002</td>
<td>1,024</td>
<td>0.1(0)</td>
<td>0.6(0.1)</td>
<td>2.4(0.8)</td>
</tr>
<tr>
<td>Ring et al. 2002</td>
<td>1,300</td>
<td>2.5(1.7)</td>
<td>6.2(2.0)</td>
<td>27.8(10.1)</td>
</tr>
</tbody>
</table>

CP > LSIL⁺ is the proportion where the conventional Pap smear result was LSIL⁺ but the liquid-based method result was negative or ASCUS. LBC > CP LSIL⁺ is the proportion where the liquid-based Pap test result was LSIL⁺ but the conventional Pap smear result was negative or ASCUS.

ThinPrep Pap with conventional cytology and 10 articles with histology as the final diagnosis “gold standard” found increases in both sensitivity and specificity with the liquid-based method. Three of the articles directly comparing ThinPrep Pap with conventional cytology were among the 10 articles with a histologic outcome. Sensitivity, relative to histology, was 68% for the conventional Pap smear and 76% for the ThinPrep Pap test, with specificity also higher for ThinPrep (86%) than for the conventional smear (79%). The increased sensitivity of LBC for CIN noted in most studies is from increased detection of all levels of cytologic abnormality ASC-US or greater. However, sensitivity of ThinPrep for CIN III+ at the ASC-US or greater threshold has been reported to be as low as 61.3% and as high as 94%, but the latter was achieved only with calling approximately 27% of the Pap tests abnormal. Only one study has found no statistically significant difference in sensitivity and specificity of the two techniques, but in this study sampling was optimized for the conventional Pap by use of a specialized collection device, removal of mucus and cellular debris from the cervical surface before sampling, and colposcopically-guided sampling to verify collection of cells from the transformation zone.

Concern that increased detection of ASC-US or greater by LBC would necessarily decrease specificity and that researchers lacked information to clarify this issue was initially a primary reason for the reluctance of organizations to recommend LBC as a replacement for the conventional smear. Specificity would be expected to decline if significant increase in the rate of ASC-US and an increase in the ASCUS to LSIL ratio were reported. LBC has been shown to increase the ASC-US rate in some but not all studies. The ASCUS:LSIL ratio drops in most studies on LBC, at least partially because the ASC-US rate does not rise as dramatically as the rate of LSIL. Additionally, the ASC-US rate tends to be higher with inexperience with the technique and falls as the cytologist becomes experienced in interpreting LBC.

Positive predictive value for histologic CIN has been shown to be higher for ASC-US/AGUS interpretations from ThinPrep Pap tests (22.8%) than from conventional smears (11.9%), and for ASCUS alone, with a markedly lower rate of equivocal LBC in the latter study when compared with conventional smears. Repeat LBC after an ASC-US Pap is less likely to again be ASC-US than when the repeat is a conventional smear. Predictive value of a cytologic

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**Table 3** SurePath Split-Sample Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>No. samples/women</th>
<th>CP &gt; LBC LSIL+ (HSIL+) (%)</th>
<th>LBC &gt; CP LSIL+ (HSIL+) (%)</th>
<th>Both LSIL+ (HSIL+) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vassilakos et al.</td>
<td>560</td>
<td>0.5</td>
<td>1.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Takahashi and Naito</td>
<td>2,000</td>
<td>0.4</td>
<td>0.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Howell et al.</td>
<td>852</td>
<td>0.8</td>
<td>1.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Geyer et al.</td>
<td>551</td>
<td>0.0</td>
<td>0.7</td>
<td>12.5</td>
</tr>
<tr>
<td>Sprenger et al.</td>
<td>2,863</td>
<td>2.0</td>
<td>5.1</td>
<td>36.2</td>
</tr>
<tr>
<td>Bishop</td>
<td>2,032</td>
<td>1.1</td>
<td>3.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Laverty et al.</td>
<td>2,064</td>
<td>3.9</td>
<td>1.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Wilbur et al.</td>
<td>277</td>
<td>1.1</td>
<td>6.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Data on file, Cell Path 1997</td>
<td>8,983</td>
<td>1.6</td>
<td>2.2</td>
<td>5.7</td>
</tr>
<tr>
<td>Stevens et al.</td>
<td>1,325</td>
<td>1.3</td>
<td>0.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Minge et al.</td>
<td>2,156</td>
<td>1.5 (0.8)</td>
<td>3.0 (0.6)</td>
<td>2.8 (0.5)</td>
</tr>
<tr>
<td>Bergeron et al.</td>
<td>500</td>
<td>9.8 (12.2)</td>
<td>12.6 (15.6)</td>
<td>46.6 (20.2)</td>
</tr>
</tbody>
</table>

CP > LSIL+ is the proportion where the conventional Pap smear result was LSIL+ but the liquid-based method result was negative or ASCUS. LBC > CP LSIL+ is the proportion where the liquid-based Pap test result was LSIL+ but the conventional Pap smear result was negative or ASCUS.

interpretation of cancer is high for both LBC and for conventional smears, but LBC was slightly more specific in one study that reported only 8.4% of the liquid-based tests with this interpretation being false positives in contrast to 12.5% for the conventional technique. However, results in a large retrospective study resulted in a different conclusion, as did a 2004 evaluation of comparative diagnostic accuracy of LBC and CP in the College of American Pathologists (CAP) Interlaboratory Comparison Program. Overall, TP preparations in the CAP program were associated with significantly lower error rate than conventional smears.

The recent Heath Technology Assessment Program meta-analysis of the six studies comparing specificity between CP and LBC found no difference. The conclusion of this meta-analysis was that LBC did not decrease specificity, particularly after cytologists mastered the technique. Although the majority of current data on LBPs is for the ThinPrep technology, available studies on the SurePath method suggest equivalent performance. However, the absence of studies directly comparing the two methods preclude definitive statements on relative performance.

### Table 4  Direct-to-Vial (Two Cohort) Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N CP</th>
<th>N LBC</th>
<th>CP LSIL+ (HSIL*) (%)</th>
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### LBC Versus CP: Other Measures

**Detection of Glandular Lesions**

The incidence of adenocarcinoma in situ (AIS) has increased over the past 20 years in young white women, but increasing detection has not yet translated into a decrease in the incidence of invasive adenocarcinoma (AC), unlike the continuing decrease in incidence in squamous cell carcinoma (SCC) that has accompanied increased detection and treatment of CIN III. Although glandular cell abnormalities are more difficult to detect on cytology than squamous cells, cervical screening does reduce the risk of cervical adenocarcinoma. Biennial screenings have been estimated to reduce the cumulative incidence of invasive adenocarcinoma by 46%, and with annual screening, a 65% reduction has been predicted.

Researchers have expressed concern that the features of endocervical lesions in LBC may be subtle compared with smears. However, four studies have shown that detection rates of glandular lesions using LBP are significantly higher than with conventional smears, and specificity for glandular abnormality was also shown to be increased. One study reported a 50% decline in the AGC rate with LBP but
a fivefold increase in the positive predictive value for AIS.89 Another reported sensitivity of a ThinPrep AGCUS/adenoacarcinoma interpretation to be 72% in detecting the combined group of cervical and endometrial adenocarcinomas compared with 41.5% for the conventional smear, and for endometrial adenocarcinomas alone (65.2% vs. 38.6%).86 With the increased rate of cervical adenocarcinoma reported in the past 2 decades, the importance of more precisely detecting AIS and cervical adenocarcinoma could not be more evident.

Specimen Adequacy
Although specimen adequacy of LBP s is generally improved because of more complete collection of exfoliated cells, random and presumably more representative transfer of exfoliated cells to slides, and improved microscopic visualization attributable to reduced overlapping, obscuring blood, and inflammation; identification of endocervical cells as a marker for sampling of the transformation zone is often more difficult than with conventional Pap tests.77,80,81 This results in some increase in the proportion of samples lacking an endocervical component; however, this has not been reported to the impact detection rates of CIN.17,40,65,76,78,81 Specimen adequacy as determined by cellularity clearly impacts sensitivity for detection of squamous intraepithelial lesions, because significantly lower sensitivity for SIL was shown for LBC slides having less than 5,000 squamous cells.92 When LBC is unsatisfactory because of partially obscuring blood or mucus, reprocessing of the remaining liquid specimen can provide a satisfactory specimen,93 although it is rarely done in routine clinical practice. TP produces a true monolayer of cells that are all spread at the same plane, whereas the SurePath method distributes cells at slightly different planes, requiring some focusing of the viewed plane. Both methods facilitate review by the cytologist when compared with CP because of significantly reduced need to focus up and down to visualize all planes.94

Presently, LBC specimens are limited by FDA approval restrictions to a 3-week shelf-life for both cytotologic and HPV DNA testing, beyond which they cannot be evaluated using either technique. However, cervical specimens archived in PreservCyt have been shown to be stable over a much longer period of time. Negative impact on the validity of PCR and Pap test results from PreservCyt has been shown with increasing time after collection, but significant impact resulting in partial DNA and cytologic degradation is only seen after several years. Additionally, no adverse effect has been shown on Hybrid Capture 2 (HC2) results.95 Clearly, the 3-week mandated shelf live is far shorter than necessary for test accuracy.

Ancillary Testing
One of the most compelling reasons for using LBC over conventional cytology is the ability to perform ancillary tests on the remaining cells in the LBC medium. The first ancillary test taken from LBC to be evaluated and proven to be useful in multiple studies was testing for HPV.80-82 The sensitivity for CIN II or III of “reflex” HPV testing of residual LBC from specimens interpreted as ASC-US reported in these studies varied from 89% to 92%.92 This high sensitivity and ease of testing the liquid-based specimen without having to bring the patient back to obtain an additional specimen established HPV testing as the “preferred” management option for women with ASC-US derived from LBC in the 2001 ASCCP Consensus Guidelines for the Management of Women with Abnormal Cervical Cytology and Cervical Cancer Precursors.99 Additionally, ALTS data documented that HPV triage was essentially equivalent to immediate colposcopy in sensitivity for CIN II or III, while decreasing colposcopic referrals by half.97 At present the only FDA-approved HPV test from LBC is Hybrid Capture 2 (HC2) [Digene, Gaithersburg, MD] from the TP PreservCyt medium. Tripath presently has an application before the FDA for approval of HC2 testing from the SurePath medium. HC2 has available both a low- and a high-risk panel. For HPV triage of ASC-US to be cost-effective, it is imperative that the sample be tested only for the high-risk panel. All women with results positive for high-risk HPV are to be referred to colposcopy. Despite the ASCCP guideline designation that HPV testing is the preferred management option for women with ASC-US, a random sample of ACOG Fellows in 2003 did not document a rapid adoption of HPV testing for ASC-US triage.100 Most of the survey participants continued to perform colposcopy for any ASC-US result even though 80% used LBC and many used HPV testing on occasion. However, triage of ASC-US by HPV testing appears to increasingly be the management option most commonly chosen in the United States.

HPV DNA testing of the residual volume from the TP Pap test has also been shown to be an excellent substitute “gold standard” in monitoring quality assurance for a cervical cytology screening program.
because target HPV positivity rates for ASC-US (40% to 55%) and LSIL/HSIL (80% and higher) indicate that the lab is correctly interpreting these Pap categories.

LBC medium can also serve as a repository for testing for Chlamydia trachomatis and Neisseria gonorrhoeae. Current U.S. guidelines recommend annual screening for C. trachomatis infection for sexually active women age 15 to 25 and for women older than 25 if they have new or multiple sex partners and have not used condoms during the previous 3 months. Additionally, screening for gonorrhea has contributed to reduction in the incidence of this sexually transmitted infection. Screening for both these infections directly from the cells remaining in the LBP medium after the preparation of the Pap test has been shown to be comparable to screening directly from a cervical swab for both ligase-chain reaction (LCR) tests and for HC2. This offers the option of performing “quadruple” screening with LBC: cytology, HPV testing, and testing for chlamydia and gonorrhea.

Screenings for other risk markers are also presently being evaluated. However, with increasing numbers of samples required for multiple testing, the cellularity and specimen quality of the sample will have to be maximized to have adequate samples for each test. Presently, from 1% to 4% of LBC samples do not have enough cells remaining in the vial after preparation of the Pap test to do the HPV test. Adding more tests to the same specimen will increase inadequacy rates for tests further down the line in preparation. New methods of collecting more cells may be necessary if multiple testing from the vial is to be successful.

**Effectiveness and Cost-Effectiveness of Introducing LBC**

The primary concern most commonly expressed about using LBC is cost. Experts have argued that in a routine screening population, disease prevalence is so small and the progression from CIN II or III to invasive cancer typically so slow that increased sensitivity reported in LBC studies is of minimal impact, but would bring many more women in for evaluation because of the increased detection of LSIL. Whether maximizing sensitivity by increasing colposcopy referral rates is most valued depends on many societal and economic issues, particularly community expectations and medicolegal risks. Although most significant lesions would be detected over time by frequent screening with CP, many women undergo infrequent screening or none at all. Therefore, if cervical cancer rates are to continue to decline, it will be crucial to increase screening rates and to maximize sensitivity of the test for the few screenings that some women obtain, because these women are at highest risk if significant cervical disease is missed and at highest risk for continued inadequate screening. Unfortunately, underscreened women, who are often indigent, are about the only remaining segment of US society that has yet to achieve third party reimbursement for LBC.

Despite the increased cost of the materials used in collecting and preparing liquid-based slides, evaluations of the cost-effectiveness of screening with LBC have determined that the actual cost of cervical screening is likely to decrease when compared with annual CP screening, but only if clinicians and the public accept prolonged screening intervals that are recommended with the use of these tests. A 2002 cost-modeling study found that biennial LBPs and “reflex HPV testing” for ASC-US was significantly more cost-effective and somewhat more protective than annual CP with routine follow-up of ASC-US by repeat cytology. The projected cost-savings of this strategy over the lifetime of a cohort of 16- to 24-year-old women was 15 billion dollars. Therefore, if the American Cancer Society recommendation that LBC can be performed every 2 years is consistently followed, the initial increased cost of the test would appear to be more than covered by the savings accrued when compared with annual conventional Pap smears. In contrast, the cost of the cervical cancer screening program will increase if the recommendations are not followed and women are over-screened.

The most comprehensive assessment of the effectiveness and the cost-effectiveness of liquid-based cytology was recently issued by the Health Technology Assessment Program (HTA). The results of the modeling analysis provide a robust argument that LBC is a cost-effective alternative to conventional cervical cancer screening, because this review of the evidence available concluded that LBC will likely reduce the number of false-negative test results, and modeling analyses indicated that this would reduce the incidence of invasive cervical cancer. Researchers also concluded that costs would be saved by reducing the number of unsatisfactory specimens and decreasing the time needed to
obtain and to evaluate the cytologic sample. Cost-effective analyses based on models of disease natural history and clinical effectiveness of each screening modality showed consistent dominance of CP screening by screening with LBC. This means that LBC was found to always be more cost-effective than conventional Pap smear testing over the same screening interval.\(^{64}\)

**United States Guidelines**

In 2002 the ACS issued new primary cervical screening guidelines, followed in 2003 by guidelines from ACOG and United States Public Services Task Force (USPSTF).\(^{8,110,111}\) All three guidelines replaced recommendations that had been in place, with only minor modifications previously, since the late 1970s. The major departure in screening recommendations among the three organizations were in the area of screening intervals, and whether to consider increased sensitivity for CIN II or III, reported for both liquid-based cytology and for HPV, in making screening interval recommendations. The USPSTF recommendations differed significantly in several areas with both the ACS and the ACOG recommendations. Only the recommendations from the ACS reflect recognition that increased sensitivity of liquid-based cytology could be the basis for lengthening the screening interval, recommending that women undergoing LBC could undergo screening every 2 years from the onset of screening until the age of 30, whereas screening should be annual if CP.\(^ {8}\) ACOG recommends annual cytology until the age of 30 for women undergoing both types of cytologic screening, preferring not to differentiate between CP and LBC.\(^ {110}\) Both organizations recommend extension of the screening interval to 2 to 3 years for women age 30 and over having three consecutive normal Pap tests.\(^ {8,110}\) Both ACS and ACOG recognized the very high sensitivity of HPV testing and cytology when combined as a primary screen in providing increased reassurance of the absence of significant disease that would allow lengthening of the screening interval.\(^ {8,110}\) The USPSTF did not change screening interval based on any of the new technologies and instead recommended that women undergo Pap tests at least every 3 years beginning with the onset of screening.\(^ {111}\) Extended screening interval options for women over the age of 30 apply only to women with normal immunity and who were not exposed to diethylstilbestrol (DES) in utero.\(^ {8,110,111}\) Therefore, women with HIV should be followed up at intervals recommended by the CDC,\(^ {112}\) and women exposed to DES should undergo annual screening.\(^ {8,110}\)

**Adoption of Liquid-Based Cytology**

The increased initial cost of LBC delayed rapid adoption of this new technology despite the early data documenting higher sensitivity and improved specimen adequacy. Early adoption was also delayed in many laboratories by the need to retrain cytopathologists and pathologists to interpret findings on the liquid-based platform.\(^ {113}\) Although conversion by clinicians to the use of LBC was initially relatively slow, within 4 years from FDA-approval of the ThinPrep Pap test, a number of factors began to converge to encourage use of a replacement for the venerable Pap smear. These included third-party payer coverage, vigorous marketing to clinicians, enthusiasm by cytopathologists and cytotechnologists for the monolayer technique, and an expanding volume of literature that was favorable to LBC.

By 2000, 96% of gynecologists and 75% of family physicians surveyed in Maryland were using LBC.\(^ {114}\) More aggressive marketing to gynecologists than to family physicians was given as the primary reason that gynecologists were more likely than family physicians to have adopted LBC in 1997, soon after FDA approval (34% vs. 5%). The ACOG survey in 2003 determined that 80% of Pap tests performed by gynecologists in the sample were LBC, with legal concerns mentioned as important determinants of practice patterns.\(^ {110}\) However, a similar survey of gynecologists, family practice physicians, and nurse practitioners in the same year in Wisconsin determined that LBC comprised only 57% of all Pap tests performed, indicating that practice specialty and locale may also be important determinations to conversion.\(^ {111}\)

**Logistics of Use**

Most laboratories that interpret cervical cytology slides have learned the differences in reading conventional and LBC slides. However, when switching over to LBC, clinicians must monitor the Pap results they are receiving over time to detect shifts in performance.\(^ {73}\) In addition, optimization of LBC may require clinicians to change cervical samplers, which can affect both the appearance and quality of specimens. A single sampler cervical brush can produce a good sample if
the squamocolumnar junction is not within a narrow cervical os; otherwise, adding an endocervical brush may be critical. If an Ayer spatula is used in combination with an endocervical brush, specimen adequacy may be enhanced by scraping the spatula against the brush in solution to free up more endocervical cells. Ayre spatulas used to collect ThinPrep samples must be plastic, because wood splinters from a wooden spatula can plug the filter.

The capability to add an HPV test to the same sample as the Pap test has resulted in a number of changes to the typical abnormal Pap management system. One of the major issues challenging many clinicians is the separate arrival of the HPV test result and the Pap report, which occurs when the cytopathology laboratory does not do HPV testing. Sending the test sample to a separate reference laboratory requires the clinician to collate the two reports before notifying the patient, which is made more difficult by the often-significant delay between the reports. Therefore, some mechanism is required that flags the ASC-US report and holds it until the HPV test result arrives.

In contrast, when the laboratory that interprets the liquid-based Pap is also the site that performs the “reflex” HPV test, there is no need to collate separate Pap and HPV test results, as the Pap may be reported directly from the testing lab as “ASC-US HPV negative” or “ASC-US HPV positive.” The other major issue that is new to cervical cancer screening when ASC-US obtained from LBC is managed by “reflex” HPV testing is the issue of “shared, or informed, decision-making” between the patient and the clinician. Shared decision-making is the term applied to the crucial role of the clinical community in creating an environment in which screening decisions and results can be discussed. In reality, this should not have been a new issue with the advent of “reflex” HPV testing from LBC, for whether to screen by any screening modality, including the Pap, involves both risks and benefits that should ideally be discussed. However, screening with the Pap has been such a “given” that little thought was given previously to educate women about the reasons for cervical screening or the sexually transmitted nature of significantly abnormal Pap results. Triage of ASC-US by testing for HPV establishes the connection and makes avoidance of the sexually transmitted nature of abnormal Pap results unavoidable. To diminish anxiety and psychological distress that may now be heightened by this association, clinicians must include patient education into the incorporation of HPV DNA testing into screening and abnormal Pap management protocols.

**Future Directions**

Future population-based analyses are needed to determine the absolute impact of LBC on cancer incidence and mortality, and to evaluate its capability in detection and prevention of adenocarcinoma. However, LBC has clearly become the dominant technique for cervical cytology screening in the United States, and societal prerogatives and preferences for the technique among cytologists are likely to ensure that LBC remains the dominant technique in the absence of other data. Molecular markers in the liquid-based specimen that may increase the specificity for detecting which women are at risk for CIN II or III+ are now being studied. For example, microarray techniques that survey the expression of large numbers of genes simultaneously when performed on remaining cells from LBC have been shown to be useful in the evaluation of cellular gene expression patterns that differ between high-grade CIN and normal, but histologically difficult cases. Additionally, the overexpression of p16 is reported to be closely associated with CIN II or III and cancer in both LBC and in similar histology, and therefore has been suggested to be a satisfactory biomarker for primary cervical screening and as a reflex test to abnormal cervical cytology. An increasing array of testing capabilities from the LBC medium will probably continue to provide further impetus to the use of a cytology platform that supports multiple testing.

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