Comparative Analysis of Cervical Cytology Screening Methods and Staining Protocols for Detection Rate and Accurate Interpretation of ASC-H:

Data From a High-Volume Laboratory in Turkey

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Background: *This study evaluated the effectiveness of the ThinPrep® Imaging System (TIS) and ThinPrep® Pap Stain (TPPS). A comparative analysis was conducted to determine the detection rates of atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H), the ASC:squamous intraepithelial lesion (SIL) ratio, biopsy follow-up for ASC-H in terms of the screening method used (manual screening [MS] vs. TIS screening [TISS]) and the staining protocol (regular Pap stain [RPS] vs. TPPS).*
Methods: *This study was performed over two periods. The RPS period included manually screened slides, whereas the TPPS period included TIS + manually screened slides. All data from the study periods were compared using statistical analysis.*
Results: *The detection rate of ASC-H was significantly higher during the TPPS period than during the RPS period (0.49% vs. 0.23%); this finding is in contrast to the insignificant difference between the screening method periods. The positive predictive value (PPV) of ASC-H cytodiagnosis for cervical intraepithelial neoplasia of grade 2 or more severe histologies was significantly different between manually screened and TIS slides (22.10% vs. 38.55%), in contrast to an insignificant difference between RPS and TPPS periods (37.14% vs. 29.77%).*
Conclusion: *Implementation of the TIS did not change the ASC-H detection rates appreciably. However, the new technology improved PPV for ASC-H cytodiagnosis and enabled the detection of true disease. Our laboratory statistics indicate that the TPPS is not a superior staining protocol and did not increase our diagnostic accuracy for ASC-H compared with RPS.* Diagn. Cytopathol. 2015;43:863–869. © 2015 Wiley Periodicals, Inc.

Key Words: cervical cytology; ASC-H; detection rate; ThinPrep® imaging system; ThinPrep® Pap stain

The Pap test is widely accepted as one of the most effective screening methods for detecting cervical precancerous lesions, which can be treated easily.[1–3] In practice, the Pap test is a complex system, and complex systems are subject to failure, particularly when they depend on human performance. Failures are caused by inadequate screening in 20–40% of Pap tests.[4]

The factors that contribute to cervical cytology screening challenges include "mistakes" in what is inherently an imperfect and highly subjective analysis,[5] visual searches for low-target prevalence,[6] inability to view every cell on any given slide,[7] monotonous and demanding activity, and a critical need to maintain high vigilance.[8,9] Correct diagnosis depends on an accurate interpretation of cells, especially small cells, which are difficult to categorize using a Pap test.[10]

ASC-H is a gray zone with regard to cytologic interpretation and reflects an uncertain diagnosis. The term was introduced

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in 2001 in the Bethesda System to define changes that are suggestive, but not diagnostic, of high-grade SIL (HSIL) in the absence of unequivocal SIL.[11] ASC-H is associated with histologic CIN2+ in approximately 60% (59%[12]−68%[13]) of women. These cells resemble immature squamous cells; they vary in size and shape and have high N/C ratios.[14] Such small cells are responsible for false-positive and false-negative reports.[15] To aid in the identification of these cells, computer-guided imaging for slide interpretation was recently developed. Only two systems are currently available for cervical cytology: the BD FocalPoint™ system and the ThinPrep® imaging system (TIS) (Hologic).[16] The TIS, approved by the U.S. Food and Drug Administration in 2003, is a fully integrated, interactive automated screening system that assists but does not replace cytotechnologists (CTs) and cytopathologists (CPs) in the primary screening and diagnosis of ThinPrep® Pap test slides.[7,8] The system consists of an image processor and automated review scopes (RSs). The slides are fully scanned by the image processor one by one. Then, the 22 fields of view (FOVs) most likely to contain abnormal cells (the largest and darkest cells) are chosen.[17] The CT reviews these FOVs (approximately 25% of the slide) saved from each slide either manually or by autoscanning using RS.[1,7,18] The TIS is designed for use with a proprietary ThinPrep® Pap Stain (Cytyc Corporation, Marlborough, MA, USA) (TPPS). This stain was developed to be "near stoichiometric" to DNA content, which is similar to Feulgen stain, and provides near-quantitative assessment of DNA content.[19] The quality of the stain allows for analysis of the integrated optical density of the nucleus, which is required to image the slide. This system combines imaging technology with human interpretive expertise.[8,9,20] Some authors have reported that computer assistance has the ability to reduce screening errors[16] and identify more abnormal cases compared to manual screening (MS) alone,[7,8,18,21–26] whereas other authors[21,26,27] have reported a decrease in the rate of SAs after using the TIS. The majority of available studies have found that the TIS has significantly higher sensitivity for histologically confirmed cervical intraepithelial neoplasia (CIN) of grade 2 or more severe histologies (CIN2+) (CIN 2 or 3 or carcinoma).[7,8,24,28] The system has been adopted by many laboratories across the world.[21,29] Although liquid-based cytology (LBC) has mostly replaced conventional Pap smears in cervical cancer screening in Turkey, computer-assisted imaging systems are still in their infancy. In Turkey, only our laboratory uses a fully automated image processor, although some centers do have the ThinPrep® Integrated Imager.

The objective of this study was to evaluate the short-term effects of implementing the TIS and TPPS in our high-volume laboratory. We specifically focused on the detection of ASC-H, which has a high positive predictive value (PPV) for the detection of clinically significant precancerous target lesions during cervical screening. For this purpose, a total of 93,492 ThinPrep® Pap tests were analyzed specifically and retrospectively for the following: a) the detection rate of overall squamous abnormalities (SAs); b) the detection rate of ASC-H; c) the ASC:SIL ratio, used as a quality-control measure;[7,30] and d) biopsy follow-up for ASC-H in terms of screening method (MS vs. TIS screening [TISS]) and staining protocol (regular Pap stain [RPS] vs. TPPS). To the best of our knowledge, this study is meaningful and differs from previously published studies in the following ways. First, this is the first report to specifically focus on and compare the effects of RPS and TPPS in LBC slides regardless of the screening method used. Second, only a few studies[21,23] in the literature have specifically focused on ASC-H during the TISS and TPPS periods. Third, this is the first report to evaluate the effects of implementing the TIS in Turkey.

Materials and Methods

This study was performed at the Acibadem Pathology Laboratory in Istanbul. The laboratory is accredited by the Joint Commission International, processes the highest number of Pap tests in Turkey, and employs 5 CTs and 4 CPs. Our laboratory introduced the TIS in January 2011. ThinPrep® slides were prepared using a ThinPrep® 5000 Processor (Hologic, Inc, Marlborough, MA, USA) and stained with RPS (Merck) during the pre-TIS period and TPPS during the post-TIS period using an automated stainer (Thermo Scientific Varistain Gemini). It is important to note that before routine use of the TIS, the manufacturer provided validation protocols for both the imager and the stain. All CTs and CPs were trained on the use of the RS and passed proficiency tests for both RS and TPPS. Following completion of the system validation, all the TP Pap test slides were processed by the TIS with 5 RSs. However, some slides were manually screened due to an insufficient number of RSs. The selection of the slides for MS was essentially performed randomly by the CTs. The assistance of the TIS was specifically stated in the reports of all cases that were processed by the imager. Each slide was read initially by the TIS. The 22 FOVs chosen by the imager were examined by a CT at an RS to locate possible abnormalities. If there was any suspicion of an abnormality in these FOVs, the slide was then screened in its entirety. The cellular changes detected in these 22 FOVs were compared with the cellular changes in the remainder of the slide, and additional marks made during MS or by autoscanning. If an abnormality was identified upon full screening, the slide was referred to a CP for diagnosis. In accordance with the manufacturer's instructions for the TIS, slides were interpreted as negative without additional screening if abnormalities were not identified in the 22 FOVs. Cytologic interpretations were made using criteria from the 2001 Bethesda System.[11]

This study was conducted over two periods for each screening method and staining protocol. The RPS period (January 2009–December 2010) included ThinPrep® slides that were manually screened. The TPPS period (January 2011–December 2012) included ThinPrep® slides that were TIS+ manually screened. The results of all cervical cytology diagnoses for the study periods were retrieved from the computer database (proprietary software called "Cellula" that was designed, built and run by Acibadem Information Technologies) retrospectively, and all cases were included in the study except unsatisfactory samples. Biopsy follow-up results (including cervical punch biopsies, endocervical curettings, loop electrocautery excision procedures, cold knife cones, and hysterectomy specimens) for ASC-H were also retrieved through computerized searches to determine the PPV. The most severe histologic diagnosis was considered the follow-up histologic diagnosis. CIN2+ was categorized as a positive reference standard. For this retrospective study, the rate of overall SAs, the rate of ASC-H, the ASC:SIL ratio, and follow-up histologic diagnoses of ASC-H category for CIN2+ during the study periods were compared between the screening methods (MS vs. TISS) and staining protocols (RPS vs. TPPS).

Statistical significance for all data tables was determined using the "Two Proportions"[31,32] and "χ^2"[33,34] analyses in Minitab Statistical Software.

Results

During the study period, 93,492 ThinPrep® Pap tests that were satisfactory for evaluation were evaluated in our laboratory. The rate of SAs was 9.59% ($n = 8{,}968$). The pre-TIS period consisted of 25,550 ThinPrep® slides stained with RPS (MS). The post-TIS period included 67,942 ThinPrep® slides stained with TPPS (TISS and MS) from the routine workload. The number of cases with SAs was 2,002 (7.83%) during the RPS period and 6,966 (10.25%) during the TPPS period ($p < 0.05$). During the TPPS period, the difference in the detection rates of SAs between MS and TISS was not significant (3,002/33,349 [9.00%] vs. 3,964/34,593 [11.45%]; $p < 0.05$). ASC-H ($n = 395$) constituted 0.42% of all Pap tests ($n = 93{,}492$) and accounted for 4.40% of all SAs ($n = 8{,}968$) during the study period.

Table I shows the detection rates of ASC-H during the staining and screening periods. The rate was significantly higher during the TPPS (Fig. 1a) period compared to the RPS (Fig. 1b) period (0.49% vs. 0.23%; $p < 0.001$). However, although the imager increased the detection rate of ASC-H compared with the manual period (180/34,593 [0.52%] vs. 155/33,349 [0.46%]), the increase in detection was not statistically significant ($p < 0.05$). ASC:SIL ratios during the staining and screening periods are summarized in Table II. Whereas the ratio was significantly decreased between the RPS and TPPS periods (1.89 vs. 1.45; $p < 0.001$), no significant difference was found between the MS and TISS periods (1.41 vs. 1.49; $p < 0.05$).

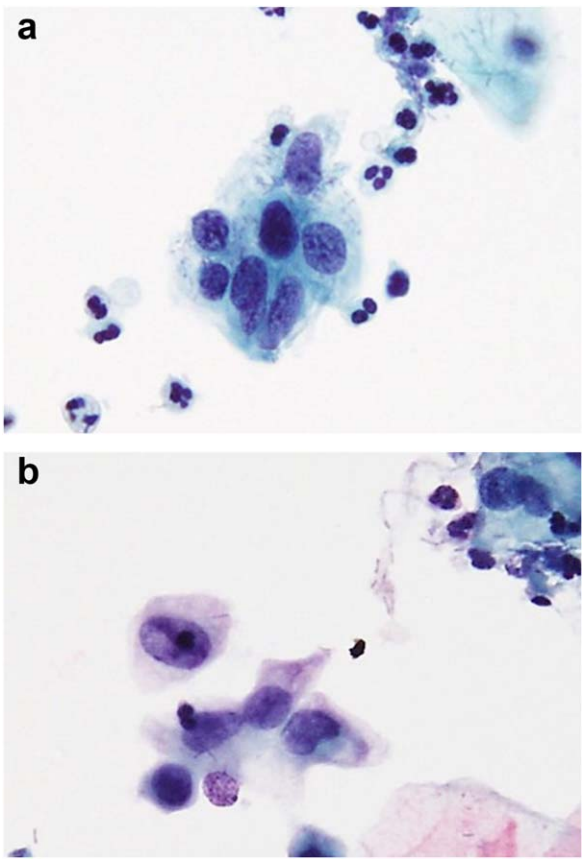

Fig. 1. Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion: (a) ThinPrep® Pap stain (original magnification 400×); (b) regular Pap stain (original magnification 400×). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

To determine the clinical significance of the increased detection rate of ASC-H, the rates of the histologically correlated cases were compared between each staining protocol and screening method. Follow-up data from subsequent biopsies were available for 213 patients (53.92%), all of whom were diagnosed with ASC-H. During the study period, the PPV for ASC-H cytology was 30.98% (66/213) in our laboratory. Biopsy correlation data for the staining and screening method periods are provided in Table III for comparison. As shown, the RPS was used to detect 60 ASC-H cases with 35 biopsies (correlation: 13 [37.14%]) and the TPPS was used to detect 335 cases with 178 biopsies (correlation: 53 [29.77%]). The significant increase in ASC-H interpretation using the TPPS compared with the RPS (0.49% vs. 0.23%; $p < 0.001$) did not reflect the PPV for CIN2+ (29.77% vs. 37.14%; $p < 0.05$). Table III shows that 21 out of 155 manually screened (22.10%) ASC-H diagnoses with 95

Table I. Comparison of ASC-H Rates Between Staining Protocols and Screening Method Periods

	ASC-H		*Total Pap tests*	
	No. of cases	*Detection rate (%)*		P *value*
Staining protocol periods				
Regular Pap stain	60	0.23	*25,550*	<0.001
ThinPrep Pap stain	335	0.49	*67,942*	
Screening method periods				
Manual screening	155	0.46	*33,349*	0.301
ThinPrep Imager system screening	180	0.52	*34,593*	

Table II. Comparison of ASC:SIL Ratios Between Staining Protocols and Screening Method Periods

	ASC:SIL	P *value*
Staining protocol periods		
Regular Pap stain	1.89 (1,311:691)	<0.001
ThinPrep Pap stain	1.45 (4,132:2,834)	
Screening method periods		
Manual screening	1.41 (1,759:1,243)	0.285
ThinPrep Imager system screening	1.49 (2,373:1,591)	

biopsies were confirmed compared with 32 out of 180 TIS screened (38.55%) ASC-H diagnoses with 83 biopsies. The difference in PPV based on the screening method was statistically significant ($p < 0.05$).

Discussion

A comparison of cervical cancer screening methods must include an evaluation of the sensitivity of CIN2+ detection, which has a strong tendency to progress into invasive carcinoma. Calculating the false-negative rate using a threshold of ASC has a stronger correlation with potential HSIL misses and better reflects the performance of the laboratory compared with low-grade SIL (LSIL).[17] For this reason, in this study, we focused on ASC-H, which has a high PPV for the detection of CIN2+.[12,13]

An unfortunate paradox of Pap test interpretation is that the higher the grade of dysplasia, the more difficult it can be to detect the abnormality. High-grade dysplastic cells tend to be smaller and thus more difficult to identify, andchromatin abnormalities may not be conspicuous.[4] In addition, abnormal cells can be sparse because the LBC specimen represents a sample of a sample.[4] Moreover, there are many morphologically similar HSILs. Therefore, not surprisingly, approximately 15% of HSIL cases are under-diagnosed and may be passed over as benign.[4,24] This study documented data for the TPPS and TIS separately, and the results also discussed separately in the following sections.

TPPS

Following the implementation of the new imager, an adjustment was required by both the CTs and the CPs to the new staining protocol. Although the TPPS is very similar in all respects to the RPS, it is possible that the proprietary stoichiometric stain, which presents darker and perhaps slightly more vivid nuclei, may have been a contributing variable in the imager cohort.[7,35,36] Roberts et al.[35] suggested that their CPs had initial adaptation problems with the TPPS that resulted in the interpretation of the darkness of some groups of cells as hyperchromasia, which is suggestive of a high-grade lesion. This issue resulted in more ThinPrep® cases being "overcalled" as possible high grade. Similarly, we experienced a significant increase in the number of cases of SAs (10.25% vs. 7.83%; $p < 0.05$) and ASC-H interpretation (0.49% vs. 0.23%; $p < 0.001$) using TPPS compared with RPS. This difference may be an indication that the "learning curve" for a new staining protocol (which has been emphasized by Lozano[7]) is partially responsible for our increased rates of ASC-H. However, this increase did not reflect a significant PPV for CIN2+ (29.77% vs. 37.14%; $p < 0.05$), in agreement with the results reported in Chivukula's study.[26] Whether the lack of a significant PPV can be clarified with an increased number of follow-up biopsies requires further study.

ASC:SIL ratios also decreased from 1.89 to 1.45 ($p < 0.001$) using the TPPS. This result indicates that we may have slightly under-reported SIL prior to using the TPPS and that the new staining protocol allowed for an increased detection of SIL.

Lozano et al.[7] suggested that the initial increase in ASC rates is partially due to the new staining protocol and partially to the focus of the TIS on "small cells." Because the data from staining protocols and screening methods were evaluated independently in our study, we confirmed that the effect of the TPPS was significant, whereas the effects of the TIS did not increase the rates of detection of ASC-H. Lapen et al.[19] reported that the TPPS produces results that are similar to those obtained using a commercially available stain (Richard–Allan) for cytologic diagnoses and that the diagnostic results from screening by the CTs showed 79.9% agreement between the TPPS and RPS. In our opinion, this rate of agreement is not sufficient. Thus, adaptation to and familiarization with this new staining protocol is necessary, and the level of experience of the screeners may play an important role in preventing conflicting results. Additionally, this finding indicates that the staining methodology plays a key role in the interpretive process. We agree with Lozano et al.[7] that cytology based on a visual representation is as much an interpretive art as a science.

TIS

When compared with MS, some authors [7,8,18,21,24–26,35–43] have noted the potential of the TIS to allow and force the

Table III. Comparison of Biopsy Confirmations (Predictive Value) Following ASC-H Diagnosis Between Staining Protocols and Screening Method Periods

	ASC-H				
	No. of cases	*No. of follow-up biopsies*	*No. of correlating biopsies*	*PPV (%)*	P *value*
Staining protocol periods					
Regular Pap stain	60	35	13	37.14	0.406
ThinPrep Pap stain	335	178	53	29.77	
Screening method periods					
Manual screening	155	95	21	22.10	0.016
ThinPrep Imager system screening	180	83	32	38.55	

CT to consider and concentrate on crucial atypical cells, enabling the detection of more diseases and reducing the false-negative rate in the laboratory; others have reported a decrease in the rate of SAs with the use of the TIS.[21,26,27] The results of our analysis showed no meaningful increase in the detection rate of SAs during the TISS period compared with MS (11.45% vs. 9.00%; $p < 0.05$).

Multipl studies have reported that the detection rate of ASC-H cells was increased using the TIS.[7,8,21,26,27,36–38,40,44] In contast, our results demonstrated that TIS primary screening did not significantly impact the ASC-H rate compared with MS (0.52% vs. 0.46%; $p < 0.05$); this result is in agreement with a similar finding by Roberts.[35] These data suggest that we had no difficulties in detecting ASC-H cells before the use of the TIS and that we did not have a serious "learning curve effect" for TIS, which has been emphasized in previous studies.[7,42]

Although the ASC:SIL ratio varies widely among and within laboratories,[45] it generally ranges between 1.3 and 3.0.[4,42] In our laboratory, the ratio was similar ($p > 0.05$) when the use of the imager (1.49) was compared with manual analysis (1.41). This result is comparable with those of other studies,[7,28,36,40,43,44] reporting the same ASC:SIL ratios before and after use of the TIS. Based on these findings, we can speculate that the implementation of the TIS did not significantly increase the cytologic detection of SAs compared to MS in our laboratory.

Although some studies have demonstrated that interpretation is not highly reproducible, ASC-H diagnoses have consistently been associated with histologic CIN2+ in 24–96% of patients.[11,12,46] In our study, the PPV for ASC-H was also within these limits (30.98%). Miller et al.[8] and Dziura et al.[21] reported that biopsy results confirmed a significant increase in the detection of CIN2+ for ASC-H cases in the imager cohort, which is in contrast to the reports of Ha et al.[40] and Koltz et al.[23] In this study, the difference in the proportion of correlated biopsies for ASC-H before and after TIS implementation was found to be significant (22.10% vs. 38.55%; $p < 0.05$). However, the increase in the detection rate of ASC-H cells did not reach the point of statistical significance when using the TIS. Moreover, our biopsy confirmation results suggest that TIS has improved the diagnostic accuracy for the cytologic ASC-H category compared with MS in our laboratory.

The data from this study are especially important because of the following: (1) We report our initial experience with the TIS and TPPS within 2 years of their introduction into a high-volume laboratory in Turkey. (2) This is the first report to specifically compare the effects of the RPS and TPPS in LBC slides regardless of the screening technique used. (3) This is one of only a few studies that have focused specifically on ASC-H that have a high PPV for the detection of clinically significant precancerous target lesions in cervical screening during both the TISS and TPPS periods. (4) This is the first report to evaluate the effects of implementing the TIS in Turkey.

However, this study has several limitations: (1) The biopsy follow-up data were only available for 53.92% of cases, all of whom were diagnosed with ASC-H. (2) Because this study was specifically focused on ASC-H, a PPV was not evaluated at the level of ASC-US, LSIL, and HSIL+. In conclusion, implementation of the TIS did not change ASC-H detection rates appreciably. However, the new technology improved the PPV for ASC-H cytodiagnosis and allowed for the detection of true disease, thereby avoiding false-positive cytologic diagnoses by our laboratory. Our laboratory statistics indicated that the TPPS is not a superior staining protocol and did not increase our diagnostic accuracy compared with RPS. In the near future, we plan to study the effect of implementing TIS and TPPS on PPV at the level of ASC-US, LSIL, and HSIL+.

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References

1. Dawson AE. Can we change the way we screen? The ThinPrep imaging system. Cancer 2004; 102:340–344.
2. Martin-Hirsch PL, Koilopoulos G Paraskevaidis E. Is it now time to evaluate the true accuracy of cervical cytology screening? A review of the literature. Eur J Gynaecol Oncol 2002; 23:363–365.
3. Renshaw AA. Measuring sensitivity in gynecologic cytology: A review. Cancer 2002; 96:210–217.
4. DeMay RM. The Pap Test. In: DeMay RM, editor. The Art & Science of Cytopathology. 2nd. ed. Vol:1. Hong Kong: ASCP Press, 2012. p 2–200.
5. Wilbur DC, Parker EM Foti JA. Location-guided screening of liquid-based cervical cytology specimens. A potential improvement in accuracy and productivity is demonstrated in a preclinical feasibility trial. Am J Clin Pathol 2002; 118:399–407.
6. Evans KK, Tambouret RH, Evered A, Wilbur DC Wolfe JM. Prevalence of abnormalities influences cytologists' error rates in screening for cervical cancer. Arch Pathol Lab Med 2011; 135:1557–1560.
7. Lozano R. Comparison of computer-assisted and manual screening of cervical cytology. Gynecol Oncol 2007; 104:134–138.
8. Miller FS, Nagel LE Kenny-Moynihan MB. Implementation of the ThinPrep® imaging system in a high-volume metropolitan laboratory. Diagn Cytopathol 2007; 35:213–217.
9. Della PP, Moresco L Giorgi RP. Health technology assessment report: Computer-assisted Pap test for cervical cancer screening. Epidemiol Prev 2012; 36:e1–e43. (Abstract).
10. Renshaw AA, Mody DR, Wang E, Haja J Colgan TJ. Hyperchromatic crowded groups in cervical cytology-differing appearances and interpretations in conventional and ThinPrep preparations. A study from the College of American Pathologists interlaboratory comparison program in cervicovaginal cytology. Arch Pathol Lab Med 2006; 130:332–336.
11. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda System: Terminology for reporting results of cervical cytology. JAMA 2002; 287:2114–2119.
12. Mokhtar GA, Delatour NL, Assiri AH, Gilliatt MA, Senterman M Islam S. Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion: Cytohistologic correlation study with diagnostic pitfalls. Acta Cytol 2008; 52:169–177.
13. Selvaggi SM. Reporting of atypical squamous cells, cannot exclude a high-grade squamous intraepithelial lesion (ASC-H) on cervical samples: Is it significant?. Diagn Cytopathol 2003; 29:38–41.
14. Nayar R Tabarra SO. Atypical squamous cells: Update on current concepts. Clin Lab Med 2003; 23:605–632.
15. Croll E, Rana DN Walton LJ. Hyperchromatic crowded cell groups in gynecological liquid-based cytology samples. Br J Biomed Sci 2010; 67:154–163.
16. Ikenberg H. Computer-assisted diagnostics in cervical cytology. Pathologe 2011; 32:476–483. (Article in German) (Abstract).
17. Elsheikh TM, Kirkpatrick JL, Cooper MK, Johnson ML, Hawkins AP Renshaw AA. Increasing cytotechnologists workload above 100 slides per day using the ThinPrep imaging system leads to significant reduction in screening accuracy. Cancer Cytopathol 2010; 118: 75–82.
18. Zhang FF, Banks HW, Langford SM Davey DD. Accuracy of ThinPrep imaging system in detecting low-grade squamous intraepithelial lesions. Arch Pathol Lab Med 2007; 131:773–776.
19. Lapen D, Mui K, Smith R Linder J. Validation of the ThinPrep® stain. Acta Cytol 2003; 47:854
20. Gibb RK,Martens MG. The use of liquid-based cytology in cervical cancer screening. Rev Obstet Gynecol 2011; 4:2–11.
21. Dziura B, Quinn S Richard K. Performance of an imaging system vs. manual screening in the detection of squamous intraepithelial lesions of the uterine cervix. Acta Cytol 2006; 50:309–311.
22. Eichhorn JH, Buckner L, Buckner SB, et al. Internet-based gynecologic telecytology with remote automated image selection. Resuls of a first-phase developmental trial. Am J Clin Pathol 2008; 129: 686–696.
23. Koltz BR, Russell DK, Lu N, Bonfiglio TA Varghese S. Effect of ThinPrep® imaging system on laboratory rate and relative sensitivity of atypical squamous cells, high-grade squamous intraepithelial lesion not excluded and high-grade squamous intraepithelial lesion interpretations. Cytojournal 2013; 10:6
24. Biscotti CV, Dawson AE, Dziura B, et al. Assisted primary screening using the automated ThinPrep imaging system. Am J Clin Pathol 2005; 123:281–287.
25. Davey E, d'Assuncao J, Irwig L, et al. Accuracy of reading liquid based cytology slides using the ThinPrep imager compared with conventional cytology: Prospective study. Bmj 2007; 335:31
26. Chivukula M, Saad RS, Elishaev E, White S, Mauser N Dabbs DJ. Introduction of the ThinPrep imaging system (TIS): Experience in a high volume academic practice. Cytojournal 2007; 4:6
27. Howard MT, Cohen DW, Underwood DL, Deeds DA Booth CN. Utilization of ASC-H, LSIL, cannot exclude HSIL (LSIL-H) and HSIL terminology following implementation of the ThinPrep Imaging System. Mod Pathol 2006; 20:71A
28. Quddus MR, Neves T, Reilly ME, Steinhoff MM Sung CJ. Does the ThinPrep Imaging system increase the detection of high-risk HPV-positive ASC-US and AGUS? The Women and Infants Hospital experience with over 200,000 cervical cytology cases. Cytojournal 2009; 6:15
29. Barroeta JE, Reilly ME, Steinhoff MM Lawrence WD. Utility of the Thin Prep Imaging system® in the detection of squamous intraepithelial abnormalities on retrospective evaluation: can we trust the imager?. Diagn Cytopathol 2012; 40:124–127.
30. Renshaw AA, Deschênes M Auger M. ASC/SIL ratio for cytotechnologists. A surrogate marker of screening sensitivity. Am J Clin Pathol 2009; 131:776–781.
31. http://support.minitab.com/en-us/minitab/17/topic-library/basic-statistics-and-graphs/hypothesis-tests/tests-of-proportions/about-2-proportions-test/
32. http://www.minitab.com/en-us/Published-Articles/Delve-Deeper-into-Survey-Data-with-Minitab-2-Sample-t-Tests,-Proportion-Tests,-ANOVA-and-Regression/
33. http://www.minitab.com/en-us/Support/Tutorials/Chi-Square-Analysis-Powerful,-Versatile,-Statistically-Objective/
34. http://support.minitab.com/en-us/minitab/17/topic-library/basic-statistics-and-graphs/tables/chi-square/chi-square-tests-in-minitab/
35. Roberts JM, Thurloe JK, Bowditch RC, et al. A three-armed trial of the ThinPrep imaging system. Diagn Cytopathol 2007; 35:96–102.
36. Papillo JL, St John TL Leiman G. Effectiveness of the ThinPrep Imaging system: Clinical experience in a low risk screening population. Diagn Cytopathol 2008; 36:155–160.
37. Duby JM DiFurio MJ. Implementation of the ThinPrep Imaging system in a tertiary military medical center. Cancer 2009; 117: 264–270.
38. Pacheco MC, Conley RC, Pennington DW Bishop JW. Concordance between original screening and final diagnosis using imager vs. manual screen of cervical liquid-based cytology slides. Acta Cytol 2008; 52:575–578.
39. Halford JA, Batty T, Boost T, et al. Comparison of the sensitivity of conventional cytology and the ThinPrep Imaging System for 1,083 biopsy confirmed high-grade squamous lesions. Diagn Cytopathol 2010; 38:318–326.
40. Ha SY, Lee YK Oh YL. Effectiveness of the ThinPrep Imaging System in the detection of abnormal cervicovaginal cytology: A practical experience in Korea. Acta Cytol 2013; 57:159–163.
41. Wilbur DC, Black-Schaffer WS, Luff RD, et al. The Becton Dickinson FocalPoint GS imaging system. Clinical trials demonstrate

significantly improved sensitivity for the detection of important cervical lesions. Am J Clin Pathol 2009; 132:767–775.

42. Thrall MJ, Russell DK, Bonfiglio TA Hoda RS. Use of the ThinPrep® Imaging System does not alter the frequency of interpreting Papanicolaou tests as atypical squamous cells of undetermined significance. Cytojournal 2008; 5:10
43. Schledermann D, Hyldebrandt T, Ejersbo D Hoelund B. Automated screening versus manual screening: A comparison of the ThinPrep imaging system and manual screening in a time study. Diagn Cytopathol 2007; 35:348–352.
44. O'Brian D, Brainard J, Chen L, Pork A Booth C. Comparison of HPV and follow-up data for ASC-H before and after implementation of the ThinPrep Imager system. Cancer Cytopathol 2006; 342
45. Renshaw AA, Auger M, Birdsong G, et al. ASC/SIL ratio for cytotechnologists: A survey of its utility in clinical practice. Diagn Cytopathol 2010; 38:180–183.
46. Nogara PR, Manfroni LA Consolaro ME. Cervical cytology of atypical squamous cells cannnot exclude high-grade squamous intraepithelial lesion (ASC-H): Histological results and recurrence after a loop electrosurgical excision procedure. Arch Gynecol Obstet 2011; 284:965–971.