tract in urethral suspension procedures for stress incontinence. Int Urogynecol J Pelvic Floor Dysfunct 1999;10:15–21.
29. Pace J, Ballard CA, Klutke J, Klutke C, Kobak W. Intraoperative transvesical cystoscopy for urogynecologic procedures. Int Urogynecol J Pelvic Floor Dysfunct 1997;8:265–9.
30. Miklos JR, Kohli N, Sze EHM, Saye WB. Percutaneous suprapubic teloscopy: A minimally invasive cystoscopic technique. Obstet Gynecol 1997;89:476–8.
31. Harris RL, Cundiff GW, Theofrastous JP, Yoon H, Bump RC, Addison WA. The value of intraoperative cystoscopy in urogynecologic and reconstructive pelvic surgery. Am J Obstet Gynecol 1997;177:1367–9.
32. Councell RB, Thorp JM, Sandridge DA, Hill ST. Assessments of laparoscopic-assisted vaginal hysterectomy. J Am Assoc Gynecol Laparosc 1994;2:49–56.
33. Timmons MC, Addison WA. Suprapubic teloscopy: Extraperitoneal intraoperative technique to demonstrate ureteral patency. Obstet Gynecol 1990;75:137–9.

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Received March 12, 1999.
Received in revised form May 17, 1999.
Accepted June 17, 1999.

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Screening for squamous intraepithelial lesions with fluorescence spectroscopy

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***Objective*: To evaluate the accuracy of fluorescence spectroscopy in screening for squamous intraepithelial lesions (SILs) and to compare its performance with that of Papanicolaou smear screening, colposcopy, cervicoscopy, cervicography, and human papillomavirus (HPV) testing.**

***Data Sources*: Receiver operating characteristic (ROC) curve analysis was used to analyze performance by fluorescence spectroscopy (primary data) and other methods (secondary data).**

***Methods of Study Selection*: In our search, 275 articles were identified in MEDLINE (1966–1996). Articles were included if the investigators had studied a population in whom low disease prevalence was expected; used either Papanicolaou smear screening and colposcopy or colposcopically directed biopsy as a standard against which the screening technique was measured, and included enough data for recalculation of reported sensitivities and specificities.**

***Tabulation, Integration, and Results*: Receiver operating characteristic curves for fluorescence spectroscopy were calculated using a Bayesian algorithm, and ROC curves for the other screening methods were constructed using meta-analytic techniques. Areas under the ROC curves and Q points were calculated. Screening colposcopy had the highest area under the curve (0.95), followed by screening cervicography (0.90), HPV testing (0.88), cervicoscopy (0.85), fluorescence spectroscopy (0.76), and Papanicolaou smear screening (0.70).**

***Conclusion*: In terms of screening for SILs, fluorescence spectroscopy performed better than the standard technique, Papanicolaou smear screening, and less well than screening colposcopy, cervicography, HPV testing, and cervicoscopy. The promise of this research technique warrants further investigation. (Obstet Gynecol 1999;94:889–96. © 1999 by The American College of Obstetricians and Gynecologists.)**

Although use of Papanicolaou smear screening has led to a substantial decrease in cervical cancer–related mortality over the last 50 years, this screening method still has disadvantages: a high false-positive rate and a typically week-long wait for results. Therefore, new technologies for screening for and diagnosis of cervical cancer and squamous intraepithelial lesions (SILs) are being evaluated. One of those, laser-induced fluorescence spectroscopy, is a noninvasive real-time technique for screening for and diagnosis of neoplasia,[1] in which a fiberoptic probe is placed on the cervix, illuminating the tissue with low-power, monochromatic light and collecting fluorescent light emitted by the tissue. The fluorescence spectrum is recorded. The shape of the spectrum is based on the number of fluorophores in the tissue.[1] Different levels of fluorescence are seen in normal, preneoplastic, and neoplastic tissue.[2]

We have been developing and testing algorithms for SIL diagnosis and screening using fluorescence spectroscopy.[3,4] For the diagnosis of SIL, we reported sensitivities of 87% for squamous epithelium, 96% for

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This study was supported by the National Science Foundation and the Whitaker Foundation. The contributions of E. Neely Atkinson, PhD, and Judy Sandella, CNP, MS, are gratefully acknowledged.

0029-7844/99/$20.00
PII S0029-7844(99)00408-1

Table 1. Performance of Papanicolaou Smear Screening

First author	Threshold	Standard		TP	FP	FN	TN	P (%)	100-Sp (%)	Se (%)	Sp (%)
		Pos	Neg								
Anderson[12]	CIN 1	Bx	Colpo and Pap, or bx	70	12	121	25	0.84	33	37	67
Bigrigg[13]	CIN 1	Bx	Colpo and Pap, or bx	668	16	266	31	0.95	34	71	66
Bolger[14]	CIN 1	Bx	Colpo and Pap, or bx	25	37	11	18	0.40	67	68	33
Chomet[15]	CIN 1	Bx	Colpo and Pap, or bx	65	15	37	26	0.71	37	64	63
Engineer[16]	CIN 1	Bx	Bx	71	87	10	303	0.17	22	87	78
Frisch[17]	CIN 1	Bx	Bx	2	2	3	21	0.18	12	43	88
Giles[18]	CIN 2	Bx	Colpo and Pap, or bx	5	9	3	182	0.04	5	60	95
Gunderson[19]	CIN 1	Bx	Bx	4	2	16	31	0.38	9	23	91
Haddad*	CIN 1	Bx	Bx	87	13	12	9	0.82	58	87	42
Hellberg[20]	CIN 2	Bx	Bx	15	3	65	15	0.82	20	19	80
Kashimura[21]	CIN 1	Bx	Bx	9	0	0	2	0.82	17	95	83
Morrison[22]	CIN 1	Bx	Bx	23	50	10	44	0.26	53	69	47
Nyirjesy[23]	CIN 1	Bx	Bx	83	26	24	0	0.80	98	77	2
Okagaki[24]	CIN 1	Bx	Bx	1269	928	264	1084	0.43	46	83	54
Parker[25]	CIN 1	Bx	Bx	154	30	20	237	0.39	12	88	88
Ramirez[26]	CIN 1	Bx	Bx	9	2	6	1	0.83	63	59	38
Reid[27]	CIN 2	Bx	Bx	12	5	11	60	0.26	9	52	91
Soost[28]	CIN 1	Bx	Bx	1205	186	454	241	0.80	44	73	56
Soutter[29†]	CIN 1	Bx	Bx	42	18	18	26	0.58	41	70	59
Soutter[29†]	CIN 1	Bx	Bx	47	19	0	2	0.69	89	99	11
Stafl[30]	CIN 2	Bx	Bx	3	5	3	15	0.23	27	50	73
Szarewski[31]	CIN 1	Bx	Colpo or bx	13	3	82	17	0.83	18	14	82
Tait[32]	CIN 1	Bx	Bx	26	14	25	0	0.78	97	51	3
Tawa[33]	CIN 1	Bx	Bx	14	25	67	291	0.20	8	18	92
Upadhyay[34]	CIN 1	Bx	Bx	238	52	2	16	0.78	76	99	24
Unweighted mean										62	
Weighted mean										73	
Unweighted mean											60
Weighted mean											63

Threshold = threshold for diagnosis of abnormality; Pos = technique used to determine presence of disease; Neg = technique(s) used to determine absence of disease; TP = number of true-positive; FP = number of false-positive; FN = number of false-negative; TN = number of true-negative; P = prevalence of disease; Sp = specificity; Se = sensitivity; CIN = cervical intraepithelial neoplasia; Bx = biopsy; Colpo = colposcopy.

* Haddad NG, Hussein IY, Livingstone JR, Smart GE. Colposcopy in teenagers [letter]. BMJ 1988;297:29–30.

† Papanicolaou smears were sent to two different laboratories.

columnar epithelium, and 78% for the transformation zone.[5] We compared the results of a clinical trial of fluorescence spectroscopy for diagnosis of SIL in a referral setting with results reported for other diagnostic techniques.[6] In the present study, fluorescence spectroscopy was used in the screening setting.

In our prior work,[6] we evaluated the discriminative ability of tests for cervical precancer using receiver operating characteristic (ROC) curve analysis, a method increasingly being used to evaluate medical tests by the Food and Drug Administration as new devices are developed.[7–10] In this study, we did ROC curve analysis using data collected in the screening setting. Fahey et al[11] recently published a meta-analysis of the Papanicolaou smear technique in screening and diagnostic settings. They estimated a sensitivity of 58% and a specificity of 68% in the combined settings. In that study, diagnostic and screening populations were combined. In the current and our previous work, we separated diagnostic from screening populations for the meta-analysis.[6]

Data Sources

Two methods of data collection were required for this study. For fluorescence spectroscopy, we used primary data collected from women in the screening setting.[5] Subjects in the clinical study were recruited using an advertisement offering a free screening Papanicolaou smear, cancer-screening gynecologic examination, colposcopic examination, and fluorescence spectroscopic measurement of the cervix. Women were scheduled for screening if they had no histories of abnormal Papanicolaou smears, had no current signs of vaginal infections, and were not pregnant. A history was obtained from each subject, and a gynecologic examination, Papanicolaou smear screening, and colposcopy were done as well. A research spectroscopic system incorporating a pulsed nitrogen laser, a fiberoptic probe, and an optical multichannel analyzer was used to record fluorescence spectra. The system measured tissue fluorescence at excitation of 337, 380, and 460 nm and has been

Table 2. Performance of Colposcopy

First author	Threshold	Standard		TP	FP	FN	TN	P (%)	100-Sp (%)	Se (%)	Sp (%)
		Pos	Neg								
Cecchini[35]	CIN 2	Bx or LEEP	Colpo and Pap, or LEEP or bx	18	591	0	2391	0.01	20	97	80
Cecchini[36]	CIN 2	Bx or LEEP	Colpo and Pap, or LEEP or bx	19	284	0	571	0.02	33	97	67
Davison[37]	CIN 1	Bx	Colpo and Pap, or bx	25	6	8	157	0.17	4	75	96
Giles[18]	CIN 1	Bx	Pap or bx	15	5	7	173	0.11	3	67	97
Hockstad[38]	CIN 1	Bx	Colpo and Pap, or bx	3	20	4	43	0.10	32	44	68
Olatunbosun[39]	CIN 1	Bx	Colpo and Pap, or bx	39	41	0	1469	0.03	3	99	97
Unweighted mean										80	
Weighted mean										86	
Unweighted mean											84
Weighted mean											83

Pap = Papanicolaou smear screening; LEEP = loop electrosurgical excision procedure; other abbreviations as in Table 1.

described in detail elsewhere.[2–5] On average, spectra were collected from two normal areas of squamous epithelium, two normal areas of columnar epithelium, and one area of the transformation zone. If detected, colposcopically abnormal sites were also measured. Approximately 10% of screening Papanicolaou smear results in the United States are abnormal.[11]

Fifty-five women were screened in this clinical trial. Spectroscopy data from one patient were lost, leaving data from 54 for analysis. All 54 women had Papanicolaou smears adequate for assessment; 50 had normal Papanicolaou smear results and four (10%) had abnormal results. One woman had a high-grade SIL, one had atypical cells of uncertain significance favoring dysplasia, and the other two had atypical cells of uncertain significance favoring human papillomavirus (HPV). The four women with abnormalities were referred for colposcopically directed biopsies. The woman with high-grade SIL was treated in our clinic with the loop electrosurgical excision procedure.

For all other screening techniques, we analyzed data from published reports identified in a MEDLINE search covering the period of 1966–1996. We used the search terms "Papanicolaou smear," "colposcopy," "cervicoscopy," "cervicography," "HPV testing," "fluorescence spectroscopy," and "polar probe." Each term was combined with "screening," "sensitivity," "specificity," "positive predictive value," "negative predictive value," and "receiver operating characteristic curve."

Studies were selected using three criteria. The intent of the test had to be a screening in a low-disease-prevalence setting; reports of studies in which women were referred with abnormal Papanicolaou smear results were excluded because we assumed that such populations would have higher disease prevalence. The standard against which the technique was measured had to be either Papanicolaou smear screening and colposcopy or colposcopically directed biopsy, and the sensitivity and specificity calculations had to be reproducible from data in the report. The first two criteria were chosen to ensure selection of studies that were similar to our fluorescence spectroscopy study in terms of population prevalence characteristics and data analysis. In all selected studies, colposcopically normal areas were not biopsied.

Two hundred seventy-five articles were identified in the MEDLINE search, 66 of which were review articles about tests without data for analysis. Of the 59 articles reviewed by Fahey et al[11] in their meta-analysis of Papanicolaou smear screening, 28 were reports of studies in which Papanicolaou smears were used for screening in a low-disease-prevalence setting, and that technique was compared with biopsy (disease presence or absence was determined with biopsy). Twenty-four[12–34] (Haddad NG, Hussein IY, Livingstone JR, Smart GE. Colposcopy in teenagers [letter]. BMJ 1988;297:29–30) of those 28 were suitable for this analysis (Table 1). In six[18,35–39] of 86 articles about colposcopy, the authors reported that colposcopy had been used for screening and sufficient information was included to permit recalculation of sensitivities and specificities against the standards (Table 2). In those, the standard was biopsy and disease absence was demonstrated by negative colposcopic and Papanicolaou smear results. Of the eight articles on cervicoscopy in the screening setting, three[40–42] were used for this analysis (Table 3). For those studies, disease presence was determined with biopsy, whereas disease absence was demonstrated by negative biopsy findings, negative colposcopic results, or a combination of other tests. In five[33,43–46] of 35 articles about cervicography, the authors reported that cervicography had been used for screening and sufficient detail was included for our analysis (Table 4). Disease presence was determined with biopsy, and disease absence was demonstrated by negative Papanicolaou smear or biopsy results or negative findings by cervicography, cervicoscopy or colposcopy. There were 20 articles about HPV testing using ViraPap (Digene Corp., Beltsville, MD), Hybrid Capture (Digene Corp.), or PCR. There would have been too few data for an ROC curve if the analysis had been limited to one type of HPV testing, so articles on

Table 3. Performance of Cervicoscopy

First author	Threshold	Standard		TP	FP	FN	TN	P (%)	100-Sp (%)	Se (%)	Sp (%)
		Pos	Neg								
Cecchini[40]	CIN2	Bx	Cyt, cervicogr, and cervicosc, or colpo or bx	7	334	1	1694	0.004	16	83	84
Megevand[41]	HPV	Bx	Pap and cervicosc, or colpo or bx	55	21	229	2121	0.12	1	19	99
Slawson[42]	HPV	Bx	Cyt and cervicogr, or colpo or bx	47	38	93	2375	0.05	2	34	98
Unweighted mean										45	
Weighted mean										25	
Unweighted mean											94
Weighted mean											94

Cyt = cytology; cervicogr = cervicography; cervicosc = cervicoscopy; HPV = human papillomavirus; Pap = Papanicolaou smear screening; other abbreviations as in Table 1.

any of these three techniques were considered. Three articles[46–48] were on techniques used in a screening setting and were suitable for analysis (Table 5). Disease presence was determined with Papanicolaou smear screening or biopsy; disease absence was demonstrated by negative Papanicolaou smear or biopsy findings or negative findings by cervicography or colposcopy. The one article found on use of the polar probe was on use of that technique in the diagnostic setting.

Tabulation and Integration

Bayesian statistical methods were used to classify primary data collected with fluorescence spectroscopy. Details of the algorithm have been reported elsewhere.[3,4] The results of the algorithm were used to determine an ROC curve and calculate the area under the curve using the Excel software program (Microsoft Corp., Redmond, WA) following the method of Metz[7] and Moses et al.[10]

For the other screening techniques, data from the published studies were used to reproduce the reported calculations of sensitivity and specificity. Receiver operating characteristic curves and respective areas under the curves were calculated using the formula described by Littenberg and Moses,[8,10] using Excel software. The method of meta-analysis is described in detail by Mitchell et al.[6]

The thresholds of abnormality varied among studies. In some studies, the presence of normal tissue was distinguished from all abnormalities (atypia, low-grade SILs, high-grade SILs, and cancer), and in other studies, the presence of normal tissue and atypia were distinguished from low-grade SILs, high-grade SILs, and cancer. Tests were considered positive if they indicated low-grade SILs, high-grade SILs, or cancer. Those thresholds were accounted for by the meta-analytic method of Littenberg and Moses.[8] In those studies, SILs were termed "cervical intraepithelial neoplasia" (CIN) and were classified as grade 1, 2, or 3. Low-grade SILs correspond to HPV or CIN 1, and high-grade SILs correspond to CIN 2 or CIN 3. Many of the studies were analyzed before the institution of the Bethesda system, so grades of CIN used by those authors are used in our tables as well.

Table 4. Performance of Cervicography

First author	Threshold	Standard		TP	FP	FN	TN	P (%)	100-Sp (%)	Se (%)	Sp (%)
		Pos	Neg								
Baldauf[43]*	CIN 1	Bx or ECC	Colpo or bx	51	135	11	1149	0.05	11	82	89
Baldauf[43]*	CIN 1	Bx or ECC	Colpo or bx	33	39	29	1245	0.05	3	53	97
Cecchini[44]	HGSIL	Bx	Pap, cervicosc, and cervicogr, or colpo or bx	5	280	3	1748	0.004	14	61	86
Coibon[45]	CIN 1	Bx	Pap and cervicogr, or bx	106	34	17	3858	0.03	1	86	99
Schneider[46]	CIN 2	Bx	Pap and cervicogr, or colpo or bx	17	82	21	847	0.04	9	45	92
Tawa[33]	CIN 1	Bx	Pap and cervicogr, or colpo or bx	72	301	9	2889	0.02	9	88	91
Unweighted mean										69	
Weighted mean										76	
Unweighted mean											92
Weighted mean											95

ECC = endocervical curettage; HGSIL = high-grade squamous intraepithelial lesions; Pap = Papanicolaou smear screening; cervicosc = cervicoscopy; cervicogr = cervicography; other abbreviations as in Table 1.

* Baldauf et al[43] reported data using both the original reporting criteria (negative findings, positive findings, technically defective cervigram) and the new criteria (negative findings, atypical findings, positive findings, technically defective cervigram).

Table 5. Performance of Human Papillomavirus Testing

First author	Test(s)	Threshold	Standard Pos	Standard Neg	TP	FP	FN	TN	P (%)	100-Sp (%)	Se (%)	Sp (%)
Cuzick[47]	PCR	CIN 1	Cyt	Cyt	43	97	85	1754	0.06	5	34	95
Schneider[46]	Hybrid Capture	HGSIL	Bx	Pap and cervicogr, or colpo or bx	19	41	19	888	0.04	4	50	96
Zazove[48]	ViraPap, PCR	LGSIL	Bx	Bx	164	2	16	18	0.90	12	91	88
Unweighted mean											58	
Weighted mean											65	
Unweighted mean												93
Weighted mean												95

PCR = polymerase chain reaction; Cyt = cytology; HGSIL = high-grade squamous intraepithelial lesions; Pap = Papanicolaou smear screening; cervicogr = cervicography; LGSIL = low-grade squamous intraepithelial lesions; other abbreviations as in Table 1.

Results

The ROC curve calculated for fluorescence spectroscopy using Bayesian statistical methods is presented in Figure 1. The area under the curve was 0.76. The ROC curves for Papanicolaou smear screening, colposcopy, cervicoscopy, cervicography, and HPV testing are shown individually in Figure 2. The curves for all screening techniques are superimposed in Figure 3. The areas under the curves were 0.70 for Papanicolaou smear screening, 0.95 for colposcopy, 0.85 for cervicoscopy, 0.90 for cervicography, and 0.88 for HPV testing. Fluorescence spectroscopy compared favorably with the other tests but outperformed Papanicolaou smear screening, the current standard screening technique.

Q points are the uppermost points in ROC curves, at which sensitivity equals specificity. They are preferred by some meta-analysts for comparisons of ROC curves because confidence intervals can be obtained. The corresponding Q points and stndard errors were as follows: Papanicolaou smear screening, 0.65 (0.04); colposcopy, 0.89 (0.05); cervicoscopy, 0.71 (0.07); cervicography, 0.83 (0.05); and HPV testing, 0.81 (0.07). A statistic could not be calculated for fluorescence spectroscopy because the ROC curve generated was from data from one study. The Q points for all other techniques were statistically significantly different from that of Papanicolaou smear screening: colposcopy, $P < .005$; cervicoscopy, $P < .05$; cervicography, $P < .005$; and HPV testing, $P < .005$.

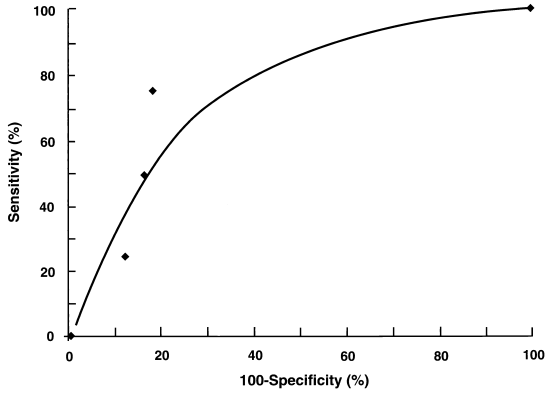

Figure 1. Receiver operating characteristic (ROC) curve for screening fluorescence spectroscopy. Dots are data points and the line is a fitted ROC curve.

Discussion

Cervical cancer is a disease for which screening is suitable because it is a serious disease for which early treatment is beneficial. Good screening tests should be easy to administer, be inexpensive, and cause minimal discomfort. Papanicolaou smear screening meets those

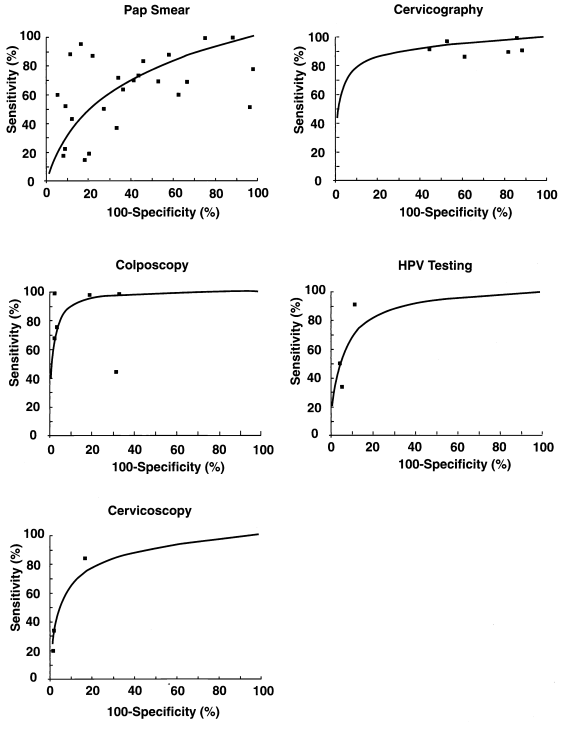

Figure 2. Receiver operating characteristic (ROC) curves for Papanicolaou (Pap) smear screening, colposcopy, cervicoscopy, cervicography, and human papillomavirus (HPV) testing. Dots are data points and lines are fitted ROC curves.

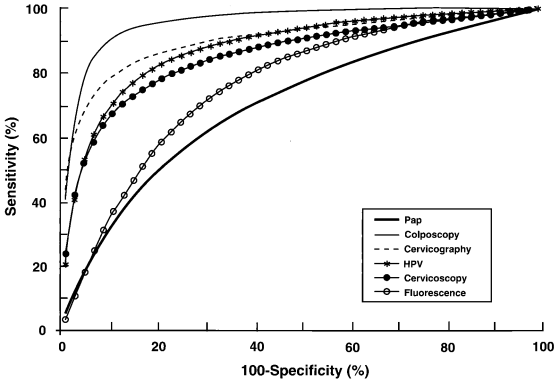

Figure 3. Superimposed receiver operating characteristic curves for all six screening techniques studied. HPV = human papillomavirus testing; Pap = Papanicolaou smear screening.

requirements, although as assessed by Fahey et al,[11] it has a sensitivity of 58% and specificity of 68%. Given these low levels, strategies that increase sensitivity and specificity may be called for. Adding a second screening test is one strategy; improving sensitivity and specificity of Papanicolaou smear screening is another.

The incidence and prevalence of cervical cancer are decreasing. Lesions are being detected in the precursor stage. In the United States, the threshold for evaluation has been reset so that women with almost any form of abnormal Papanicolaou smear are now referred for colposcopy, which has increased the cost of cervical cancer screening.

In our analysis, screening colposcopy was an excellent discriminator, outperforming fluorescence spectroscopy, cervicography, HPV testing, cervicoscopy, and Papanicolaou smear screening. Colposcopy, however, is expensive, requires training, and is labor-intensive and therefore probably should not be considered as a screening test. Cervicography and HPV testing also perform well in the screening setting. Cervicography, like colposcopy, is highly dependent on good visual skills, is expensive, and is labor- and equipment-intensive. Human papillomavirus testing is not dependent on good visual skills, but it might not be cost-effective.

In our trial, in which Papanicolaou smear screening and colposcopy were used as the standard, fluorescence spectroscopy outperformed Papanicolaou smear screening in screening for SILs. This work is preliminary and is based on only one study, but the screening technique shows promise when compared with existing techniques. Studies of screening colposcopy and fluorescence spectroscopy using biopsy as a standard are needed. Screening fluorescence spectroscopy will need to be subjected to randomized multicenter clinical trials so that it may be determined whether it is a useful and cost-effective adjuvant to Papanicolaou smear screening. More important, any new method needs to be subjected to cost-effectiveness analysis before it is introduced into medical practice.

A potential criticism of the clinical measurements in this screening study is that each woman underwent colposcopy before fluorescence spectroscopy, which provided assurance that the cervix of a woman with negative Papanicolaou smear findings truly was clinically disease free. Our probe is the size of a pencil and measures a 2-mm area. Our goal was to test our algorithm, so we wanted to be sure we were placing the probe on normal tissue.

Fluorescence spectroscopy makes real-time diagnosis possible at the time of patient screening. Women then can be treated at screening visits, saving women and the health care system money and time that would have been spent on return visits for colposcopy and colposcopically directed biopsies and for treatment, and saving women the 1- to 2-week anxiety-producing period in which results are awaited, as well as costs of time off work, child care, and parking. Our cost-effectiveness analysis showed that in the diagnostic setting, fluorescence spectroscopy could save the United States $625 million annually.[49] We are pursuing a similar cost-effectiveness analysis of fluorescence spectroscopy in the screening setting.

Another advantage of fluorescence spectroscopy is its ease of use. In the United States, most Papanicolaou smear screening is done by physicians, physician assistants, and nurse practitioners. In rural areas and some underserved urban settings, screening is done by registered nurses. In developing countries, much of the screening is done by nondegreed trained health care workers. In some settings, visual inspection of the cervix is the only affordable option. In other settings, health care workers do Papanicolaou smear screening. Fluorescence spectroscopy involves simply the placement of a probe on the cervix, so it is technically easier to do than Papanicolaou smear screening and could be used by less trained members of the health care team, further reducing costs. We found that with fluorescence spectroscopy, a hospital aide can obtain the same results as a physician or nurse practitioner can (unpublished data). The algorithms work without a priori knowledge of the presence of SILs, and thus expertise in recognizing lesions is not necessary.[3]

Although our data suggest that fluorescence spectroscopy might outperform Papanicolaou smear screening in detecting SILs, Papanicolaou smear screening does have an advantage in that it permits sampling of the endocervical canal. The flat fluorescence spectroscopy probe used in this study cannot—a major limitation to the use of the technology in the screening setting. Our team is working on strategies for assessing the endocervical canal spectroscopically. Also, the current probe

measures only a small area of the cervix, another barrier for use in screening. The probe should be capable of measuring the surface of many different sizes and shapes of cervices. Those issues will have to be explored extensively before the technology is used in larger screening trials.

The research-level fluorescence spectroscopy device performs well, but the design of a commercial prototype that performs as well and meets the stringent requirements of the Food and Drug Administration is a challenge to industry. Making probes that can be sterilized readily and that can sample the whole cervix adequately will be equally challenging. For society to benefit maximally from this technology, the device must be priced so the savings in health care dollars from the fewer clinic visits are realized. Our group estimates that devices could be made for as little as $3600.

With high value placed on streamlining procedures and conserving resources, exciting opportunities lie ahead for women and physicians willing to explore the benefit optical technologies might bring.

References

1. Richards-Kortum R, Mitchell MF, Ramanujam N, Mahadevan A, Thomsen S. In vivo fluorescence spectroscopy: Potential for noninvasive, automated diagnosis of cervical intraepithelial neoplasia and use as a surrogate endpoint biomarker. J Cell Biochem Suppl 1994;19:111–9.
2. Ramanujam N, Mitchell MF, Mahadevan A, Thomsen S, Richards-Kortum R. In vivo diagnosis of cervical intraepithelial neoplasia (CIN) using 337-nm-excited laser-induced fluorescence. Proc Natl Acad Sci U S A 1994;91:10193–7.
3. Ramanujam N, Mitchell MF, Mahadevan-Jansen A, Thomsen SL, Staerkel G, Malpica A, et al. Cervical pre-cancer detection using a multivariate statistical algorithm based on laser induced fluorescence spectra at multiple excitation wavelengths. Photochem Photobiol 1996;64:720–35.
4. Tumer K, Ramanujam N, Ghosh J, Richards-Kortum R. Ensembles of radial basis function networks for spectroscopic detection of cervical pre-cancer. IEEE Trans Biomed Eng 1998;45:953–61.
5. Brookner CK, Utzinger U, Staerkel G, Richards-Kortum R, Mitchell MF. Cervical fluorescence of normal women. Lasers Surg Med 1999;24:29–37.
6. Mitchell MF, Cantor SB, Ramanujam N, Tortolero-Luna G, Richards-Kortum R. Fluorescence spectroscopy for the diagnosis of squamous intraepithelial lesions of the cervix. Obstet Gynecol 1999;93:462–70.
7. Metz CE. Basic principles of ROC analysis. Semin Nucl Med 1978;8:283–98.
8. Littenberg B, Moses LE. Estimating diagnostic accuracy from multiple conflicting reports: A new meta-analytic method. Med Decis Making 1993;13:313–21.
9. Swets JA. Measuring the accuracy of diagnostic systems. Science 1988;240:1285–93.
10. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: Data-analytic approaches and some additional considerations. Stat Med 1993;12:1293–316.
11. Fahey MT, Irwig L, Macaskill P. Meta-analysis of Pap test accuracy. Am J Epidemiol 1995;141:680–9.
12. Anderson DJ, Flannelly GM, Kitchener HC, Fisher PM, Mann EM, Campbell MK, et al. Mild and moderate dyskaryosis: Can women be selected on the basis of social criteria? BMJ 1992;305:84–7.
13. Bigrigg MA, Codling BW, Pearson P, Read MD, Swingler GR. Colposcopic diagnosis and treatment of cervical dysplasia at a single clinic visit. Experience of low-voltage diathermy loop in 1000 patients. Lancet 1990;336:229–31.
14. Bolger BS, Lewis BV. A prospective study of colposcopy in women with dyskaryosis or koilocytosis. Br J Obstet Gynaecol 1988;95:1117–9.
15. Chomet J. Screening for cervical cancer: A new scope for general practitioners? Results of the first year of colposcopy in general practice. BMJ 1987;294:1326–8.
16. Engineer AD, Misra JS. The role of routine outpatient cytologic screening for early detection of carcinoma of the cervix in India. Diagn Cytopathol 1987;3:30–4.
17. Frisch LE, Parmar H, Buckley LD, Chalem SA. Improving the sensitivity of cervical cytologic screening. Acta Cytol 1990;34:136–9.
18. Giles JA, Hudson E, Crow J, Williams D, Walker P. Colposcopic assessment of cervical cytology screening. BMJ 1988;286:1096–102.
19. Gunderson JH, Schauberger CW, Rowe NR. The Papanicolaou smear and the cervicogram. J Reprod Med 1988;33:46–8.
20. Hellberg D, Axelsson O, Gad A, Nilsson S. Conservative management of the abnormal smear during pregnancy. A long-term follow-up. Acta Obstet Gynecol Scand 1987;66:195–9.
21. Kashimura M, Matsuura Y, Shinohara M, Baba S, Obara K, Fujiwara H, et al. Comparative study of cytology and punch biopsy in cervical intraepithelial neoplasia during pregnancy. A preliminary report. Acta Cytol 1991;35:100–4.
22. Morrison BW, Erickson ER, Doshi N, Russo JF. The significance of atypical cervical smears. J Reprod Med 1988;33:809–12.
23. Nyirjesy I. Atypical or suspicious cervical smears. JAMA 1972;222:691–3.
24. Okagaki T, Zelterman D. Information discrimination and divergence in cytology. Acta Cytol 1991;35:25–9.
25. Parker A. A comparison of preoperative cervical cytology with subsequent histology. N Z Med J 1986;99:414–6.
26. Ramirez EJ, Hernandez E, Miyazawa K. Cervical conization findings in women with dysplastic cervical cytology and normal colposcopy. J Reprod Med 1990;35:359–61.
27. Reid R, Greenberg MD, Lorincz A, Jenson AB, Laverty CR, Husain M, et al. Should cervical cytologic testing be augmented by cervicography or human papillomavirus deoxyribonucleic acid detection? Am J Obstet Gynecol 1991;164:1461–9.
28. Soost HJ, Lange HJ, Lehmacher W, Ruffing-Kullmann B. The validation of cervical cytology. Acta Cytol 1991;35:8–14.
29. Soutter WP, Wisdom S, Brough AK, Monaghan JM. Should patients with mild atypia in a cervical smear be referred for colposcopy? Br J Obstet Gynaecol 1986;93:70–4.
30. Stafl A. Cervicography: A new method for cervical cancer detection. Am J Obstet Gynecol 1981;139:815–25.
31. Szarewski A, Cuzick J, Edwards R, Butler B, Singer A. The use of cervicography in a primary screening service. Br J Obstet Gynaecol 1991;98:313–7.
32. Tait IA, Balawattegama A, Rees E. Screening for cervical dysplasia in department of genitourinary medicine. Genitourin Med 1988;64:255–8.
33. Tawa K, Forsythe A, Cove JK, Saltz A, Peters HW, Watring WG. A comparison of the Papanicolaou smear and the cervicogram: Sensitivity, specificity and cost analysis. Obstet Gynecol 1988;71:229–35.

34. Upadhyay SN, Jha RS, Sinha TK, Mishra NK. Accuracy of cytology in screening for cervical cancer. Indian J Med Res 1984;80:457–62.
35. Cecchini S, Bonardi R, Iossa A, Zappa M, Ciatto S. Colposcopy as a primary screening test for cervical cancer. Tumori 1997;83:810–3.
36. Cecchini S, Iossa A, Bonardi R, Ciatto S, Cariaggi P. Comparing two modalities of management of women with cytologic evidence of squamous or glandular atypia: Early repeat cytology or colposcopy. Tumori 1997;83:732–4.
37. Davison JM, Marty JJ. Detecting premalignant cervical lesions. Contribution of screening colposcopy to cytology. J Reprod Med 1994;39:388–92.
38. Hockstad RL. A comparison of simultaneous cervical cytology, HPV testing, and colposcopy. Fam Pract Res J 1992;12:53–60.
39. Olatunbosun OA, Okonofua FE, Ayangade SO. Screening for cervical neoplasia in an African population: Simultaneous use of cytology and colposcopy. Int J Gynaecol Obstet 1991;36:39–42.
40. Cecchini S, Bonardi R, Mazotta A, Grazzini G, Iossa A, Ciatto S. Testing cervicography and cervicoscopy as screening tests for cervical cancer. Tumori 1993;79:22–5.
41. Megevand E, Denny L, Dehaeck K, Soeters R, Bloch B. Acetic acid visualization of the cervix: An alternative to cytologic screening. Obstet Gynecol 1996;88:383–6.
42. Slawson DC, Bennett JH, Herman JM. Are Papanicolaou smears enough? Acetic acid washes of the cervix as adjunctive therapy: A HARNET study. Harrisburg Area Research Network. J Fam Pract 1992;35:271–7.
43. Baldauf JJ, Dreyfus M, Lehmann M, Ritter J, Philippe E. Cervical cancer screening with cervicography and cytology. Eur J Obstet Gynecol Reprod Biol 1995;58:33–9.
44. Cecchini S, Iossa A, Bonardi R, Gustavino C, Ciatto S. Evaluation of the sensitivity of cervicography in a consecutive colposcopic series. Tumori 1992;78:211–3.
45. Coibon M, Autier P, Vandam P, Delovelle A, Huet F, Hertens D, et al. Is there a role for cervicography in the detection of premalignant lesions of the cervix uteri? Br J Cancer 1994;70:125–8.
46. Schneider A, Zahm DM, Kirchmayr R, Schneider VL. Screening for cervical intraepithelial neoplasia grade 2/3: Validity of cytologic study, cervicography, and human papillomavirus detection. Am J Obstet Gynecol 1996;174:1534–41.
47. Cuzick J, Szarewski A, Terry G, Ho L, Hanby A, Maddox P, et al. Human papillomavirus testing in primary cervical screening. Lancet 1995;345:1533–6.
48. Zazove P, Reed BD, Gregoire L, Gorenflo DW, Lancaster WD, Ruffin MT, et al. Presence of human papillomavirus infection of the uterine cervix as determined by different detection methods in a low-risk community-based population. Arch Fam Med 1993;2:1250–8.
49. Cantor SB, Mitchell MF, Tortolero-Luna G, Bratka CS, Bodurka DC, Richards-Kortum R. Cost-effectiveness analysis of diagnosis and management of cervical squamous intraepithelial lesions. Obstet Gynecol 1998;91:270–7.

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Received March 17, 1999.
Received in revised form April 30, 1999.
Accepted May 13, 1999.

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