

# Technology Matters: How the Pap Test Protects Your Patients

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The Pap test is arguably the most significant technological advancement contributing to the decrease in the incidence of cervical cancer in the United States over the past 30 years. But despite its role in reducing this incidence rate, the Pap test does have its limitations. For instance, while Pap screening is very specific, it's not very sensitive, with reported sensitivities ranging from 20% to 80% depending on the method used.<sup>1-4</sup> With these drawbacks in mind, improving cervical cancer screening methods has been a main focus so that the progress already achieved in combating one of the leading causes of death among women can continue.

## Improvements in Cervical Cancer Screening and Current Guidelines

In order to enhance the diagnostic capabilities of the Pap test, new technologies have been developed since its implementation, including the ability to test for human papillomavirus (HPV) and the improvement of the Pap test with the introduction of liquid based cytology and imaging technologies.<sup>2</sup> High-risk HPV testing, which is more sensitive and less specific than cytology at detecting dysplasia or malignancy, has proven to be a useful adjunct to perform with the Pap in certain age groups.<sup>5</sup> Liquid-based cytology has also improved sensitivity of the Pap itself.<sup>1</sup>

As diagnostic accuracy has improved due to these new technologies, so too have cervical cancer screening guidelines undergone numerous revisions to reflect these advancements.

While many screening options are acceptable for women aged 30 to 65, ACOG and other organizations prefer co-testing every 5 years.<sup>5</sup> Cytology alone via Pap testing every 3 years is also acceptable, but co-testing is preferred<sup>5-7</sup> since women with a negative cytological screening test and a negative high-risk HPV test are at an extremely low risk of developing CIN2, CIN3, or cancer over the next several years.<sup>5-7</sup> Additionally the United States Preventive Services Task Force (USPSTF) recently included HPV screening alone at a 5-year interval as an acceptable option for women aged 30 and above, and societies including SGO, ASCCP, and ACOG have provided interim guidance on the use of HPV screening alone.<sup>8</sup>

## Liquid-Based Cytology: A Key Advancement in Cervical Cancer Screening

Although both liquid-based and conventional methods of Pap testing are acceptable to use for cervical cancer screening, they are not equal. In response to the poor sensitivities observed with the conventional Pap, the liquid-based collection method was developed.<sup>1,9</sup> Current liquid-based techniques boast improved sensitivity for the detection of HSIL and LSIL, improved detection of adenocarcinomas, and have the ability to perform out-of-the vial testing, such as co-testing for HPV or sexually transmitted infections without obtaining an additional specimen.<sup>1</sup>

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Due to the benefits of this technology, over 90% of Pap tests in the United States are performed using liquid-based cytology over conventional cytology.<sup>9</sup> For both liquid-based and conventional methods, the initial collection is similar. In each case, exfoliated cells are collected from the transformation zone of the cervix using a brush or spatula collection device.<sup>5</sup> In the liquid-based technique, these cells are transferred to a vial of liquid preservative for later processing in a laboratory. In the conventional technique, the cells are transferred directly to a slide and fixed.<sup>5</sup> The poor sensitivities observed with conventional Paps have been largely attributed to sampling errors or inadequate slide preparation.<sup>9</sup> Only a small portion of the sample is actually evaluated, as the majority is discarded with the sampling device.<sup>9</sup> In fact, the amount transferred with conventional cytology varies widely, from just 6.5 up to 62.5%.<sup>10</sup>

To address these shortcomings, the first liquid-based cytology assay, the ThinPrep® Pap test, was approved by the FDA in 1996, and the second liquid-based test, SurePath™, was approved by the FDA in 1999.<sup>9</sup>

Liquid-based cytology represents an improvement over conventional Pap tests in part because it results in homogenous cell sampling during transfer, which can reduce sampling errors and improve specimen quality. This also aids in making slide interpretation easier, whether by a trained pathologist or computer-assisted technology.<sup>1,9</sup> Additional benefits of liquid-based cytology include immediate fixation, an accurate representation of the entire specimen, decreased obscuring elements,

and the ability to produce multiple reproducible slides. This improvement in sensitivity allowed by liquid-based cytology has contributed to extensions of the screening interval from 1 to 3-5 years.<sup>7</sup>

### The Clinical Benefits of the ThinPrep® Pap Test

ThinPrep®, the first FDA-approved, liquid-based cytology, is the preferred method of testing in the United States, accounting for over 80% of Pap tests performed and over 650 million tests completed globally<sup>11</sup> and is used in over 90% of the Top 50 U.S. Best Hospitals for Gynecology.<sup>12</sup> This technology has been extensively studied in over 170 different clinical trials and has consistently been shown to improve outcomes for women as compared to use of conventional cytology.<sup>13</sup> As reported by the College of American Pathologists, ThinPrep® has resulted in increased HSIL detection, increased LSIL detection, and improved sensitivity for cervical adenocarcinoma when compared to conventional testing methods.<sup>14,15</sup> This test is also approved for use with several FDA-approved HPV testing methods and numerous sexually transmitted infection tests (Table 1).<sup>16</sup>

ThinPrep® is performed by first obtaining a sample of cells from the patient's cervix using a broom-type or endocervical brush/plastic spatula combination device.<sup>16</sup> The sampling device is immersed and rinsed in a liquid vial, consisting of 20 mL of ThinPrep®'s PreservCyt solution.<sup>16</sup> This sample is then placed into a ThinPrep® cytology processor, which serves to break up mucus, blood, and other debris.<sup>16</sup> The fluid currents are strong

### Tips for Collecting ThinPrep® Samples

Although ThinPrep® is the superior choice for Pap tests, boasting optimal sensitivity and specificity for the detection of dysplasia and cancer, test accuracy depends on following proper instructions for use. Sampling errors, or false-negative Pap tests that are free of abnormal cells, can occur due to inadequate patient preparation or sampling technique errors.<sup>41</sup> Understanding how to avoid these errors can maximize accuracy and minimize the number of insufficient Pap tests collected.

First, prepare the patient. Patients can be educated over the phone during appointment scheduling or by online alerts when scheduling online.<sup>41</sup> Women should be told the following:

- Abstain from intercourse, douching, tampons, or intravaginal medication for at least 48 hours prior to the examination.<sup>41</sup>
- Do not schedule the Pap during heavy menstrual bleeding.<sup>41,47</sup>
- Ideally, schedule approximately 2 weeks after the first day of her last menstrual period.<sup>41,47</sup>

Clinicians need to ensure the specimen is labeled properly so that the specimen is matched with the correct patient. Other relevant history should be obtained and provided to the pathologist, such as prior abnormal Pap tests, previous cervical treatment, current pregnancy, or current hormone use.<sup>41</sup>

When sampling, the clinician should use the approved sampling device provided.<sup>41</sup> ThinPrep® uses a broom-type or endocervical brush/plastic spatula combination collection devices.<sup>16</sup> When inserting the speculum, lukewarm water should be considered

in lieu of lubricant, as this has the least risk to the quality of the Pap.<sup>41,48</sup> For this same reason, it's also recommended that the Pap be performed prior to bimanual examination.<sup>41</sup>

If lubricant is used, the following tips are recommended:

- Lubricant should be used sparingly, using a dime-sized amount, and applied only to the exterior sides of the speculum, avoiding the tip.<sup>41,48,49</sup>
- Lubricants containing thickening agents, such as carbomer or Carbopol® polymers, are most likely to interfere with the ThinPrep® Pap and should be avoided.<sup>12</sup> Water-based lubrication is preferable.<sup>47</sup>

Prior to obtaining the sample, excessive blood, mucus, or discharge should be blotted from the cervix.<sup>41,47</sup> The removal should be performed with a folded gauze pad on a ring forceps.<sup>47</sup> The cervix should not be cleaned with saline as this could result in an acellular specimen.<sup>47</sup> If significant inflammation or infection is present, the physician should consider rescheduling the Pap after treatment of the infection.<sup>41</sup> The specimen should be immersed in the liquid medium immediately after sampling.<sup>41</sup>

The liquid medium (PreservCyt Solution) should be stored between 15°C (59°F) and 30°C (86°F). After sampling, the PreservCyt Solution can be stored up to 6 weeks.<sup>16</sup> The clinician should also ensure that the liquid is not expired.

Finally, providers need to remember that HPV testing and sexually transmitted infection screening can be performed using the same vial, with any of the FDA-approved HPV or gonorrhea and chlamydia assays.

enough to separate out the debris, but gentle enough to protect the integrity of the cells.<sup>16</sup> The cells are then collected on a ThinPrep® Pap test filter, which prevents the cells from becoming too scant or too dense.<sup>16</sup> The resulting optimal layer of cells are then transferred to a glass slide, which is then placed into a fixative solution.<sup>16</sup> The slide is then evaluated by a pathologist appropriately trained in the interpretation of ThinPrep® prepared slides.<sup>16</sup>

Compared to SurePath™, the alternate liquid-based cytology method, the use of ThinPrep ensures that virtually 100% of the cervical cellular sample is preserved.<sup>16</sup> With ThinPrep®, the slide is created directly from the PreservCyt solution, with minimal transfer.<sup>16</sup> SurePath™, on the other hand, must be transferred from the initial vial to a separate tube prior to slide preparation.<sup>17</sup> The transfer can result in a loss of up to 33% of epithelial cells, potentially compromising the accuracy of the Pap.<sup>17</sup>

### Improved Detection of Cervical Dysplasia

When compared to other Pap techniques, the most significant benefit of the ThinPrep® method is the improved detection of cervical dysplasia and malignancy. A prospective, multicenter clinical trial of over 7,000 patients encompassing three screening centers and three hospitals was conducted to compare the ThinPrep® 2000 to the conventional Pap smear.<sup>16,18</sup> In this trial, the conventional Pap was performed first for each patient and the remaining sample was used for ThinPrep® liquid-based cytology.<sup>16,18</sup> An independent pathologist then reviewed slides for any discrepant cases. ThinPrep® was found to be just as accurate or more accurate than conventional cytology among all participating sites.<sup>16,18</sup>

Figure 1: HSIL Reporting Rate by Pap Type  
The ThinPrep Pap® identifies more HSIL than other Pap methods.

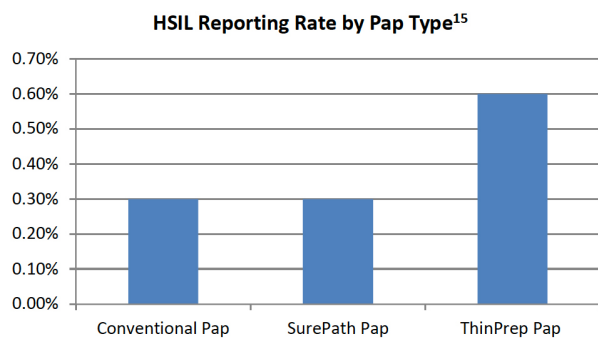
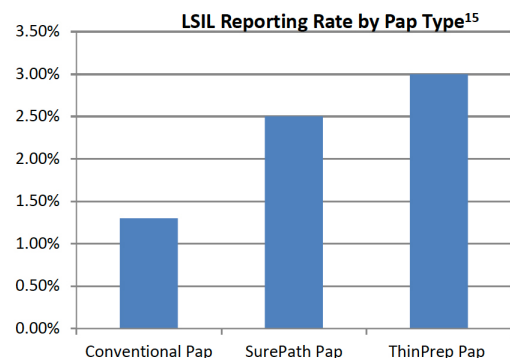


Figure 2: LSIL Reporting Rate by Pap Type  
The ThinPrep Pap® identifies more LSIL than other Pap methods



Another multi-site clinical study evaluated ThinPrep® versus conventional Pap for the detection of HSIL and greater sensitivity.<sup>16,19</sup> Conventional Pap had a detection rate of 511 out of 20,917 compared to 399 out of 10,226 for ThinPrep®, achieving a 59.7% increase in HSIL detection with ThinPrep.<sup>16,19</sup> A statistically significant increase in LSIL detection was also achieved.<sup>16,19</sup>

A New England study revealed that ThinPrep® led to a 71.65% increased detection rate of LSIL and a 102.54% increased detection rate of HSIL when compared to conventional cytology.<sup>20</sup>

Other trials have replicated these findings with liquid-based cytology, achieving improvements of up to 200% or greater in the detection of LSIL and HSIL when compared to conventional cytology.<sup>15,21-26</sup> Among 679 laboratories using a combination of conventional and liquid preparations, Eversole et al. observed that the detection rate of both LSIL and HSIL was higher for not only liquid-based cytology in general, but was highest with the ThinPrep® system.<sup>15</sup>

Although it was not a direct comparison, a study of the ProPath database confirmed the superiority of ThinPrep® compared to SurePath™ in the detection of cervical cancer precursors. A 2014 review of over 100,000 Pap specimens in the ProPath database evaluated clients that had switched from SurePath™ testing to ThinPrep®, comparing 2 years of SurePath™ results to 2 years of ThinPrep® results.<sup>27</sup> ThinPrep® testing resulted in a significantly higher rate of HSIL, ASC-HG, and LSIL detection in 16 out of 18 clients.<sup>27</sup> Although no head-to-head comparison was done, both cohorts exhibited similar demographics, and over 90% of specimens were evaluated by the same pathologists.<sup>27</sup>

### Better Adenocarcinoma Detection

Another area improved by the ThinPrep® technology is that of adenocarcinoma detection. While cervical cancer incidence as a whole has been decreasing since the arrival of the Pap smear, adenocarcinoma has remained a significant concern.<sup>14</sup> Over the past 35 years, the rate of new adenocarcinoma diagnoses has risen by 32.2% in the United States.<sup>14</sup> Traditionally, the conventional Pap was better at diagnosing squamous cell carcinomas due to the ease of sampling the ectocervix compared to the endocervix,<sup>14</sup> but liquid-based cytology—in addition to its superior performance at detecting squamous cell carcinomas and its precursors—is better at identifying glandular abnormalities. ThinPrep® in particular, has been recognized by the FDA for this indication.<sup>16</sup>

Numerous clinical trials have also shown that liquid-based cytology is better at diagnosing adenocarcinoma of the cervix.<sup>28-32</sup> In 2002, Hecht et al showed that the positive predictive value of AGUS with a ThinPrep® Pap was 22%, compared to just 15% with conventional Pap testing.<sup>33</sup> And Schorge et al showed that the ThinPrep® achieved a 65.2% sensitivity at detecting adenocarcinoma of the cervix, while the sensitivity of conventional Pap reached only 41.5%.<sup>32</sup>

Currently, ThinPrep® is the only Pap test that is FDA-approved for the improved ability to detect cervical glandular disease, compared to conventional Pap methods.<sup>16</sup> ThinPrep® is also endorsed by the Society of Gynecologic Oncology for this indication and is deemed to produce “more reliable results” when it comes to glandular abnormalities.<sup>34</sup>

### Fewer Insufficient or Unsatisfactory Results

In addition to improving diagnostic accuracy of cervical dysplasia and malignancy, liquid-based cytology methods such as ThinPrep® offer a decreased number of unsatisfactory Pap results compared to conventional cytology. Aside from the inconvenience of repeating a Pap test, for both patient and provider, insufficient Pap tests worsen clinical outcomes.<sup>35,36</sup> Unsatisfactory results are associated with up to a 4-fold higher risk for CIN2 or greater when compared to normal Pap test results.<sup>35</sup> Other trials have found that over a quarter of unsatisfactory Pap tests were from patients with a history of previous cervical epithelial abnormalities.<sup>36</sup> Since it has been shown that over 30% of women do not follow up after an insufficient Pap, this has potentially devastating consequences.<sup>36</sup>

The use of ThinPrep® and other liquid cytology methods can reduce the likelihood of unsatisfactory Pap tests.<sup>37-39</sup> A 2018 study showed that unsatisfactory results occurred with 7.1% of conventional Pap smears, compared with just 1.61% of liquid-based methods.<sup>37</sup> The most common reason for unsatisfactory tests is too few squamous cells.<sup>38</sup> According to Bethesda guidelines, adequate squamous cellularity for conventional smears requires at least 8,000 to 12,000 well-preserved and well-visualized squamous epithelial cells, while for liquid-based tests, that number is only 5,000 cells.<sup>40</sup> Other reasons for unsatisfactory results include an air-drying artifact, which does not occur with liquid-based methods, as well as inadequate patient preparation, sampling technique errors, intermittent shedding of abnormal cells, inflammation, blood, or foreign materials such as lubricant.<sup>38,41</sup> Improvements in the ease of collection and interpretation of slides with liquid-based cytology result in less sample reprocessing and, by extension, fewer rescheduled patients, which greatly improves patient care.<sup>42</sup>

### Enhanced Accuracy with ThinPrep® Digital Imaging

Digital imaging technologies have further advanced the sensitivity and specificity of liquid-based cytology, improving the detection of cervical dysplasia and malignancy. Both ThinPrep® and SurePath™ have developed digital imaging technologies. The ThinPrep Imaging System was approved by the FDA in 2003. Trials have shown that digital imaging modalities can improve the detection of HSIL by up to 38% and LSIL by up to 46% compared to manual screening.<sup>26,43-45</sup>

A trial of over 50,000 ThinPrep® Pap tests showed that the ThinPrep® Imaging System achieved a significant increase in detecting HSIL and greater lesions when compared to manual screening.<sup>44</sup> After implementation of the ThinPrep® Imaging System, one institution found they achieved a 37% increase in LSIL detection, 42% increase in HSIL detection, and cut their false-negative rate in half.<sup>45</sup> The ThinPrep® Imaging System has also been found to decrease the number of ASCUS results, further decreasing unnecessary follow-up procedures.<sup>45</sup>

Figure 3: ThinPrep® Imaging System Improves LSIL and HSIL Detection  
The ThinPrep Pap® imaging system improves detection of both LSIL and HSIL when compared to manual review of specimens, as evidenced by multiple trials.

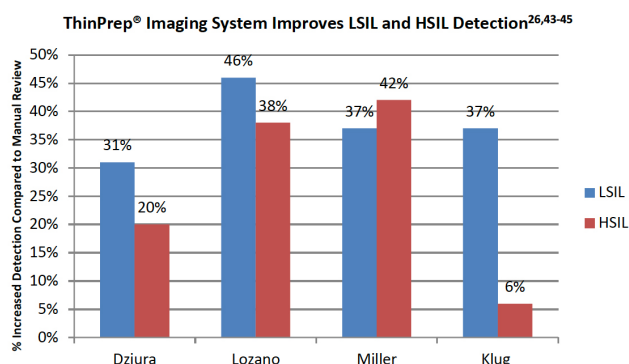


Figure 4: ThinPrep Pap® Imaging System Reduces Unsatisfactory Paps

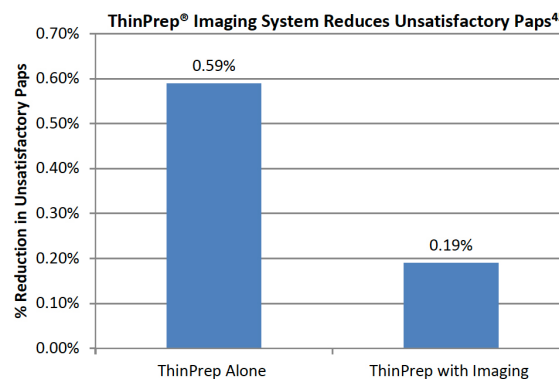
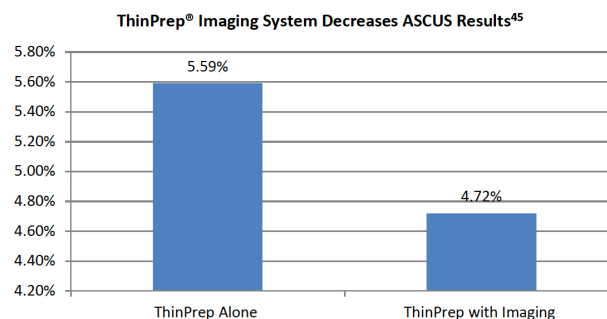


Figure 5: ThinPrep Pap® Imaging System Decreases ASCUS results



The following graphs illustrate the improvements observed using ThinPrep® imaging technology. Although HPV has been shown to be more sensitive for the detection of cervical dysplasia, there is evidence that high-quality cytology with imaging can exceed the sensitivity of high-risk HPV testing.<sup>46</sup> A 2018 study

**Table 1: Benefits of the ThinPrep Pap®**

The ThinPrep Pap® exhibits improved specimen adequacy, improved detection of HSIL, and improved detection of glandular disease. In addition, it is compatible with all of the currently FDA-approved HPV tests and numerous STD screening modalities.

Multifaceted Functionality	ThinPrep® Pap <sup>16</sup>
FDA Approval	1996
Improved Specimen Adequacy	Yes
Improved HSIL Detection	Yes
Glandular Disease Labeling Indication	Yes
Adjunctive Aptima® Trichomonas vaginalis (TV) Approval/Clearance	Yes
Adjunctive CT/NG Approval/Clearance	For All FDA-Approved CT/NG Tests
Shelf Life: Aptima® HPV Assay	15 weeks
Cervista® HPV Assay	24 weeks
Digene® HC2 Assay	12 weeks
Cobas® HPV Assay	24 weeks

out of Magee-Womens Hospital analyzed cervical screening data over a 13-year period, comparing ThinPrep®'s liquid-based cytology with computer-assisted ThinPrep® Imaging System to HPV testing.<sup>46</sup> Researchers compared over 300,000 co-testing results and concluded that liquid-based cytology using the ThinPrep® system was better than HPV testing in predicting CIN3, adenocarcinoma in situ, and cervical malignancies.<sup>46</sup> Out of 129 cervical cancers diagnosed,

76.3% were preceded by a positive HPV result while 83.3% were preceded by a positive cytology result.<sup>46</sup> HPV-negative, cytology-positive results preceded over 13% of the cervical cancers and 7.2% of the CIN3 and AIS identified.<sup>46</sup>

### Convenience of ThinPrep®: One Vial Testing for HPV and STIs

In addition to the benefits of improved cervical dysplasia and cervical cancer detection, ThinPrep® has the distinct advantage of being able to use a single specimen for HPV testing and sexually transmitted screening in addition to cytology.<sup>5</sup> One sample can be used to test for HPV, using any of the FDA-approved HPV tests, as well as to test for gonorrhea, chlamydia, and trichomonas.<sup>5</sup> Not only does this option enable providers to cut supply costs, but it can also help decrease the number of repeat appointments for add-on tests, making it more convenient for both providers and patients.

### Conclusion

While the Pap has been instrumental in decreasing the incidence of cervical cancer and its precursors for women around the world, not all Pap testing is created equal. Liquid-based cytology has led to improved detection of dysplasia and cervical malignancy and fewer unsatisfactory or insufficient results. ThinPrep®, the first FDA-approved and most widely used liquid-based cytological testing method, has the additional benefit of being compatible with most approved HPV testing devices and many different STI screening devices. This makes it an optimal cytological choice when performing co-testing for women aged 30 years and above. Even more importantly, the ThinPrep® technology will continue to contribute to the decrease in the incidence of cervical cancer.

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## Author Biography

### Dr. Darren Wheeler

Dr. Wheeler received his medical degree and completed his residency in Anatomic Pathology at the University of Washington in Seattle and completed a fellowship in Gynecologic Pathology at the Johns Hopkins Hospital in Baltimore, Maryland. Before joining Quest Diagnostics in Las Vegas, he served two years as a consultant for the Gynecologic and Breast Pathology Department at the Armed Forces Institute of Pathology (AFIP) in Washington, D.C. Based on his work there, Dr. Wheeler was the recipient of the Young Investigator Award in 2006 by the International Society of Gynecological Pathologists. He currently serves on multiple speaker bureaus for women's health pathology-related topics including cervical cancer screening. He continues to perform subspecialty consultation for Quest Diagnostics in Gynecologic and Breast Pathology in Las Vegas and serves as the Regional Medical Director of Anatomic Pathology, overseeing multiple practices for Quest Diagnostics and AmeriPath throughout the Western U.S.

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