Comparison of Performance of Conventional and ThinPrep Gynecologic Preparations in the College of American Pathologists Gynecologic Cytology Program

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• ***Context.*—Results of clinical trials suggest that interpretation of liquid-based cytology preparations is more accurate and is associated with less screening error than interpretation of conventional preparations.**

***Objective.*—In this study, the performance of participants in interpreting ThinPrep (TP) preparations was compared with participants' performance on conventional Papanicolaou tests in the College of American Pathologists Interlaboratory Comparison Program in Cervicovaginal Cytology (PAP).**

***Design.*—The results of the PAP from the year 2002 were reviewed, and the discordancies to series and exact-match error rates for the 2 cytologic methods were compared.**

***Results.*—For this study, a total of 89 815 interpretations from conventional smears and 20 886 interpretations from TP samples were analyzed. Overall, interpretations of TP preparations had both significantly fewer false-positive (1.6%) and false-negative (1.3%) rates than those of conventional smears ($P = .001$ and $P = .02$, respectively) for validated or validated-equivalent slides, as assessed by concordance with the correct diagnostic series. In this assessment of concordance to series, interpretations of educational TP and conventional preparations were similar, except for high-grade squamous intraepithelial lesion, in which the performance was significantly worse for educational TP preparations (false-negative rate of 8.1% vs 4.1% for conventional smears, $P < .001$). When interpretations were matched to the exact diagnosis, validated-equivalent TP preparations were generally more accurate for diagnoses in the 100 series and 200 series than were conventional smears. Notably, for the reference diagnosis of squamous cell carcinoma, the exact-match error rate on validated equivalent TP slides was significantly greater than that of conventional slides (44.5% vs 23.1%, $P < .001$). Interpretations of educational TP preparations also had a significantly higher error rate in matching to the exact reference diagnosis for squamous cell carcinoma (33.7% vs 22.8%, $P = .007$).**

***Conclusions.*—Overall, TP preparations in this program were associated with significantly lower error rates than conventional smears for both validated and educational cases. However, unlike the negative for intraepithelial lesion and malignancy, not otherwise specified, low-grade squamous intraepithelial lesion, and adenocarcinoma cytodiagnostic challenges, participants' responses indicated some difficulty in recognizing high-grade squamous intraepithelial lesion and squamous cell carcinoma.**

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The last several years have seen an increased use of liquid-based cytology (LBC) for gynecologic cytology, including ThinPrep (TP) (Cytyc Corporation, Boxborough, Mass). The primary reason for this change is that studies indicate that LBC has an increased sensitivity for low-grade (LSIL) and high-grade (HSIL) squamous intraepithelial lesions, without increasing the rate of detection of atypical squamous cells of undetermined significance.[1–13] Consequently, use of the TP technique characteristically leads to a decrease in the atypical squamous cells of undetermined significance–squamous intraepithelial lesion ratio.[4,7,9,14] A recent sensitivity study of TP for cervical and endometrial adenocarcinomas concluded that TP also is superior to conventional preparations in detecting these less common malignancies.[15] Many studies have suggested that this increased sensitivity is due to improved sampling by this method, resulting in fewer compromised or inadequate preparations.[4,5,7–9,13,16] In addition, results of several clinical trials have suggested that interpretation of LBC preparations is more accurate and/or precise and is associated with less frequent screening error than interpretation of conventional preparations.[1,2,5,6,17,18] The ability of TP to increase detection of squamous intraepithelial le-

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sions has been confirmed in subsequent histologic biopsy validation studies.[2,4,7,19,20]

Studies of the screening sensitivity of LBC as compared to that of conventional preparations were initially few and were performed in the context of industry-sponsored clinical trials or in academic centers.[1,10–12,21–23] Subsequent reports of large clinical laboratories' experience with TP have now appeared and seem to confirm these initial studies.[3,4,7,13] The College of American Pathologists (CAP) Interlaboratory Comparison Program in Cervicovaginal Cytology (PAP) provides another opportunity to compare the relative performance of TP methodology with that of conventional tests.

The PAP is a program in which pathologists and cytotechnologists from a wide range of practice settings interpret a full spectrum of gynecologic cytology material. The program has been using conventional preparations for more than 10 years and has been using LBC preparations for the last several years. This program is able to assess participants' interpretations of the TP technique. Currently, LBC slides in the PAP have been restricted to TP slides, but SurePath slides (by TriPath, Burlington, NC) are now being introduced as well. We sought to compare the performance of participants on TP preparations with participants' performance on conventional tests in the PAP.

MATERIALS AND METHODS

The PAP program is a quarterly, mailed, glass-slide quality improvement program. The CAP Laboratory Accreditation Program requires that all laboratories evaluating gynecologic cytology enroll in the PAP or an equivalent glass-slide program. Cytology laboratories of all types participate, with the largest number (approximately 60%) being hospital laboratories. In addition, independent laboratories, federal and government laboratories, university laboratories, and others (such as those associated with a group practice or physician's office) also participate.

Participants generously contribute slides to the program. Submitted slides with a diagnosis of LSIL or higher must be confirmed by biopsy. After receipt and accessioning into the program, the slides are reviewed by at least 3 experienced cytopathologists from the CAP Cytopathology Resource Committee. Before acceptance into the program, each slide must be judged to be of good technical quality and an excellent example of the reference diagnosis. All 3 cytopathologist reviewers must agree on the exact target diagnosis, and this diagnosis must agree with the submitted biopsy diagnosis prior to accepting a slide for circulation into an educational set.

The PAP program consists of 5 glass slides of cervicovaginal material mailed 4 times per year. The coded answer sheets have diagnostic menus using terminology modified from the Bethesda System. Referenced slides are placed into 1 of 3 selection series: the 000 category for unsatisfactory slides; the 100 series for negative for intraepithelial lesion and malignancy, not otherwise specified (NILM-NOS), infections, and reparative conditions; and the 200 series for epithelial cell abnormalities and carcinoma (Table 1).

Validated slides must meet specific performance requirements. To be validated, each slide must achieve at least a 90% level of agreement with the correct selection series, with a minimum of 20 correct responses. The standard of error of this percentage must be, at most, 5%. During the study period, additional criteria were added for LSIL and 100 series slides. For LSIL slides, cases must achieve at least a 70% concordance to the exact reference interpretation. Similarly, for other 100 series slides, cases must achieve at least a 50% concordance to the exact reference interpretation. Slides that have been reviewed by the CAP cytopathology committee and that have commenced circulation among participating laboratories but have not obtained validation status are designated ''educational.''

Table 1. Diagnostic Menu From the College of American Pathologists Interlaboratory Comparison Program in Cervicovaginal Cytology

Reference Diagnosis*
000 Unsatisfactory
101 NILM-NOS
111 Fungal organisms consistent with *Candida*
113 *Trichomonas vaginalis*
115 Cellular changes consistent with herpesvirus
120 Reparative changes
121 Atrophic vaginitis
127 Follicular cervicitis
201 LSIL
211 HSIL
220 Adenocarcinoma in situ
221 Squamous cell carcinoma
225 Adenocarcinoma
226 HSIL/carcinoma
227 Nonepithelial neoplasm

* NILM-NOS indicates negative for intraepithelial lesion and malignancy, not otherwise specified; LSIL, low-grade squamous intraepithelial lesion; and HSIL, high-grade squamous intraepithelial lesion.

During 2002, none of the circulating TP slides were designated as validated, because participants had not been given sufficient advance notice that graded sets contained TP slides. The PAP required that advance notice be given to all participants prior to their review of validated slides, because laboratory performance on these slides is monitored. However, TP slides that had met the criteria for validation could be identified retrospectively and labeled ''validated-equivalent'' slides, and thus could be compared with validated conventional slides. These validated-equivalent TP slides were included in educational slide sets of the PAP, unlike validated conventional slides, which were placed into recognizable, graded (validated) slide sets. The remaining TP cases, which had not reached validated equivalency, were recognized as educational slides.

The results of the PAP from 4 mailings in 2002 were reviewed. We used both cytotechnologist and pathologist responses on conventional and TP slides in this study. The analysis included slides only if there were at least 5 responses per slide, and if the reference diagnosis had at least 100 responses. The reference diagnosis of 226 (HSIL/carcinoma, not otherwise specified) was not used in this analysis because these criteria were not met. Responses were analyzed at 2 levels of agreement with the reference diagnosis of the slide. In the first analysis, participant responses were examined with respect to their discordancy from the series of the reference diagnosis. Discordant responses were responses that placed a slide with a 100 series reference diagnosis in the 200 series (false positive) or a slide with a 200 series reference diagnosis in the 000 or 100 series (false negative). In the second agreement analysis, the proportion of exact matches, that is, responses correctly identifying a slide to the exact reference diagnosis, was determined for each diagnostic category. In this exact-match analysis, a response that did not place a slide in the correct diagnostic category was labeled an exact-match error. The exact-match error rate of each diagnostic category was identified. A singular exception was that a response of 226 (HSIL/carcinoma, not otherwise specified) was considered to be both concordant to series and an exact match for either 211 (HSIL), 221 (squamous cell carcinoma [SCC]), or 225 (adenocarcinoma).

Statistical analysis was performed using the 2-sample *t* test for each set of slides paired by reference diagnostic category and validation status using S-PLUS 6 for windows. This compares the mean error rates for conventional slides with that of TP slides for each set of pairwise comparisons. *P* values of all significance tests are reported in Tables 2 and 3.

Table 2. Discordant* Response Rates by Preparation Type on Validated or Validated-Equivalent Slides and Educational Slides (2002 PAP)

Reference Diagnosis†	Validated or Validated-Equivalent Slides			Educational Slides		
	Conventional Mean, %	ThinPrep Mean, %	*P*	Conventional Mean, %	ThinPrep Mean, %	*P*
False-Positive Rates (Discordant Response of 200 Series)						
101 NILM-NOS	3.9	2.1	.06	7.0	5.7	.25
111 Fungal organisms consistent with *Candida*	2.2	1.1	.15	3.5	2.8	.44
113 *Trichomonas vaginalis*	2.2	1.9	.57	3.8	4.0	.91
115 Cellular changes consistent with herpesvirus	1.5	0.6	.44	2.2	0.9	.26
120 Reparative changes	6.4	0	NS‡	14.1	11.3	.60
100 Series	3.2	1.6	.001	6.1	4.4	.02
False-Negative Rates (Discordant Response of 000/100 Series)						
201 LSIL	3.4	1.5	.009	7.5	5.3	.09
211 HSIL	1.9	1.1	.10	4.1	8.1	<.001
221 Squamous cell carcinoma	1.1	1.0	.83	2.3	4.7	.14
225 Adenocarcinoma	1.9	1.3	.51	8.4	6.0	.32
200 Series	2.1	1.3	.02	5.9	6.5	.36

* Discordant response for 100 series slides includes any 200 series response; discordant response for 200 series slides includes any 000/100 series response.

† NILM-NOS indicates negative for intraepithelial lesion and malignancy, not otherwise specified; LSIL, low-grade squamous intraepithelial lesion; and HSIL, high-grade squamous intraepithelial lesion.

‡ Because of the small number of validated-equivalent ThinPrep slides for diagnosis 120, no formal statistical test was carried out.

RESULTS

A total of 89 815 responses from conventional preparations and 20 886 responses from TP samples were available for analysis in the study. A similar average number of responses was generated for both conventional slides and TP slides. Both cytotechnologist and pathologist interpretations were combined in these responses because only minor differences existed between these 2 groups' responses and trends were very similar.

Table 2 shows the discordancy rates (ie, response in an incorrect reference diagnostic series) for both TP and conventional slides. ThinPrep preparations were associated with both significantly fewer false-positive (1.6%) and false-negative rates (1.3%) than conventional tests ($P = .001$ and $P = .02$, respectively) in interpretations of validated or validated-equivalent slides (Table 2). For educational slides, the false-positive rates of interpretations on TP preparations (4.4%) were significantly lower than the false-positive rates of conventional tests ($P = .02$), but the false-negative rates (6.5%) were not significantly different ($P = .36$).

The performance of participants on the 2 preparation types varied by reference diagnosis. For validated and validated-equivalent slides, TP preparations had consistently greater accuracy for all diagnoses in the 100 series than did conventional preparations, but because of reduced statistical power from smaller sample sizes, none of the individual differences were statistically significant. For 200 series slides, TP preparations were significantly more accurate for LSIL ($P = .009$); a similar trend was noted for HSIL, SCC, and adenocarcinoma, but did not reach statistical significance. In contrast, for educational slides, responses on HSIL slides were significantly less accurate for TP preparations than for conventional slides, with a false-negative rate of 8.1% versus 4.1% ($P < .001$). A similar trend was evident for educational slides and a reference diagnosis of SCC, in which TP preparations appeared to have a higher false-negative rate of 4.7% compared to 2.3%, although the difference was not statistically significant ($P = .14$). For all other reference diagnoses, responses on TP preparations generally showed better performance, although no differences were statistically significant.

Slide performance to the exact diagnosis is summarized in Table 3. For validated or validated-equivalent slides, TP preparations overall had significantly lower error rates than the conventional preparations for the 100 series group (9.5% vs 14.5%, $P < .001$). A similar trend was seen in the 200 series group (17.4% vs 19.2%), but did not reach statistical significance. Exact-match-rate errors for all cytodiagnostic categories are less or equivalent in TP preparations than in conventional preparations, with one notable exception. The error rate of respondents for cytodiagnosis 221 (SCC, 44.5%) was higher in TP slide preparations than in conventional preparations (23.1%, $P < .001$). The proportion of exact-match errors on validated-equivalent SCC TP slides within the 200 series responses were LSIL (4%), HSIL (75%), adenocarcinoma in situ (8%), and adenocarcinoma (13%). For educational cases, TP preparations overall had marginally lower or equivalent error rates, including for all series 100 and 200 groupings. The exact-match rate for respondents on TP slides was significantly worse for cytodiagnostic category 113 (*Trichomonas vaginalis*) and, again, category 221 (SCC). The proportion of exact-match errors on educational SCC TP slides within the 200 series responses were LSIL (4%), HSIL (72%), adenocarcinoma in situ (3%), and adenocarcinoma (21%). Error rates were higher for cytodiagnoses 120 (reparative changes) and 211 (HSIL), but the difference was not significant.

COMMENT

The PAP offers a unique data set that permits comparison of the performance of participants on conventional and TP preparations. The program has included conventional preparations for more than 10 years and TP preparations for the last several years.[24] Currently, it includes literally millions of interpretations of thousands of slides over a prolonged period of time. The interpretations are

Table 3. Error Rates for Exact Matches* by Preparation Type on Validated and Validated-Equivalent, and Educational Slides (2002 PAP).

Reference Diagnosis†	Validated or Validated-Equivalent Error Rates From Exact Matches			Educational Error Rates From Exact Matches		
	Conventional Mean, %	ThinPrep Mean, %	*P*	Conventional Mean, %	ThinPrep Mean, %	*P*
101 NILM-NOS	15.5	10.3	.01	20.6	17.3	.11
111 Fungal organisms consistent with *Candida*	13.3	8.2	.01	22.0	14.7	.01
113 *Trichomonas vaginalis*	11.3	11.0	.88	12.3	18.7	.02
115 Cellular changes consistent with herpesvirus	7.4	0.9	.07	8.1	6.0	.42
120 Reparative changes	31.5	24.1	NS‡	42.7	54.4	.20
100 Series	14.5	9.5	<.001	20.2	17.2	.03
201 LSIL	9.3	8.3	.41	17.3	11.8	.004
211 HSIL	23.0	23.9	.65	26.3	26.8	.82
221 Squamous cell carcinoma	23.1	44.5	<.001	22.8	33.7	.007
225 Adenocarcinoma	20.9	16.2	.20	30.1	18.6	.007
200 Series	19.2	17.4	.12	23.2	21.8	.31
Overall	**17.2**	**14.2**	**<.001**	**21.7**	**19.8**	**.05**

* Error in exact match is any response not identical to the reference diagnostic category.

† NILM-NOS indicates negative for intraepithelial lesion and malignancy, not otherwise specified; LSIL, low-grade squamous intraepithelial lesion; and HSIL, high-grade squamous intraepithelial lesion.

‡ Because of the small number of validated-equivalent ThinPrep slides for diagnosis 120, no formal statistical test was carried out.

not limited to a single or small number of institutions composed primarily or exclusively of academic cytologists, but instead are provided by practicing pathologists and cytotechnologists in a wide variety of laboratory settings. This set of responses or interpretations may be a better reflection of the current standard of interpretation of gynecologic cytology than that of smaller investigative trials and studies, although the PAP interpretations are made in a testing mode and do not mimic day-to-day practice.

The methodology used in this study has important limitations. Participation in the program, including the LBC portion, is voluntary. This self-selection does represent a potential bias, since participants have been self-selected on the basis of interest and, possibly, prior experience. Second, the program itself cannot ensure that those participants in the TP portion of PAP are specifically certified in the interpretation of TP preparations. (Such specific training for TP is a requirement prior to the implementation of this technique in the laboratory.) Consequently, this study cannot identify any difference in performance between those participants who had received specific training and those who did not. The results of this study may include interpretations by participants who have not been fully trained in this method. Nevertheless, the demonstrated performance of participants on the validated-equivalent TP slides (Tables 2 and 3) suggests that the impact of this potential bias was limited. Third, some of the TP slides in the program are drawn from additional slides made from remaining liquid in the vial. While each slide is reviewed and accepted individually by the committee, it is possible that some slides could have fewer abnormal cells than the original slide.

This study permits the identification of the accuracy of both conventional and TP preparations for each cytodiagnostic category, since an external standard (the reference diagnosis established by 3 members of the Cytopathology Resource Committee) is available in each case. Furthermore, in the series 200 cytodiagnoses, this external standard is also confirmed by subsequent histologic biopsy. The study is capable only of comparing respondents' screening/interpretation on conventional and TP slides, and does not compare the different sampling performances of these 2 techniques.

In general, the participants' data from validated and validated-equivalent slides show that TP accuracy is superior to that of conventional preparations, as assessed by either concordance to series 100 or 200 diagnoses (Table 2) or exact-match rates by series (Table 3). The accuracy of TP preparations is either equivalent or superior to conventional preparations for all 100 series cytodiagnoses (NILM-NOS, *Candida*, *Trichomonas*, cellular changes consistent with herpesvirus, and reparative changes), LSIL, and adenocarcinoma. Data from the educational slides show a similar trend for the accuracy of TP for the diagnoses NILM-NOS, *Candida*, cellular changes consistent with herpesvirus, reparative changes, LSIL, and adenocarcinoma in both concordant series (Table 2) and exact-match analyses (Table 3). Interestingly, among the educational cases diagnosed as NILM-NOS (series 100), participants were more likely to make an exact-match error in the diagnosis of *Trichomonas* (18.7%) as compared to conventional preparations (12.3%, $P = .02$).

Examination of the data of the most significant cytodiagnostic categories of HSIL and SCC reveals some interesting findings. On validated or validated-equivalent slides, false-negative rates (discordant responses of series 100 cytodiagnoses) for HSIL and SCC are equivalent on both TP and conventional preparations. On educational slides, however, the false-negative rate is higher for HSIL (<.001) and is trending higher in the case of SCC (Table 2). In the exact-match analysis of Table 3, SCC cases exhibit a higher error rate for both validated-equivalent and educational TP slides, although not reaching statistical significance in the latter category. The clinical significance of a response of LSIL, HSIL, adenocarcinoma in situ, or adenocarcinoma on an SCC slide (ie, an exact-match error within the 200 series) initially may appear to be minimal in the screening situation, since the preferred management pathway for any of these cytointerpretations includes referral for colposcopic assessment, with the exception of LSIL in some circumstances. Nevertheless, there are significant differences in the management algorithms for some of these cytointerpretive categories, as outlined by

the recent Consensus Guidelines of the American Society of Colposcopy and Cervical Pathology.[25] For example, endocervical sampling is mandatory in the management of a woman with a cytointerpretation of atypical glandular cells of unknown significance, whereas endocervical sampling is discretionary in the management of some women with LSIL or HSIL.

These findings in the educational slide component suggest that there is increased difficulty in detecting some cases of HSIL and SCC in TP preparations, in contrast to other cytodiagnostic categories. These HSIL and SCC TP cases, which are more difficult to identify, would likely fail to fulfill the validation criteria and not achieve validation or graded status. Nevertheless, all educational cases, both conventional and TP, have biopsy confirmation and have been reviewed by 3 pathologists to confirm the cytologic findings. This implies that there may be specific patterns of HSIL and SCC in TP preparations that are more difficult for the general cytologist to identify.

Additional studies of slides from the PAP are underway to define the features of these troublesome cases more precisely. There are some suggestions from the literature as to the possible origins for diagnostic difficulty in recognizing HSIL and SCC in TP preparations. Unlike LSIL morphology, which is virtually identical in conventional and TP preparations, HSIL cytomorphology has more subtle distinctive features in LBC preparations.[26] The authors of this prior study noted that HSIL in TP preparations more frequently presents as isolated smaller cells with a decreased nuclear size. Few data are available regarding the comparative difficulty in making a diagnosis of invasive SCC in conventional versus TP preparations due to the low prevalence of this cytodiagnostic category in screened populations.[4,5,7,22] A study of a large cohort of high-risk Costa Rican women suggested that the detection of SCC by TP may be challenging, since TP preparations were interpreted as invasive carcinoma in only 2 of 11 cases of invasive carcinoma, whereas conventional preparations identified 6 cases.[2] Squamous cell carcinoma may be overlooked in TP preparations because cells of nonkeratinizing SCC may resemble benign squamous metaplasia at low magnification, and the typical tumor diathesis of invasive malignancy is altered in TP and assumes the pattern of ''a clinging diathesis.''[26] In addition, TP preparations of SCC are often of low cellularity.[27]

The apparent increased difficulty in the interpretation of invasive SCC and HSIL in TP preparations may have significance both for educational or proficiency testing programs and in routine clinical practice. Previously, a study using PAP data showed that the precision of the diagnosis of HSIL, adenocarcinoma, and SCC on conventional preparations is significantly lower than the precision of the benign diagnoses and LSIL, even though the former diagnoses are the clinically most important diagnoses that can be made in a Papanicolaou test.[28] The current study suggests that the performance of participants on TP preparations for HSIL and SCC may face additional challenges over that for conventional preparations. Whether the challenge posed by TP preparations in the cytodiagnostic categories of HSIL and SCC is inherent to the technique itself or due to insufficient training and/or experience of participants cannot be determined. One study of the value of specific TP training concluded that prior exposure to TP preparations, and not overall work experience, correlates with interpretive performance on TP.[29] The rapidity of implementation of TP preparations, and consequently familiarity with the technique, has varied among large community hospitals and academic laboratories. In this study, however, any difference in performance by participants from the various laboratory settings cannot be determined.

In conclusion, overall TP preparations in the PAP generally are associated with significantly lower error rates than conventional smears for both validated and educational cases. However, interpretations of educational HSIL and SCC TP preparations are subject to a higher false-negative rate than educational conventional preparations, even though slides prepared by both methods have satisfied identical criteria for acceptance into the program. Similarly, participants were less able to recognize SCC in educational TP slides than in conventional slides, as shown by a higher error rate for exact matching to diagnosis. The reasons for these discrepant performances by TP slides are currently being investigated through a cytomorphologic study of TP HSIL and SCC slides.

References

1. Lee KR, Ashfaq R, Birdsong GG, Corkill ME, McIntosh KM, Inhorn SL. Comparison of conventional Papanicolaou smears and a fluid-based, thin-layer system for cervical cancer screening. *Obstet Gynecol.* 1997;90:278–284.
2. Hutchinson ML, Zahniser DJ, Sherman ME, et al. Utility of liquid-based cytology for cervical carcinoma screening: results of a population-based study conducted in a region of Costa Rica with a high incidence of cervical carcinoma. *Cancer (Cancer Cytopathol).* 1999;87:48–55.
3. Roberts JM, Gurley AM, Thurloe JK, Bowditch R, Laverty CRA. Evaluation of the ThinPrep Pap test as an adjunct to the conventional Pap smear. *Med J Aust.* 1997;167:466–469.
4. Limaye A, Connor AJ, Huang X, Luff R. Comparative analysis of conventional Papanicolaou tests and a fluid-based thin-layer method. *Arch Pathol Lab Med.* 2003;127:200–204.
5. Bernstein SJ, Sanchez-Ramos L, Ndubisi B. Liquid-based cervical cytologic smear study and conventional Papanicolaou smears: a metaanalysis of prospective studies comparing cytologic diagnosis and sample adequacy. *Am J Obstet Gynecol.* 2001;185:308–317.
6. Wilbur DC, Cibas ES, Merritt S, James LP, Berger BM, Bonfiglio TA. ThinPrep™ processor clinical trials demonstrate an increased detection rate of abnormal cervical cytologic specimens. *Am J Clin Pathol.* 1994;101:209–214.
7. Diaz-Rosario LA, Kabawat SE. Performance of a fluid-based, thin-layer Papanicolaou smear method in the clinical setting of an independent laboratory and an outpatient screening population in New England. *Arch Pathol Lab Med.* 1999;123:817–821.
8. Moss SM, Gray A, Legood R, Henstock E. Evaluation of HPV/LBC cervical screening pilot studies: first report to the Department of Health on evaluation of LBC (December 2002). Available at: http://www.cancerscreening.nhs.uk/cervical/lbc-pilot-evaluation.pdf. Accessed March 31, 2003.
9. Bolick DR, Hellman DJ. Laboratory implementation and efficacy assessment of the ThinPrep cervical cancer screening system. *Acta Cytol.* 1998;42:209–213.
10. Corkill M, Knapp D, Hutchinson ML. Improved accuracy for cervical cytology with the ThinPrep method and the endocervical brush-spatula collection procedure. *J Lower Genital Tract Dis.* 1998;2:12–16.
11. Papillo JL, Zarka MA, St John TL. Evaluation of the ThinPrep Pap test in clinical practice: a seven-month, 16,314-case experience in northern Vermont. *Acta Cytol.* 1998;42:203–208.
12. Sherman ME, Mendoza M, Lee KR, et al. Performance of liquid-based, thin-layer cervical cytology: correlation with reference diagnoses and human papillomavirus testing. *Mod Pathol.* 1998;11:837–843.
13. Weintraub J, Morabia A. Efficacy of a liquid-based thin layer method for cervical cancer screening in a population with a low incidence of cervical cancer. *Diagn Cytopathol.* 2000;22:52–59.
14. Park IA, Lee SN, Chae SW, Park KH, Kim JW, Lee HP. Comparing the accuracy of ThinPrep Pap tests and conventional Papanicolaou smears on the basis of the histologic diagnosis. *Acta Cytol.* 2001;45:525–531.
15. Schorge JO, Saboorian MH, Hynan L, Ashfaq R. ThinPrep detection of cervical and endometrial adenocarcinoma: a retrospective cohort study. *Cancer (Cancer Cytopathol).* 2002;96:338–343.
16. Hutchinson ML, Isenstein LM, Goodman A, et al. Homogeneous sampling accounts for the increased diagnostic accuracy using the ThinPrep processor. *Am J Clin Pathol.* 1994;101:215–219.
17. Chhieng DC, Talley LI, Roberson J, et al. Interobserver variability: comparison between liquid-based and conventional preparations in gynecologic cytology. *Cancer (Cytopathol).* 2002;96:67–73.
18. Sidawy MK, Tabbara SO. Reactive change and atypical squamous cells of undetermined significance in Papanicolaou smears: a cytohistologic correlation. *Diagn Cytopathol.* 1993;9:423–429.

19. Yeoh GPS, Chan KW, Lauder I, Lam MB. Evaluation of the ThinPrep Papanicolaou test in clinical practice: 6-month study of 16,541 cases with histological correlation in 220 cases. *Hong Kong Med J.* 1999;5:233–239.

20. Carpenter AB, Davey DD. ThinPrep Pap Test™ performance and biopsy follow-up in a university hospital. *Cancer (Cancer Cytopathol).* 1999;87:105–112.

21. Hutchinson ML, Agarwal P, Denault T, et al. A new look at cervical cytology: ThinPrep multicenter trial results. *Acta Cytol.* 1992;36:499–504.

22. Wilbur DC, Cibas ES, Merritt S, et al. ThinPrep processor clinical trials demonstrate an increased detection rate of abnormal cervical cytologic specimens. *Am J Clin Pathol.* 1994;101:1–7.

23. Zahniser DJ, Sullivan PJ. Cytyc Corporation. *Acta Cytol.* 1996;40:37–44.

24. Davey DD, Nielsen ML, Frable WJ, Rosenstock W, Lowell DM, Kraemer BB. Improving accuracy in gynecologic cytology. *Arch Pathol Lab Med.* 1993; 117:1193–1198.

25. Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ. 2001 consensus guidelines for the management of women with cervical cytological abnormalities. *J Lower Genital Tract Dis.* 2002;6:127–143.

26. Wilbur DC, Dubeshter B, Angel C, Atkison KM. Use of thin-layer preparations for gynecologic smears with emphasis on the cytomorphology of high-grade intraepithelial lesions and carcinomas. *Diagn Cytopathol.* 1996;14:201–211.

27. Clark SB, Dawson AE. Invasive squamous-cell carcinoma in ThinPrep specimens: diagnostic clues in the cellular pattern. *Diagn Cytopathol.* 2002;26:1–4.

28. Renshaw AA, Davey DD, Birdsong GG, et al. Precision in gynecologic cytologic interpretation: a study from the College of American Pathologists Interlaboratory Comparison Program in Cervicovaginal Cytology. *Arch Pathol Lab Med.* 2003;127:1413–1420.

29. Iverson DK. Impact of training on cytotechnologists' interpretation of gynecologic thin-layer preparations. *Diagn Cytopathol.* 1998;18:230–235.