Performance and Reproducibility of Gynecologic Cytology Interpretation Using the FocalPoint System

Results of the RODEO Study Team

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ABSTRACT

Objectives: To assess whether automated screening in the cytologic examination of Papanicolaou smear slides results in smaller margins of error than manual screening.

Methods: We compared cytotechnologists' performance and reproducibility of manual and automated screening of 10,165 consecutive cervical cytology slides examined at Barretos Cancer Hospital using the FocalPoint system.

Results: In total, 83% of atypical squamous cells of undetermined significance and greater were classified as quintiles 1 and 2; no high-grade squamous intraepithelial lesions and greater were observed in quintile 5. No statistically significant differences were found between manual and automated screening, using cervical biopsy specimens as the gold standard.

Conclusions: FocalPoint safely screened high-grade lesions, which can be valuable for high-workload routines.

Upon completion of this activity you will be able to:
- critically analyze automated gynecologic cytology screening systems.
- design gynecologic screening that is appropriate to the local or regional health care setting where it is applied.
- outline ways that automation can be applied as a tool for cytology internal quality control.

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The World Health Organization estimates that more than 69.05 million Brazilian women older than 15 years are at risk of developing cervical cancer.[1] In Brazil, prevention is accomplished through a Papanicolaou (Pap) smear following routine cytologic screening established by the Ministry of Health of Brazil in 1988.[2,3] For several reasons, estimates of cancer incidence and mortality have remained virtually unchanged in the past decades in Brazil.

The manual screening of Pap smear slides by a cytotechnologist is a monotonous activity, leading to fatigue, which can result in morphologic changes, misinterpretation, and false-negative results. The number of slides examined daily must be low (40-50 per day) to avoid errors. Cytotechnologists differ in productivity, screening time, and accuracy in interpreting the results of the slides, which can vary by day of the week and even (morning or afternoon) time of day.[4]

To try to reduce false-negative results, new technologies for the preparation and screening of slides of cervical cytology specimens are currently available. Liquid-based cytology (LBC) was designed to reduce the overlapping of cells and facilitate the detection of abnormalities in automated screening.[5] In the well-known SurePath (TriPath Imaging, Burlington, NC) method, preparation of cells 13 mm in diameter is obtained without undesirable losses of material and cellular crowding.[5] This type of cell preparation maintains a high standard of quality, while automated screening is believed to improve a process fraught with cognitive difficulties.

One of the most used automated screening systems worldwide is the BD FocalPoint GS Imaging System (FPGS) (BD, Burlington, NC), which can evaluate both LBC and conventional preparations.[6] The use of these devices is presumed to serve as a primary screening tool with important improvements in internal quality control, which ensures cytologic examination routines with smaller margins of error.

Taking into account the potential usefulness of computer-assisted evaluation of LBC preparations routinely examined at Barretos Cancer Hospital, we sought to evaluate FocalPoint performance to identify and classify cervical injuries safely and critically analyze the introduction of the robot as an internal quality control device.

Materials and Methods

The cytologic samples were collected from May 2010 through August 2011 from the following sources: women referred to the Barretos Cancer Hospital who had a previous suspicious examination elsewhere, women examined in mobile units of the Preventing Cancer Hospital of Barretos, and women who had gynecologic consultations in the municipalities that send their tests to the sector of pathology at Barretos Cancer Hospital. The mean (SD) age was 45 (13.9) years (range, 13-96 years). We analyzed 10,165 cervical cytology cases prepared by the SurePath liquid-based method.

Study Design

The screening of the slides and statistical analyses were independently performed by professionals from the Barretos Cancer Hospital. In the first round, the cytotechnologists evaluated 10,165 slides prepared in the liquid-based SurePath method with a light microscope under routine conditions. Then, all slides were analyzed by the FocalPoint system, which classified the cellular changes into quintiles as previously reported.[6,7] Briefly, this classification was made in accordance with the probability of abnormality of each slide. There are 5 quintiles, with quintile 1 having the highest probability of abnormality and 5 having the least.[6,7] We

introduced quintile 99 to identify those cases that were classified as quintile 5 but had no image available for review, as well as those cases classified as Process Review, which means that the cellular alterations found by the computer were not able to be classified within the morphologic parameters recorded in the system and needed to be reviewed manually by the cytotechnologist/cytopathologist.

After about a year of manual screening, the same group of cytotechnologists conducted microscope-automated screening in the Guided Station of the FocalPoint system. The cases with cytologic changes in the manual and automated arms (atypical squamous cells of undetermined significance and greater [ASC-US+]) were reviewed by a group of 6 cytopathologists, keeping the same proportion of cases from the first round for each cytopathologist in both arms. Analyses of sensitivity and specificity were performed exclusively for patients who underwent biopsy of the cervix.

Ethics

Participants gave informed consent to participate in the study, which was approved by the ethics committee of Barretos Cancer Hospital (No. 244/2009).

Conflict of Interest

BD Brazil (São Paulo) supported part of the study with the SurePath collection kits and equipment. The study design, the screening of the slides, and statistical analyses were performed independently by professionals from the Barretos Cancer Hospital.

Results

Of the total 10,165 slides, 9,847 (96.9%) qualified for revision, and 318 (3.1%) cases were not classified by FocalPoint (manual revision was suggested by the computer—quintile 99).

The classification into quintiles of cases read by cytotechnologists in the automated arm was analyzed, and the results are listed in ❚Table 1❚. Most cases scored ASCUS+ by cytotechnologists were classified as quintile 1; 90% and 33% of high-grade squamous intraepithelial lesions (HSIL) and adeno/squamous cell carcinoma were classified as quintiles 1 and 2, respectively; and the rest of the cases of adeno/squamous cell carcinoma were selected for screening of the entire slide. Cases of invasive carcinomas that were not selected in quintiles 1 and 2 were classified as quintile 5 without opening images (in our routine, we renamed this quintile 99). Generally, quintile 99 represented cases in which cellular changes were so numerous and so pleomorphic that FocalPoint provided an alert that the slides should be fully reviewed by the observer.

▮Table 1▮
FocalPoint Classification According to the Quintiles Distribution

Quintile	FocalPoint Cytologic Diagnoses, No. (%)							
	Negative, No. (%)	ASCUS	ASC-H	LSIL	HSIL	Adeno/CEC	AGC	Total, No. (%)
1	1,516 (16.3)	59 (55.7)	74 (64.9)	115 (72.8)	101 (84.2)	0	6 (46.2)	1,871 (19.0)
2	1,809 (19.4)	24 (22.6)	16 (14.0)	23 (14.6)	7 (5.8)	1 (33.3)	2 (15.4)	1,882 (19.1)
3	1,891 (20.3)	9 (8.5)	10 (8.8)	11 (7.0)	3 (2.5)	0	1 (7.7)	1,925 (19.6)
4	1,889 (20.2)	6 (5.7)	6 (5.3)	4 (2.5)	2 (1.7)	0	2 (15.4)	1,909 (19.4)
5	1,814 (19.4)	1 (0.9)	5 (4.4)	2 (1.3)	0	0	0	1,822 (18.5)
99[a]	410 (4.4)	7 (6.6)	3 (2.6)	3 (1.9)	7 (5.8)	2 (66.7)	2 (15.4)	434 (4.4)
Total	9,329 (100)	106 (100)	114 (100)	158 (100)	120 (100)	3 (100)	13 (100)	9,843 (100)

Adeno/CEC, adenocarcinoma/cell squamous carcinoma; AGC, atypical glandular cell; ASC-H, atypical squamous cells of undetermined significance not excluding high-grade lesion; ASCUS, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.
[a] Quintile 5 without opening images; in our routine we renamed this quintile 99.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated from patients who had a biopsy of the cervix. ▮Table 2▮ shows the results for cytotechnologist screening alone and the completed process involving cytotechnologists' screening and cytopathologists' final result.

Discussion

We evaluated FocalPoint's performance in classifying into quintiles LBC slides that were read by cytotechnologists. Most of the high-grade lesions, as well as ASCUS+ alterations, were classified as quintile 1 or 2, which endorses the usefulness of FocalPoint for screening and for quality control tools. HSIL and carcinomas not classified as quintile 1 or 2 were allocated to quintile 99. All these results clearly show that FocalPoint has an excellent discriminatory power to classify cases with cytologic abnormalities.

FocalPoint ranked in quintiles all slides within standard screening (review: slides into which FocalPoint separates the images to be read in Guided Stations). This classification is applied according to the probability of abnormal cells present in each slide analyzed. Quintile 1 represents the highest probability of abnormality, with quintiles 4 and 5 representing the least likely.

The results of this study correlated, in part, with the data of other studies. In a study conducted by Parker et al,[7] 90% of HSIL and 83% of HSIL+ (HSIL, adenocarcinoma in situ [AIS], and carcinoma) were classified as quintiles 1 and 2. Wilbur et al[8] evaluated 12,313 slides and found that 700 of 1,275 ASCUS+ were classified as quintile 1, as well as 94.6% of HSIL+ (HSIL, AIS, and carcinoma) in the first 2 quintiles. These data are important to ratify the discriminatory power and reliability of FocalPoint that can be expected under routine conditions.

To evaluate the sensitivity, specificity, PPV, and NPV of automated and manual screening, we used the biopsy result as the gold standard. No statistical significance was

▮Table 2▮
Accuracy of Manual and Automated Cytology Reading to Predict CIN2+ (Biopsy) Using HSIL+ as the Cytologic Criterion[a]

Characteristic	Manual Screening	Computer-Assisted Screening
Without cytopathologist review	n = 337	n = 337
Sensitivity	52.8 (44.8-60.7)	45.3 (37.5-53.4)
Specificity	81.8 (75.3-87.2)	85.8 (79.8-90.6)
Positive predictive value	72.7 (63.6-80.5)	74.5 (64.7-82.8)
Negative predictive value	65.5 (58.8-71.7)	63.2 (56.2-69.3)
AUC (ROC curve) (*1[b])	0.67 (0.62-0.72)	0.66 (0.60-0.71)
With cytopathologist review	n = 337	n = 334
Sensitivity	59.6 (51.6-67.3)	60.4 (52.3-68.0)
Specificity	83.0 (76.6-88.2)	76.0 (69.0-82.1)
Positive predictive value	76.2 (67.8-83.3)	69.6 (61.2-77.1)
Negative predictive value	69.2 (62.5-75.4)	67.9 (60.8-74.3)
AUC (ROC curve) (*2[c])	0.71 (0.66-0.76)	0.68 (0.63-0.73)

AUC, area under curve; CIN2+, cervical intraepithelial neoplasia grade 2 and more; HSIL+, high-grade squamous intraepithelial lesion and greater; ROC, receiver operating characteristic.
[a] Values are presented as % (95% confidence interval) unless otherwise indicated. Cytologic cutoff: HSIL+; biopsy: CIN2+.
[b] Comparison of manual and computer-assisted screening AUCs: P = .47.
[c] Comparison of manual and computer-assisted screening: AUCs: P = .21.

found between the 2 screening methods, using criteria for cervical intraepithelial neoplasia grade 2 or more (CIN2+) biopsy specimens as a cutoff for both arms, with and without cytopathologist revision. Even without a significant difference, however, the sensitivity was approximately 50% and specificity was approximately 80%, numbers that reflect the performance of Pap cytology testing under standard conditions.[9] The cytotechnologists who participated in the study are experienced in detecting abnormalities in gynecologic cytology, which may explain the similarity of the results of the 2 screening techniques and without cytopathologist interference. Moreover, it is known that a good screening method for cervical cancer should be efficient to detect those who really have a cervical intraepithelial lesion because a false-positive result can cause anxiety for the patient and more government spending on additional tests to detect

cervical cancer, whereas a false-negative result generates a false sense of security that can lead to neglecting events that are critical for the woman's life.[10] The PPV is preferred to evaluate the screening test efficiency, and in this study, the PPV results were notable: the PPV performance ranged from 72.7% to 74.5% for cytotechnologists and from 76.2% to 69.9% for cytopathologists in manual and automated screening, respectively, using HSIL+ cytologic criteria.

The sensitivity and specificity of a technique can be calculated in several ways without always using biopsy as the gold standard. In a UK study examining 73,266 SurePath and ThinPrep slides (Hologic-Cytyc, Marlborough, MA) that compared manual screening with automated screening with the ThinPrep Imaging System and FPGS, the authors concluded that automated screening was 8% less sensitive than manual screening for CIN2+.[11] Our results, however, are in agreement with a study in Finland, a country with an active national program tracking rare cases of cervical cancer. Anttila et al[12] also found no statistically significant differences between manual and automated screening. Another study in 2 large laboratories in Ontario, Canada, had similarities with the current study. Colgan and colleagues[13] compared the performance of FPGS and manual screening in 10,233 cases and found no differences in detecting low-grade squamous intraepithelial lesions and greater (LSIL+) (including HSIL and invasive carcinomas), but they found higher false-negative rates for LSIL and ASC-US in FPGS than with manual screening.

Cengel et al[14] compared SurePath slides in manual and automated screening and concluded that the sensitivity of the automated method was better when it was used as the gold standard for manual screening (96%) rather than using biopsy of the cervix (93%). This unique way of evaluating the performance of a method can be subject to criticism. However, considering that manual tracing has been used for decades in millions of annual tests, the premise of the work has provided a new vision of how to evaluate the introduction of a new method. In 1 study that implemented FPGS in Connecticut, slides in a SurePath liquid base read in the 16 months preceding implementation of FPGS were used as the gold standard, resulting in an increase in the detection of ASCUS and LSIL with automated screening.[15] In 302 cases prepared in liquid-based ThinPrep, high levels of satisfactory samples for screening were demonstrated, even after patients had received radiation therapy, with a PPV of 25% for LSIL and 100% for carcinoma.[16]

The advent of human papillomavirus (HPV) vaccination is likely to decrease precancerous lesions due to decreased severe injuries. In this scenario, the low NPVs and PPVs of conventional cytology will be even lower, which further complicates the recognition by cytotechnologists of cellular changes that require new logistics and new features, such as

automated screening combined with the HPV test, to act with the efficiency expected.[17]

Recently, Sweeney and Wilbur[18] evaluated the FocalPoint utility for cytotechnologist productivity. Because it is very difficult to recruit and train new cytotechnologists and because the vaccine era will decrease the (already) low sensitivity of cytology (it is presumed that high-grade abnormalities will diminish), FPGS could help improve workload without a decline in the quality of results. The authors found that productivity after implementation of FPGS increased gradually with a period of implementation.[15]

To the best of our knowledge, this is the first study in South America that demonstrates the utility of FocalPoint in cytologic screening. Even without major differences between automated and manual screening, the use of FocalPoint in the daily routine of a cytology laboratory is valuable and also helps to avoid possible false results in routine screening, especially in centers where the cytotechnologists' workload is high (80-100 slides per day). Resources assessed are also suitable for internal quality control, overcoming the current system proposed by Brazilian health authorities that requires the revision of all ASCUS+, unsatisfactory smears, and 10% of negative cases. Although important, this system of quality control leaves aside the causes that give rise to false-negative results, passing off this serious problem by checking only 10% of patient samples selected within a given period.

The use of FocalPoint has shown that it can prevent HSIL+ false-negative cases from being released, with the possibility to be correct in real time and thereby reducing diagnostic distortions. Identifying errors and their causes offers the possibility of a continuous education process where internal control is just one more element in the role of quality assurance in cytology.

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