Effectiveness of the ThinPrep Imaging System:
Clinical Experience in a Low Risk Screening Population

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The Cytyc ThinPrep Imaging System was FDA approved based on a multi-institutional clinical trial, in which the HSIL+ prevalence rate was 0.7%. This study determines the effectiveness of the Imager in clinical practice at an academic medical center with a historical HSIL+ rate of 0.25%. Cytological interpretations were compared for two 12-month periods pre- and post-Imager implementation. Data was compiled by cytologic diagnoses, and variations in prevalence rates were analyzed for statistical significance. Interpretations of ASC-US, ASC-H, and LSIL were correlated with Digene Hybrid Capture2 High Risk HPV DNA testing; interpretations of ASC-H, LSIL, and HSIL+ were correlated with subsequent surgical follow-up. ASC-US, ASC-H, and LSIL detection rates increased 34, 48, and 29%, respectively, with the Imager ($P < 0.001$*); whereas the detection of HSIL increased 24% (*$P < 0.051$*). Surgical correlation revealed no statistical differences in the positive predictive value (PPV) for ASC-H and LSIL. However, an increase in the PPV of HSIL was found (*$P < 0.05$*). High risk HPV results were lower for ASC-US (*$P < 0.001$*), but statistically equivalent for ASC-H and LSIL. Results of surgical correlation and HPV testing validated an increase in detection rates of ASC-H, LSIL, and HSIL, as well as increased PPV of HSIL with the ThinPrep Imaging System.* Diagn. Cytopathol. 2008;36:155–160.

Key Words: ThinPrep Imaging System; cervical cytology; ThinPrep Pap test; automated screening; HPV

The Cytyc ThinPrep Imaging System® (Cytyc Corporation, Marlborough, MA), also referred to as the Imager, received approval from the Food and Drug Administration in June 2003 based on the results of manufacturer internal studies coupled with data from a multi-institutional clinical trial. The clinical trial was a two-armed study comparing the cytological interpretations of 9,950 manually reviewed ThinPrep slides, with the cytological interpretation of the same slide set after Imager review. Clinical trial results showed increased sensitivity with the Imager for ASC-US+ and an increase in specificity for HSIL. The prevalence rate for HSIL+ in the four institutions participating in the trial ranged between 0.4% and 1.1%, with an average HSIL+ prevalence rate of 0.7%, a relatively high-risk screening population.

The purpose of this study was to determine the effectiveness of the Imager in actual clinical use over a 1-year period in a low-risk screening population at a large academic medical center with a historical HSIL+ rate of 0.25%.

Materials/Methods

After completing validation studies and review scope training, the ThinPrep Imaging System was implemented at Fletcher Allen Health Care on July 1, 2005. Cytological interpretations for ThinPrep Pap tests were compared in an IRB approved retrospective study for two 12-month periods, pre and post-Imager implementation (July 2004 to June 2005 vs. July 2005 to June 2006).

Data was compiled by cytological diagnoses, and variations in prevalence rates between the two time periods were analyzed for statistical significance. Interpretations of ASC-US, ASC-H, and LSIL were correlated with results of Hybrid Capture® 2 High Risk HPV DNA testing (Digene Corporation, Gaithersburg, MD). Interpretations of ASC-H, LSIL, and HSIL were correlated with subsequent surgical follow-up.

Specimen adequacy was evaluated using two parameters; the percentage of cases reported as unsatisfactory for

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Received 3 May 2007; Accepted 30 October 2007
DOI 10.1002/dc.20779
Published online in Wiley InterScience (www.interscience.wiley.com).

Table I. Epithelial Cell Abnormalities

Diagnosis	*Pre-Imager n = 54,565*		*Post-Imager n = 55,547*		*% Change*	*P-Value*
ASC-US	3.62%	(1974)	4.83%	(2,685)	+34%	<0.001
ASC-H	0.34%	(184)	0.50%	(277)	+48%	<0.001
LSIL	2.07%	(1130)	2.68%	(1,489)	+29%	<0.001
HSIL	0.28%	(151)	0.34%	(190)	+24%	=0.051
AGC	0.09%	(48)	0.08%	(42)	−14%	NSS
Carcinoma	0.02%	(11)	0.02%	(9)	−20%	NSS
All ASC	3.95%	(2158)	5.33%	(2,962)	+35%	<0.001
All SIL	2.35%	(1281)	3.02%	(1,679)	+29%	<0.001
ASC/SIL	1.68		1.76		+5%	NSS

ASC-US indicates atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells, cannot rule out HSIL; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; AGC, atypical glandular cells; All ASC, ASC-US + ASC-H; All SIL, LSIL + HSIL; NSS, not statistically significant.

Table II. Surgical Correlation

		Cases with Biopsies		*Benign*		*CIN I*		*CIN II/III*		*P-Value*
ASC-H	Pre-Imager	50%	(92/184)	47.8%	(44)	8.7%	(8)	43.5%	(40)	NSS
	Post-Imager	51%	(141/277)	46.1%	(65)	6.4%	(9)	47.5%	(67)	
LSIL	Pre-Imager	44%	(495/1130)	46.1%	(228)	31.5%	(156)	22.4%	(111)	NSS
	Post-Imager	41%	(604/1489)	46.0%	(278)	32.6%	(197)	21.4%	(129)	
HSIL	Pre-Imager	58%	(88/151)	19.3%	(17)	5.7%	(5)	75.0%	(66)	<0.05
	Post-Imager	64%	(122/190)	9.8%	(12)	4.1%	(5)	86.1%	(105)	

ASC-H indicates atypical squamous cells, cannot rule out HSIL; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; NSS, not statistically significant.

evaluation, and the percentage of cases lacking a transformation zone component. Data was also analyzed to compare the presence of infectious agents and the number of cases with endometrial cells in women over the age of 40. Quality control records were compared to determine the false negative fraction for each of the two study periods.

Results

The pre-Imager control group consisted of 54,565 manually evaluated ThinPrep Pap tests. The post-Imager arm of the study consisted of 58,351 cases evaluated utilizing the ThinPrep Imaging System. While our overall test volume increased 7% during the year following implementation, patient demographics remained stable. The age distribution in the pre-Imager group was 13–96 years, with a median age of 39. The age range in the post-Imager study group was 13–97 years, with a median age of 40. The make-up of testing personnel (cytotechnologists and cytopathologists) remained stable during the 2-year study period.

Of the post-Imager cases, 2,804 (4.8%) could not be evaluated by the Imager due to coverslipping, staining or biological reasons (e.g., extremely dark staining atrophic smears, excessive blood, inflammation, and/or bacteria). These rejected cases were manually evaluated and removed from the study, leaving a total 55,547 ThinPrep Pap tests in the post-Imager arm of the study, which compares closely with the pre-Imager control group.

Identification of Epithelial Cell Abnormalities

Collectively, the interpretation of all levels of SIL increased by 29% and was statistically significant at the level of $P < 0.001$. Individually, the increase in LSIL was 29% ($P < 0.001$), whereas the interpretation of HSIL increased by 24% ($P = 0.051$). With a 34% increase in ASC-US and a 48% in ASC-H ($P < 0.001$), the increase in the ASC/SIL ratio was not statistically significant. The number and percentage of cases identified as glandular lesions and carcinoma were small, but comparable for the two time periods (Table I).

Surgical Correlation

Pap tests reported as ASC-H, LSIL, and HSIL were correlated with subsequent biopsy results, as available. Surgical correlation rates for ASC-H and LSIL were comparable with pre-Imager levels and validated the increased detection reported earlier. Surgical correlation rates for HSIL were statistically higher in the post-Imager study group (75.0% vs. 86.1%, $P < 0.05$), indicating a higher positive predictive value for cases of HSIL evaluated with the Imager (Table II).

HPV Correlation

HPV testing at Fletcher Allen Health Care is not performed by automatic reflex, but requires an order from the patient's provider. Our review revealed that 64–69% of ASC-US, 22% of ASC-H, and 14–16% of LSIL specimens were submitted for HPV testing. The lower percent-

Table III. Digene Hybrid Capture 2 High-Risk HPV DNA Correlation

		Cases with HPV testing		*HR HPV positive*		*P-Value*
ASC-US	Pre-Imager	63.7%	(1,258/1,974)	51.8%	(652)	<0.001
	Post-Imager	68.9%	(1,851/2,685)	43.1%	(798)	
ASC-H	Pre-Imager	22.3%	(41/184)	73.2%	(30)	NSS
	Post-Imager	22.0%	(61/277)	63.9%	(39)	
LSIL	Pre-Imager	13.8%	(156/1,130)	80.1%	(125)	NSS
	Post-Imager	16.4%	(244/1,489)	84.0%	(205)	

ASC-US indicates atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells, cannot rule out HSIL; LSIL, low-grade squamous intraepithelial lesion; HR HPV, high-risk human papilloma virus; NSS, not statistically significant.

Table IV. Specimen Adequacy, Infectious Agents, and Endometrial Cells

Diagnosis	*Pre-Imager n = 54,565*		*Post-Imager n = 55,547*		*% Change*	*P-Value*
Unsatisfactory	1.67%	(911)	1.58%	(876)	−6%	NSS
T-zone Absent	7.74%	(4222)	7.96%	(4420)	+3%	NSS
Shift in flora	6.95%	(3791)	7.65%	(4251)	+10%	<0.001
Fungus	4.40%	(2402)	4.53%	(2514)	+3%	<0.05
Trichomonas	0.14%	(78)	0.13%	(73)	−8%	NSS
Actinomyces	0.06%	(31)	0.03%	(18)	−43%	NSS
Herpes	0.02%	(13)	0.03%	(14)	+6%	NSS
EMC 40–50	1.72%	(936)	1.38%	(764)	−20%	<0.001
EMC >50	0.30%	(161)	0.36%	(201)	+23%	NSS
All EMC >40	2.01%	(1097)	1.74%	(965)	−14%	<0.001

T-zone indicates transformation zone component; EMC 40–50, endometrial cells in women 40–50 years: EMC >50, endometrial cells in women over 50 years: All EMC >40, all women over age 40 with endometrial cells present; NSS, not statistically significant.

age of HPV testing for patients with ASC-H and LSIL reflects clinical practice and the fact that HPV testing is not the preferred management route put forth by the ASCCP Consensus Guidelines for the management of these women. We found no statistical difference between HPV positivity rates in the pre and post-Imager study groups following a cytologic diagnosis of ASC-H and LSIL. However, a statistically significant decrease in HPV positivity (51.8% vs. 43.1%, $P < 0.001$) was seen following a cytologic diagnosis of ASC-US (Table III).

Specimen Adequacy, Infectious Agents, and Endometrial Cells

Even though the evaluation of 77% of the negative slides in the post-Imager study group was limited to 22 fields of view (with only 23% selected for full manual review), the difference in specimen adequacy was not statistically different for a diagnosis of unsatisfactory for evaluation or for the presence of transformation zone component.

The percentage of cases reported with shift in flora and fungal organisms was higher in the post-Imager study group ($P < 0.001$ and $P < 0.05$, respectively); whereas, the identification of *trichomonas vaginalis*, *Actinomyces*, and herpes simplex virus were not statistically different from the pre-Imager control group.

The presence of endometrial cells in women over age 40 was lower in the post-Imager study group ($P < 0.001$). This decrease was only seen in the 40–50 age group. No statistical difference was seen in the identification of endometrial cells in women over age 50 (Table IV).

Quality Control Data

During the 12-month period prior to Imager implementation, the laboratory's False Negative Fraction (FNF) was 2.75 compared with 2.70 during the post-Imager study period, a decrease of 1.8% which was not statically significant. Of the 4,692 cases diagnosed with Epithelial Cell Abnormalities, 11 errors were attributed to the Imager (9 ASC-US and 2 LSIL).

Discussion

The Cytyc ThinPrep Imaging System received approval from the Food and Drug Administration in June 2003 based, in part, on the results of a multi-institutional clinical trial. The clinical trial was conducted in four diverse laboratories, all of which reported a historical rate of HSIL+ of greater than 0.4% (range 0.4%–1.1%, average 0.7%).[1] The limited number of studies published to date in full manuscript form comparing pre and post-Imager implementation data have been conducted in laboratories with a historical HSIL+ rate ranging between 0.34% and 0.58%.[2–4]

As with the implementation of any new technology, studies in one type of laboratory do not always transfer to laboratories with a different make-up, be it size, location or patient population. The study reported here specifically looks at the effectiveness of the Imager in a low-risk

screening population in a large academic medical center with a historical rate of HSIL+ of 0.25%. This study provides new information for laboratories with similar patient populations. It may also serve as a model in the years ahead as the population of HPV vaccinated patients matures and the prevalence of HSIL is predicted to decline.

On behalf of the institutions participating in the multicenter clinical trial, Biscotti et al. reported a statistical increase in the sensitivity of ASC-US+ with the Imager, but failed to show statistical improvement in either LSIL+ or HSIL+.[5] Dizura et al. showed an increase in the detection rates of ASC-US and LSIL+, but not HSIL+; where as Lozano reported an increase in ASC-US, LSIL, and HSIL+.[2,3] Miller et al. reported an increase in LSIL and HSIL, but unlike other studies found a statistically significant decrease in ASC-US.[4] In our study, statistically significant increases were seen in the detection of ASC-US, ASC-H, and LSIL, with HSIL nearing significance at $P = 0.051$.

Biscotti et al. reported a statistical increase in HSIL specificity; whereas Dizura et al., Lozano and Miller et al. failed to show statistical improvements in the PPV of a cytologic diagnosis of HSIL.[2–5] Fletcher Allen Health Care (FAHC) serves as a regional center for cytology testing, with 23% of our Pap test population receiving follow-up surgical care at community hospitals rather than at our institution. Even with this limitation, 64% of our HSIL patients received surgical follow-up at FAHC and we were able to show a statically significant improvement in the positive predictive value of a cytologic diagnosis of HSIL ($P < 0.05$).

Several other studies showing improved sensitivity have been presented at professional meetings and published in abstract form.[6–11] Most of these abstracts report only on the incidence pre and post implementation of the ThinPrep Imaging System, but are lacking diagnostic correlation with either HPV testing and/or surgical follow-up. The study reported here is one of the larger studies to date from a single institution that includes both HPV and surgical correlation to validate the findings of a 29% increase in detection of squamous intraepithelial lesions (LSIL+) and a 12% increase in the positive predictive value of HSIL.

With regard to the increased incidence of ASC-US in this study, concurrent or subsequent HPV DNA testing did not support an increase in disease detection. While detection of ASC-US increased 34% (3.62–4.83%), HPV positivity following a diagnosis of ASC-US decreased by 17% (51.8–43.1%). This would suggest an overcalling of reactive or metaplastic changes as ASC-US. This finding is not unique to our study, and points to the importance of HPV reflex testing for samples reported as ASC-US utilizing the ThinPrep Imaging System.

In an abstract specific to this topic, Geyer et al. reports an increase in ASC-US (2.4–3.2%, $P < 0.005$), with a drop in the HPV positivity (45.5–27%, $P < 0.003$).[12] Dziura et al. reported a 9.5% decrease in HPV positivity when looking at reflex testing for ASC-US and ASC-H combined (53.9–48.4%).[2] Lozano's raw data also calculates to a decrease (48–35%) following a diagnosis of "atypical squamous cells."[3] In contrast, Miller et al. reported an ASC-US rate of 5.59% pre-Imager and 4.72% post-Imager, with HPV positivity rates of 35.87% and 39.75%, respectively.[4] Similarly, Ashfaq et al. reported an ASC-US rate of 5.9% pre-Imager and 5.0% post-Imager with HPV positivity rates of 49.4% and 57.1%, respectively.[13]

Both Dziura et al. and Lozano reported a decrease in the ASC rate over time indicating an initial learning curve. Dziura et al. associated the learning curve to familiarity with the Image Review Scopes and the type of cells presented in the 22 fields of view. In our laboratory, the learning curve appeared to be associated more with becoming accustomed to the proprietary ThinPrep Imager Stain, which was darker than our previous stain. If our experience holds true, it would seem that the closer the proprietary ThinPrep Imager stain is to the intensity of the stain previously used by a laboratory, the less effect the stain would have on the laboratory's rate of ASC-US or the corresponding ASC/SIL ratio.

With statistical increases in ASC-US and ASC-H, as well as in LSIL and HSIL, our ASC/SIL ratio increased by 5% but this increase was not statistically significant. Dziura et al. reported only a slight increase; where as Lozano's data calculates to an 11% increase that was statically significant.[2,3] In contrast, Miller et al. data calculates to a 38% decrease ($P < 0.001$).[4] Of the abstracts cited previously in this paper, there is a spectrum of results with some studies reporting an increase, some a decrease and some where the ratio is unchanged. Likewise in a multicenter study of ten laboratories reported by Linder et al., a cumulative decrease in the ASC/SIL ratio from 1.59 to 1.28 was seen; however, within that study seven laboratories reported a decrease, two were unchanged and one laboratory showed an increase.[14] This variability of results may support the stain intensity issue discussed earlier.

Even though the evaluations of the majority of negative slides are limited to 22 fields of view with the ThinPrep Imaging System, the evaluation of specimen adequacy was not compromised in our study. The percentage of unsatisfactory cases decreased 6% (1.67–1.58%) and the percentage of specimens lacking a transformation zone component increased by 3% (7.74–7.96%). Neither of these two changes was statistically significant. Results from the clinical trial were more dramatic and showed a decrease in the unsatisfactory rate (0.7–0.3%) and an

increase in cases lacking a transformation zone component (12.4–14.5%), both at $P < 0.001$.[1]

Results from the clinical trial show no statistical difference in the identification of infectious organisms. The percentage of cases in our study reported with shift in flora and fungal organisms was statistically higher in the post-Imager study group ($P < 0.001$ and $P < 0.05$, respectively); whereas, the identification of *Trichomonas vaginalis*, *Actinomyces* and herpes simplex virus were not statistically different from the pre-Imager control group.

Our study was limited in the number and percentage of cases with glandular abnormalities and invasive carcinomas. Studies by Sabo et al. and Friedlander et al. address the issue of glandular abnormalities and unusual neoplasia through review of the Pap tests evaluated prior to a surgical confirmation of disease. Combining the data from these studies shows that 85/86 (99%) Pap tests evaluated with the ThinPrep Imaging System contained abnormal cells within the 22 fields of view.[15–18]

Other studies have not reported specifically on the identification of endometrial cells in women over the age of 40. We found this diagnosis to be lower in the post-Imager study group ($P < 0.001$). However, the decrease was only seen in the 40–50 age group. No statistical difference was seen in the identification of endometrial cells in women over the age of 50. Larger and/or multi-institutional studies specifically addressing the effectiveness of the ThinPrep Imaging System with glandular cells and glandular lesions are warranted.

In our study, the false negative fraction decreased slightly from 2.75 to 2.70 utilizing the Imager. Other studies have also reported decreases in error rates and false negative fractions.[4,8,19–21] The largest study looking specifically at false negative fractions was conducted by Chase and included quality control rescreening of 26,113 manual cases and 37,639 imaged cases.[21] In the manual control group 69 cases of LSIL were identified; whereas there were 55 LSIL identified among the imaged slides. The false negative fractions were calculated at 7.21 and 4.01, respectively, a 44% decrease that was significant at the level of $P < 0.001$.

Fletcher Allen Health Care implemented the ThinPrep Imaging System as a quality initiative not as a productivity tool. However, a 10–30% increase in individual slide screening productivity afforded us by the ThinPrep Imaging System allowed us to broaden our high-risk QC pool and increase quality control rescreening from 10 to 20%, as well as to bring on a new client (increasing our annual volume 5,000 cases/yr) without additional staffing or increasing our turn around time. Cytotechnologists reported the ability to evaluate slides in a more efficient manner with less fatigue. Productivity savings provided cytotechnologists with the ability to spend more time on abnormal cases, while maintaining their commitment to assisting on FNA procedures, educating students and participating in research studies. Reports of increased productivity have ranged from zero to greater than 100%.[1,3,4,21] The Chase study showed a significant reduction in false negative fraction, and did so in a laboratory where the slide productivity concordantly increased from 9.8 slides/hr to 12.8 slides/hr, an increase of 31%.[21]

Although cost effectiveness and operation of the ThinPrep Imaging System was not the focus of this study, it should be noted that the ThinPrep Imaging System adds to the cost of Pap testing. In our laboratory, the increased price to the patient was less than $8.00/test. In our experience, the daily operation of the ThinPrep Imaging System was simple and reliable. The Imager provides walk-away processing with a maximum throughput of 400 slides in 24 hr. Our laboratory's volume of 200–250 slides/day was readily accommodated without any changes in staff scheduling. While two mechanical downtimes were experienced during the first 6 mo of operation, no further downtimes have occurred over 18 mo of subsequent operation.

The data reported here supports the original findings of the multicenter clinical trial. It further establishes the increased effectiveness of the ThinPrep Imaging System in detecting squamous intraepithelial lesions in clinical practice in a laboratory with a low-risk screening population. The increased rate of detection was not only measured by incidence, but was validated through correlation with Digene High Risk HPV DNA testing and/or surgical biopsy, as was the increased positive predictive value for HSIL. We can conclude from this study that the ThinPrep Imaging System is statically more effective than manual screening within our laboratory and within our patient population.

At this time, all published reports on the ThinPrep Imaging System have emanated from the USA,[1–21] Europe,[22,23] and Austraila.[24,25] However, the results of these studies may also be of interest to the practice of cytology in developing countries, where cervical cancer screening varies from regions in which no screening programs exists to areas where sophisticated manual screening occurs. Imaging of cervical samples could prove useful in areas where appropriate infrastructure exists, but where the limiting factor to increased screening is the supply of trained and experienced cytotechnologists; the increase in productivity seen in almost all published studies could be critical to such programs. Further, in areas where screening may be limited to two to three cervical samples in the lifetime of a woman[26]; the improved detection rate offered by imaging of liquid based material could bring this limited screening to its full potential.

Acknowledgments

Fletcher Allen Health Care has previously received financial support for clinical trials involving the manual review

of ThinPrep Pap test slides and Ms. Papillo has previously served as a consultant to Cytyc Corporation. No financial support was received for the ThinPrep Imaging System study reported here.

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