Int J Gynecol Cancer 2003, **13,** 804–811

A real time optoelectronic device as an adjunct to the Pap smear for cervical screening: A multicenter evaluation

A. SINGER*, M. COPPLESON†, K. CANFELL‡, V. SKLADNEV‡, G. MACKELLAR‡, N. PISAL* & A. DEERY§

*Departments of Gynaecology, *The Whittington Hospital, London, UK and †Royal Prince Alfred Hospital for Women and Babies, Sydney, Australia; ‡Polartechnics Limited, Sydney, Australia; and §The Royal Free Hospital, London, UK*

Abstract. Singer A, Coppleson M, Canfell K, Skladnev V, Mackellar G, Pisal N, Deery A. A real time optoelectronic device as an adjunct to the Pap smear for cervical screening: A multicenter evaluation. *Int J Gynecol Cancer* 2003;**13:**804–811.

We report on the results from a multicenter trial for a real time optoelectronic device as an adjunct to the Pap smear for cervical screening. TruScreen (Polartechnics Limited, Sydney, Australia) is an automated device which measures the response to optical and electrical stimulation of the cervix and returns a screening result in real time. Analysis was performed on a group of 651 subjects recruited at 10 centers. Cytology and histology analyses were performed by centralized laboratories, with the cytology classification performed according to the Bethesda 2001 system. The sensitivities for histologically confirmed CIN 2/3 lesions by TruScreen, Pap, and TruScreen/Pap combined were 70% (95% CI: 67–74), 69% (CI: 65–72), and 93% (CI: 91–95), respectively. For histologically reported CIN 1, the sensitivities of the TruScreen, Pap, and combined test were 67% (CI: 63–70), 45% (CI: 41–49), and 87% (CI: 84–89). The improvement in sensitivity for the combined test compared to the Pap smear alone was significant ($P = 0.002$). Because TruScreen and cytology detect partly different but overlapping groups of CIN cases, the adjunctive combination provides very high CIN detection rates.

KEYWORDS: cervical screening, optoelectronic device, real time screening.

Address correspondence and reprint requests to: Professor Albert Singer, Department of Gynaecology, The Whittington Hospital, London N19 5NF, UK. E-mail: albert.singer@whittington.nhs.uk.

Contributors: Albert Singer, Malcolm Coppleson and Karen Canfell designed the study, analyzed the results, and drafted the paper. Victor Skladnev and Geoff Mackellar were responsible for the design of the TruScreen expert system, and provided an encrypted output version of the device for the study. Narendra Pisal critically revised the paper. Alastair Deery provided centralized review readings for histologic results.

Conflict of Interest Statement: This study was funded by Polartechnics Limited, Sydney, Australia. Professor Singer, Dr. Pisal and The Whittington Hospital are recipients of research grants from Polartechnics Limited. Professor Singer is a member of the Polartechnics Limited Scientific Advisory Committee and receives honoraria in recognition of this role. Professor Coppleson was formerly Medical Director of Polartechnics Limited. Cytologic analysis was performed under contract with the participating laboratory.

Organized cytologic screening programs have been successful in reducing overall mortality from cervical cancer[1]. However, a single cytologic smear suffers from sensitivity limitations[2] and the success of current screening programs relies heavily on multiple retesting for the detection of slowly developing cervical intraepithelial neoplastic (CIN) lesions. As many as 47% of women who develop cervical cancer may report an adequate screening history[3], demonstrating that cytologic sampling and analysis techniques are not fail-safe, even when multiple tests are performed over a period of years. The adjunctive use of a complementary test technology has the potential to improve detection rates for high grade intraepithelial lesions and in turn to increase overall screening sensitivity for CIN. Adjunctive test methodologies currently under

evaluation include human papillomavirus (HPV) DNA testing and optical or optoelectronic detection devices. Optically based devices offer the advantage of real time diagnosis, allowing the clinician to immediately counsel and manage the patient.

The TruScreen [Polarprobe] (Polartechnics, Sydney, Australia) is a real time device using electrical and optical signals to classify cervical tissue with an expert system approach[4,5]. An expert system is a computerized device programmed to mimic the diagnostic capability of human specialists. The TruScreen incorporates a portable console connected to a probe-shaped handpiece (Fig. 1). The distal tip of the handpiece is covered with a 5-mm diameter single use sensor element designed to protect against cross-infection, that is applied to the cervix. The device uses a combination of biosensors including directly reflected light, backscattered light, and electrical decay curves. Tissue is illuminated at four discrete wavelengths in the visible and infrared regions of the spectrum. In addition, the system incorporates electrical measurements of decay curves where the rate of electrical decay is inversely proportional to the degree of abnormality on the cervix. Pulses of 0.8 V are applied for 100 microseconds, and the electrical decay curve is assessed by sampling the magnitude at various points and by integrating the area underneath the curve. The optical and electrical measurements are repeated at the rate of 14 times per second and various parameters are extracted from each of the biosensor signals. The information is filtered, sampled, and processed by a microcomputer within a portable console to extract the parameters of greatest value for tissue discrimination. Tissue discrimination software classifies the tissue on the basis of the values of the multiple parameters.

During the examination, "stop/go" lights on the handpiece tell the operator to move the tip of the probe to a tissue spot, stop for the measurement to be performed, and then proceed to the next tissue spot. This sequence is repeated until the ectocervix and the portion of the lower endocervix exposed by the vaginal speculum have been covered. After the operator has signaled completion of the examination by pressing a button on the handpiece, the screening result is calculated and printed from the console. TruScreen is capable of classifying approximately 16 different basic cervical tissue types as well as transitions between different tissue types[4]. The expert system has been "trained" to recognize various normal and abnormal cervical tissue types using a previously obtained database of over 1500 patients collected from a geographically diverse range of centers. The system has been designed to recognize tissue changes characteristic of preneoplastic disease, and therefore the training dataset for abnormal tissue including lesions manifesting cellular differentiation abnormalities, abnormal mitotic figures, and/or nuclear changes. The device is not trained to recognize the cytopathic changes associated with HPV infection as abnormal, unless these are also associated with preneoplastic changes. This gives the device the potential to distinguish between latent HPV infection (including infection with low risk viral types) and the changes associated with progressive infection with high risk HPV types. Following primary classification, the specific tissue types are grouped in a manner useful for cervical screening, and hence the "worst case" tissue

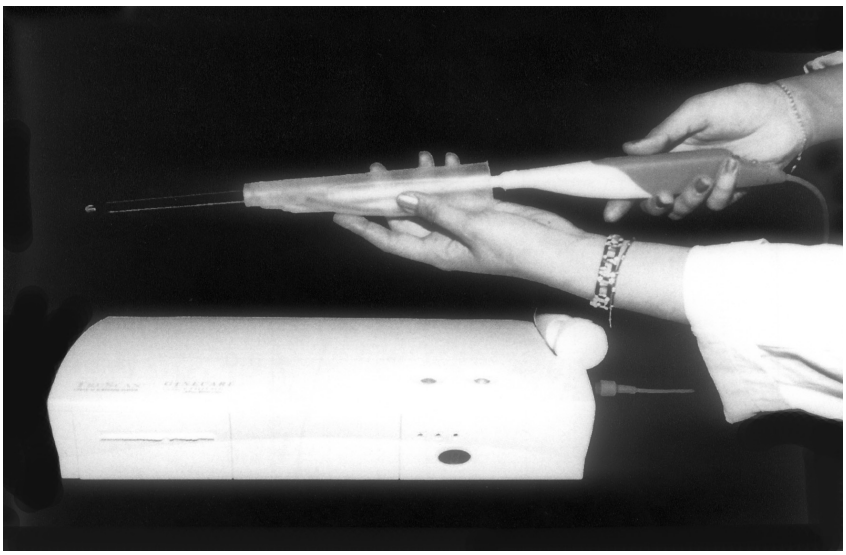

Fig. 1. The TruScreen Real Time Optoelectronic Device.The TruScreen system consists of a portable console, a handpiece and a single use sensor. The photograph depicts the single use sensor being fitted to the handpiece.

type seen on the cervix determines the final device output. The initial model of the TruScreen returns one of two possible final patient screening results: "normal" (normal squamous epithelium, columnar epithelium, physiologic metaplasia, or latent HPV-related changes) or "abnormal" (CIN 1–3, invasive cancer).

This study examined TruScreen performance as an adjunct to the Pap smear in the hands of multiple users and in two countries. Adjunctive use in this context involves performing the two tests during the same session and considering the results of both tests when determining management. If either or both tests are positive for detection of an abnormality, immediate colposcopy should be considered. In general, the most conservative evaluation of the adjunctive benefits of a new test involves an assessment of performance in the presence of a high quality cytologic smear. The quality of the smear is known to be influenced by sampling methodology, control of smear reading processes, and the cytologic classification system. In this study, sampling was performed by experienced gynecologists, reading was performed in a quality-controlled laboratory setting, and the recently published Bethesda 2001 system[6] was used for cytological classification.

Patients and methods

Objectives

The objectives of the study were to assess the sensitivity and specificity of a combined test regime where TruScreen is used adjunctively with the Pap smear, and to compare these results with those obtained using the Pap smear alone.

Participants

The study involved the recruitment of 769 subjects in 10 centers in the UK and Australia. Ethics committee approval was obtained in each institution with all subjects providing signed informed consent. Two groups of subjects were used: I) volunteers recruited via advertising in Sydney and London, with advertising performed through local and national press and leaflet handouts in urban shopping centers. Volunteers were asked to attend one of seven participating family planning or gynecological practices (in Sydney) or the colposcopy clinic at the Whittington Hospital (in London) for a 10–20 minute study session, which included the TruScreen examination and sampling for the Pap smear followed by colposcopy. Volunteers were compensated for time and travel costs, as appropriate to the setting. If a suspected abnormality was identified colposcopically, volunteers were referred for further management including biopsy and/or treatment, as appropriate; II) patients referred to the colposcopy clinic for the evaluation of a previous borderline/ASCUS or abnormal Pap smear, follow-up after treatment, or evaluation of another gynecological condition unrelated to cervical smear status. The dual-test TruScreen/Pap screening procedure was performed prior to colposcopy, with biopsy and/or treatment performed in the same session if clinically indicated. This "enriched" population had a higher underlying CIN prevalence rate and thus increased the statistical power of the assessment of test sensitivities. Participating colposcopy clinics were the Whittington and Whipps Cross Hospitals, London, UK; and Royal Prince Alfred Hospital for Women and Babies and the Royal Hospital for Women, Sydney, Australia.

All subjects were over 18 years of age and were willing and able to sign the informed consent. Exclusion criteria for the study were a recent (<6 weeks) Pap smear, current menstrual period, current or recent pregnancy (<4 months postdelivery), previous total hysterectomy, and surgical treatment to the cervix within the previous 3 months.

Sample size calculation

The study sample size was calculated on the basis of an ability to detect an absolute CIN 2/3 sensitivity difference of at least 10% between the combined TruScreen/Pap test and the Pap smear alone. In order to perform a prior calculation of the sample size, the following assumptions were made: study enrichment rate of 25%, underlying CIN 2/3 prevalences of 0.5% and 25% in the volunteer and colposcopy clinic populations, and a Pap smear sensitivity of 70% for CIN 2/3 detection.

Elimination of bias

The TruScreen and Pap smear tests were performed without the aid of colposcopic visualization, in order to duplicate routine use in the primary care setting. In routine use the TruScreen returns an instantaneous result on a printout, but for the purposes of the study the result was encrypted using a predetermined coding protocol, and the encryption coding was varied throughout the study to prevent clinician decoding of the result. The encryption coding was performed in order to eliminate possible verification bias associated with prior knowledge of the TruScreen

result while performing colposcopy and at the time of making the decision on the biopsy site.

Cytology analysis

Cytology samples were collected using a plastic cervical broom which was rotated with the central bristles positioned in the canal, to obtain both endocervical and ectocervical samples. In accordance with standard practice[7,8] and at the clinician's discretion, a cytobrush was also used for deeper canal sampling. The cellular sample was prepared according to standard clinical procedures. Cytology analysis for all centers was performed by a centralized independent laboratory (Douglass Hanly Moir Laboratory, Sydney, Australia). Slides were read as per standard screener/checker laboratory procedures and were subject to the laboratory's usual quality control systems. Before sending to the laboratory, slides were recoded in order to mask the center of origin and clinician. The slide codes were assigned in a random fashion in order to prevent unmasking due to batching effects. A maximum 20% in each batch of slides sent to the laboratory was obtained from the colposcopy clinic population. This ensured that the laboratory evaluated all slides in a screening context, even though the study population was artificially enriched with a higher disease loading through the inclusion of the colposcopy clinic patients. The information provided on the Pap smear request form was standardized and controlled, and included only the patient age, menopausal status, last menstrual period, and whether or not an IUD was placed *in situ*. In accordance with the Bethesda 2001 cytology classification system for cytology analysis[6], atypical squamous cells (ASC) were interpreted as either ASC-H (ASC – cannot exclude high grade) or ASC-US (ASC – Uncertain Significance). For the reporting of Pap smear performance results, an abnormality threshold of ASC-H was used. The choice of the Bethesda 2001 system used in conjunction with a quality controlled screener/checker laboratory program provided a high quality screening Pap smear for the study comparison.

Colposcopy and biopsy procedures

Colposcopy was performed with 3–5% aqueous acetic acid and Lugol's iodine solution. The colposcopic impression was recorded, and biopsies were taken of any colposcopically suspicious areas according to local clinical guidelines, although clinicians were encouraged to consider biopsying even marginally suspicious areas. If more than one suspicious area was observed, multiple punch biopsies were taken. A separate histology slide was prepared for each punch biopsy taken.

Histology analysis

Histology slides from all participating centers were sent to the Royal Free Hospital, London, for review by one of the authors (AD). Slides were recoded such that the reviewing histologist was not aware of the center of origin or whether the patient was originally recruited via volunteer-based advertising or through the colposcopy clinic referral system. In addition, the histologist was not given any associated clinical information about the patient such as TruScreen, Pap smear, or colposcopy results or patient history.

The CIN 1–3 histologic classification system was used as the reference standard for the study in preference to the dichotomous low and high grade squamous intraepithelial lesion (LSIL/HSIL) classification for two reasons. Firstly, review histology was performed in the UK, where the CIN classification is routinely used. Secondly, the histologic classification of LSIL includes potentially benign HPV-related changes, which the TruScreen device is not designed to flag as abnormal. For this study therefore only lesions with verified preneoplastic changes (ie, CIN 1–3) were included in the abnormal category.

Data entry and analysis

After decoding the slide reference codes and the TruScreen encrypted result, data entry was performed by trained personnel. All study data were entered into the ClinTrial database package (ClinSoft Inc., Lexington, MA, USA). Re-entry of 10% of the data, selected at random, was performed for data verification purposes. Analysis was performed using the STATA statistical software package (Stata Corp., College Station, TX, USA).

Statistics

Point estimates and 95% CIs for sensitivity and specificity results were calculated for each screening test and for the adjunctive test combination. Tests for paired samples were used to derive point estimates and confidence intervals for the differences between screening test performances, and McNemar's χ^2 test was used to derive the associated *P*-values for the significance of the differences.

Results

A total of 769 subjects were recruited into the study. An unequivocal reference diagnosis was obtained for 85% of subjects, and therefore these 651 subjects were included in the analysis of results. The reasons for a lack of unequivocal reference diagnosis were predominately that a biopsy was taken but slides were not available for independent review or a colposcopic impression of CIN 1–3 was recorded, but no biopsy was taken during the study session. In a small portion of study subjects (0.3%) histology was unsatisfactory. Of the remaining 651 subjects used for the analysis, 485 (75%) were volunteers and 166 (25%) were colposcopy clinic patients. A total of 141 (22%) were recruited in the UK and 510 (78%) were recruited in Australia. One hundred twenty eight (18%) were biopsied, with the remainder allocated a reference diagnosis of either "Normal" or "HPV effect/Atypia" according to the colposcopic impression. Within the volunteer population, the underlying prevalences of CIN 2/3 and CIN 1 according to the reference diagnosis were 0.6% and 1.0%, respectively. Within the colposcopy clinic population, the prevalences of CIN 2/3 and CIN 1 were 31% and 14%, reflecting the referral policies and the relatively high risk inner-city referral zones for the colposcopy clinics participating in the study.

The number of cases correctly classified by each screening regime under study (TruScreen, Pap, and the combined test) are given in Table 1. Point estimates for sensitivity and specificity, with 95% confidence intervals and corresponding false negative and false positive rates, are given in Table 2. Unsatisfactory examination rates for both the Pap smear and TruScreen were 0.6%.

The absolute improvement in the point estimate of CIN 2/3 sensitivity for the combined test (sensitivity 93%) vs. Pap alone (sensitivity 70%) was 24% (95% CI: 11–37; $P = 0.002$) for the significance of the difference. The corresponding relative reduction in the false negative rate for CIN 2/3 was 77%. For CIN 1, the absolute improvement in sensitivity for the combined test (sensitivity 87%) vs. Pap alone (sensitivity 45%) was 42% (95% CI: 18–66; $P = 0.002$) for the significance of the difference. The corresponding relative reduction in the false negative rate for CIN 1 was 76%. The absolute decrease in specificity for the combined test (specificity 80%) vs. the Pap alone (specificity 95%) was 15% (95% CI: 11–19; $P < 0.001$) for the significance of the difference.

The Negative Predictive Value (NPV) of a screening test is the ratio of true screen-negative results to all screen-negative results. Similarly, the Positive Predictive Value (PPV) is the ratio of true screen-positive results to all screen-positive results. Both measures are intrinsically dependent on the prevalence of disease in the population, as well as the sensitivity and specificity of the screening test. For a low prevalence disease such as CIN, the NPV will tend towards very high values (>99%) for any test, since most of the screen- negatives will be true negatives in the low prevalence scenario. Because of the dependence of NPV and PPV on population prevalence, they cannot be estimated from our study, due to the enriched design.

Figure 2 depicts the study results for the detection of CIN 2/3 lesions on the same diagram as the corresponding Receiver Operating Characteristic (ROC) curve for cytology. The ROC curve is the most comprehensive method of assessing the performance of a screening test, as it shows the dynamic trade-off between sensitivity and specificity as the threshold for calling the test result "positive" is moved. The cytology ROC curve was derived from the US Association for Health Care Policy and Research meta-analysis of Pap smear results[2] and thus represents the performance of the "standard" Pap smear. As the sensitivity/specificity trade-off is adjusted, the operating point on the ROC moves along the curve. The study smear result is shown to have superior

Table 1. Classification of cervical status by each screening regime

		Number correctly classified (%)		
Reference diagnosis[a]	Total in population	TruScreen	Pap	TruScreen/Pap combined
CIN 2/3	54	38 (70%)	37 (69%)	50 (93%)
CIN 1	30	20 (67%)	13 (43%)	26 (87%)
HPV effect/atypia	152	100 (66%)	145 (95%)	98 (64%)
Normal	415	338 (81%)	396 (95%)	332 (80%)

CIN, Cervical Intraepithelial Neoplasia.

[a]The CIN 1–3 histological classification system was used as the reference standard for the study because the histological classification of LSIL includes benign HPV-related changes, which the TruScreen device is not designed to flag as abnormal. Therefore, only lesions with verified preneoplastic changes were included in the abnormal category.

Table 2. Sensitivity, specificity, false positive, and false negative results for each screening regime[a]

	TruScreen	Pap	TruScreen/Pap combined
Sensitivity for CIN 2/3	70% (CI: 67–74)	69% (CI: 65–72)	93% (CI: 91–95)
Corresponding false negative rate for CIN 2/3	30%	31%	7%
Sensitivity for CIN 1	67% (CI: 63–70)	45%[b] (CI: 41–49)	87% (CI: 84–89)
Corresponding false negative rate for CIN 1	33%	55%[b]	13%
Specificity for Normal	81% (CI: 78–84)	95% (CI: 94–96)	80% (CI: 76–84)
Corresponding false positive rate for Normal	19%	5%	20%

[a]CIN = Cervical Intraepithelial Neoplasia; CI = 95% Confidence Interval.
[b]One Pap smear in this histologically determined category was unsatisfactory. The case was discounted for the analysis of Pap smear sensitivity and false negative rate, but not for the analysis of the combined test where the TruScreen result for that case was taken to represent the adjunctive outcome.

performance when compared to the standard Pap smear, since the data point representing the performance of the study smear is above that of the standard curve, and the confidence intervals do not overlap the standard curve. Similarly, the combined TruScreen/Pap test is shown to have superior performance to the standard smear, as represented by the curve. However, the trade-off between sensitivity and specificity for the combined test is adjusted towards higher sensitivity and lower specificity, as represented by its positioning in the uppermost sector of the ROC diagram.

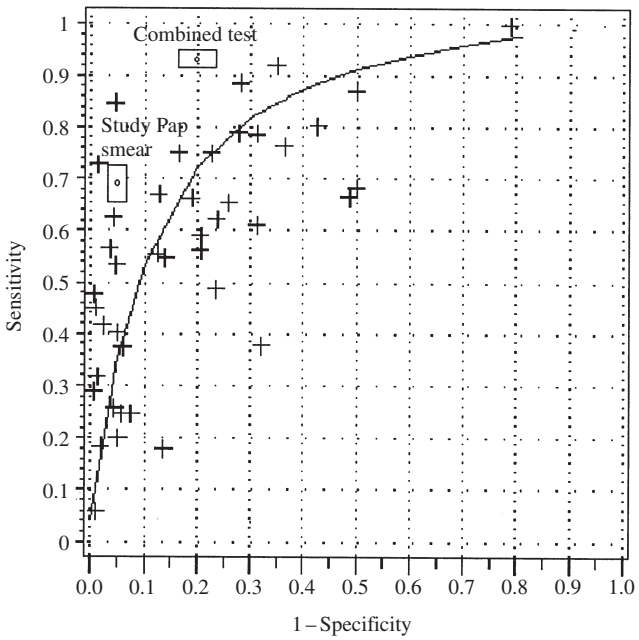

Fig. 2. Summary ROC curve of Pap smear studies reporting on CIN 2/3 threshold from AHCPR report[(2)].As the sensitivity/specificity trade-off is adjusted, the operating point on the ROC moves along the curve. Individual study results included in the AHCPR meta-analysis of Pap smear results are shown (+). Point estimates and 95% confidence interval boxes for the study Pap smear and combined test results are shown for comparison.

Discussion

The use of the two tests in combination provides a very high overall screening sensitivity (over 90% for CIN 2/3), since the TruScreen provides a second opportunity to detect CIN lesions missed by cytology. In practice, the use of the two tests in combination can result in the early diagnosis and management of abnormalities (Fig. 3), since a TruScreen-detected abnormality can be dealt with immediately by further investigation or referral as appropriate. If no abnormality is detected by the TruScreen, the results of the Pap smear, when returned negative, will confirm the normal diagnosis. However, the cost of an increased sensitivity is a decrease in specificity when the two tests are combined. The results of the study demonstrate that for the individual woman, the use of the two tests in conjunction provides a very high degree of assurance that no significant cervical abnormality is present if both tests are negative. From a public health perspective, the benefits of a higher overall sensitivity leading to earlier treatment and a simplified management path facilitated by the adjunctive use of TruScreen must be balanced against a higher referral rate to colposcopy and the costs associated with performing an additional test.

Furthermore, the overall sensitivity for high grade lesions when the TruScreen is used as a single screening test was shown to be equivalent to that of a high quality screening Pap smear, albeit with an associated specificity loss. This result suggests that TruScreen also has potential in developing world regions without organized cytologic screening programs. The device is a possible alternative to direct visual inspection (DVI) conducted after the application of acetic acid solution for use in see-and-treat programs in which women are immediately treated with cryotherapy or loop electrosurgical excision. Results of DVI performance studies are highly variable and appear to depend on the training of clinical personnel. Variable

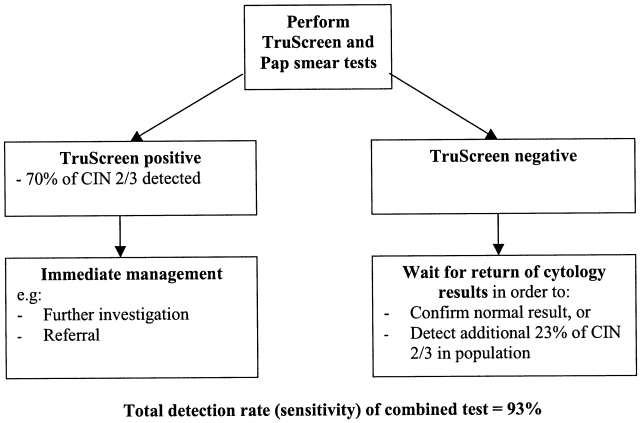

Fig. 3. Possible management protocol using the Pap smear and TruScreen tests adjunctively.

factors likely to influence the accuracy of DVI include training procedures, interscreener variation, screener fatigue, amount of acetic acid solution applied, and exposure time[9]. In contrast, the use of an automated test should minimize training requirements and assist in the standardization of results. Further studies in low resource settings are required to assess the comparative performance of TruScreen and DVI.

In this study, the screening population was enriched with subjects recruited from the colposcopy clinic environment, which has a higher underlying prevalence of disease. In general, for diseases of relatively low prevalence, enrichment allows a more precise determination of test sensitivity since more cases are available for the analysis. This is because in the presence of a reliable reference standard, calculations of sensitivity and specificity are independent of the prevalence of disease in the population, except insofar as prevalence affects the calculation of sample size. However, in an enriched study design, an imperfect reference standard may lead to an underestimation of both sensitivity and specificity[2,10]. Histology is recognized as the diagnostic standard for cervical preneoplastic disease. However, histology is known to be subject to interobserver variability, with the consistency of results varying across the spectrum of CIN and a higher agreement observed for normal and CIN 2/3 results than observed for CIN 1[11,12]. For this reason, analysis by a single expert histologist was used as the study reference standard, in order to establish internal consistency of the results. Because the study was designed to evaluate performance in a screening setting, measures were taken to ensure that slides from subjects recruited in the colposcopy clinic were evaluated in the same way as for subjects recruited from the general population.

The group of cases classified as "HPV effect/atypia" by the reference diagnosis is likely to predominantly comprise low oncogenic risk HPV infections or reactive or atrophic changes. Because the issue of whether such cases should be "flagged" by a screening test is somewhat controversial, we have not included these cases in the sensitivity calculations, which use histologically confirmed CIN as the only basis for assessment.

The study used the Bethesda 2001 system for the classification of cytologic results, which has been designed to maintain consistency between laboratories for the detection of squamous intraepithelial lesions while improving cytological specificity. A key feature of Bethesda 2001 is the subclassification of atypical squamous cells (ASC) into either ASC-H (ASC – cannot exclude high grade) or ASC-US (ASC – Uncertain Significance). The introduction of these subclassifications allows a differentiation of management strategies, with management guidelines recommending immediate colposcopy for ASC-H, whereas ASC-US management may involve either repeat cytology, HPV DNA testing, or colposcopy[13]. The Pap smear unsatisfactory rate for the study was 0.6%, as compared to an overall rate of 9.6% in the UK NHS Cervical Screening Program in 2000–2001[14], presumably reflecting the high quality of cytologic sampling and analysis in the study. The TruScreen "inadequate examination" rate was also 0.6%. The TruScreen software classifies an examination as inadequate if an insufficient number of cervical tissue "spots" have been assessed. However, it should be noted that in normal clinical use the TruScreen output will not be encrypted and any inadequate results can be dealt with by immediately repeating the examination.

A potential limitation of our study was the use of conventional rather than newer liquid based cytologic techniques. However, any impact on the results of the study is likely to be mitigated by the use of a high quality conventional smear in a quality assured setting. A recent review of liquid-based cytology concluded that the technology has the potential to dramatically reduce the unsatisfactory rate of the smear, but that an increase in the rate of high grade CIN detection is not established[15]. The very low unsatisfactory rate observed in our study confirms the high quality of the study smear.

In conclusion, the results of this study suggest that TruScreen operates as a viable adjunctive test when used together with cervical cytology for screening. The TruScreen and Pap smear utilize different measurement approaches; the automated device uses *in vivo* stimulation and measurement of tissue response

whereas cytology involves *in vitro* pathologic analysis of cellular changes. As a result, groups of CIN lesions detected by TruScreen and by cytology are partly, but not wholly, overlapping. Therefore, almost all CIN lesions can be detected when the TruScreen device is adjunctively combined with the Pap smear.

Acknowledgments

We thank Douglass Hanly Moir Laboratories, Sydney, for cytology analysis; Sacha Macansh, Megan Smith, and their staff at Polartechnics for clinical and technical support; Gill Wallace for coordination of histology review; Jules Lee for coordination of cytology review; and the following clinicians who conducted TruScreen, Pap smear, and colposcopy examinations: Narendra Pisal, Heather Evans, Carl Chow, and Tony Hollingsworth at the Whittington and Whipps Cross Hospitals, London; Chris Dalrymple at the Royal Prince Alfred Hospital for Women and Babies, Sydney; Neville Hacker and Michael Campion at the Royal Hospital for Women, Sydney; Edith Weisberg and Lynne Wray at the Family Planning Association, Sydney; and the following practice-based clinicians in Sydney: Michael Campion, Gabrielle Casper, Chris Dalrymple, Michael Fortune, David Itzkowic, and Richard Reid.

References

1 Quinn M, Babb P, Jones J, Allen E, on behalf of the United Kingdom Association of Cancer Registries. Effect of screening on incidence of and mortality from cancer of cervix in England: Evaluation based on routinely collected statistics. *BMJ* 1999;**318:**904–8.

2 McCrory DC, Mather DB, Bastian L *et al.* Evaluation of cervical cytology. Evidence Report/Technology Assessment No. 5 (Prepared by Dule University under Contract No. 290-97-0014). AHCPR Publication No. 99-E010. Rockville, MD. USA: Agency for Health Care Policy and Research. February 1999.

3 Sung HY, Kearney KA, Miller M, Kinney W, Sawaya GF, Hiatt RA. Papanicolaou smear history and diagnosis of invasive cervical carcinoma among members of a large prepaid health plan. *Cancer* 2000;**88:**2283–9.

4 Coppleson M, Canfell K, Skladnev V. The Polarprobe – An instantaneous optoelectronic approach to cervical screening. *CME J Gynecol Oncol* 2000;**5:**31–8.

5 Coppleson M, Reid BL, Skladnev VN, Dalrymple JC. An electronic approach to the detection of pre-cancer and cancer of the uterine cervix: a preliminary evaluation of Polarprobe. *Int J Gynecol Cancer* 1994;**4:**79–83.

6 Solomon D, Davey D, Kurman R *et al.* The 2001 Bethesda System. Terminology for reporting results of cervical cytology. *JAMA* 2002;**287:**2114–9.

7 NHS Cervical Screening Program. Resource pack for training smear takers. Publication no. 9, 1998.

8 Commonwealth of Australia Department of Health and Family Services. Screening for the prevention of cervical cancer. Publication no. 1031, 1998.

9 Denny L, Kuhn L, Pollack A, Wright TC Jr. Direct visual inspection for cervical cancer screening: an analysis of factors influencing test performance. *Cancer* 2002;**94:** 1699–707.

10 Boyko EJ. Meta-analysis of Pap test accuracy. *Am J Epidemiol* 1996;**143:**406–7.

11 Ismail SM, Colclough AB, Dinnen JS *et al.* Observer variation in histopathological diagnosis and grading of cervical intraepithelial neoplasia. *BMJ* 1989;**298:** 707–10.

12 Robertson AJ, Anderson JM, Beck JS *et al.* Observer variability in histopathological reporting of cervical biopsy specimens. *J Clin Pathol* 1989;**42:**231–8.

13 Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ for the 2001 ASCCP-Sponsored Consensus Conference. 2001. Consensus guidelines for the management of women with cervical cytological abnormalities. *JAMA* 2002;**287:**2120–9.

14 UK Department of Health. *Report of the Cervical Screening Program*, Bulletin 2001/22, September, 2001.

15 Broadstock M. Liquid-based cytology – an alternative international view. *Cytopathology* 2001;**12:**141–3.

Accepted for publication July 15, 2003.