

Cervical Cancer Screening

DIANE SOLOMON* AND MARK SCHIFFMAN†

*Division of Cancer Prevention and †Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland

I. Introduction

Cervical cancer mortality in the United States has decreased since the 1950s by over 70% [1]. The decrease is attributed largely to the introduction of the Papanicolaou test in the 1940s. Cervical cancer, once the number one cancer killer of women, now ranks tenth in cancer deaths for women in the U.S. An estimated 15,000 women are still diagnosed each year with cervical cancer and approximately 4800 will die of their disease. However, worldwide, cervical cancer is the third most common cancer in women behind breast and colon cancer, and it ranks first in many developing countries that lack screening programs [2].

The accessibility of the cervix to direct examination and the relatively slow progression to cervical cancer from recognized and treatable precursor lesions make cervical neoplasia an ideal target for screening and prevention efforts. The success of screening has been demonstrated most directly and convincingly in Scandinavia. Countries with formal screening programs with wide population coverage experienced substantial drops in incidence and mortality while neighboring countries with limited population screening did not [3,4].

An empirical evaluation of screening programs in eight countries [5] as well as a mathematical model developed by Eddy [6] found that screening every 3 years affords appreciably more protection compared with screening every 5 or 10 years. However, in this evaluation, little protection was gained by screening annually compared with every three years.

In Canada, Great Britain, and many European countries, screening recommendations range from every 3–5 years. In the U.S., consensus recommendations adopted by the American Cancer Society, National Cancer Institute, American College of Obstetricians and Gynecologists, and others call for three consecutive annual screening tests for women who have initiated sexual activity or have reached age 18. If the results of these three tests are negative, the screening interval may be extended at the discretion of the clinician.

Historically, unscreened subpopulations of women in the U.S. include older women, uninsured and impoverished women, minority women (particularly Hispanic and older African-American women), and women residing in rural areas [7]. Some of these patterns are changing whereas others are not. In the 1994 National Health Interview Survey of the U.S. population [8], 77% of women reported having had a Pap test in the past 3 years. Age remains a factor; screening was higher among women 18–44 (82%) compared to women 65 and older (57%). However, there were no marked differences between African-Americans, Hispanic whites, and non-Hispanic whites, or metropolitan versus nonmetropolitan residents in the 18–44 age group. Socioeconomic measures continue to show significant differ-

ences in screening coverage; women who did not complete high school and whose family income was less than \$20,000 reported lower rates of screening compared to women with education beyond high school or family income exceeding \$20,000 [8].

In many developing countries, screening is available to only a small segment of the population through urban clinics or hospitals, or not at all [9]. Obstacles to comprehensive cervical cancer screening include lack of public and clinician awareness of cervical cancer as a health problem, lack of awareness of the benefits of screening, inadequate numbers of trained clinicians, inadequate supplies, inadequate laboratory facilities and personnel to evaluate specimens, loss to follow-up, and inadequate treatment facilities [10]. For such countries, comprehensive cytologic screening performed at regular intervals is unattainable at the present time. Other approaches to screening must be considered, such as limiting the age range for screening, limiting screening to a single test for women at the maximally beneficial age (*e.g.*, between the ages of 30–35), or utilizing noncytologic approaches to screening that do not require an extensive infrastructure of trained personnel.

II. Papanicolaou Test

The Papanicolaou (Pap) test is currently the most widely utilized cervical cancer screening technique in the U.S. as well as internationally. Named for George Papanicolaou, one of the originators of cervical cytologic diagnosis, the test involves gently scraping cells from the surface of the cervix and evaluating the fixed and stained sample microscopically to detect abnormal morphologic cell changes. Although there are new technologies currently available and others in development that may dramatically alter screening in the future, the Papanicolaou test is still the standard of care and serves as a paradigm to discuss components of a screening process.

A. Specimen Collection

Obtaining an adequate specimen is an essential step that requires some training and experience. The clinician should visually inspect the cervix and identify the "squamous columnar junction" where the smooth squamous surface of the ectocervix changes to the cobblestone-like glandular lining of the endocervix which leads into the uterine cavity. Sampling should be directed to this ring of tissue, as this is the region where the majority of cervical lesions arise. In comparison to a spatula alone, it has been demonstrated that use of either a combination of a spatula and a cervical brush or a broom-shaped device that samples both the ectocervix and endocervix simultaneously results in increased detection of abnormalities [11].

Table 74.1
Cervical Diagnostic Terminology

Dysplasia	Atypia	HPV	Mild dysplasia	Moderate dysplasia	Severe dysplasia	CIS
CIN	Atypia	HPV	CIN 1	CIN 2	CIN 3	
Bethesda	ASCUS	LSIL		HSIL		

In the conventional Pap “smear,” the cellular sample collected on the instrument(s) is spread over the surface of a glass slide. The object is to quickly but evenly spread the material over the slide, thinning out large clumps but avoiding excessive manipulation that can damage cells. Studies have shown that more than half of the material collected on the sampling instrument is not transferred to the glass slide but remains on the device and is therefore lost for microscopic analysis [12]. After smearing, rapid fixation of the specimen by alcohol immersion or spray is essential to preserve morphologic detail. Air-drying of the sample may limit the interpretability of the specimen.

B. Laboratory Evaluation and Diagnosis

Once accessioned in the laboratory, the slides are stained using a polychrome process that was developed by Papanicolaou and bears his name. When optimally performed, it results in excellent nuclear detail and cytoplasmic transparency that allows visualization through areas of overlapping cells.

Specimen adequacy is assessed microscopically based on a number of parameters including number and types of epithelial cells present, morphologic preservation, and presence of obscuring factors, such as blood, inflammation, or air-drying, that may limit microscopic visualization of the cells [13]. An “adequate” specimen consists of well-preserved, evenly distributed squamous and glandular cells. The presence of both epithelial cell types provides indirect evidence that the squamocolumnar junction has been sampled.

The process of diagnostic evaluation of a Pap test is highly labor-intensive and subjective. A cervical specimen may consist of over 100,000 cells of which only a small number may be abnormal. The process of microscopic screening is performed by trained cytotechnologists who must be able to detect the rare abnormal cell amidst thousands of cytologically normal cells. Any identified abnormal or questionable cytologic changes are then referred to a pathologist for diagnostic interpretation.

Pap test results may be reported using a variety of terminology systems. A translation table [Table 74.1] is helpful to convert from one nomenclature to another. At the time of the emergence of cytology as a diagnostic discipline in the 1940s–1950s, Dr. George Papanicolaou devised a numeric classification (I–V) to communicate the degree of confidence that cancer cells were present in a specimen. As used initially by Papanicolaou, the numeric designations represented the following: Class I—benign; Class II—minor cellular abnormalities considered benign; Class III—cells suspicious for but not diagnostic of cancer; Class IV—cells fairly conclusive for malignancy; and Class V—cells diagnostic of cancer.

As the field of cytology expanded, numeric designations largely gave way to terminology systems that included a designation of the degree of abnormality identified, for example the four grades of dysplasia (mild, moderate, severe, and carcinoma-*in situ* (CIS)). Richart introduced the term cervical intraepithelial neoplasia (CIN), grades 1, 2 and 3, to promote the concept of a disease continuum of precursors to invasive cancer [14]. The morphologic criteria for the three grades of CIN are based on tissue architecture: the proportional thickness of the epithelium involved by disorderly growth and cytologic atypia. Mild and moderate dysplasia roughly correspond to CIN 1 and CIN 2, respectively. However, CIN 3 encompasses severe dysplasia and CIS, thus eliminating a difficult and sometimes arbitrary diagnostic distinction between almost vs complete full-thickness abnormality.

Koilocytosis, a descriptive diagnostic term indicating cellular changes of perinuclear cytoplasmic cavitation, was recognized by Meisels to be a manifestation of genital human papillomavirus (HPV) infection [15]. Initially, HPV cellular changes were considered distinct from “true” dysplasia or CIN and not part of the precursor pathway to cervical cancer. However, as techniques for identifying HPV became more sensitive, HPV DNA was found in the vast majority of cervical neoplasias studied [16]. The pathogenesis of cervical neoplasia and cervical cancer is now known to be due to HPV, based on epidemiologic, virologic, and experimental evidence. Therefore, isolation of “koilocytotic atypia” or “HPV effect” as a separate distinct entity from dysplasia/CIN is no longer biologically valid.

The Bethesda System, developed at a National Cancer Institute workshop in 1988 [17] and refined in 1991 [18], collapses the cytologic diagnostic subcategories of intraepithelial lesions into low- and high-grade squamous intraepithelial lesions, abbreviated as LSIL and HSIL, respectively. This division is based on the concept of HPV-induced cellular changes as discrete processes of (1) LSIL as acute infection with any HPV type resulting in mild, usually transient cytologic effects, and (2) HSIL as the result of persistent infection with predominantly oncogenic HPV types and the interplay of a variety of factors, including host immune response, that poses a substantial risk of invasion [19]. While the CIN classification remains widely used in cervical histopathology, the Bethesda System (TBS) is more commonly used to report Pap test results.

The Bethesda System also introduced the term “atypical squamous cells of undetermined significance” (ASCUS) to reflect equivocal, abnormal changes that are quantitatively or qualitatively insufficient to establish a definitive diagnosis of SIL. ASCUS is not a single diagnostic entity and is therefore associated with highly variable clinical outcomes. It does represent an improvement, however, over older classifications that used “atypia” to encompass reactive changes and HPV-associated cell changes in addition to equivocal findings. In the Bethesda System, reactive changes are categorized as “benign” and HPV changes are subsumed under SIL.

Abnormal Pap test results are not evenly distributed among the diagnostic categories described above. Rather, in a screened population such as that in the U.S., the distribution of abnormalities resembles a pyramid with relatively few cancers at the top and millions of low grade and equivocal diagnoses comprising the very broad base (Fig. 74.1). In the U.S., cancers represent

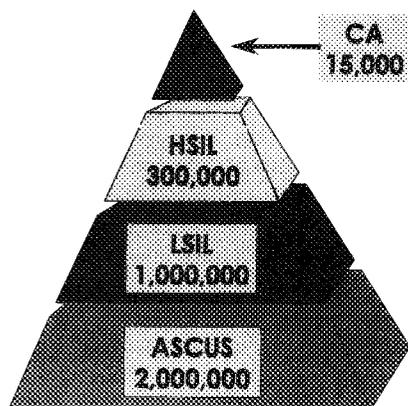


Fig. 74.1 Cervical lesions: pyramid of diagnoses.

far less than one-tenth of 1% of diagnoses and high-grade lesions constitute approximately six-tenths of 1% [20,21]. By contrast, LSIL and ASCUS account for an estimated 6% of all Pap test results, which translates to 3 million women in the U.S. annually.

C. Screening Test Characteristics

A screening test can be evaluated by several parameters. In the 2×2 screening table (Table 74.2), the results of a dichotomous screening test are presented compared to the disease state of the population screened; for example, HSIL or above (HSIL+) versus not. Four test outcomes are possible: A represents true-positives (positive results in individuals with HSIL+); D is the number of true-negatives (negative results in individuals without HSIL+); B reflects false-positives (positive results in individuals without HSIL+); and C corresponds to false-negatives (negative results in individuals with HSIL+).

Sensitivity [$A / (A + C)$] is the proportion of diseased individuals correctly detected by a positive test. Specificity [$D / (B + D)$] is the proportion of disease-free individuals who receive a negative test result. Positive predictive value [$A / (A + B)$] indicates the percentage of positive test results that correctly identify the presence of disease. Negative predictive value [$D / (C + D)$] reflects the percentage of negative tests correctly indicating the absence of disease (*i.e.*, the reassurance provided by a negative test).

The sensitivity of the Papanicolaou test for high-grade lesions or cancer is estimated to be up to 70–80% (specificity 94–97%) [22,23]. Test sensitivity must be distinguished from program sensitivity. The former is a measure of the sensitivity of a single test at one point in time. The latter is the sensitivity of a series of tests at intervals determined by the screening program to detect an abnormality at any single test event. Repeat screening at regular intervals therefore compensates somewhat for the limitations of the sensitivity of the technique.

In the context of cervical screening, two main types of error contribute to lower sensitivity. Sampling error occurs when a cervical lesion is present but cells representative of the abnormality are not present on the glass slide specimen. Sampling error may occur if either the lesion is not sampled or if abnormal cells collected on the sampling implement are not transferred to

Table 74.2
Schematic Outcomes of a Diagnostic Test

Test result	Disease		Total
	Present	Absent	
Positive	A	B	A + B
Negative	C	D	C + D
Total	A + C	B + D	

the slide. Factors that contribute to sampling error include small size of the lesion, inaccessible location of the lesion (high in the endocervical canal, for example), or inappropriate sampling technique. Laboratory error occurs when cells diagnostic of an intraepithelial lesion or carcinoma are present in the specimen but are not identified as abnormal when the result is reported. Factors that may contribute to laboratory error include presence of only a few abnormal cells, small size of the abnormal cells, presence of inflammation or blood obscuring cells, or diagnostic misinterpretation of the significance of identified cell abnormalities. Even under optimal screening conditions, sampling and laboratory error cannot be entirely eliminated.

D. Threshold for Further Follow-up

The objective of cervical cancer screening is to prevent the development of invasive cervical cancer, ideally by effectively identifying and treating the minimal number of women with histologically confirmed precursor lesions. In order to identify such women, the screening test threshold for further evaluation could be set at a cytologic diagnosis of “high-grade lesion.” This cut-point would yield a high percentage of confirmed high-grade tissue lesions among the women evaluated (a high positive predictive value of a positive result). However, many of the women who harbor a true high-grade tissue lesion may be “missed” because the severity of a lesion may be undercalled on the screening test. In two large studies, one-fourth to over one-half of prevalent cases of high-grade neoplasia were associated with cytologic diagnoses of ASCUS or LSIL [24,25].

Lowering the test threshold for further evaluation, to LSIL or ASCUS for example, improves sensitivity and NPV (reassurance of a negative result) of the screening process at the expense of a loss of specificity. As can be seen from the pyramid of abnormal cytology diagnoses in Figure 74.1, lowering the cut-point for further evaluation from HSIL to ASCUS increases by a factor of ten the number of women referred to follow-up.

The screening test threshold for follow-up and/or treatment of cervical abnormalities will vary depending on prevailing management paradigms, medicolegal issues, economic factors, and societal expectations. In countries where sensitivity is emphasized over specificity, lesser abnormalities will trigger additional follow-up compared to countries that favor a more cost-effective approach to screening.

The trade-off of sensitivity and specificity for a given test is graphically depicted by Receiver Operating Characteristic (ROC) curves that plot sensitivity and (1-specificity) along the Y- and X-axis respectively, as the test cut-points change. ROC

curves are useful tools to compare the performance of a given test at different thresholds, as well as to compare different tests or combinations of tests [26].

E. Follow-up and Management of Abnormalities

Screening cannot be effective without follow-up of abnormal results and treatment of lesions as appropriate. Loss to follow-up is a significant problem. In two studies [27,28] 13 and 15% of cervical cancers that occurred in women who had ever had a Pap test were attributed to lack of either patient notification or patient compliance with recommended treatment. "One-stop" screening, diagnosis, and treatment clinics have been established in a few high-risk areas to address this problem [29,30]. However, this is a labor-intensive approach to screening that cannot feasibly be applied as yet on a large scale.

In the U.S., high-grade cytologic lesions are managed by visual evaluation of the cervix with magnification (colposcopy), directed biopsy, and—in women with histologically-confirmed HSIL—destruction or removal of the lesion and transformation zone of the cervix. However, there is currently no consensus as to the appropriate management of women with LSIL or ASCUS, which comprise the vast majority of abnormal Pap smear results. Options include immediate colposcopy and directed biopsy as with high-grade lesions versus follow-up with repeat cytology every 4–6 months, with colposcopy indicated only if an abnormality persists.

Most low-grade changes regress spontaneously; only a minority of such lesions would progress without treatment. However, currently there is no way to determine morphologically which patients are at risk. The available data indicate that for many specimens demonstrating ASCUS, patients do not have a significant lesion and follow-up smears will be normal. In 25–60% of patients, however, further evaluation will detect a squamous intraepithelial lesion. The majority of these lesions are low grade; only 15–30% are high-grade [31,32]. Of note, the yield of high-grade lesions is increased in cases of ASCUS involving atypical metaplastic cells [33].

As discussed in the next section, future studies may provide a molecular basis to distinguish true precursors of neoplasia from minor lesions of no significant clinical import; this would allow a more coherent and rational approach to diagnosis and management of women. For example, HPV testing may have utility to identify which women with equivocal Pap test results are at greatest risk of a significant lesion.

III. New Cervical Cancer Screening Techniques

The cervical/vaginal Pap smear has been tremendously successful in reducing the death rate from cervical cancer. However, as with any medical test, the Pap smear has limitations, particularly with respect to false-negative screening results.

Interest has focused on development of technologies to enhance the accuracy of cervical cancer screening. Some of these techniques are directed at improving the sampling and specimen quality, others are focused on improving the laboratory microscopic screening process, and some techniques are visual or molecular rather than microscopic.

A. Techniques to Improve Sampling and Specimen Quality

As noted earlier, with conventional smear techniques only a fraction of the cellular material collected from the cervix is transferred to the glass slide. By contrast, liquid-based collection, in which the implement is vigorously rinsed in a vial of preservative/fixative, recovers much more of the cervical sample [12]. The vial is then transported to the laboratory where the specimen is agitated to disaggregate cell clumps and a subsample of cell material is deposited on a glass slide in a fairly uniform, thin layer. The method of subsampling and cell transfer to the glass slide varies depending on the particular device. ThinPrep 2000 (Cytoc, Boxborough, MA) is a semiautomated single-sample processor that uses suction filtration. CytoRich (AutoCyte Inc., Elon College, NC) utilizes centrifugation, sedimentation through a density gradient, and filtration to process multiple samples at a time. These techniques cost \$10–20 more than a conventional Pap smear.

Clinical trials comparing conventional smears and "residual-to-vial" (after a smear has been made) liquid-based preparations have shown equal or greater sensitivity of the thin-layer preparations in detection of low-grade lesions [34,35]. Some studies also claim equal or increased sensitivity for high-grade lesions [24,36,37].

Liquid-based collection eliminates vagaries of collector-operator errors of uneven or incomplete transfer of cellular material or air-drying artifact. Improved fixation and presentation of the even distribution of material in a more uniform fashion may make detection of abnormal cells easier. Another theoretical advantage of liquid-based collection is that residual specimen would be available for additional testing as may be appropriate. Several studies have noted the potential advantage of "reflex" HPV testing in the setting of a low-grade or equivocal cytology result [38,39]. The ability to test for HPV from the same cytologic sample would eliminate the need for an additional patient visit to collect a separate sample. Ongoing studies are evaluating the cost-effectiveness of such a management approach.

B. Computerized Screening Technologies

These devices utilize computer image analysis technology to screen cervical cytology specimens in an effort to reduce false-negative results. Two instruments have received FDA approval for rescreening (secondary screening) of previously evaluated specimens determined to be negative by routine manual screening: Papnet (AutoCyte) and AutoPap (NeoPath Inc., Redmond, WA). Only AutoPap is also FDA approved for use in initial (primary) screening of cervical specimens.

Used in a rescreening mode, AutoPap identifies approximately 20% of previously diagnosed "negative" cases as most likely to contain an abnormality. These cases undergo repeat manual screening by the cytotechnologist. Papnet analysis generates a digital tape of images of the most abnormal cells or cell groups as identified by the computer. The tape is reviewed by a cytotechnologist at a computer monitor workstation. In some cases, an abnormality may be diagnosed based on review of the digital images; in other cases, an abnormality may be suspected and the glass slide may be selected for manual microscopic review.

Compared to random 10% quality control rescreening, both computer rescreening devices increase detection of abnormalities in cases previously diagnosed as negative. Using 100% rescreening as the reference standard, AutoPap, set to select 20% of slides for review, identified 77% of LSIL and above [40] (7.7 times more than a random 10% review). Papnet assisted rescreening sensitivity for LSIL and above is estimated to be in the range of 85% [41] (8.5 times more than a random 10% review). However, this increased sensitivity is primarily for ASCUS and LSIL diagnoses and comes at significant cost. Used in a secondary screening mode, these technologies are cost-effective only if incorporated into a less frequent screening strategy [41].

Operating as a primary screener, the AutoPap computer identifies approximately 25% of cases—those with the lowest rank score—as least likely to contain an abnormality; these slides are not reviewed by a cytotechnologist. The remaining 75% of specimens undergo manual microscopic screening. In addition, of those cases reviewed as “negative” by the cytotechnologist, a subset with the highest rank score as determined by the computer are then subjected to a second round of manual screening.

Although not FDA-approved for use in primary screening, a study comparing primary Papnet screening to conventional microscopic screening showed promising results [22].

C. Nonmicroscopic Screening Technologies

In addition to the efforts to improve cytologic screening, several adjunctive screening technologies are being considered in an effort to improve cervical screening sensitivity. These can be categorized as: (1) visual evaluation techniques; (2) electro-optical probes; and (3) testing for molecular markers.

1. Visual Evaluation Technologies

The colposcope was first developed in 1925 in Germany to visually evaluate the cervical epithelium for abnormal changes. Five percent acetic acid is usually applied to the cervix during the examination to enhance the contrast between normal and abnormal tissue. Although colposcopy is used for primary screening in some countries such as Switzerland, in most areas colposcopy is not an economically feasible primary screening tool due to the relatively high price of the procedure which requires highly trained colposcopists. In certain high-risk populations, colposcopy may be used as a screening technique. However, colposcopy is generally restricted to patients with a previously identified abnormality, to direct tissue biopsy to the most abnormal area of the cervix, and to visually evaluate the location and extent of a lesion prior to therapy. It is worth noting that the practice of colposcopy has not been standardized, leading to uncertain intercolposcopist variability.

Cervicography utilizes a 35-mm camera with a fixed focal-distance telephoto macrolens to take a photographic image of the cervix that can be sent off-site for diagnostic interpretation by expert readers. Several early studies evaluating the sensitivity of cervicography plus cytology in comparison to cytology alone found that the addition of cervicography increases screening sensitivity, primarily for low-grade lesions, but with unacceptable loss of screening specificity [42–44].

In a large population-based screening study in Costa Rica, Schneider *et al.* compared the results of cytology, cervicography, and HPV testing, alone and in combination, for 8460 women [45]. If women with positive screening cervicography were referred to colposcopy, all 11 invasive cancers would have been detected. However, the sensitivity for high-grade intraepithelial lesions was only 48%. The technique was logistically feasible and inexpensive but had limited utility in postmenopausal women due to the migration of the squamocolumnar junction into the endocervical canal beyond the visual range of cervicography.

Visual inspection (VI) is a very low-cost approach to screening that may be an option for areas that do not have access to comprehensive cervical cytological screening [46]. VI, at its most basic, consists of looking at the untreated cervix for visual signs of a high-grade lesion or cancer. VI may be enhanced by cervical application of acetic acid (termed VIA) and the use of low-power magnification (termed VIAM) to detect acetowhite lesions. Use of VI or VIAM alone, without cytologic screening, is unlikely to achieve the accuracy of the Pap test or even cervicography. However, VI may prove to be a cost-effective approach to decrease cervical mortality in countries that cannot afford a comprehensive cytological screening program [47].

2. Electro-optical Probe Devices

Several electro-optical probe devices are currently under development or in clinical trials; none, at this writing, are FDA approved. This technology is based on measurable differences in the physical properties of electrical decay and light scatter of normal and abnormal epithelium [48]. The devices typically consist of a small desktop processor and a sterilizable or disposable fiber-optic probe that is inserted into the vagina. The probe emits a mild electrical and/or optical stimulus to the surface of the cervix and then measures the voltage decay or light transmission and scatter properties of the tissue. Immediate results are available to the operator and theoretically could be used either in a primary screening mode to select women to be evaluated by colposcopy or in a triage mode to direct colposcopic biopsy to the most abnormal areas of the cervix.

3. Molecular Markers: HPV Testing

As mentioned earlier, the pathogenesis of cervical neoplasia and cervical cancer is known to be due to HPV, based on epidemiologic, virologic, and experimental evidence. While there are over 90 HPV types, including those that cause cutaneous warts, approximately 30 types infect the anogenital tract. About half of the anogenital HPV types have been identified in cervical cancers and are termed “oncogenic” or “cancer associated” types; the remainder are classified as “low risk.” Although HPV infection of sexually active women is common, cervical cancer is not; therefore, other factors, including the host immune response, determine the course of infection and the potential to develop significant cervical disease.

HPV testing is based on detection of HPV DNA in cervical specimens, as clinically useful serologic assays for the full range of oncogenic HPV types have not yet been fully validated. Advances in HPV DNA testing methodology now allow testing directly from residual liquid-based cytology specimens

(PreservCyt, Cytoc) or a separately collected sample. Studies comparing polymerase chain reaction (PCR)-based and Hybrid Capture (HC)-based HPV detection systems show excellent agreement between PCR results and the newest generation HC test (HC II) using a 1.0-pg/ml cutoff [49].

Several screening strategies utilizing HPV testing may be considered. These scenarios can be categorized broadly as: (1) primary screening, in addition to, or as a substitute for cervical cytology; or (2) secondary testing following an ASCUS cytologic abnormality, to clarify the cytologic diagnosis or to triage women for further colposcopic evaluation.

In young sexually active women, the high prevalence of HPV infection, often not associated with significant cervical disease, probably precludes use of HPV testing as a primary screening strategy in this setting. However, HPV DNA prevalence declines sharply with age while the sensitivity of HPV DNA for cervical neoplasia remains high. Therefore, the positive predictive value of finding HPV DNA rises with age. Moreover, the accuracy of Pap smear cytology declines with age due to sampling false negatives (as the squamocolumnar junction migrates into the endocervical canal) and false positives (associated with atrophic (estrogen-depleted) cellular changes). Thus, HPV testing may potentially be a cost-effective, primary screening strategy in older women [50]. Evaluation of the strategy is underway in at least two European countries.

In well-screened populations, the number of ASCUS and LSIL cases detected by cytology will greatly outnumber high-grade lesions and cancer. While there is general consensus (in the U.S.) that such diagnoses warrant increased monitoring, it is not clear whether colposcopy and biopsy or more frequent cytologic sampling represents optimal management. There is a trade-off between aggressive follow-up of cytologic changes that, in the majority of women, would regress spontaneously and underdiagnosis of the minority of women at risk for a significant HSIL or cancer. Sherman *et al.* have demonstrated that HPV testing may clarify inconclusive cytologic diagnoses by separating true lesions from mimics unrelated to cervical neoplasia [51]. HPV testing may also help to identify which women harbor occult HSIL at the time of an ASCUS diagnosis [52], or possibly predict which low grade lesions will progress over time to HSIL. Currently, a multicenter, prospective clinical trial sponsored by the National Cancer Institute is underway to evaluate the potential role of HPV testing in the management of ASCUS and LSIL.

D. Evaluation of New Technologies

Many of these new technologies are well beyond the financial capabilities of developing countries that are seeking to establish or improve existing screening programs. However, using ROC curve and cost-effectiveness analyses, one might develop a more rationally based screening program that may improve sensitivity at no/little extra cost. Using a new technology or a combination of technologies will increase the cost of a screening event; however, the gain in sensitivity may allow less frequent screening that theoretically could result in cost-neutral implementation.

At this writing it is not clear which technology or combination of methodologies will emerge as new standards of care in the U.S. or internationally. A cost-effectiveness analysis of the

three FDA-approved technologies to improve the accuracy of cytology screening finds that although each enhancement increases the sensitivity of screening, the marginal benefit in terms of lives saved compared to conventional annual screening is small, and the costs are relatively high [41]. However, the study points out that as technologies evolve and/or less frequent screening strategies are considered, the cost-effectiveness ratios may shift in favor of new approaches to screening.

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