Pathology (August 2013) **45(5)**, pp. 474–477

ANATOMICAL PATHOLOGY

A comparison of ThinPrep Imager-assisted with manual screening, and its place in the New Zealand cervical cancer screening program

MEE LING YEONG*†, ELIZABETH PRINGLE†, JOANNA STEWART‡ AND ERIN RETTER†

*Departments of *Histology, and †Cytology, Diagnostic Medlab Auckland, Ellerslie, Auckland, and ‡Epidemiology and Biostatistics, School of Population Health, Faculty of Medical and Health Sciences, University of Auckland, Tâmaki Campus, Glen Innes, Auckland, New Zealand*

Summary

Aims: Overseas studies have shown equivalent sensitivity and specificity between computer-assisted screening and manual screening, with increased screener productivity. This study was undertaken to test these in a New Zealand laboratory setting.

Methods: A total of 9232 slides were read manually alone, and following ThinPrep Imager-assisted screening, and the results compared. Two senior screeners and a cytopathologist reviewed the slides with discordant results.

Results: The detection rate for abnormalities was 7.30% for Imager-assisted screening and 7.83% for manual screening. The concordance in diagnosis of abnormalities ranged from 72.7% to 100% with the lowest concordance for high-grade abnormalities diagnosed by Imager-assisted screening. The rate of unsatisfactory smears with Imager-assisted screening is half that of manual screening. There was a screener productivity increase of 140%. In all but one case, abnormal cells were identified by the Imager but screeners varied in their interpretations.

Conclusions: Overall, Imager-assisted screening was as sensitive as manual screening, and more sensitive for high-grade lesions, with a halving of the rate of unsatisfactory smears. In the setting of the New Zealand cervical screening program, the initial screen by the Imager removes the need for a second, rapid rescreen required by the program for manual screening.

Key words: Concordance, manual screening, screening program, ThinPrep Imager.

Received 4 July 2012, revised 10 January, accepted 20 January 2013

INTRODUCTION

Screening for cervical cancer by microscopic examination of a smear sample spread directly onto a slide (conventional smear) has been in practice for several decades and until recently had remained largely unchanged. The screening of conventional smears is relatively insensitive, with only a reported 50% pick-up rate of abnormalities for each smear sample. Liquid-based cytology was developed to address some of the inherent difficulties resulting from the presence of blood, mucus and cellular debris.

A further development became available in 2003 with the introduction of computerised ThinPrep Imager (TPI; Hologic, USA) assisted screening, which operates on the principle of a highly standardised stoichiometric stain which stains nuclei with varying intensity depending on DNA content. The Imager scans the slide and marks 22 fields of vision (FOV) with the most densely stained nuclei. A screener assesses these fields and if no abnormal cells are identified, the slide is reported as normal. The presence of abnormal cells in any of the FOV would trigger a full screen and progress to further assessment.

The adoption of automated screening is a significant departure from manual screening and several reports which compare the two methods found equivalent sensitivity with a higher detection rate for high grade abnormalities with automated screening.[1–10] One finding that is consistent in most studies, if not all, is the significant increase in productivity, in many cases in the order of 100%.

The New Zealand cervical cancer screening program (NCSP) was established in 1991.[11] Between 1991 and 2000, the mortality from this cancer was reduced by 45.7%.[12] The screening process in this country follows strict guidelines, which are influenced by the relative insensitivity inherent in manual screening. An initial (primary) screener screens a smear, which is again assessed by a second screener who performs a rapid review (rapid reviewer). If no abnormality is detected by either screener, the smear is reported as normal. If an abnormality is detected by either screener, the smear is assessed by another senior scientist (collator) who performs a full screen, prior to referring the material to a cytopathologist for final reporting. Specific follow-up recommendations established by the NCSP accompany each smear (NCSP guidelines).

Thus, in the NZ cervical cancer screening program, a minimum of two screeners assess a smear if it is regarded as normal, while a smear with an abnormality is assessed by a total of four trained personnel.

The advent of automated screening presented the possibility of reducing the initial manual screeners from two to one, with the Imager performing the role of primary screener, while another screener assesses the 22 FOV.

The potential for reducing the staffing requirements for screeners while maintaining the same standards in screening was a critically important issue in light of the difficulty most laboratories experience in recruiting skilled screener staff, and the funding constraints that NZ laboratories were experiencing.

Our laboratory, Diagnostic Medlab (DML), processes about 130 000 cervical smears annually. Prior to 1 July 2009, when DML converted to 100% liquid-based cytology (LBC), about 40% were ThinPrep liquid-based samples. With up to 60 000 LBC samples a year, and an average of 10 years of experience among screeners in assessing ThinPrep samples, DML was in a

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: 10.1097/PAT.0b013e3283631d63

good position to pilot a study of automated screening in New Zealand.

AIMS AND OBJECTIVES

The objectives of this study were three-fold. The first was to investigate concordance of TPI-assisted screening and manual screening of the same LBC samples in the setting of our laboratory. The second was to determine if automated screening could be successfully adapted to the specific Operational Policy and Quality Standards (OP&QS) set out by the NCSP.[13] The third objective was to study the potential productivity gains of automated screening and, in line with this productivity, whether there were any ergonomic issues resulting from working with automation.

MATERIALS AND METHODS

As this study conforms to the standards established by the National Health and Medical Research Council (NHMRC) for ethical quality review,[14] ethics committee approval was not sought.

Prior to the utilisation of the TPI system, a two-step validation process was undertaken, according to guidelines established for ThinPrep Stain validation[15] and the TPI System (TPIS) validation.[16]

For the first step, a total of 100 consecutive slides with a wide range of diagnoses including inflammatory and specific infections, low grade and high grade intraepithelial lesions, abnormal squamous cells of uncertain significance, squamous and adenocarcinomas were stained with the ThinPrep stain, screened, and compared with the original diagnoses utilising the standard laboratory PAP stain. All screeners were blinded to the original diagnoses.

For the TPIS validation protocol, the same 100 slides were processed by the Imager and reviewed by a screener viewing the 22 FOV. This involved placing the slide on the review scope, which read the unique numeric identifier, with appropriate aligning of the fiducial markings present on each slide, which prompted the Imager to retrieve the coordinates of the 22 FOV. If no abnormalities were detected upon screening all FOV, the slide was signed out as normal. The detection of any abnormalities resulted in a full review, which was performed by a senior screener, using his/her own light microscope or the review scope.

All DML screeners and cytopathologists underwent training to read the stoichiometric stain required for LBC samples processed by the TPI. Technical staff was also trained in the highly standardised stain used in these samples. Six screeners of varying years of experience were trained in the screening of slides that were processed by the Imager and to screen these using the review microscopes.

All ThinPrep samples that were registered in the laboratory over a period of about 3 months from July to October 2008 were used for the study. These slides were stained with the standardised TPI stain and were processed through the TPIS. The slides were then screened manually in compliance with the NCSP OP&QS, using the standard procedure: primary screening, rapid review and reported as normal if no abnormalities were detected. A full rescreen by a senior screener was performed if there was an abnormality, and the slides referred to a cytopathologist for final reporting. Full rescreens were also performed on all cases where the risk of abnormality was known to be higher than that of the total screening population, where a full review is required by the OP&QS. These were smears from women with previous abnormal smears, suspicious clinical conditions, abnormal bleeding, observed cervical abnormalities, or women with immunosuppression. Cervical smears taken at sexually transmitted infection, colposcopy and oncology clinics, and unsatisfactory smears also require a full rescreen.

Following manual screening and reporting, the slides were cleaned of all screeners' marks, and read by the six screeners trained to use the review scopes. All screeners were blinded to the original reports. The Imager-screened slides were usually read a few days after the original manual reading. A screener looked at the 22 FOV identified by the Imager. If all FOV were normal, the slide was reported as normal with no further review. If any FOV showed an abnormality, the slide was fully rescreened by a second, senior screener, who then referred this to the cytopathologist for final reporting. This pattern of screening yielded two separate sets of results for Imager-assisted screening and manual screening for comparison at the conclusion of the study.

Slides that were processed and rejected by the Imager were manually screened and these were excluded from the study. In these cases, the Imager generated a report, providing information for the rejection. Additionally, each screener using Imager-assisted screening recorded the number of slides screened and the hours taken to screen these, and any ergonomic issues encountered.

All cytology reports were issued using the 2001 Bethesda System. Only reports generated by manual screening were reported to the NCSP.

Two senior scientists and a cytopathologist reviewed the slides that had discordant results. The reviews were conducted independently and then as a panel to reach a consensus. The reviews determined (1) if abnormal cells were detected and marked by the Imager and (2) the cytological diagnosis, applying standard morphological criteria.

For the final assessment of discordant diagnosis rates between Imager-assisted and manual screening, similar diagnoses that carry the same follow-up and management recommendations were regarded as concordant. Atypical squamous cells, possible high grade (ASH) was ranked similar to high grade squamous lesion, cervical intraepithelial neoplasia 2 or 3 (HS1), as both carry a recommendation for colposcopy; low grade squamous intraepithelial lesion (LS) was ranked similar to atypical squamous cells of undetermined significance (ASL), which prior to the review in guidelines resulted in a recommendation for a review in 6 months; and low grade squamous lesion with possible high grade lesion (LS/ASH) was ranked similar to HS1, both resulting in a recommendation for colposcopy.

The final discordant results were calculated after excluding these similar results in each category.

Results are discussed in four categories: Category 1, LS by TPI compared with ASH or HS1 by manual screening; Category 2, ASH or HS1 by TPI compared with LS by manual screening; Category 3, ASL by TPI compared with ASH/HS1 by manual screening; and Category 4: normal/inflammatory smears by TPI compared with any abnormal by manual screening. The results of the reviewers' evaluation are discussed.

Category 4 indicates an overall pick-up rate for abnormalities between the two arms of the study. Categories 1, 2 and 3 reflect the discordance of grade of abnormality where abnormalities were identified in both arms of the study.

RESULTS

The total number of cases available for reading by the TPI was 9455. Of these, 223 slides (2.4%) were rejected by the TPI and were read manually, disqualifying these from the study. A final total of 9232 slides were read successfully (Table 1).

Of these, 674 (7.3%) were identified as abnormal by TPI-assisted screening. An additional 49 cases were identified as abnormal by manual screening (7.8%). These abnormalities are summarised in Table 2 and detailed in Table 3, category 4.

Where an abnormality was detected in both arms of the study, in a proportion of the cases there was discordance in the interpretation of the type of abnormality, which is detailed in categories 1, 2, 3 (Table 3).

In category 1 (TPI LS versus manual ASH or HS1), reviewers agreed that six of the 10 cases fulfilled the cytological criteria for LS. The remaining four cases were considered possible high grade lesions (ASH or HS1).

In category 2 (TPI ASH/HS1 versus manual LS), reviewers identified all nine cases as being high grade lesions (either ASH or HS1).

Table 1 Number of cases read in the study

Total number of cases	9455
Total read successfully	9232
Unable to be read	223
Percentage unreadable	2.4%

Table 2 Abnormality rates by Imager-assisted screening and manual screening

Screening	*n*
Imager-assisted	
Total normal	8558
Total abnormal	674
Percentage abnormal	7.30%
Manual	
Total normal	8509
Total abnormal	723
Percentage abnormal	7.83%

In category 3 (TPI ASL versus manual ASH/HS1), reviewers agreed that four of seven cases were normal, one was an ASL and one was an ASH. One case could not be reviewed as the case slide was missing.

In category 4 (TPI normal versus manual abnormalities), the reviewers agreed that 38 of the total 49 cases were normal/inflammatory. The remainder were categorised as ASL (3), LS (3), AC4 (1). One AG (abnormal glandular cells) identified by manual screening was interpreted by the panel as showing endometrial cells only and included in the 38 normal/inflammatory group.

One case was interpreted by Imager-assisted screening as normal, but manual screening identified a single group of degenerate glandular cells that was reported as endocervical adenocarcinoma (AC4), subsequently confirmed by histology. This group of cells was not identified by the Imager. Four cases were not available for panel review.

In New Zealand, an adequacy code is used to denote the presence (S1) or absence (S2) of endocervical cells. TPI screening identified 719 cases as S2, against 537 by manual screening.

The number of smears showing insufficient numbers of squamous cells (unsatisfactory smears) by manual screening was 155 (1.68%) compared to 76 (0.82%) by TPI screening.

On an average day and using manual screening, a screener could comfortably screen about 50 ThinPrep slides as well as perform the usual laboratory duties required of them. Using the Imager, the range of slides the screeners were able to process per day was 86 – 140.6 with an average 120. This did not include screening slides that required a full rescreen, which was performed by a second screener.

No ergonomic issues were reported specific to the use of Imager-assisted screening.

DISCUSSION

In the study, 223 (2.4%) were labelled 'imaging not successful' by the TPIS. To enable the successful imaging of a slide, fiducial markings must be free from scratches or other defects, coverslips must be properly placed, and the cover slip media dry, slides must be clean and free of fingerprints, dust, debris and bubbles. The slide must be appropriately labelled and the label applied smoothly without overhang. Slides with dense bacterial vaginosis infection cannot be imaged.[17] In their Imaging System clinical trial, Biscotti *et al.*[3] showed an 'imaging not successful' rate of 7.1%. The low rate in this study reflects the care taken in the cover slipping and labelling process. Those slides that were not readable by the Imager were manually screened and excluded from the study.

The abnormality pick-up rate was 7.3% for TPI-assisted screening and 7.8% for manual screening. Among the abnormalities detected in both arms, if the diagnostic categories with only single cases were excluded, the concordance in diagnosis ranged from 72.73% to 99.97% with an overall concordance rate of 99.03%.

In all bar one case, panel review showed that abnormal cells were marked by the TPIS; the discordance in the arms of the study was a result of screener interpretation. The reviewers noted that single, small cells seen in high grade abnormalities were marked by the Imager, thus drawing the screeners' attention to these cells which may be hard to locate. This category yielded the lowest concordance rates between TPI and manual screening, with TPI screening showing a higher sensitivity for high grade lesions. This has been the finding in other studies.[1,5–7,9,18]

The one case in which the Imager failed to detect an abnormality was where manual screening identified a single group of degenerate glandular cells, which was reported as abnormal glandular cells. This was subsequently demonstrated by histology to have come from an adenocarcinoma. It is likely that the cells were not detected by the Imager because of their degenerate nature; however, no meaningful conclusions can be drawn from this one case in regard to the accuracy of Imager-assisted screening in detecting abnormal glandular cells. In a study of 39 cases identified as atypical glandular cells (AGC) or adenocarcinoma by manual screening, Imager assisted screening had failed to detect seven of these.[19] However, of the seven cases, only one was demonstrated to be adenocarcinoma. In four of the remaining six cases in which follow-up was available, two had subsequent normal readings, one had a hysterectomy which showed benign changes and one had a further result of AGC with no additional information. Two other studies have demonstrated that the Imager is effective in detecting abnormal glandular cells.[20,21]

Table 3 Discordant diagnoses and reviewer assessments

Category (*n*)	Diagnosis by TPI	Diagnosis by manual screening (*n*)	Reviewer assessment (*n*)
1 (10)	LS	ASH	LS (6), ASH/HS1 (4)
2 (9)	ASH/HS1	LS	ASH/HS1 (9)
3 (7)	ASL	ASH/HS1	Normal (4), ASL (1), ASH (1) 1 case not reviewed
4 (49)	Normal/Inflammatory	ASL (35), LS (10), ASH (2), AG (1), AC4 (1)	Normal/Inflammatory (38), ASL (3), LS(3), AC4 (1) 4 cases not reviewed

AC4, abnormal glandular cells consistent with adenocarcinoma; AG, atypical endocervical cells present; ASH, atypical squamous cells, possible high grade; ASL, atypical squamous cells of undetermined significance; HS1, high grade squamous lesion, cervical intraepithelial neoplasia 2 or 3; LS, low grade squamous intraepithelial lesion.

The cytology results were not compared with the corresponding histological diagnosis because histological assessment is subject to similar observer variables to cytological analysis, the histology samples are often taken at a time distant from the smear sample, and there are possible sampling differences between the histological and cytological specimens, leading to apparently discordant reports. Furthermore, the study was primarily intended to be a comparison of manual screening against TPI-assisted cytology screening from the perspective of the screener, in particular how TPI-assisted screening affects the screener's ability to detect and assess cytological abnormalities.

Our overall concordance rates are higher than in other studies. This may be due to the collective experience of a large group of experienced screeners in the laboratory. At the time of the study, there were 31 screeners who averaged 10–30 years in screening experience, with collective experience being one of the largest world-wide in screening ThinPrep liquid-based samples, of over 10 years since 1997.

The productivity using TPI-assisted screening increased from 50 LBC samples a day by manual screening to up to 140 a day with an average of 120 a day, while maintaining other activities in a screener's normal day. This represents a productivity increase of 140%. This does not take into account a proportion of full rescreens that are required if an abnormality is encountered which is performed by a second screener.

The NCSP requires a comment on the presence or absence of endocervical cells as a guide to smear takers. The adequacy category S2 which signals the absence of endocervical cells is more frequent in TPI-assisted screening, as these cells, if normal, would not be marked by the Imager. In these cases, the screener may perform a quick search for endocervical cells outside the FOV in order to comment on this.

The rate of unsatisfactory smears is halved from 1.68% to 0.82% by Imager-assisted screening. We consider this to be due to the Imager's ability to identify potentially abnormal cells even in material of limited cellularity.

The study lends further support to the increasing number of studies available that TPI-assisted cervical cancer screening is equivalent to manual screening, in many cases, with lower unsatisfactory smear rates, and higher detection of both low grade and high grade abnormalities.[1,4–7,9,18,22] These conclusions contrast with the MAVARIC study that concluded that Imager-assisted screening is less sensitive with an inconsequential increase in specificity compared to manual screening.[23]

TPI-assisted screening can be safely and successfully adapted for screening in the New Zealand setting, following the guidelines of the NCSP OP&QS. In this setting, with manual screening, a slide with an abnormality is assessed by four people before the report is issued or two if it is normal.

The introduction of an initial screen by the TPI removes the requirement for a rapid rescreen, but a second, senior screener should perform a full screen following the detection of an abnormality.

Our study has shown that the successful identification of abnormalities lies in the combined resources of the Imager and screener. Automation with the TPIS introduces a standardised and consistent first step in the screening for cervical abnormalities, but screener vigilance and expertise play a critical and integral role in the correct interpretation of cell abnormalities thus identified.

Acknowledgements: We thank Hologic for their contribution of materials, equipment and technical assistance for the study. We acknowledge Dr A. Farnsworth and Mrs A. Richards (Douglass Hanly Moir, Sydney, Australia) for their assistance and valuable advice, and Ms Alexis Brook, Amy Tam and Gael Westein for administrative services.

Conflicts of interest and sources of funding: Hologic supplied the ThinPrep Imager, materials and staff training for ThinPrep Imager-assisted screening.

Address for correspondence: Dr M. L. Yeong, Departments of Histology and Cytology, Diagnostic Medlab Auckland, 10 Harrison Road, Ellerslie, Auckland 1060, New Zealand. E-mail: myeong@dml.co.nz

References

1. 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: 309–11.
2. Bolger N, Heffron C, Regan I. Implementation and evaluation of a new automated interactive Image analysis system. *Acta Cytol* 2006; 50: 483–91.
3. Biscotti C, Dawson A, Dziura B. Assisted primary screening using the automated ThinPrep Imaging System. *Am J Clin Pathol* 2005; 123: 281–7.
4. Schledermann D, Hyldebrandt T, Ejersbo D. Automated screening versus manual screening. *Diagn Cytopathol* 2007; 35: 348–52.
5. Lozano R. Comparison of computer-assisted and manual screening of cervical cytology. *Gynecol Oncol* 2007; 104: 134–8.
6. Miller F, Nagel L, Kenny-Moynihan M. Implementation of the ThinPrep Imaging System in a high-volume Metropolitan laboratory. *Diagn Cytopathol* 2007; 35: 213–7.
7. Chivukula M, Saad R, Elishaev E. Introduction of the Thin Prep Imaging System (TIS): experience in a high volume academic practice. *CytoJournal* 2007; 4: 6.
8. Davey E, Erwig L, Macaskill P. Cervical cytology reading times: a comparison between ThinPrep Imager and conventional methods. *Diagn Cytopathol* 2007; 35: 550–4.
9. Papillo J, St. John T, Leiman G. Effectiveness of the ThinPrep Imaging System: Clinical experience in a low risk screening population. *Diagn Cytopathol* 2008; 36: 155–60.
10. Roberts J, Thurloe J, Bowditch R. A three-armed trial of the ThinPrep Imaging System. *Diagn Cytopathol* 2007; 35: 96–102.
11. National Screening Unit. *Cervical Screening in New Zealand. A Brief Statistical Review of the First Decade*. Wellington, NZ: National Cervical Screening Programme, Ministry of Health, Feb 2005. www.healthywomen.org.nz
12. Cervical Cancer Audit and the University of Auckland. *Cervical Cancer Audit Report. Screening of Women with Cervical Cancer 2000–2002*. Wellington, NZ; Ministry of Health, Nov 2004. www.moh.govt.nz/cervicalcanceraudit
13. Health Funding Authority. *National Cervical Screening Programme Interim Operational Policy and Quality Standards, October 2000*. Auckland: Health Funding Authority, Oct 2000. www.moh.govt.nz.
14. National Health and Medical Research Council. *When Does Quality Assurance in Health Care Require Independent Ethical Review? Advice to Institutions, Human Research Ethics Committees and Health Care Professionals*. Canberra: National Health and Medical Research Council, Feb 2003.
15. ThinPrep Imaging System Implementation Guide. A Step-by-Step Preparation Workbook. Section 2 – Stain Validation; 2.1–2.8.
16. ThinPrep Imaging System Implementation Guide. A Step-by-Step Preparation Workbook. Section 3 – System Validation; 3.1–3.8
17. ThinPrep Imaging System. Image Processor Operator's Manual.
18. Halford JA, Batty T, Duhig J, Lee C. Comparison of the sensitivity of conventional cytology and the ThinPrep Imaging System for 1,083 biopsy confirmed high-grade squamous lesions. *Diagn Cytopathol* 2009; 38: 318–26.
19. Jayamohan Y, Karabakhtsian R, Banks H, Davey D. Accuracy of ThinPrep Imaging System in detecting atypical glandular cells. *Diagn Cytopathol* 2009; 37: 479–82.
20. Sabo D, Shorie J, Biscotti C. Detection of adenocarcinoma using the ThinPrep Imaging System. *Cancer* 2008; 114: 7–12.
21. Friedlander MA, Rudomina D, Lin O. Effectiveness of the ThinPrep Imaging System in the detection of adenocarcinoma of the gynecologic system. *Cancer* 2008; 114: 7–12.
22. Barroeta JE, Reilly ME, Steinhoff MM, Lawrence WD. Utility of the Thin Prep Imaging System in the detection of squamous intraepithelial abnormalities of retrospective evaluation: can we trust the imager? *Diagn Cytopathol* 2010; 40: 124–7.
23. Kitchener HC, Blanks R, Dunn G, Gunn L. Automation assisted versus manual reading of cervical cytology (MAVARIC): a randomized controlled trial. *Lancet Oncol* 2011; 12: 56–64.