Chapter 10: Cervical Cancer Screening Using Visualization Techniques

Thomas C. Wright, Jr.

There is a resurgence of interest in the use of visual techniques to identify cervical intraepithelial neoplasia (CIN). These visual techniques can be divided into two general categories. One is the simple visual screening method, such as direct visual inspection (DVI), during which the cervix is visualized with either the naked eye or a low-power magnification device after the application of a solution of 3% to 5% acetic acid that is used as a chemical contrast agent to highlight regions of CIN. DVI has been evaluated in a number of large clinical trials and is considered by some to be a possible alternative to cervical cytology for primary cervical cancer screening in low-resource settings. The advantages of DVI compared with cervical cytology for these settings are that it is inexpensive, it does not require a laboratory infrastructure, and it provides an immediate result, allowing the use of “screen and treat” protocols. The major disadvantage of DVI is that it is relatively nonspecific and that its sensitivity is low compared with testing for human papillomavirus. The other category of visual techniques includes devices that use electro-optical sensors and light of specific wavelengths produced by lasers or specialized light sources to identify and localize regions of CIN on the cervix. Although these “high-technology” devices are not yet in routine clinical use, several groups and companies have such devices in clinical trials. [J Natl Cancer Inst Monogr 2003;31:66–71]

Over the last several decades, visualization techniques based on identifying cervical lesions using light of various wavelengths have been developed. These techniques could potentially be used for cervical cancer screening, either as an adjunct to cervical cytology or as a replacement for cytology. There are two general categories of visualization techniques.

The first general category of visualization techniques includes approaches that use broad-band light (i.e., the entire spectrum of light composed of both wavelengths that are visible and nonvisible to the naked eye) to illuminate the cervix (Table 1). These techniques include direct visual inspection (DVI), which is the inspection of the cervix after the application of a dilute solution of 3%-5% acetic acid (also known as visual inspection, the acetic acid test, cervicoscopy, and visual inspection with acetic acid [VIA]); the Schiller’s iodine test, in which the cervix is inspected with the naked eye after the application of Lugol’s iodine; speculoscopy, which is the inspection of the cervix after the application of a 3%-5% solution of acetic acid using a low (×4)-magnification device and a special chemiluminescent light; and cervicography, which requires that a photograph be obtained of the cervix after the application of a 3%-5% solution of acetic acid and that the photograph be interpreted by a specially trained expert.

The second general category of visualization techniques includes the methods that use specific wavelengths of light produced by lasers or specialized light sources and electro-optical sensors to detect cervical disease. These high-technology devices are designed to measure a variety of different parameters including 1) endogenous fluorescence, which is light that is produced or emitted by molecules within the cervical tissue when they are exposed to various wavelengths of incident light; 2) the uptake of exogenously applied fluorescent compounds by the cervix or the increases in naturally occurring fluorescence molecules that are induced within the cervical tissue by exogenously applied compounds, like 5-aminolevulinic acid-induced porphyrin fluorescence (1); 3) other parameters, such as the intrinsic electrical resistance of the cervix or the interactions between cervical tissues and specific wavelengths of light or electrical impulses; or 4) a computer-assisted image analysis of reflectance images. Some of the instruments under development that use electro-optical sensors measure a single parameter, whereas others measure multiple parameters. The devices then predict the underlying tissue histology from these biophysical measurements using mathematic algorithms.

There is currently substantially more information on the performance of the simple visual techniques such as DVI than there is for the devices incorporating electro-optical sensors. However, there is considerable interest in the development of the new high-technology devices and a number of devices are in clinical trials. This chapter reviews the recent studies evaluating visual screening methods for primary screening and outlines the key issues that need to be addressed in epidemiologic studies.

SIMPLE VISUAL TECHNIQUES

Simple visual screening techniques are highly controversial. In large part the controversy surrounding these methods stems from the fact that they were first introduced for cervical cancer screening in the 1930s by Schiller (2), but they were largely abandoned once cervical cytology became widely available because of their poor specificity. Therefore, the renewed interest in these techniques as screening methods for low-resource settings is viewed with skepticism by some who perceive them as providing a lower standard of care for women living in the poor regions of the world than is considered acceptable for women living in developed countries.

A variety of different terms have been used to refer to the process of applying a dilute solution of 3%-5% acetic acid to the cervix and then inspecting it using either the naked eye or a hand-held low-magnification device. These terms include direct DVI, VIA (when magnification is not used), visual inspection with acetic acid and magnification or VIAM (when magnifica-
tion is used), aided visual inspection, cervicoscopy, the vinegar acid test, and the acetic acid test (3–7). Recently, a task force of the International Academy of Cytology recommended that the term DVI be used for the process of inspecting the cervix with the naked eye after the application of 3%–5% acetic acid (8).

The task force believed that the term DVI was reasonably descriptive and was preferable to the term VIA, since it allows a clear distinction between this single technique and a number of other visual screening techniques, such as colposcopy, cervicography, and speculoscopy, all of which are techniques that are based on visually inspecting the cervix after the application of a dilute solution of 3%–5% acetic acid. Similar confusion regarding terminology is present with respect to the inspection of the cervix after the application of Lugol's iodine. This method has been widely known for more than 50 years by the two terms, “Schiller's iodine test” and “Lugol's iodine test.” However, some groups have recently begun using the term “visual inspection with Lugol's iodine” (VILI) to refer to this method.

DVI has been evaluated in a number of relatively large clinical trials. Nine of the largest studies that have evaluated the performance of DVI in a screening setting are shown in Table 2. These studies have included a total of more than 21,000 participants. The weighted average sensitivity of DVI for the detection of women with high-grade cervical disease (biopsy-confirmed cervical intraepithelial neoplasia [CIN] 2 and 3 high-grade squamous intraepithelial lesions [HSILs], HSILs on cytology, or invasive cervical cancer) is 0.80 and the specificity is 0.80. The average positive predictive values and negative predictive values are 0.14 and 0.99, respectively. When reviewing these studies, it is clear that there is considerable variation in the performance of the test in different settings. In some studies, the sensitivity of DVI has been reported to be as high as 0.96, whereas in others, it is as low as 0.65. In some instances, the variations in performance may reflect a failure to adjust for verification bias. The specificity of DVI has also varied considerably in the different studies. DVI is a relatively subjective test, and variations in training may account for some of the differences observed in the various clinical studies.

One problem encountered with visual screening techniques is that, with increasing age, the squamocolumnar junction migrates inward from the readily visible portion of the exocervix toward the endocervical canal (9). Because most CIN2 and CIN3 lesions occur immediately adjacent to the squamocolumnar junction, this means that the lesions would be expected to become progressively more difficult to identify with visual methods in older women.

When comparing the performance of DVI as a screening test with that of cervical cytology, it is important to recognize that there is considerable controversy in the literature regarding the performance of cervical cytology as a screening test. One meta-analysis (10) of the performance of cytology reported that the sensitivity of a conventional cervical cytology for identifying

<table>
<thead>
<tr>
<th>Method</th>
<th>Contrast agent</th>
<th>Special equipment</th>
<th>Other terms used for method</th>
</tr>
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<tbody>
<tr>
<td>Direct visual inspection</td>
<td>3%–5% acetic acid</td>
<td>Performed either with or without a low-magnification hand-held device</td>
<td>Acetic acid test, Vinegar test, Cervicoscopy, Aided visual inspection, Visual inspection with acetic acid—without magnification, Visual inspection with acetic acid and magnification</td>
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<tr>
<td>Schiller's iodine test</td>
<td>Lugol's iodine solution</td>
<td>None</td>
<td>Lugol's iodine test, visual inspection with Lugol's iodine</td>
</tr>
<tr>
<td>Speculoscopy</td>
<td>3%–5% acetic acid</td>
<td>Low-magnification device; chemiluminescent light stick</td>
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</tr>
<tr>
<td>Cervicography</td>
<td>3%–5% acetic acid</td>
<td>35-mm camera</td>
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<thead>
<tr>
<th>Author (Year)</th>
<th>Country</th>
<th>No. of participants</th>
<th>For detection of high-grade disease*</th>
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<tbody>
<tr>
<td>Ottaviano (1982)†</td>
<td>Italy</td>
<td>2400</td>
<td>Sensitivity 0.94, Specificity 0.90, PPV 0.20, NPV 0.999</td>
</tr>
<tr>
<td>Cecchini (1993)†</td>
<td>Italy</td>
<td>2105</td>
<td>Sensitivity 0.88, Specificity 0.75, PPV 0.01, NPV 0.999</td>
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<tr>
<td>Megevand (1996)†</td>
<td>South Africa</td>
<td>2426</td>
<td>Sensitivity 0.65, Specificity 0.98, PPV 0.26, NPV 0.995</td>
</tr>
<tr>
<td>Sankaranarayanan (1998)†</td>
<td>India</td>
<td>3000</td>
<td>Sensitivity 0.90, Specificity 0.91, PPV 0.15, NPV 0.998</td>
</tr>
<tr>
<td>Sankaranarayanan (1999)†</td>
<td>India</td>
<td>1351</td>
<td>Sensitivity 0.96, Specificity 0.66, PPV 0.13, NPV 0.996</td>
</tr>
<tr>
<td>Zimbabwe Project (1999)</td>
<td>Zimbabwe</td>
<td>2148</td>
<td>Sensitivity 0.77, Specificity 0.65, PPV 0.19, NPV 0.963</td>
</tr>
<tr>
<td>Denny (2000)†</td>
<td>South Africa</td>
<td>1335</td>
<td>Sensitivity 0.67, Specificity 0.85, PPV 0.11, NPV 0.988</td>
</tr>
<tr>
<td>Belinson (2001)†</td>
<td>China</td>
<td>1997</td>
<td>Sensitivity 0.71, Specificity 0.74, PPV 0.11, NPV 0.983</td>
</tr>
<tr>
<td>Denny (2002)†</td>
<td>South Africa</td>
<td>2698</td>
<td>Sensitivity 0.73, Specificity 0.78, PPV 0.13, NPV 0.984</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>2698</td>
<td>Sensitivity 0.76, Specificity 0.74, PPV 0.12, NPV 0.986</td>
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<tr>
<td></td>
<td>Average</td>
<td></td>
<td>Sensitivity 0.80, Specificity 0.80, PPV 0.14, NPV 0.989</td>
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<tr>
<td></td>
<td>Weighted average</td>
<td></td>
<td>Sensitivity 0.80, Specificity 0.81, PPV 0.14, NPV 0.989</td>
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* CIN2, CIN3, HSIL, or invasive cervical cancer. 
† Histology used to determine presence of high-grade disease. [modified from references (3,4,6,7,13,22–25)].
women with biopsy-confirmed CIN of any grade or cancer was 0.74 and the specificity was 0.68 when the cutoff for referral to colposcopy was atypical squamous cells or higher. However, recent large screening studies have frequently reported a somewhat better performance. In a study from South Africa (7), conventional cervical cytology had a sensitivity of 0.81 and a specificity of 0.88 for the detection of biopsy-confirmed CIN2 and CIN3 or cancer. Similarly, in a Costa Rican (11) study, the sensitivity of a conventional cervical cytology for the detection of biopsy-confirmed CIN2 and CIN3 or cancer was 0.78 and the specificity was 0.95. Overall, it appears that DVI has a sensitivity that is equivalent to that of cervical cytology, but that the specificity is markedly lower.

The lower specificity of DVI compared with cytology will have a considerable impact on the logistics of incorporating DVI into routine cervical cancer screening programs, since it means that large numbers of women will be classified as having a positive screening test and will require either additional evaluation or possibly treatment. When comparing DVI with human papillomavirus (HPV)-DNA testing for screening it is important to recognize that although HPV-DNA testing also has a relatively low specificity when applied to the general screening population, simple visual screening methods have the additional limitation that they have a much lower sensitivity than does HPV-DNA testing. Moreover, the positive predictive value of HPV-DNA testing can be increased by restricting the testing to selected populations, such as women over the age of 35 years (12). Although one study (13) has demonstrated that DVI is significantly more specific when used in postmenopausal as compared with premenopausal women, to date clinically meaningful subpopulations for whom simple visual techniques have a higher positive or negative predictive value have not been identified. Because of their low positive predictive value, new strategies for managing women with abnormal visual screening tests will need to be developed before these methods can be introduced into routine clinical care.

There is considerable interest in using DVI as a possible alternative to cytology for cervical cancer screening in low-resource settings. This interest has been stimulated by a realization that cytology is simply not a viable option for most of the world. Because DVI does not require highly trained cytotechnicians or a central laboratory and provides an immediate result, it is perceived as overcoming many of the barriers that have blocked the use of cervical cytology. It is important to recognize, however, that there is currently rather limited information on how DVI will perform when introduced into widespread use in low-resource settings. The results that are shown in Table 2 were obtained in highly controlled research settings with dramatically increased resources for training, quality-control procedures, and follow-up compared with what would be available in a routine screening program in a low-resource setting. For example, our study from South Africa (14) found a sensitivity of 0.81 and a specificity of 0.88 for conventional cervical cytology. It is extremely unlikely that this level of performance would ever be obtained in a routine service setting. The fact that the real world performance of any of the different screening tests, when performed as a routine service in a low-resource setting, is essentially unknown should provide a sobering reality check to those contemplating widespread implementation of screening programs based on the results obtained in highly controlled research settings.

**Key Issues Relating to Simple Visual Techniques**

**Screening Test**

**Terminology and definitions.** We need a standardized terminology for the visual screening methods and clear and reproducible definitions of what constitutes a positive screening test. Using different definitions of what constitutes a positive screening test has serious repercussions, since it can have a profound impact on the performance of DVI. One recent study (13) demonstrated that, when the definition of a positive visual screening test included all acetowhite (e.g., areas that appear white after the application of a 3% to 5% solution of acetic acid) lesions of the cervix, the sensitivity for detecting biopsy-confirmed CIN2 and CIN3 was 0.70 and the specificity was 0.79. When the definition of a positive test was redefined to include only acetowhite lesions with well-circumscribed borders, which is the definition being used in many large clinical trials, the sensitivity dropped to 0.58 and the specificity increased to 0.84 (13).

To develop standardized definitions of what constitutes a positive screening test, we need a better understanding of the impact that different definitions of test positivity have on test performance. Although several studies have been published on this topic, the results of these studies are somewhat conflicting and additional studies are needed. To determine what constitutes the best definition of a positive screening test, we need careful evaluations of the reproducibility of different criteria. In one recently completed study (15) the interobserver variability of experts evaluating the cervix after the application of acetic acid using low-magnification cervical photographs was measured. A moderate to substantial degree of agreement was observed (15). However, this study measured the performance of experts evaluating selected static images rather than of clinicians working under field conditions, and a considerably lower level of agreement might be observed in routine clinical practice. It is also unclear whether or not different definitions of what constitutes a positive screening test will be needed to obtain optimal performance in different populations. It is quite possible that this will be the case and that one definition will be appropriate for younger women and another for older women. It is also possible that different definitions will be used in different locations where there are varying resources available for the evaluation and treatment of women with a positive screening test. Studies need to be designed to address these issues.

**Factors influencing test performance.** Although it appears clear that DVI has a sensitivity that is consistently equivalent to that of conventional cytology and that sensitivity is relatively reproducible between studies, the specificity of DVI has varied dramatically between studies. The reasons for this marked variation in specificity are unknown, but possible factors that might influence test performance include the definitions of what constitutes a positive test result discussed above: the demographic characteristics of the population screened, the presence of coexistent non-neoplastic cervical diseases, the use of magnification, the different approaches to training, and the different skill levels of the clinicians performing the test. There is very limited information on the role of covariates that might impact performance. These covariates include cervicitis, bacterial vaginosis, and oral and injectable contraceptives. In the South African study by Denny et al. (13), even though there was a very high prevalence of sexually transmitted infections (20% high-risk
types of HPV, 7% human immunodeficiency virus [HIV] seropositivity, 2% Neisseria gonorrhoeae, 4% Chlamydia trachomatis, and 19% Trichomonas vaginalis), no significant differences in sensitivity and specificity of DVI were observed in the presence or absence of infection with any agent except for HIV. There was a significant reduction in specificity but no change in sensitivity among HIV-seropositive women. Clearly, additional studies are needed to formally address how various factors impact test performance. The studies that address this issue need to involve actual clinical screening examinations rather than simply photographs of the cervix, and need to be designed in such a way as to limit verification bias.

Impact of training on test performance. It is unlikely that the performance of the visual screening methods when done under routine clinical conditions will be equivalent to that obtained when the test is done in highly controlled clinical research trials. The impact that training and experience have on test performance requires investigation. Several groups currently running clinical trials are finding that the performance of individual screeners varies considerably. Some screeners tend to classify more cases as being positive, even though they receive the exact same training as the other screeners. Of equal concern is that individual performance appears to be quite variable. On numerous occasions, we have observed in our South African trials that immediately after we have provided additional training to a specific provider because quality-control measures indicate that their performance is not adequate, the additional training results in a temporary increase in their test positivity rate. Specific important questions that need to be addressed include whether there is a learning curve such that providers who have done some fixed number of examinations are more accurate than those who have done a lower number. Similarly, what is the impact of training on test performance and what is the minimal level of training required to obtain competency? A number of organizations have developed basic DVI training programs that include in-depth training manuals and collections of annotated digital images. There is also consideration being given to developing web-based training programs for settings with internet access.

Quality control of visual screening methods. Compared with cervical cytology, visual screening methods are much more difficult to quality control in the field. Standardization is particularly difficult because not only is the interpretation of visual patterns highly subjective, but also, unlike cytology, there is no permanent record of the appearance of the cervix to allow screeners and their supervisors to review selected cases. A number of approaches are being evaluated as possible quality-control methods for DVI. These include a video recording of selected cases and taking static 35-mm photographs for later review with a trainer or supervisor. Studies need to be conducted to determine the efficacy of such measures for quality control, and effective measures need to be evaluated under field conditions.

Performance of the test when done serially or when used to detect incident or recurrent and persistent disease. Almost all studies of DVI have evaluated the impact of a single screening and have been done in unscreened or poorly screened populations. However, it appears from health-policy modeling studies that it would be best if DVI could be done serially at some defined time interval. For example, a recent modeling study (16) that incorporated data from South Africa found that a screening strategy that incorporated a single lifetime screen at age 35 years with immediate treatment of all women who were DVI positive would have reduced a woman’s lifetime risk of developing invasive cervical cancer by only 26%. More frequent screening using this same strategy could result in greater reductions, with an estimated 69% reduction in cervical cancer reduction when women are screened at 5-year intervals, provided that the performance of the screening test remains constant. Women who have received treatments such as cryotherapy for abnormal screening test results are at a particularly high risk of having recurrent and persistent CIN and require some form of surveillance after treatment. Unless the infrastructure for cervical cytology or HPV-DNA testing is developed for following women after treatment, it will be necessary to use visual screening to screen women after treatment in settings where this approach is used for primary screening. Unfortunately, there is no information available on the performance of DVI when done serially or its performance for detecting recurrent or persistent disease. It is expected that the performance of visual screening will be worse in these settings than in the large published screening trials. This is because the lesions being identified in the screening trials are typically large prevalent lesions. These lesions should be easier to identify than would be smaller persistent or incident lesions that would predominate in a previously screened population. Additional studies are needed to evaluate the performance of DVI when done serially or to detect persistent CIN.

Incorporating DVI Into Cervical Cancer-Prevention Strategies

A major limitation of DVI is its poor specificity. In many studies, 20%–30% of the women screened have been classified as DVI positive. Therefore, novel management strategies need to be developed to handle the large numbers of test-positive women.

Health-policy modeling. Several groups have developed health-policy models to help evaluate the costs and expected outcomes that would be obtained with different screening strategies (16,17). However, these studies have been rather limited and additional studies are needed. These studies need to evaluate novel cervical cancer-prevention strategies, including those that combine DVI with other screening tests to enhance specificity and to reduce overtreatment and evaluation.

Evaluating the safety and efficacy of “screen and treat” programs. One of the most attractive strategies to incorporate DVI into cervical cancer-prevention programs for low-resource settings is a “simple screen and treat” model, in which all of the women who are screen positive receive immediate treatment using cryotherapy (14). Before advocating the adoption of such a radical program, it is critical that both the short- and intermediate-term safety and efficacy of such programs be evaluated, preferably in randomized controlled clinical trials. These trials also need to evaluate the impact of the programs on HIV transmission and the long-term incidence of CIN in the treated populations.

Cervicography

Cervicography has been evaluated both as a primary screening method and as an adjunct to other screening methods in several large clinical studies. These studies have shown that, when used alone, cervicography lacks sufficient sensitivity for
the detection of high-grade disease (CIN2 and CIN3) to be considered as an acceptable primary screening method (7,18). Moreover, the performance of cervicography is particularly poor in older women in their 40s and 50s who would be expected to represent the bulk of the women being screened in the low-resource settings where a noncytologic technique such as cervicography might be particularly helpful (18). Although it appears that cervicography will not be acceptable as a primary screening method, it is unclear whether cervicography could have clinical use in selected clinical settings when used as an adjunct to other screening methods. In a recent analysis of data from the National Cancer Institute’s Costa Rica study (Ferreccio C, Bratti MC, Sherman ME, Herrero R, Wacholder S, Hildesheim A, et al: unpublished data), a useful synergy was observed when conventional cervical cytology was combined with cervicography for primary screening.

**KEY ISSUES RELATING TO CERVICOGRAPHY**

**Performance as Adjunctive Screening Test**

We need in-depth analyses of how cervicography will perform as an adjunctive test in conjunction with other tests, such as cervical cytology, HPV-DNA testing, or other biomarkers. It is likely that this information can be provided from the reanalyses of data from large screening trials that have already been conducted and have incorporated cervicography. However, should potential be shown in these reanalyses, consideration should be given to incorporating cervicography into the large screening trials currently being conducted around the world.

**Development of Newer Technology for Performing Cervicography**

The use of 35-mm photographs for cervicography seems to be outdated since the advent of digital imaging systems. Digital systems would be expected to reduce the costs of performing cervicography (by reducing film and processing costs) and would provide the opportunity for "telemedicine"-based screening and of centralized image analysis of digital images. Both of these approaches might be expected to improve the performance of cervicography. The development of image-analysis programs that automatically evaluate cervical images is a more ambitious project than the development of a digital cervical camera and would require considerable levels of funding. However, with ongoing improvements in computer-based image analysis, the development of such programs may be feasible, although it is unlikely that they will improve the performance of the test.

**DEVICES INCORPORATING ELECTRO-OPTICAL SENSORS**

Devices incorporating electro-optical sensors are currently under development by a number of companies, academic centers, and federal agencies. These devices are being evaluated for four possible clinical indications: 1) as adjuncts to cervical cytology, where the device will be used in addition to a cervical cytology for primary cervical cancer screening; 2) for triage of women with an abnormal cervical cytology, much as colposcopy or HPV-DNA is used; 3) as a method to localize sites for cervical biopsies; and 4) as a primary screening device that could provide an alternative or replacement to cervical cytology.

The most extensively studied approach is of fluorescence spectroscopy. There are a number of studies (19,20) demonstrating the feasibility of using fluorescence spectroscopy for identifying CIN2 and CIN3. Fluorescence refers to a process in which light of specific wavelengths (referred to as the excitation wavelength) is focused on tissue. Molecules within the tissue, such as nicotinamide adenine dinucleotide phosphate (NADPH), flavin adenine dinucleotide (FAD), porphyrins, collagen, and elastin, interact with the incident light, become "excited" (i.e., are raised to a higher energy state), and subsequently release very small amounts of light of given wavelengths (referred to as the emission wavelength) that can be measured using highly sensitive electro-optical sensors. The fluorescence that is produced when a tissue is irradiated is a complex signal of various emission wavelengths that is dependent on the excitation wavelengths and the molecular composition of the tissue. Fluorescence signals obtained from regions of CIN2 and CIN3 are substantially altered compared with those obtained from regions of normal squamous epithelium. However, because of the wide variations in the fluorescence produced by different patients and by different regions on the cervix, complex mathematical algorithms have had to be developed for analyzing the fluorescence signals to reproducibly discriminate between normal and neoplastic tissue (21). To enhance the performance of devices using fluorescence spectroscopy, some companies are incorporating other modalities such as image analysis of reflectance images into their devices.

Devices incorporating electro-optical sensors include devices that require contact with the cervix and those that do not, as well as devices that interrogate relatively small (≤5-mm diameter) regions of the cervix and devices that interrogate the entire transformation zone. None of these devices are currently approved by the Food and Drug Administration for marketing in the United States. Some of the companies that are actively pursuing the development of these devices are Polartechniques, Inc. (Sydney, Australia), which makes Polarprobe/Truscan, a pencil-sized, contact device that is designed to assist in cervical cancer screening, and MediSpectra (Lexington, MA) and SpectRx (Norcross, GA), who are developing devices using fluorescence spectroscopy for “real-time” imaging of the entire cervix.

**KEY ISSUES RELATING TO DEVICES INCORPORATING ELECTRO-OPTICAL SENSORS**

**Exploratory Phase of Development**

A number of different approaches are being contemplated, including devices based purely on fluorescence spectroscopy, electrical impedance measurements (i.e., measuring the resistance that the tissue provides to the movement of an electrical current through it), the Raman effect (i.e., a form of spectroscopy that is based on light scattering that provides a measure of the molecular composition of a tissue by determining changes in the wavelength of light as it passes through a tissue), other forms of spectroscopy, reflectance image processing, and devices that incorporate multiple methods. Although small feasibility trials have demonstrated that experimental or commercial prototype devices using these methods can identify CIN2 and CIN3, there remains considerable exploratory-phase research to be done to investigate different approaches. Multiple research initiatives are needed to develop novel devices incorporating electro-optical sensors. Several research initiatives are already under way in both the public and private sectors, but additional studies are needed.
Clinical Trials

No large-scale clinical trials have been published to document the clinical performance in terms of standard diagnostic test characteristics of devices incorporating electro-optical sensors. These trials are clearly needed before determining whether such devices have clinical use. Large-scale clinical trials for regulatory approval purposes are either under way or being planned for several devices. The results of these trials are expected within the next 18–24 months. It will also be very important for epidemiologists to run separate validation trials of the new technologies and to help define the relevant clinical protocols so that the utility of these devices compared with other methods can be assessed.

Developing a Commercial Device

Once clinical trials have determined that a specific type of device can provide clinical utility for a given indication, the device will need to be redesigned into a feasible commercial product. In many instances, this redesigning will necessitate exchanging research-grade components for less expensive commercial-grade components, standardizing and validating software and components, and designing the instrument suitable for a clinical environment.

Research Into the Biophysical Basis of Fluorescence Spectroscopy

The biochemical and structural differences between normal and neoplastic tissue that allow devices based on fluorescence or other forms of spectroscopy to discriminate between CIN and normal tissue are poorly understood. Research initiatives are changing research-grade components for less expensive commercial-grade components, standardizing and validating software and components, so that the utility of these devices compared with other methods can be assessed.

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NOTE

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