

A Three-Armed Trial of the ThinPrep Imaging System

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We compared the performance of the ThinPrep (TP) Imaging System (TIS) with manual reading of TP slides (TPM) and with manual reading of the paired conventional Pap smear (PS) in terms of sensitivity for and positive predictive value (PPV) of high-grade disease and productivity.

The study consisted of 11,416 routine PS and paired TP slides as well as 103 confirmed abnormal TP slides.

In terms of sensitivity for the detection of biopsy-confirmed high-grade disease, overall there was no statistically significant difference between TIS-screened TP (TPI) and TPM (81.1% vs. 86.8%). For the routine cases, TPI was significantly more sensitive than PS (73.4% vs. 57.8%).

In terms of PPVs for the cytologic prediction of high-grade disease, there was no statistically significant difference among TPI, TPM, and PS (75.6%, 73.9%, and 84.6%). For cytologic reports of possible high-grade disease, the PPVs were equivalent for TPI (45.0%) and TPM (37.0%) and there was no significant difference in PPVs between TPI and PS (61.3%). For TP slides, TIS screening showed a 27% productivity gain when compared with manual screening and a 54% productivity gain when compared with manual screening of PS slides.

Use of TIS showed productivity benefits when compared with TPM and both productivity and sensitivity benefits over use of PS. Diagn. Cytopathol. 2007;35:96–102. © 2007 Wiley-Liss, Inc.

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Liquid based cytology (LBC) has provided the opportunity to standardise the Pap test slide in a way, which was never possible with the conventional Pap smear (PS). In a decade of routine use, we and others have shown significant advantages in utilising LBC technology

with manual reading of LBC slides.^{1–3} The ThinPrep Imaging System (TIS), which was FDA approved in 2003 is an interactive automated screening system, enabling a proportion of TP slides to be archived as negative without full human screening. In the trial on which FDA approval was based, TIS-assisted screening showed equivalent sensitivity for the detection of high-grade squamous intraepithelial lesion (HSIL) to full manual reading of TP slides and showed a higher specificity for a prediction of HSIL. There were significant productivity gains.⁴

In Australia, LBC is used as an adjunct to PS (i.e., the PS slide is prepared first and the residual material on the sampling implement is placed in the TP vial), rather than in direct-to-vial mode as in USA and elsewhere. In 2002, the Australian Government, through its Medical Services Advisory Committee, determined that there was insufficient evidence to provide funding for LBC.⁵ Patients therefore choose to have the additional test and bear the cost themselves. At Lavery Pathology we have been offering adjunctive TP since mid 1996 and were the first Australian laboratory to do so. Since that time, we have received over 600,000 TP samples. Thirty to forty percent of women having a PS have a TP test as well. We reported our early results; in our first 35,560 specimens, there was a 12% increase in detection of high-grade lesions as a result of the addition of TP, with no loss of specificity and a 94% reduction in unsatisfactory reports.¹ Benefits of this order of magnitude have continued since that time.

Cytologist numbers in Australia are not increasing to meet workplace demands, partly because of the perceptions that the job is both tedious and stressful and partly because of a reduction in the number of training programs at universities in Australia. Any technology with the potential to improve productivity without sacrificing quality is therefore worth considering.

When TIS became available in Australia, we decided to undertake a trial of the system in our laboratory. Our primary aim was to compare TIS with current normal practice, that is manual screening of TP slides, in terms of

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sensitivity, specificity, and productivity. As a secondary aim, we compared TIS with manual screening of PS.

Methodology

Six weeks prior to commencement of the trial of TIS, the TP Stain was introduced into the laboratory and a validation process was undertaken, according to Cytyc Corporation's protocol. Nineteen of 34 screening staff were trained on TIS. They were selected to represent the general range of skill and experience within our laboratory. Screening experience ranged from 3 to 37 yr.

Over a 9-wk period (February to April 2005), 11,416 routinely received samples were processed through the three arms of the trial: PS (manually read), manually read TP (TPM), and imager-processed TP (TPI) (Fig. 1). In addition, 103 extra TP slides were added to the TPM and TPI arms to ensure the presence of sufficient abnormalities. These 103 TP slides were prepared from our TP vial archive and were all from women with histologically confirmed high-grade abnormalities (HSIL, adenocarcinoma in situ (AIS), or carcinoma). Seventy one were HSIL, 3 HSIL + AIS, 9 AIS, 15 adenocarcinoma, and 5 squamous cell carcinoma (SCC). Each of these slides was checked prior to the study by two senior cytologists to confirm that diagnostic high-grade material was present on each slide. These 103 seeds were introduced in a random fashion to the routine workload, with dummy request forms and clinical data to prevent recognition of the seeded cases as such. The pathologists were aware that seeding was occurring but could not identify seeded cases. Cytologists were unaware that seeding was occurring. No seeds were introduced to the PS arm.

Each TP slide was first processed through the TPI arm. A cytologist at a review scope examined just the 22 fields chosen by the imager. A determination was first made whether the slide was satisfactory for assessment and then, whether the slide was negative or not. If there was any suspicion of abnormality in the 22 fields or the slide was suspected of being unsatisfactory for assessment, the slide was completely screened, as per Cytyc protocol. If abnormality was found on full screening, the slide was checked by a senior cytologist and then referred to a pathologist for a TPI report. The TP slide was then completely cleaned and processed through the TPM arm, being read by one or more cytologists and seen by a pathologist if any degree of abnormality was found, before a TPM report was made. The PS was read in the same fashion. Identical clinical information and medical history were available in each arm. Each slide was reported using the Australian Modified Bethesda System 2004 (AMBS 2004)⁶ (Table I). For the purposes of the trial, each of the three reports was entered separately into a database. The report for the referring practitioner was a combined report incorporating the most serious findings of the three re-

ports. For each patient, a different cytologist was involved with each arm of the trial, with no knowledge of the results of the other two arms. At the time of the trial, we had fewer than three full-time equivalent gynecological cytopathologists in the department. Hence in some cases, pathologist interpretation of each of the three arms may not have been totally independent.

Our main outcome measure was histologic high-grade disease. Histologic follow-up was obtained from our own gynecological histopathology service as well as from Pap test registers. The worst histopathology result within 9 months of the end of the trial was recorded. Follow-up was confined to final cytologic reports in the high-grade and possible high-grade categories (HSIL, Possible HSIL, AIS, Possible AIS/Adenocarcinoma, Squamous cell carcinoma, Adenocarcinoma), because these are the only categories in which there was a uniform recommendation for colposcopy. Comparisons based on histologic follow-up of cytologic reports of LSIL, Possible LSIL, and Atypical glandular cells of undetermined significance were not undertaken because of the bias introduced by the selective nature of the subset biopsied.

For confirmed high-grade disease, the cytology reports in each arm were classified into three categories:

1. Correct cytologic reports: high-grade or possible high-grade cytologic reports.
2. Cytologic undercalls: cytologic reports of LSIL, Possible LSIL, or Atypical glandular cells of undetermined significance.
3. False negatives (FN): cytologic reports of Negative or Unsatisfactory.

Sensitivity calculations were based on the proportion of histologic high-grade cases in which a correct cytologic report was made.

The finding of a FN (because of follow-up of high-grade or possible high-grade cytologic reports in another arm or arms) prompted review of the appropriate slide. In broad terms, a FN report was attributed to sampling error, in which the abnormality was not represented on the slide despite careful retrospective review; or to screening/interpretation error, in which the cytologist or pathologist failed to see or appreciate the nature of abnormal cells which were present.

Specificity for each arm was expressed in terms of a positive predictive value (PPV) for cytologic reports in the high-grade and possible high-grade categories. The seeds in the two TP arms were excluded from these calculations.

Although histologic follow-up was not sought for the Possible LSIL and LSIL categories, we recorded the rates of reporting of these categories for each arm. We also recorded the proportion of reports of 'No endocervical component present.'

Finally, productivity was assessed by comparing the average screening time per slide. Each cytologist was

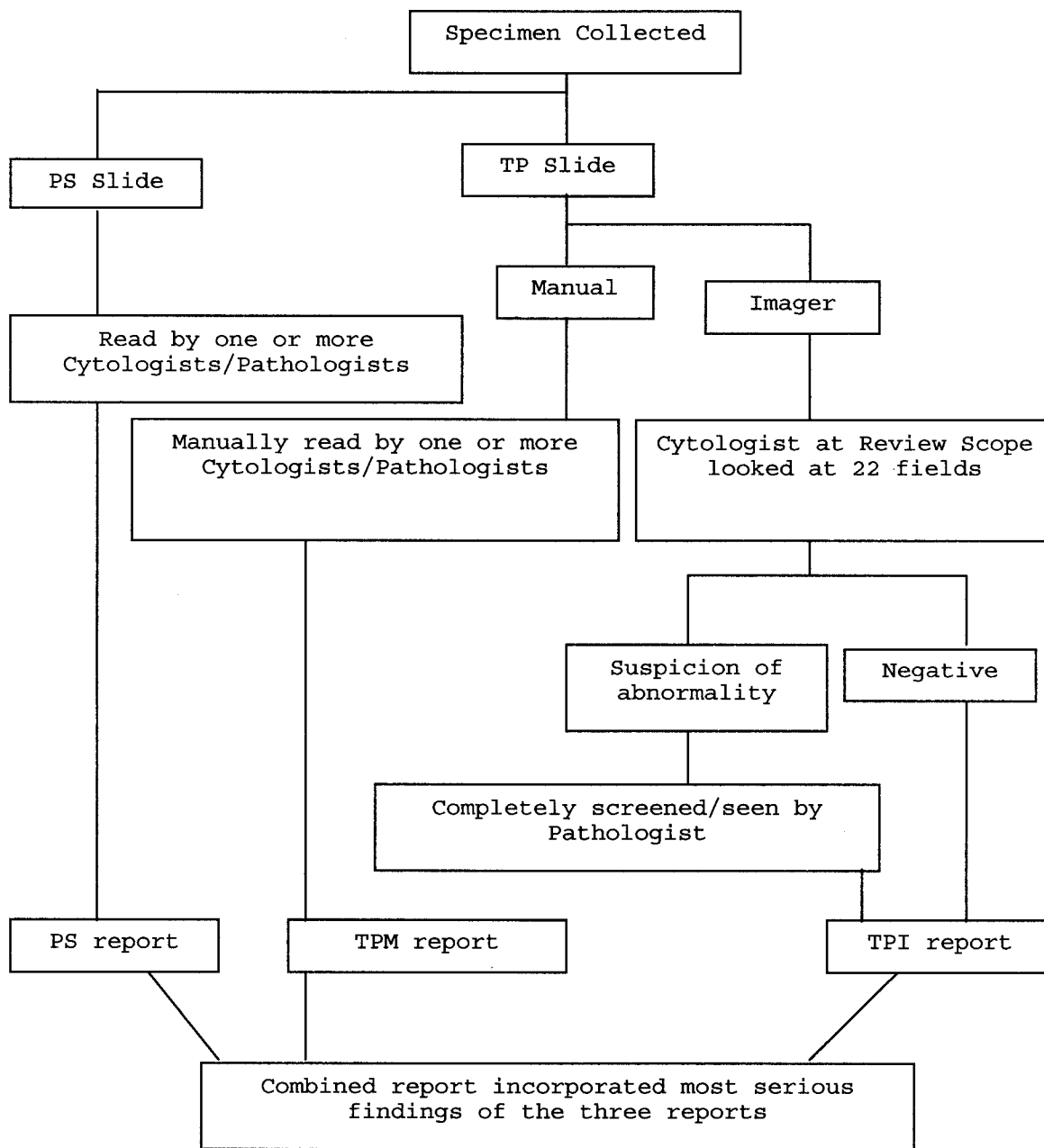


Fig. 1. Flow diagram illustrating the conduct of the trial.

required to record the time taken screening slides. For the TPI arm this included both time at the review scope and time spent fully screening those slides which required it. Time spent checking previously screened slides was not included. The times were totalled and an average screening time per slide obtained.

Results

Of all TP slides, 96.3% were able to be processed by TIS. TP slides were rejected by the imager for three rea-

sons: poor cellularity, excessive blood and technical problems, in particular the presence of air bubbles under the coverslip. Rejected slides were excluded from the analyses which follow.

Eighty-four percent of TP slides in the TPI arm were deemed negative without full human screening. The remaining 16% were fully screened by a cytologist.

Table II shows the cytologic reports made, in each of the three arms, for the 109 histologically confirmed high-grade lesions from the routine workload. Table III shows

Table I. Australian Modified Bethesda System 2004 With TBS Equivalent and Standard Recommendations

AMBS 2004	TBS 2001	Recommendation
Squamous abnormalities		
Possible LSIL	ASC-US	No uniform recommendation
LSIL	LSIL	Colposcopy in some circumstances
Possible HSIL	ASC-H	
HSIL	HSIL	Colposcopy
SCC	SCC	Colposcopy
Glandular abnormalities		
Atypical endocervical/glandular cells of undetermined significance	Atypical endocervical/glandular cells of undetermined significance	Repeat smear ^a
Possible high-grade glandular lesion	Atypical glandular cells probably neoplastic	Colposcopy
Endocervical adenocarcinoma in situ	Endocervical adenocarcinoma in situ	Colposcopy
Adenocarcinoma	Adenocarcinoma	Colposcopy

^aThis was the recommendation at the time of trial. The current recommendation is colposcopy.

Table II. Cytologic Reports for 109 Biopsy-Confirmed High-Grade Lesions in 11,416 Routine Cases

	TPI	TPM	PS
Negative/Unsat	10	3	28
Possible LSIL	5	3	5
LSIL	14	8	13
Possible HSIL	16	23	16
HSIL	60	66	41
SCC	1	1	1
Atypical glandular cells	0	0	0
Possible high-grade glandular lesion	2	4	3
AIS	1	1	2
Adenocarcinoma	0	0	0
	109	109	109

Table III. Cytologic Reports for 103 Biopsy-Confirmed High-Grade Seeded TP Slides

	TPI	TPM
Negative/Unsatisfactory	4	6
Possible LSIL	3	3
LSIL	4	5
Possible HSIL	7	6
HSIL	53	56
SCC	9	9
Atypical glandular cells	0	0
Possible high-grade glandular lesion	3	0
AIS	8	5
Adenocarcinoma	12	13
	103	103

the cytologic reports made, in each of the two TP arms, for the 103 seeded high-grade cases. Table IV combines these two sets of data for the two TP arms, to show an overall sensitivity (including routine cases and seeds) for the correct report of high-grade disease. Overall sensitivity for the TPM arm was 86.8% and for the TPI arm 81.1% ($P > 0.05$). Table V summarizes the data in Table II for TPI and PS arms, to show sensitivities of 73.4% and 57.8%, respectively, in the 11,416 routine cases ($P = 0.016$). Table VI shows the sensitivities for all histologically confirmed high-grade cases, by histologic result.

Table IV. Cytologic Reports by Category for 212 Biopsy-Confirmed High-Grade Lesions in TPI and TPM Arms, Including Both Routine Cases and Seeded Slides

Report category	TPI (%)	TPM (%)
False negative (negative/unsatisfactory)	14 (6.6)	9 (4.2)
Cytologic undercall (possible LSIL/LSIL/atypical glandular cells)	26 (12.3)	19 (9.0)
High-grade or possible high-grade (HSIL, possible HSIL, SCC, possible high-grade glandular lesion, AIS, adenocarcinoma)	172 (81.1)	184 (86.8)
Total	212 (100)	212 (100)

Table V. Cytologic Reports by Category for 109 Biopsy-Confirmed High-Grade Lesions in TPI and PS Arms, Including Only Routine Cases

Report category	TPI (%)	PS (%)
False negative (negative/unsatisfactory)	10 (9.2)	28 (25.7)
Cytologic undercall (possible LSIL/LSIL/atypical glandular cells)	19 (17.4)	18 (16.5)
High-grade or possible high-grade (HSIL, possible HSIL, SCC, possible high-grade glandular lesion, AIS adenocarcinoma)	80 (73.4)	63 (57.8)
Total	109 (100)	109 (100)

We compared the number of FN reports in each arm. When seeds are included (Table IV), there were 14 false negatives in the TPI arm and 9 FN in the TPM arm ($P > 0.05$). This included 3 (2 of them seeds) which were FN on both. Without seeds (Table V), there were 10 FN in the TPI arm and 28 FN in the PS arm ($P < 0.001$), including 4 which were FN on both.

Examination of the 14 FN (10 HSIL, 4 AIS) in the TPI arm revealed one (HSIL) to be a so-called 'location error,'⁷ in that, even on careful retrospective review, no abnormality of any degree can be identified in any one of the 22 FOV presented to the cytologist at the review scope. In 11 cases (8 HSIL, 3 AIS), abnormality was present in the 22 fields on review, but the cytologist at the review scope did not recognise this and made the

Table VI. Number (Percentage) of Each Histologic Category With Correct Cytologic Report, i.e., High-Grade or Possible High-Grade (Routine and Seeded Cases for TPI and TPM Arms and Routine Cases Only for PS arm)

	TPI (%)	TPM (%)	PS (%)
HSIL	138/174 (79)	151/174 (87)	57/103 (55)
SCC	6/6 (100)	6/6 (100)	1/1 (100)
AIS	7/11 (64)	7/11 (64)	2/2 (100)
AC	18/18 (100)	17/18 (94)	3/3 (100)
HSIL + AIS	3/3 (100)	3/3 (100)	0/0 (100)

Table VII. Positive Predictive Values (PPV) for Cytologic Reports of High-Grade Disease in 11,416 Routine Cases

	TPI	TPM	PS
Total no.	85	98	55
No. (%) with histo follow-up	82 (96.5)	92 (93.9)	52 (94.5)
No. with high-grade histology	62	68	44
Positive predictive value for those with histo follow-up (%)	75.6	73.9	84.6
PPV 2004 (%)	N/A	80	84

incorrect decision to archive the slide as negative. In two cases (1 AIS, 1 HSIL), the cytologist recognised the possibility of an abnormality in the 22 fields, made the correct decision to fully screen the slide, but then failed to appreciate the presence of a high-grade abnormality on the slide, reporting it as Negative.

The TPM arm had 9 FN (4 HSIL, 4 AIS, 1 adenocarcinoma) and all of these were screening errors i.e. abnormality was present on the slide but was either missed or misinterpreted on screening. Eight (4 HSIL, 4 AIS) were reported as Negative and one (adenocarcinoma) as Unsatisfactory (because of insufficient cellular material).

There was a total of 28 FN (all HSIL) on the PS arm. One half of these were screening errors in which an abnormality present was either missed or misinterpreted. The other 50% were sampling errors, in which, even on careful retrospective review, no abnormality can be seen on the PS slide, indicating that, while the abnormality was sampled (cells were present on the TP slide), abnormal cells were not present on the conventional PS. Thirteen of these were reported Negative and one Unsatisfactory (because of insufficient cellular material).

Tables VII and VIII present the PPVs for cytologic reports in the high-grade and possible high-grade categories respectively. PPVs for our laboratory in 2004 are presented in both tables, for comparison. For cytologic high-grade reports, there was no statistically significant difference between TPI and TPM ($P > 0.05$) and between TPI and PS ($P > 0.05$). Comparison with 2004 shows results similar to the trial results.

For possible high-grade cytologic reports, there was no statistically significant difference between TPI and TPM ($P > 0.05$), or between TPI and PS ($P > 0.05$). However,

Table VIII. PPV for Cytologic Reports of Possible High-Grade Disease in 11,416 Routine Cases

	TPI	TPM	PS
Total no.	49	82	38
No. (%) with histo follow-up	40 (81.6)	73 (89.0)	31 (81.6)
No. with high-grade histology	18	27	19
Positive predictive value for those with histo follow-up (%)	45.0	37.0	61.3
PPV 2004 (%)	N/A	66	60

Table IX. Rates of Reporting of LSIL Possible LSIL for 11, 416 Routine Cases

Report	TPI (%)	TPM (%)	PS (%)
Possible LSIL	3.8	4.5	1.8
LSIL	2.9	2.7	1.6

there was a significant difference between TPM and PS ($P = 0.023$).

Comparison with 2004 shows a higher PPV for TP in 2004, to a value equivalent to the PPV for PS, both in 2004 and in the trial.

Table IX shows reporting rates for Possible LSIL and LSIL categories. Both TPI and TPM show an increase in Possible LSIL and LSIL reporting over the PS. The rates were similar for TPI and TPM.

An endocervical component was absent in 31.3% of TPI arm reports, 28.9% of TPM arm reports, and 16% of PS arm reports.

Mean screening times per slide for each arm were as follows: PS 7.40 min, TPM 4.71 min, and TPI 3.42 min.

Discussion

In undertaking this trial, we hoped to obtain a clear answer to our question: “Should we continue to screen TP slides manually or utilize TIS?” We believed that if TIS-assisted screening did not sacrifice sensitivity or specificity for high-grade lesions and enabled improvement in productivity, then we would institute TIS as a routine part of our laboratory process. A secondary aim was to compare performance of TIS-processed TP slides with the performance of the conventional PS, read in the conventional manual fashion.

Overall, TPI and TPM showed equivalent sensitivities for the detection of high-grade disease and TPI sensitivity was significantly higher than that of PS.

Sensitivity for each arm of the trial depended on the type of histologic high-grade abnormality. Sensitivities for SCC, adenocarcinoma, and combined lesions were very high in both TP arms, while sensitivity for the detection of AIS was relatively lower, at 64% for each TP arm. We have previously found that detection of AIS on TP presents some new challenges, including a smaller

amount of abnormal material on the slide and a reduction in the classical architectural features seen on PS.⁸ While the former may possibly be rectified by the use of direct-to-vial TP, the latter necessitates specific educational activities and ongoing training and reinforcement. Interestingly, a small study of cervical glandular lesions published only as an abstract, showed that while TIS-assisted screening effectively detected these lesions, pure AIS cases had relatively few FOV containing atypical glandular cells, compared to invasive adenocarcinoma cases.⁹ Meaningful comparison with PS arm for these less common lesions is not possible because of the very small numbers in the routine caseload.

The total number of FN reports in TPI arm and TPM arm did not significantly differ. There were three broad categories of FN in the TPI arm. One case was a 'location error'⁷ and this slide has been made available to Cytoc Corporation for analysis. Most of the FN reports were due to failure by the cytologist at the review scope to identify that abnormal material of some degree was present in at least one of the 22 FOV. While we cannot accurately retrospectively analyze the thinking of the cytologist at the time of viewing the slide at the review scope, careful analysis of the cases suggests two possible contributing mechanisms: abnormal material is not necessarily centered in the FOV and the 22 FOV do not necessarily show the worst material on the slide. Both these factors were taught and reinforced during the Cytoc training program for cytologists, undertaken prior to commencement of the trial. However despite this training, it appears that these factors necessitate a shift in the thinking and/or screening technique of the cytologist and so require considerable reinforcement during the learning process. That the abnormal cells are not necessarily centred in the FOV requires cytologists to modify their typical search pattern. Typically, during screening, cytologists examine most of the field only in peripheral vision, and only one or two areas within each field are fixated in foveal vision for close attention. An abnormal cell is less likely to be detected by peripheral vision if it is toward the edge of the field, an effect that in routine screening may be compensated for by overlap of adjacent screening fields.¹⁰ In TIS-assisted screening, the cytologist must make an effort to search beyond the centre of the field, attending to several parts of the field in turn. Such a search pattern includes elements of a serial search, which is slower and more laborious than cytologists' typical search pattern. During times of fatigue or distraction, the cytologist may slip back into the accustomed peripheral vision search pattern and so miss abnormal cells near the edge of the field. That the worst material is not necessarily represented in the 22 FOV requires awareness by the cytologist that minor abnormality in a FOV may herald more severe abnormality elsewhere.

In a small minority of cases, the cytologist made the correct decision to fully screen the slide, but then failed to appreciate the presence of a high-grade abnormality on the slide. This probably cannot be attributed to any factors in the TIS process, but probably represents screening error as occurs in routine manual screening.

False negatives in the TPM arm were all due to either screening or interpretation errors by the cytologist or pathologist. In no cases was there a sampling error i.e., in every case abnormality was present on the slide.

The number of PS FN reports was significantly higher than for TPI (for the routine caseload) and included both sampling and screening/interpretation errors. This is in contrast to both TP arms, in which there were no sampling errors. These data lend support to the claim that the use of TP reduces both sampling error and screening/interpretation error when compared with PS.

The PPVs were very similar for the three trial arms for high-grade cytologic-reports. These PPVs were similar to the PPVs for high-grade cytologic reports obtained for TP and PS in 2004.

For possible high-grade cytology reports, there was no significant difference in the PPV between TPI and TPM or between TPI and PS. However, the PPV for TPM was significantly lower than the PPV for PS. Our own experience and published Australian literature suggest that the PPV for possible high-grade reports is in the order of 30–70%.^{11,12} The PS PPV was at the upper end of this range and this may relate to the relatively low sensitivity of the PS in this trial. The PPVs for TPI and TPM were in the mid to lower range and both were lower than the TP PPV obtained in our laboratory in 2004. We believe the major reason for this interesting anomaly is the new TP stain. While this stain is very similar in all respects to the traditional Pap stain, it is subtly but noticeably darker. We believe our cytologists had some initial teething problems with the new stain, interpreting the darkness of some groups of cells as hyperchromasia, suggestive of a high-grade lesion. This resulted in more TP cases (in both arms) being 'overcalled' as possible high-grade. The effect of the new stain was more marked in the TPM arm because all groups and sheets were seen, providing greater opportunity to 'overcall' when compared with the TPI arm, in which relatively fewer such groups were seen by the cytologist. If our hypothesis is correct, we anticipate that with continued familiarization, the PPV for TP will increase. We plan to carefully monitor this trend.

We have been aware, since we first introduced TP in 1996, that its use increases the reporting of Possible LSIL and LSIL categories. This appeared to be maintained with the use of TPI. Again it is our intention to closely monitor any trend in this area.

In analyzing productivity issues, over 96% of all TP slides were able to be processed by TIS, leaving fewer

than 4% to require full manual screening. Of the slides able to be processed by TIS, use of TIS-assisted screening reduced the average screening time per slide by 27%. When we compared TIS-assisted screening of TP slides with manual screening of PS, the reduction in mean screening time was 54%. These productivity gains were lower than we would have anticipated. Once again we continue to monitor this parameter and would anticipate with increased familiarization with TIS, mean screening times would reduce. Anecdotally we are already noticing this trend.

Comparison with the clinical trial data on which FDA approval of TIS was based⁴ was undertaken. TIS in that trial showed equivalent sensitivity for HSIL to manual TP screening, as did our study, but in contrast to our results, a prediction of HSIL in the trial carried a higher specificity than manual TP screening. These results were based on adjudicated cytologic opinions as the 'gold standard,' while our 'gold standard' was histology. In addition, our productivity gain was modest when compared with their reported doubling of cytologists' daily workload. A recently published study comparing manual and imager-read TP slides showed increased sensitivity for TIS with no loss of specificity. However, as the manual TP cohort was historical, some of the sensitivity improvements may be attributed to the effect of recent intensive TIS training.¹³ We are unaware of any published trial comparing TIS with PS.

Our trial revealed that, under our normal laboratory conditions, TIS-assisted screening of TP slides showed no reduction in sensitivity for the detection of high-grade disease, compared to manual screening of TP slides. There was no difference in specificity of reports of high-grade or possible high-grade disease. There was however a reduction in the specificity of reports of possible high-grade disease compared to 2004 and this is an area of continued study for us. The productivity gain was modest but real and we anticipate further productivity gains in the future. In view of this generally favourable outcome, we made the decision to utilise TIS as our preferred screening mechanism of TP slides in our laboratory.

Although comparison between TPI and PS was a secondary aim of this trial, we have shown that TIS-assisted screening of TP slides showed significantly improved sensitivity for the detection of high-grade disease over the conventional PS. Specificity was not reduced in high-

grade or possible high-grade categories. Productivity gains were significant. These data may prove useful in future determinations in Australia regarding the replacement of the conventional Pap smear by LBC.

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