CANCER
CYTOPATHOLOGY

A Feasibility Study of the Use of the AutoPap Screening System as a Primary Screening and Location-Guided Rescreening Device

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The authors thank Ilaria Poggesi for kindly reviewing the article.

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Received April 24, 2002; revision received September 6, 2002; accepted October 21, 2002.

DOI 10.1002/cncr.11077

BACKGROUND. The AutoPap 300 QC system (Tripath Imaging, Inc., Burlington, NC) is an automated device that was designed to screen conventionally prepared cervical smears and, more recently, thin-layer slide preparations. The system has been tested in large clinical trials.

METHODS. A total of 14,145 cervical smears obtained from participants in the Florence screening program were eligible for the study. Smears were processed first with the AutoPap system and were classified into three different categories: 1) no further review (NFR), 2) review, and 3) process review (PR). Conventional manual reading was performed by 10 experienced cytopathologists.

RESULTS. After AutoPap processing, 2398 smears were classified as NFR (16.9%), and 1818 smears were classified as PR (12.8%). Overall, there were 188 inadequate smears (1.3%) at conventional review and 125 inadequate smears (0.88%) at AutoPap review. Six-month repeat smears were prompted by 330 conventional reviews (2.3%) and by 222 AutoPap reviews (1.56%). Similarly, referral to colposcopy was prompted by 179 conventional reviews (1.2%) and by 147 AutoPap reviews (1.0%). Overall, 32 patients were diagnosed with high-grade cervical intraepithelial neoplasia as a result of assessment. Conventional reading detected 31 patients (28 patients were referred for colposcopy, and 3 patients were referred for repeat cytology), and the AutoPap system detected 30 patients (27 patients were referred for colposcopy, and 3 patients were referred for repeat cytology).

CONCLUSIONS. The current experience suggested that conventional reading and AutoPap reading of cervical smears had essentially the same sensitivity, with slightly greater specificity for the AutoPap system. Thus, comparisons of the AutoPap system and conventional reading should focus mainly on cost analysis. ***Cancer (Cancer Cytopathol)* 2003;99:129–34.** *© 2003 American Cancer Society.*

KEYWORDS: AutoPap, location-guided screening, automated device, Papanicolaou (Pap) smears.

The AutoPap Primary Screening System (APSS; Tripath Imaging, Inc., Burlington, NC) is an automated device that was designed to screen conventional cervical smears[1] and, more recently, thin-layer specimens. The APSS, which first was approved by the U.S. Food and Drug Administration as a method for quality control,[2–5] has been tested in large clinical trials. Its use in primary screening also has been suggested, because it may improve accuracy while reducing laboratory workload.[6,7]

Since April 2000, the APSS has been at disposal of the Centro per lo Studio e la Prevenzione Oncologica in Florence, Italy. After proper training of the laboratory staff, the system was tested in a controlled, prospective study. The performances of conventional reading and

AutoPap-assisted reading were compared, and the feasibility of employing the AutoPap system in primary screening has been discussed.

MATERIALS AND METHODS

In total, 14,145 consecutive smears from the Florence screening program were considered for the study. Smears were processed first with the AutoPap system according to manufacturer recommendations.[8] Smears were classified by the system according to three different categories: 1) no further review (NFR) (slides with a low probability of abnormality), 2) review (smears with a greater likelihood of abnormality), and 3) process review (PR) (smears that failed processing). In review smears, the system selected field of vision (FOV) locations of potentially abnormal cells. FOVs were printed on a smear map in the report sheet. No FOVs were selected for review smears with scant cellularity or for PR smears.

Conventional smear reading was performed by 10 experienced cytopathologists (each with at least 10 years of experience). Each cytopathologist read a randomly selected smear subset. Smears were reported according to 1991 Bethesda system.[9] Three to 4 days after conventional smear reading, smears with an AutoPap report other than NFR were reread by the same cytopathologist who had performed conventional reading without any knowledge of the results from the first reading report.

Reading was directed to FOVs that were selected by the AutoPap machine based on a printed scheme of the instrument. Reading of the whole smear was performed only if 1) evidence from FOVs was insufficient for diagnosis, or 2) no FOVs were selected.

The worst report between conventional reading and AutoPap-assisted reading was considered for further patient management. According to the current screening protocol, patients with smears that were reported as atypical squamous cells of undetermined significance (ASCUS) favoring a reactive process were invited to have a repeat smear after 6 months and were referred to colposcopy if persistent ASCUS or a more severe abnormality was evidenced. Smears reported as ASCUS favoring squamous intraepithelial lesion (SIL) or a more severe abnormality were referred immediately for colposcopy. Patients with colposcopy negative, low-grade SIL (LSIL) were categorized as negative for the purposes of the study; whereas patients with colposcopy negative, high-grade SIL (HSIL) were followed with repeat cytology (6 months). Histologic diagnosis at directed punch biopsy (or on loop excision specimen, if more severe) was the reference standard for purposes of the study.

The APSS also provides for dividing each set of processed smears (approximately 200 smears) into quintile ranks of increasing cell abnormality. This information was available to the cytologist who interpreted the AutoPap-assisted readings.

Conventional readings and AutoPap-assisted readings were compared first according to the issued diagnostic report. The two procedures were compared in terms of 1) the rate of abnormal smears (in which patients were advised to have a 6-months repeat smear or were referred to colposcopy) and 2) the proportion of high-grade cervical intraepithelial neoplasia (CIN) detected as a direct consequence of the cytologic report at each procedure. Slides that showed high-grade CIN in which one reading method prompted colposcopy and the other reading method prompted only repeat cytology were considered true-positive for both procedures, assuming that, in the latter eventuality, a cytologic abnormality would persist at 6 months, prompting a referral for colposcopy.

The cost of AutoPap-assisted reading (inclusive of material and assistant operator) and the cost of conventional reading were determined. On the basis of the results obtained, a cost-outcome analysis was performed, considering the follow unitary costs: 1) €20 for each Papanicolaou (Pap) smear repeated, 2) €50 for each assessment, 3) €70,000 for the real cost for each reader with an annual workload of 7500 smears, 4) €216,912 for the annual cost of the AutoPap system, and 6) €4000 per year (for 25,000 smears per year) or €10,000 per year (for 60,000 smears per year) for a part-time assistant operator to work the AutoPap machine (slide preparation with bar codes, uploading and unloading the instrument, and printing).

The estimate of reading time cost savings with AutoPap-assisted reading has been calculated based on the following considerations: 1) NFR, no manual screening, and only time (1 minute) for reporting and attending to quality-control procedures; 2) PR, 6 minutes and 30 seconds for manual reading; 3) review, 90% screening of only 15 marked FOVs, 4 minutes and 10 seconds; and 4) 10% screening of the whole slide (entire slides were screened when at least one of the following conditions were identified: abnormal cells, questionable abnormalities, and questionable cell patterns). Time for manual reading was added to the time necessary for screening FOVs. The time per smear read was determined according to an average of 100 smears for each reader for both procedures. An extra 2 minutes for each smear read was considered for 1) reporting and 1) attending to quality-control procedures, both depending on the number of smears read.

The overall cost of the 2 compared procedures were calculated according to 1) 25,000 smears per year (the minimum standard for quality in European guidelines[10])

TABLE 1
Distribution of Cytologic Reports from Conventional and AutoPap-Assisted Reading (14,145 smears)

	AutoPap-assisted reading[a]										
	Review										
Conventional reading	Neg	ASCUS-R	ASCUS-S/AGUS	LSIL	HSIL	CA	Unsat	NFR	PR	Total	%
Neg	9290	38	7	0	0	0	22	2365	1726	13,448	95.07
ASCUS-R	140	126	3	0	0	0	1	19	41	330	2.33
ASCUS-S/AGUS	16	13	53	1	0	0	0	3	7	93	0.65
LSIL	3	3	13	25	0	0	0	3	11	58	0.41
HSIL	0	1	1	3	19	0	0	0	3	27	0.19
CA	0	0	0	0	0	1	0	0	0	1	0.007
Unsat	78	0	0	0	0	0	72	8	30	188	1.32
Total	9527	181	77	29	19	1	95	2398	1818	—	—
%	67.3	1.28	0.54	0.20	0.13	0.007	0.67	16.9	12.8	—	—

Neg: negative; ASCUS-R: atypical squamous cells of undetermined significance (ASCUS) favoring a reactive process; ASCUS-S: atypical squamous cells of undetermined significance favoring squamous intraepithelial lesion or a more severe abnormality; AGUS: atypical glands of undetermined significance; LSIL: low-grade Squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; CA: carcinoma; Unsat: unsatisfactory; NFR: no further review; PR: process review.

[a] The AutoPap Primary Screening System (Tripath Imaging, Inc., Burlington, NC).

TABLE 2
Distribution of 32 Patients with a Histologic Diagnosis of Grade 2–3 Cervical Intraepithelial Neoplasia or Cervical Carcinoma According to Cytologic Reports from Conventional and AutoPap-Assisted Reading

	AutoPap-assisted reading[a]								
	Review								
Conventional reading	Neg	ASCUS-R	ASCUS-S/AGUS	LSIL	HSIL	CA	NFR	PR	Total
Neg	0	0	1[b]	0	0	0	0	0	1
ASCUS-R	0	3	0	0	0	0	0	0	3
ASCUS-S/AGUS	1[c]	0	4	0	0	0	0	1	6
LSIL	0	0	2	2	0	0	1[c]	1	6
HSIL	0	0	1	2	11	0	0	1	15
CA	0	0	0	0	0	1	0	0	1
Total	1	3	8	4	11	1	1	3	—

Neg: negative; ASCUS-R: atypical squamous cells of undetermined significance (ASCUS) favoring a reactive process; ASCUS-S: atypical squamous cells of undetermined significance favoring squamous intraepithelial lesion or a more severe abnormality; AGUS: atypical glands of undetermined significance; LSIL: low-grade Squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; CA: carcinoma; NFR: no further review; PR: process review.

[a] The AutoPap Primary Screening System (Tripath Imaging, Inc., Burlington, NC).

[b] Histologic Grade 2–3 cervical intraepithelial neoplasia was lost at conventional reading.

[c] Histologic Grade 2–3 cervical intraepithelial neoplasia was lost at AutoPap-assisted reading.

and 2) 60,000 smears per year (the maximum AutoPap unit workload per year), including the costs of processing (for AutoPap), reading (NFR excluded for AutoPap), and further procedures (6-month repeat smear, colposcopy, and biopsy) generated by abnormal cytology. The cost/outcome evaluation was based on the cost per processed smear and the cost per high-grade CIN detected at biopsy. Personnel costs were based on real expenditures. Three different NFR rates also were also considered: 20%, 25%, and 30%.

RESULTS

After AutoPap processing, 2398 smears were classified as NFR (16.9%), and 1818 smears were classified as PR (12.8%). Table 1 shows the distribution of cytologic reports from conventional reading and AutoPap-assisted reading. One hundred eighty-eight conventionally read smears were unsatisfactory (1.3%), and 125 AutoPap-read smears were unsatisfactory (0.88%), with a statistically significant difference (chi-square test, 12.4; 1 degree of freedom; $P < 0.001$). ASCUS was

TABLE 3
Distribution of Patients with Histologically Confirmed Cervical Intraepithelial Neoplasia or Cervical Carcinoma According to AutoPap Attribution to Quintiles of Decreasing Cell Abnormality

	AutoPap categories[a]							
Final histologic outcome	Review/quintile ranks							
	1	2	3	4	5	NFR	PR	Total
CIN-1	23	3	7	1	9	1	7	51
CIN2–3	23	0	1	0	3	1	3	31
Carcinoma	0	0	0	0	1	0	0	1

NFR: no further review; PR: process review; CIN-1: Grade 1 cervical intraepithelial neoplasia (CIN); CIN2–3: Grade 2–3 CIN.
[a] The AutoPap Primary Screening System (Tripath Imaging, Inc., Burlington, NC).

TABLE 4
Experimental and Estimated Workload Attributable to AutoPap-Assisted Reading or Conventional Reading for the Purposes of Cost Analysis

		AutoPap-assisted reading[a]			
			Estimated workload		
Conventional reading	%	Study results (%)	NFR 20%	NFR 25%	NFR 30%
NFR	—	16.9	—	—	—
PR	—	12.8	10	10	10
Read/reviewed	100	70.3	70.0	65.0	60.0
ASCUS-R (6-month repeat)	2.3	1.6	1.6	1.6	1.6
Colposcopy assessed	1.2	1.0	1.0	1.0	1.0
CIN > Grade 2 detected	0.22	0.21	0.21	0.21	0.21

NFR 20%: no further review required for 20% of specimens; PR: process review; ASCUS-R: atypical squamous cells of undetermined significance favoring a reactive process; CIN: cervical intraepithelial neoplasia.
[a] The AutoPap Primary Screening System (Tripath Imaging, Inc., Burlington, NC).

reported more frequently in conventional readings. Three hundred thirty conventional reports (2.3%) prompted 6-month repeat smears, and 222 AutoPap reports (1.56%) prompted 6-month repeat smears, a statistically significant difference (chi-square test, 21.1; 1 degree of freedom; $P < 0.01$). Similarly, 179 conventional reports (1.2%) prompted referral to colposcopy, and 147 AutoPap reports (1.0%) prompted referral to colposcopy, a difference of borderline significance (chi-square test, 3.2; 1 degree of freedom; $P = 0,07$).

Thirty-two patients with Grade 2–3 CIN (CIN-2–CIN-3) were diagnosed at assessment. Table 2 reports the distribution of these patients by cytologic report at the two compared procedures. Conventional reading detected 31 patients (28 patients referred to colposcopy and 3 patients referred to repeat cytology), and AutoPap-assisted reading detected 30 patients (27 patients referred to colposcopy and 3 patients referred to repeat cytology).

Table 3 shows the distribution of patients by final outcome and AutoPap quintile attribution. Twenty-three of 31 patients with CIN-2–CIN-3 were classified in the first AutoPap quintile (highest level of cell abnormality).

Table 4 shows the workload attributable to conventional reading and AutoPap-assisted reading on which the cost analysis was based. On the basis of our results, the estimated reading time saved for 20% NFR, 25% NFR, and 30% NFR, respectively, was 35.1%, 38.0%, and 40.9%.

Table 5 show the cost estimates for workloads of either 25,000 smears per year or 60,000 smears per year at the best conditions obtained in the last part of this study (20% NFR and 10% PR). For the scenario of 25,000 smears per year, overall costs and cost per CIN $\geq$ Grade 2 detected were € 259,833 and €4724 for conventional reading and €392,959 and €7414 for AutoPap-assisted reading, respectively. The corresponding costs for the scenario of 60,000 smears per year were €623,600 and €4724 for conventional reading and €639,825 and €5078 for AutoPap-assisted reading, respectively. A cost analysis was conducted for the three different NFR rates (20%, 25%, and 30%). AutoPap

TABLE 5
Sample Cost/Outcome Analyses for a Scenario of 25,000 Smears per Year and a Scenario of 60,000 Smears per Year: Cost in Euros (€) per Cervical Intraepithelial Neoplasia Grade > 2 Detected

	Scenario with 25,000 smears/yr		Scenario with 60,000 smears/yr	
Measure	Conventional reading	AutoPap-assisted reading (NFR 20%)[a]	Conventional reading	AutoPap-assisted reading (NFR 20%)
AutoPap cost	None	€216,912	None	€216,912
Assisting unit	None	€4000	None	€10,000
Reading	€233,333	€151,547	€560,000	€363,713
Repeat cytology	€11,500	€8000	€27,600	€19,200
Assessment	€15,000	€12,500	€36,000	€30,000
Total	€259,833	€392,959	€623,600	€639,825
> CIN2 detected (no.)	55	53	132	126
Cost per > CIN2 detected	€4724	€7414	€4724	€5077

NFR 20%: no further review required for 20% of specimens; CIN2: Grade 2 cervical intraepithelial neoplasia.
[a] The AutoPap Primary Screening System (Tripath Imaging, Inc., Burlington, NC).

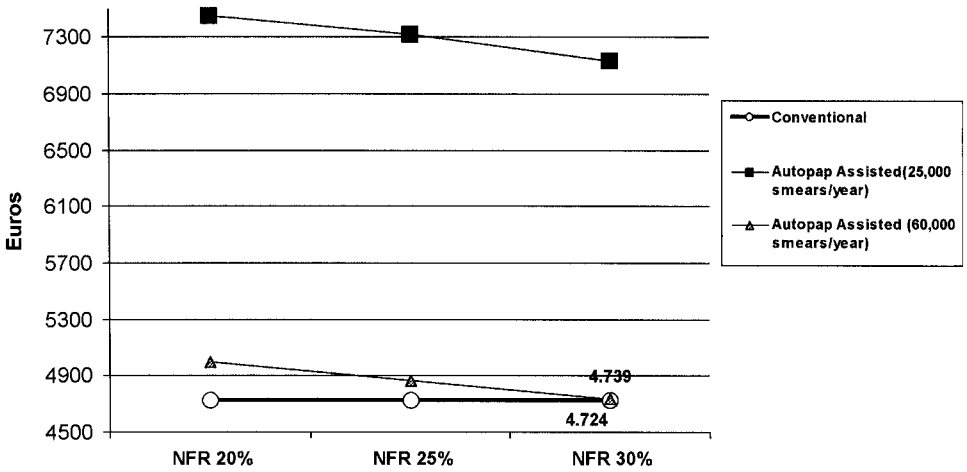

FIGURE 1. Examples of cost/outcome analyses of the cost per cervical intraepithelial neoplasia > Grade 2 detected in scenarios for 25,000 smears per year and 60,000 smears per year for different expected no further review (NFR) rates using the AutoPap Primary Screening System (Tripath Imaging, Inc., Burlington, NC) compared with conventional screening.

data are shown in Figure 1 for the scenarios of 25,000 smears per year and 60,000 smears per year. In both scenarios, the influence of the NFR rate is evident, but AutoPap-assisted reading costs are higher compared with conventional reading costs, with the highest cost effect observed for the scenario of 25,000 smears per year. Only with a 30% NFR rate and a scenario of 60,000 smears per year does it seem possible to achieve similar costs.

DISCUSSION

The main advantage expected from AutoPap-assisted reading was the exclusion of a relevant number of smears (classified as NFR) from conventional reading, sparing considerable cost. In the current experience, the proportion of NFR smears was 16.95%, quite low with respect to the 25% figure currently promised by the manufacturer. This may depend in part on the high rate of smears classified as PR in the current experience that may have been due to the suboptimal quality of processed smears (bubbles, cover slides, and staining). An attempt to improve smear processing quality and to adjust the system tolerance to smear processing artifacts was done during the study; and, in the final period of the study, the PR rate was reduced to 10%, an improved (although still high) value compared with other experiences.[8] Because of the progressive reduction in the PR rate, the NFR rate had increased by the end of the study, although only to 20%. According to the point of view of conventional reading, the quality of smears in our setting was quite good, and a further, major improvement in the PR rate seems unlikely. A not insignificant PR rate is unavoidable and should be considered a limit of the AutoPap system.

Comparisons of cytologic reports from conventional and AutoPap-assisted reading have very little relevance, because neither procedure can be used as a

reference standard, and comparisons of accuracy should be based mainly on the final outcome: that is, the detection of CIN $\geq$ Grade 2. Another relevant indicator of performance is the rate of actionable reports (e.g., reports that prompt a 6-month repeat smear or immediate referral for colposcopy), because they have considerable impact on overall costs: The actionable report rate was significantly lower for AutoPap-assisted reading compared with conventional reading in the current study.

The current experience suggests that conventional and AutoPap-assisted reading have essentially the same sensitivity and that AutoPap-assisted reading has slightly greater specificity. For this reason, comparison of AutoPap-assisted and conventional reading should focus mainly on cost analysis.

Cost analysis in the current study was careful and reliable, although it is evident that, in different settings/countries, staff costs are different, personnel other than cytopathologists are employed for reading, and the cost of quality control as well as the rate of abnormal smears are variable. However, the essential scheme of cost analysis may be used for other settings, provided that local unitary costs are defined carefully.

The cost of the AutoPap machine is a major, fixed cost determinant. Low workloads will maximize the impact on overall costs; however, assuming the maximum workload, the cost of AutoPap-assisted reading in the current experience was slightly higher compared with conventional reading. Only with the hypothesis of an NFR rate of 30%, which hardly may be expected, were the costs similar to conventional reading. Because AutoPap provides categories of the degree of cell abnormality (quintiles), this also may be proposed as a criterion to select patients for conventional reading (e.g., excluded from reading the fifth quintile, which is associated with lesser cell abnormalities). However, in the current experience, such an option did not seem to be rewarding: Four of 28 patients who were diagnosed with CIN $>$ Grade 2 were classified in the fifth quintile, and limiting conventional reading to quintiles 1–4 would miss 14.2% of CIN lesions $>$ Grade 2.

AutoPap-assisted reading of cervical smears reduces the need for conventional reading, and its use may be proposed as an alternative method to conventional reading for settings in which sufficient numbers of readers are not available or when implementing a new program with newly employed staff. Adoption of microscopes with automatic positioning to selected FOVs may reduce reading time further, although the cost-benefit balance of this costly technology also needs to be considered carefully.

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