

## TruScreen: a new ally in cervical cancer screening

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In Italy, screening for cervical cancer takes place in rather different health care settings, with significant differences between one region and another with regard to methodologies and practices. Currently, several cytology screening programs are in force both at regional and local level, and the number of areas involved is constantly increasing.

However, even those regions where organized screening programs are operational see a substantial percentage of Pap smears carried out in private sector centers. Attending for screening once a year is recommended by many gynecologists; the gynecological examination usually involves an objective clinical examination and cytology sampling, as well as colposcopy whenever it is indicated.

Cytology has been used as the screening method for cancer of the uterine cervix for over fifty years, and yet little has been published, with respect to Italy, in the way of data concerning the accuracy (sensitivity and specificity) of that technique in detecting pre-cancerous and cancerous pathologies.

The most important international study recently appeared on this subject was a meta-analysis conducted by researchers from Duke University (in the United States). The authors of this meta-analytic review examined all the studies on the accuracy of cytology, which were conducted following predefined standards, appeared in the literature [1].

Duke University researchers pointed out that cytological testing, when conducted in a screening context for the detection of high-grade pre-cancer, showed a sensitivity close to 50% - well below expectations.

The performance limitations of the Papanicolaou smear shown by the international meta-analytic review probably apply to Italy as well, all the more so on account of a non-homogeneous quality of screening procedures, resulting from both territorial and infrastructural factors.

In order to fix these limitations, some suggestions have been presented for introducing the adjunctive use of complementary testing techniques that can both increase detection rates for high-grade intraepithelial lesions and improve the overall sensitivity of the screening process in detecting all CIN lesions. These adjunctive test methodologies include HPV DNA testing and optical or optoelectronic detection devices. Optoelectronic devices offer the advantage of real time diagnosis, allowing the clinician to immediately counsel and manage the patient.

TruScreen (developed by Polartechnics, Sydney, Australia), previously known as Polarprobe, is a tool capable of providing the operator with real time feedback. It uses electrical and optical signals to classify cervical tissue with an "expert system" approach. An expert system is a computerized device programmed to mimic the scientific judgment and diagnostic skills of expert physicians.

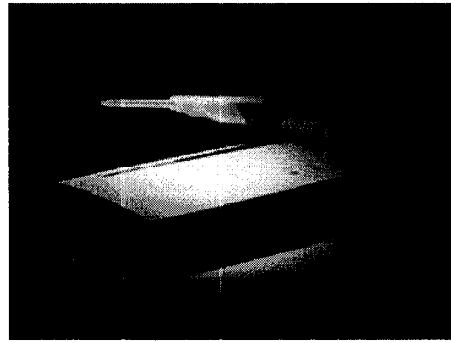


Figure 1

The TruScreen system consists of a portable console connected to a pen-shaped handpiece (Figure 1). The tip of the handpiece is covered with one single-use biosensor - for each patient who is examined.

The operator places the tip of the handpiece in direct contact with many different tissue spots on the uterine cervix, following a predetermined protocol and a topographic scanning path. The device gives the operator an overall assessment of the cervix by providing a hard copy printout of the test results at the end of the examination.

The overall assessment, summarized by the system's algorithm in terms of "normal" or "abnormal", entails a probability estimate indicating how likely it is that pre-neoplastic or neoplastic lesions of the uterine cervix have been detected. When the result is "normal", the physician is in a position to reassure the patient immediately and to wait for cytology testing to confirm the result. When the result is "abnormal", however, it is possible to promptly conduct secondary tests (appropriate biopsies, colposcopy, see and treat techniques).

Tissue is illuminated at four discrete wavelengths in the visible and infrared regions of the spectrum and stimulated by means of very low level voltage pulses (not detected by human beings) that give rise to electrical decay curves. This operating principle makes TruScreen a truly complementary technique to cytology, not just a modified version of the screening operating principle. In fact, unlike cytology - which only allows to examine cells - it offers the advantage of exploring tissue in its structural complexity (cells, extracellular matrix, blood vessels, etc...).

TruScreen is the result of more than ten years of research and development efforts by world-famous experts in many international centers.

As far as screening accuracy is concerned, a recent study coordinated by Professor Albert Singer of the Whittington Hospital, London, proves that the sensitivity of TruScreen is 70% for histologically confirmed CIN 2/3 lesions and 67% for CIN 1 lesions [2]. By contrast, the sensitivity of high-quality cytology was found to be 69% in detecting CIN 2/3 lesions and as little as 45% in detecting CIN 1 lesions.

The use of the two tests in combination (TruScreen and Pap test), on the other hand, led to an improvement in performance: the sensitivities of the TruScreen/Pap combined test were 93% for CIN 2/3 lesions and 87% for CIN 1 lesions respectively.

This study shows that TruScreen and cytology detect partly different but overlapping groups of CIN lesions; as a result, the adjunctive combination leads to higher CIN detection rates.

Conversely, for colposcopically or histologically normal patients the specificity of TruScreen was 81%, compared with a better specificity shown by the Pap test (95%). With the use of the two tests in conjunction, the overall specificity was found to be 80%.

In Italy the TruScreen system has been available for about a year. It is already in operation in a few hospitals and private gynecologic centers, where it is used as an adjunct to the conventional Pap test.

We now briefly report on the results of trials for TruScreen conducted in three different gynecologic centers.

The use of TruScreen in conjunction with the Pap test was considered for those patients who attended for screening in the three centers. Follow-up procedures stayed the same, in accordance with the usual guidelines as for the routine outpatient activities, when the Pap test returned a positive result. In those cases the TruScreen examination did not add or take any information, but thanks to the real-time results obtained, the physician was offered an opportunity to promptly decide on further investigation if needed.

On the other hand, the results obtained with the TruScreen examination were considered when the Pap smear returned negative results. For 437 patients out of 525 (83%), TruScreen confirmed the "normal" cytology diagnosis. Among these "double negative" cases, colposcopy turned out to be normal for 96% of the subjects. For the remaining 4%, colposcopy detected minor changes. This suggests that when both the TruScreen examination and the Pap test return a "normal" result, the gynecologist is in a position to provide the patient with a high degree of assurance that no significant cervical abnormality is present.

For 88 subjects out of 525 (17%) TruScreen detected abnormality, while cytology returned negative or "normal" results. Of these, 24 results (27%) were found to be major changes by colposcopic examination. Consequently, TruScreen detected a substantial number of cases that would have gone unnoticed if cytology screening had been performed alone. It follows that these patients, with more accurate screening, might benefit from a close follow-up session or early treatment.

In the absence of both histologic confirmation data and of an appropriate double-blind protocol for Pap test and colposcopy procedures, it is clearly not our purpose here to draw any conclusions on the subject of "sensitivity" or "specificity" - for that we refer to the above-mentioned paper and the prospective Italian reports. We simply wish to suggest one way to use a technique that proves to be effectively complementary to the Pap test and to enhance screening accuracy in everyday outpatient practice.

Another interesting aspect of TruScreen is related to those patients with ASCUS or unsatisfactory cytology results. For 25 subjects out of the 37 with ASCUS or unsatisfactory cytology results (67%), the TruScreen examination returned a "normal" diagnosis. Of these, 19 results (76%) were in agreement with the colposcopic diagnosis. However, 6 subjects (24%) were shown to be colposcopically abnormal; of these, two CIN 2/3 results and one CIN 1 result were histologically confirmed. For 12 subjects out of the 37 subjects with ASCUS or unsatisfactory cytology results (33%), TruScreen returned an "abnormal" diagnosis. For 11 subjects out of these (92%), the results were colposcopically confirmed; of these, one CIN 2/3 result and two CIN 1 results were histologically confirmed. On the whole, for ASCUS or unsatisfactory cytology results, TruScreen returned results that proved to be accurate for 30 subjects out of 37 (81%).

In conclusion, our experience suggests that TruScreen holds the potential to both detect lesions that might be missed by cytology alone and clarify unsatisfactory or ASCUS cytology results.

With regard to patients, they can benefit from more rapid follow-up and early treatment. We also noticed that the women were happy with the real time results, which are now available using TruScreen. In summary, TruScreen technology seems to have a high potential to improve and standardize the screening of the cervical carcinoma.