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Regulatory Closure of Cervical Cytology Laboratories:

Recommendations for a Public Health Response

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Contents

Introduction 2
Cervical Cancer Screening in the United States 2
Clinical Quality Assurance 5
Laboratory Regulations and Enforcement 5
Guidelines for a Public Health Response to Closure of a Cervical Cytology Laboratory 9
Conclusion 14
References 14
Appendix A. False Negatives and False Negative Rates (FNRs): A Review 16
Appendix B. Automated Rescreening of Pap Smear Slides 19

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Regulatory Closure of Cervical Cytology Laboratories:

Recommendations for a Public Health Response

Summary

The Papanicolaou test—or Pap smear test—is one of the most effective cancer screening tests available, and its ability to detect premalignant conditions has contributed to the decline in cervical cancer morbidity and mortality in the United States since its development in 1941. The success of this screening test has created confidence among women, health-care providers, and public health officials. However, this screening tool is not perfect: false-negative findings are a special concern because they can delay necessary follow-up of and treatment for women who have cervical cancer precursor lesions or invasive cervical cancer. Recent media attention has focused on cytology laboratories that have been closed as a result of deficiencies (including a high proportion of false-negative reports), and in some states legal action has been taken against individual laboratories. With the advent of revised federal regulations implementing the Clinical Laboratory Improvement Amendments (CLIA) of 1988, scrutiny of the quality of cytology laboratory practice has increased. Between 1992 and 1994, a total of 10 cytology laboratories were closed by regulatory action of the Health Care Financing Administration because they were considered a threat to the public's health. Although such closures represent <1% of CLIA-certified cytology laboratories, the attendant publicity may trigger anxiety among women. Public health officials must respond to those concerns with appropriate clinical and community actions to ensure the health and safety of women whose Pap smears were evaluated by the closed laboratories.

There are no published recommendations to help develop a public health response to the regulatory closure of a cervical cytology laboratory. In April 1994, the Association of State and Territorial Public Health Laboratory Directors, through a cooperative agreement with CDC, convened a working group to provide background on the current practice of clinical cervical cytology in the United States, summarize the CLIA regulations that established specific quality assurance standards for this specialty, and recommend actions that a public health agency may initiate to deliver a measured response to laboratory closings and other regulatory sanctions. This report includes this background and summary of the workshop. The working group made three recommendations: (a) public health officials should plan for a cervical cytology laboratory closure, then, when a laboratory is closed by regulatory action, they should (b) assess the severity of the situation and determine an appropriate response and (c) provide accurate, timely information to the public.

INTRODUCTION

Screening for cervical cancer has been an important means of reducing morbidity and mortality from this disease in the United States. This report describes cervical cancer screening in the United States, steps ensuring the clinical quality of this screening test, and regulations concerning the quality of work performed in cervical cytology laboratories. Problems suspected or detected in cervical cytology laboratories and the procedures for closure or other sanction of a cervical cytology laboratory are discussed. These recommendations are intended for public health officials and other health services administrators who must address regulatory closure of a cervical cytology laboratory in their jurisdictions. The report also provides guidance when less stringent regulatory sanctions are imposed or when media coverage of laboratory difficulties provoke public concern.

These recommendations were developed by a working group convened by the Association of State and Territorial Public Health Laboratory Directors (ASTPHLD) through a cooperative agreement with CDC. The working group included representatives of federal agencies, state public health departments, professional cytology organizations, medical organizations, and a consumer representative. ASTPHLD and CDC charged the working group to describe the practice of clinical cervical cytology in the United States, summarize regulations pertaining to practices of cervical cytology laboratories, and recommend appropriate responses by public health agencies to regulatory closings. The working group met in April 1994 and again in October 1995 to discuss the report and to develop recommendations for a public health response.

Because each locality has special concerns, the recommendations in this report are broad. Community variables include the composition of the patient population, the availability of records or patient information (to enable rescreening of Pap smear slides previously reported or to obtain new patient specimens for testing), the extent of the problems evident in a laboratory, and duration of the problems. Despite these variables, these recommendations can help local public health agencies respond effectively to a laboratory closure as public, regulatory, and legal interest in the quality of cytology laboratories increases. This report is intended to enable public health agencies to prepare for situations in which concerns about laboratory quality affect public confidence in cervical cytologic screening.

CERVICAL CANCER SCREENING IN THE UNITED STATES

Effect of Cervical Cancer Screening on the Health of Women

In 1941, Drs. George Papanicolaou and Herbert Traut first described their use of a "vaginal smear technique" in assessing patients for uterine and cervical cancers (*1*). Since the introduction of this technique—now known as the Pap smear test—the mortality rate from invasive cervical cancer has declined by 70% (*2*), which makes the Pap smear test one of the most successful cancer screening tests (*3*). Nonetheless, cervical cancer is currently the eighth leading cause of cancer deaths and the third leading cause of gynecologic cancer deaths among U.S. women (*4*), and the American Cancer Society estimates that 4,900 U.S. women will die of invasive cervical cancer in 1997 (*5*). Most of these deaths will occur among women who have never had a Pap

smear test or have not had that test in the past 5 years. To decrease the morbidity and mortality rates of cervical cancer, a Healthy People 2000 health objective is to increase regular cervical cancer screening of women, particularly women at high risk for this disease (*6*).

The success of cervical cancer screening in detecting the disease early is based on the ability of clinicians to collect adequate samples of cervical cells for a Pap smear and the ability of cytotechnologists and anatomic pathologists to identify morphological lesions in the smear. The earlier that precancerous or cancerous lesions are identified, the more likely that treatment to prevent or cure the disease will be effective. Each year, hundreds of thousands of cases of precursor lesions of cervical cancer that were initially identified by a Pap smear test are diagnosed and successfully treated (*7*). Because cervical cancer is usually asymptomatic early in its development, the primary way to detect this disease is to perform Pap smear tests regularly.

Accuracy of Cervical Cancer Screening

Although cervical cancer screening has been highly successful in reducing the morbidity and mortality rates from this disease, the Pap smear test has limitations. In particular, the accuracy of this test is limited by the occurrence of *clinical false positives*, a positive test result for a person who does not have cervical abnormalities, and *clinical false negatives*, a negative test result for a person who actually has cervical abnormalities. False positives may be difficult to determine, because a positive test result that is not confirmed by subsequent tissue biopsy may represent regression of cervical abnormalities rather than a false-positive test result. A more serious problem is false negatives. In cervical cytology, a clinical false negative is a negative Pap smear test result in the months preceding or concomitant with a positive tissue biopsy diagnosis of dysplasia, intraepithelial neoplasia, or cervical carcinoma. A negative Pap smear test result is (a) a diagnosis of negative or within normal limits or (b) any diagnosis in the Bethesda System (TBS) category of benign cellular changes or reactive changes. A clinical false negative can be caused by a sampling error or a laboratory error.

In a *sampling false negative*, a patient's lesion is not represented by abnormal cells on the slide because the lesion was not sampled or because the abnormal cells were not transferred to the slide. Sampling error can be caused by small lesion size, a lesion at an inaccessible site on the cervix or vagina, or inappropriate sampling technique.

In a *laboratory false negative*, cells representative of a precancerous lesion or carcinoma are present in the specimen to be examined but are not identified as abnormal; that is, the test is incorrectly reported as negative. In cervical cytology, this error can be caused by the presence of only a few abnormal cells in the specimen, obscuring inflammatory elements (e.g., cells, bacteria, or debris) or blood in the specimen, improper laboratory techniques for screening, or inattention of laboratory personnel to the slides they screen.

A laboratory false negative is identified when positive cells (i.e., cells representative of an intraepithelial lesion or carcinoma) are found on rescreening of a Pap smear slide initially reported as negative. For an external review of a laboratory's performance by a regulatory or accreditation agency, a review diagnosis of atypical cells of undetermined significance (ACUS)* for a specimen initially diagnosed as negative

*ACUS includes TBS categories of atypical squamous cells of undetermined significance and atypical glandular cells of undetermined significance.

should not be considered a false-negative result. For internal laboratory quality assurance, however, a lower threshold might be used and a review diagnosis of ACUS may be considered a false-negative result (Appendix A).

Laboratory interpretation is constrained by the quality of the smears provided. If sampling is inadequate, laboratory analysis of specimens will be compromised. Any Pap smear specimen perceived to be unsatisfactory (e.g., one obscured by blood) should be identified by laboratory personnel as such, and the health-care provider who obtained the specimen should be notified that it is not acceptable for evaluation. When given Pap smears that have no abnormal cells, however, laboratory personnel cannot determine whether the lack of abnormal cells is due to inadequate sampling or is truly representative of a patient's cervical cells.

The *false-negative rate* (FNR) represents the percentage of persons with a condition but who have false-negative test results for that condition. A laboratory FNR is based on random rescreening of a sufficient percentage of a laboratory's cases previously screened as negative or within normal limits. Generally, <1% of rescreened slides will be found to have squamous intraepithelial lesions (SIL) (e.g., human papillomavirus-associated changes, dysplasia, carcinoma in situ, or cervical intraepithelial neoplasia) or invasive carcinoma (i.e., >99% of negative Pap smears are truly negative).

A laboratory FNR is calculated with the formula FN/(FN+TP), where FN is the number of false-negative cases and TP is the number of true-positive cases detected on the initial slide screening. For example, during an initial screening of 1,000 slides, a laboratory detects 20 positive cases; on rescreening of the 980 slides originally determined to be negative, five additional positive cases are found. This laboratory's FNR for these 1,000 smears is [5/(5+20)] x 100 = 20%. The estimated minimum achievable laboratory FNR for traditional (i.e., manual) screening is 5% (*8–11*). A laboratory FNR of >20% may indicate a problem and warrant further investigation.

The slide review for determining a laboratory FNR is random and is not focused on high-risk cases or on negative slides from patients having recently diagnosed high-grade lesions. Although a nonrandom (i.e., focused) review is useful in identifying problem areas (e.g., specific laboratory staff or laboratory practices), only a random rescreening can be used to calculate a laboratory's FNR or to compare performances between laboratories. Rescreening should be performed similarly to the initial screening (the entire coverslipped area of the slide is examined field by field); exhaustive searching does not replicate the normal practice of routine screening. Computer-assisted rescreening of previously diagnosed negative smears has recently been approved by the U.S. Food and Drug Administration (Appendix B).

Other Measures of Laboratory Performance

FNR is one measure of laboratory performance; it should not be the only factor considered during laboratory review and inspection. Other measures of a laboratory's performance include how many slides employees evaluate, the quality of the working environment, the presence of internal quality control and quality assurance reviews, whether laboratory standards and guidelines are defined, the quality of internal communication between laboratory personnel, and the currentness of cytology practices.

The Importance of Routine, Periodic Pap Smear Tests

Despite clinical (sampling and laboratory) limitations, the Pap smear test is one of the most effective tools in the prevention and early detection of cervical cancer. Routine, periodic testing compensates for the inherent FNR of a single slide interpretation. For example, if a laboratory FNR is 25%, then over 3 years of annual slide screening, the probability of not detecting a lesion in all three samples (assuming independent probabilities) is small (0.25 x 0.25 x 0.25 = 0.016) (i.e., the sensitivity of the Pap smear test when three smears are used is 98.4%). Therefore, health-care providers and public health officials must emphasize the importance of routine, periodic Pap smear tests for all women.

CLINICAL QUALITY ASSURANCE

This report focuses on the evaluation of Pap smears in qualified laboratories. However, quality assurance entails other considerations as well. The following steps must be performed and monitored correctly and adequately for the Pap smear test to be reliable:

- Patients must be properly examined and cervical cells must be sampled
- Specimens must be properly collected and labeled
- Laboratory requisition forms must be complete and contain sufficient information
- Pap smears must be evaluated in a certified laboratory
- Laboratory reports must be reviewed to identify patients who require follow-up
- Health-care providers and their patients must be notified of the screening results and any follow-up indicated
- Appropriate follow-up must be taken
- Any substantive discrepancies between clinical, cytologic, and histological findings must be resolved by the referring clinician and an anatomic pathologist.

LABORATORY REGULATIONS AND ENFORCEMENT

In the 1980s, intensive media coverage of poor cytology laboratory practices and charges of lax enforcement of federal regulations contributed to the passage of the Clinical Laboratory Improvement Amendments (CLIA) in 1988 and the regulations that now define standards of cytology laboratory practice in the United States. CLIA and its attendant regulations serve as a baseline, through inspections and certification, for assessing the quality of laboratory work. The regulations allow for enforcement of CLIA standards and for corrective measures when laboratories fail to meet these standards.

The Health Care Financing Administration (HCFA) and CDC are responsible for establishing and implementing the CLIA regulations, and HCFA is responsible for enforcing the regulations. CDC provides technical and scientific support to HCFA. The

HCFA central office in Baltimore, Maryland, establishes CLIA program policies and oversees and coordinates the work of the 10 HCFA regional offices. The regional offices are responsible for enforcing the CLIA regulations among the cytology laboratories in their jurisdictions.

Personnel

The two categories of laboratory professionals involved in evaluating Pap smears are cytotechnologists and anatomic pathologists. Cytotechnologists must have completed an accredited training program. Program graduates who also have a baccalaureate degree (with an emphasis on biology) may sit for an examination administered by the American Society of Clinical Pathologists to become a registered cytotechnologist.

The pathologist must be a doctor of medicine (M.D.) or doctor of osteopathy (D.O.), have successfully completed at least 4 years of pathology residency training, be certified or qualified for certification in anatomic pathology by the American Board of Pathology or the American Osteopathic Board of Pathology, and be licensed in the state in which he or she practices. An anatomic pathologist who has acquired additional training or experience in cytopathology may seek certification in cytopathology from the American Board of Pathology.

CLIA regulations emphasize that skilled laboratory personnel are necessary in ensuring the accuracy of Pap smear interpretation and limit the workload of cytotechnologists and anatomic pathologists to help avoid mistakes caused by fatigue or haste. In addition, CLIA requires proficiency testing of each cytotechnologist and pathologist. Although some state laboratory licensure and accreditation programs include proficiency testing for these personnel, only one state (Maryland) has a program approved under CLIA. Whether annual proficiency tests can identify personnel whose work is submarginal has not yet been determined.

Laboratories

Cytology laboratories may be based at a hospital or other patient-care facility, be part of a group pathology practice, or function independently; the number of personnel may vary substantially (e.g., from 1 to >100). As of November 1997, a total of 3,700 cytology laboratories were registered under CLIA.

U.S. cytology laboratories are inspected at least biennially to certify that they meet CLIA regulations and that they are eligible to participate in Medicare and Medicaid. If accreditation and state programs have standards equivalent to or more stringent than the CLIA minimum standards, CLIA regulations allow laboratory accreditation inspections in place of HCFA biennial inspections and allow state licensure in place of HCFA biennial inspections and certification. HCFA and CDC review each program and determine whether it is adequate to replace HCFA inspection activities. Each year, HCFA also inspects on-site a sample (approximately 5%) of the laboratories accredited or licensed by these programs (i.e., the accreditation and state programs). As of November 1977, 74% of U.S. cytology laboratories were accredited by HCFA-approved programs (e.g., the accreditation programs of the College of American Pathologists and the Joint Commission on Accreditation of Healthcare Organizations).

In addition to conducting routine, biennial surveys, HCFA may initiate specialized surveys. A specialized survey may be conducted to verify biennial survey findings or to investigate a complaint about any laboratory, including an accredited laboratory or a laboratory in a CLIA-exempt state (i.e., a state-licensed laboratory).

Biennial Inspection

HCFA assigns responsibility for biennial inspection to state survey agencies. HCFA trains state agency surveyors about the CLIA regulations applicable to laboratories and about the policies and procedures for conducting inspections. HCFA has developed written survey procedures and guidelines to assist state agency surveyors in conducting inspections. The agency also advises laboratories on how to improve performance and internal monitoring systems.

If laboratory deficiencies are found during an inspection, the state survey agency may request a specialized review by HCFA, which includes a retrospective slide review, or recommend that HCFA initiate sanctions against the laboratory. Sanctions are intended to deter negative practices and to establish laboratory compliance with CLIA regulations as quickly as possible. HCFA will request a plan of correction from the laboratory, determine whether to use sanctions, and, if so, determine what kind of sanction should be used. The latter decision is based on perceived or potential threat to public health and safety and on the severity of the laboratory's deficiencies. Before HCFA imposes any sanctions, the laboratory is given the opportunity to correct its problems. The laboratory can also request an appeals hearing from HCFA if it wishes to challenge the findings of the state agency surveyor.

For cytology laboratories with substantial deficiencies, HCFA can initiate two types of sanctions: principal and alternate. Principal sanctions include limiting, suspending, or revoking a laboratory's CLIA certificate to analyze Pap smear slides. Alternate sanctions include directing a plan of correction, monitoring activities on-site, suspending all or part of Medicare payments for certain tests (e.g., Pap smear tests), and imposing a civil monetary penalty. HCFA may request a list of the laboratory's clients (i.e., clinicians who send specimens to the laboratory for interpretation) to notify them of the sanctions taken against the laboratory. Instead of or in addition to sanctions, HCFA may enjoin a laboratory in a civil suit or proceed with criminal sanctions against the owner, operator, or employees.

HCFA maintains a national registry of sanctioned laboratories that is available to the public. The 10 HCFA regional offices can provide a list of these sanctioned laboratories.

Specialized Surveys

HCFA contracts with an independent organization to conduct specialized surveys of cytology laboratories. A specialized survey does not necessarily imply a laboratory problem. Although some specialized surveys are conducted to investigate specific complaints about or perceived problems at a laboratory, other specialized surveys are conducted at randomly selected laboratories or to verify findings of a state survey agency. The surveys are on-site, announced (except those conducted to investigate a complaint), and conducted during the laboratory's normal working hours. The contractor evaluates compliance with relevant CLIA regulations by reviewing management of tests, general and specialized quality control, quality assurance policies

and procedures, and personnel responsibilities. The contractor cytotechnologists rescreen specimens, then compare their findings with the laboratory's reported results. This approach allows the contractor to assess smear fixation and staining quality, the cellularity of specimens, the integrity of specimen identification, and the accuracy of the laboratory's results.

Specimens for rescreening and related requisitions and reports for review are randomly selected but include a sampling of cases evaluated by each laboratory cytotechnologist and anatomic pathologist. The contractor reviews at least 0.1% of the laboratory's annual volume but a minimum of 100 specimens. Both negative and nonnegative cases are included. During rescreening, the contract cytotechnologists note substantial discrepancies between their analyses and the laboratory's results. Substantial discrepancies are those that may adversely affect patient care, such as:

- A rescreening diagnosis of SIL or invasive carcinoma for a specimen the laboratory originally reported as negative or within normal limits
- Cases unsatisfactory for evaluation but which the laboratory reported as normal or negative
- A rescreening diagnosis of negative or within normal limits for a specimen the laboratory originally diagnosed as SIL or invasive carcinoma.

Because laboratories report results differently, the contract cytotechnologists must understand the classification system of the laboratory under review and use the same criteria in diagnosing specimens and determining discrepancies.

If the number or nature of discrepancies is substantial, HCFA may request that the contractor rescreen more specimens and have the contractor anatomic pathologist travel to the laboratory to oversee the extended review. Findings that might trigger such a request include the following:

- A real or potential threat to public health and safety
- Cases in which the laboratory's diagnosis was negative or within normal limits but the contractor's interpretration was SIL or invasive carcinoma
- Cases in which the laboratory cytotechnologist and contractor cytotechnologist interpreted specimens as high-grade SIL but the laboratory pathologist interpreted as negative or within normal limits.

At the conclusion of the specialized survey, the contractor usually shares the results of the survey with the laboratory director. At this meeting, the laboratory's deficiencies are discussed and a summary of discrepancies identified during rescreening is provided. The contractor forwards its findings to HCFA, which then pursues any necessary actions. The contractor makes no decisions about sanctions. As a result of HCFA's review of findings from specialized surveys, since 1989, from 7.3% to 22.2% of cytology laboratories have been sanctioned each fiscal year (Table 1).

TABLE 1. Results of specialized surveys of cytology laboratories, United States, fiscal years 1989–1990 through 1995–1996

	Fiscal years									
	1989–1990		1991–1992		1993–1994		1995–1996		Total	
Category	No.	%	No.	%	No.	%	No.	%	No.	%
Laboratories surveyed	41	100.0	41	100.0	72	100.0	109	100.0	263	100.0
Laboratories found to have condition-level deficiencies*	18	43.9	19	46.3	30	41.7	41	37.6	108	41.1
Laboratories with CLIA certification that was limited, suspended, or revoked	NA†		NA		8	11.1	4	3.7	12	4.6
Laboratories that were no longer permitted to participate in Medicare	5	12.2	3	7.3	8	11.1	4	3.7	20	7.6

*A condition-level deficiency is one in which if a condition is remedied, the deficiency will no longer exist.
†Not applicable. The Clinical Laboratory Improvement Amendments (CLIA) of 1988 went into effect September 1992.

Source: Health Care Financing Administration.

GUIDELINES FOR A PUBLIC HEALTH RESPONSE TO CLOSURE OF A CERVICAL CYTOLOGY LABORATORY

When a cervical cytology laboratory is forced to close, is cited for substantial problems, or voluntarily discontinues screening of Pap smear samples, the goals of the local public health agency are to protect the health and safety of the public and to avert undue anxiety in the community. These goals can be achieved by (a) having a plan for such an event, and when laboratory closure does occur, (b) evaluating the extent of the problem and determining an appropriate response and (c) providing accurate, timely information to the public.

Even if the HCFA sanction is not as severe as closure, a public health response may be warranted. In addition, sanctions may not be initiated if past problems have been corrected or if a laboratory voluntarily discontinues screening of Pap smear samples. Nonetheless, minor deficiencies and past problems may cause concern in a community. Thus, public health agencies must be prepared to coordinate a community response when problems in cervical cytology laboratories are identified.

Plan for a Laboratory Closure Initiated by HCFA

The most important task for public health officials who want to respond effectively to closure of a cervical cytology laboratory is to plan a course of action. Such a plan will ensure the response from public health agencies will be coordinated, knowledgeable, timely, and reassuring. This contingency plan should address (a) the responsibilities of involved organizations and the means of communication between them, (b) relevant laws and regulations, and (c) the continuance of Pap smear slide screening.

The state public health department may be the most appropriate organization to initiate developing this plan. The state survey agency responsible for inspecting cytology laboratories and relevant community groups should be closely involved in the planning. In some states, public health agencies and health facility regulatory agencies function under an umbrella organization, and collaboration is relatively easy to achieve. In other states, however, coordination between public health agencies, health facility regulatory agencies, and community groups requires vigorous effort.

Responsibilities and Communication Lines

The contingency plan should detail the responsibilities of all organizations concerned with closure of cervical cytology laboratories, including the public health agencies, health facility regulatory agencies, laboratory professional organizations, medical societies, and community groups. The means of communication between these organizations should be outlined.

Relevant Federal, State, and Local Laws and Regulations

Statutes and ordinances governing retention of laboratory slides and medical records may be more stringent at some levels than others. For example, CLIA regulations require cytology laboratories to retain slides for 5 years, but some states require slides to be held longer. The contingency plan should reflect both the most stringent and the most recent laws and regulations applicable to cervical cytology laboratories, patient confidentiality, notification responsibilities, and other issues.

Continued Pap Smear Slide Screening

If a laboratory's certification or license to analyze Pap smear slides is restricted or revoked, a means of continuing cervical cancer screening will be necessary. The contingency plan should include an assessment of Pap smear testing services available in the area and a list of laboratories that may be available to undertake additional slide analysis. The assessment and list should be frequently updated, because the testing capacity may be limited in some areas and local laboratories may not always be able to assume an increased workload.

Assess the Extent of the Problem and Determine an Appropriate Response

In determining an appropriate response to an actual laboratory closure, public health officials need to assess the extent to which the laboratory's noncompliance with CLIA regulations affected test results. The HCFA report based on the specialized survey can be used to determine whether diagnostic errors were associated with certain laboratory employees or within a specific period. A HCFA laboratory surveyor or a laboratory professional knowledgeable about CLIA regulations can review the HCFA report with public health officials to determine what approach to take to the laboratory closure—prospective or retrospective. The method that promises to be more productive should be chosen, but the working group convened by ASTPHLD and CDC advocates the prospective method as the better strategy to ensure women's health and safety and to respond to public concerns about the implications of the HCFA closure.

Prospective Approach

In the prospective approach, women whose most recent Pap smear was evaluated by the closed laboratory are advised to have a repeat Pap smear. This approach allows a woman's current cervical cytologic status to be assessed. Changes since the patient's last Pap smear, as well as lesions that were present but missed during the last Pap smear, may be identified. Among patients whose Pap smear slides were incorrectly analyzed, many may be due for their next routine Pap smear test. The U.S. Preventive Services Task Force recommends Pap smear screening at least every 3 years for all women who are or have been sexually active and who have a cervix (*12*). The American Cancer Society recommends that all women who are or have been sexually active or who are ≥18 years of age have an annual Pap smear and pelvic examination; the society also suggests that after a woman has three or more consecutive, satisfactory, normal annual examinations, the Pap smear could be performed less frequently at the discretion of her physician (*13*). The National Cancer Institute, the American College of Obstetricians and Gynecologists, the American Medical Association, the American Nurses Association, the American Academy of Family Practices, and the American Medical Women's Association have identical or similar recommendations as the American Cancer Society (*13*).

To be effective, the prospective approach relies on women returning for a repeat Pap smear test. To attain the largest possible response, public health officials need to consider how to reach the patients and address their concerns about costs and confidentiality. Regardless of how vigorous the notification campaign or how well patients' concerns are addressed, however, not all women will be reached, nor will all respond.

Public health officials have a specific role in coordinating patient notification and follow-up. Many physicians and managed-care organizations already have protocols for notification and follow-up, and public health officials can use these protocols. Public health officials must ensure follow-up of women traditionally hard to reach. For example, mainstream media may not reach women in minority groups because of language barriers. The plan should also address how to track women who may have moved since their last Pap smear test, how to handle refusals for a repeat Pap smear test, and what criteria to use to determine a woman as lost to follow-up.

Public health officials will need to determine who will perform and pay for the additional Pap smear tests. The decision may depend on the policies of the health insurers in the area, the laboratory's insurance liability limits and fiscal responsibilities, whether patients are due for their next routine Pap smear test, and other considerations. Maintaining patient confidentiality and the confidentiality of the health-care provider–patient relationship should also be a priority of the prospective approach. Providers who have sent Pap smear slides to the closed laboratory can be recruited to encourage their patients to return for another screening. In this way, confidentialities can be kept intact. These concerns—cost and confidentiality—can be discussed when patients are first notified that they should return for a repeat Pap smear test.

Retrospective Approach

The retrospective approach involves having laboratory professionals rescreen Pap smear slides submitted to a laboratory during a specified period. Although it may be less effective and less advantageous than the prospective approach because a

patient's current cervical cytology status is unknown, the retrospective approach can identify criteria for a more productive, targeted slide rescreen or indicate that accurate specimen interpretation is problematic across the cytology laboratory. For example, problem cases may be clustered in association with a few health-care providers who see patients at high risk for cervical cancer, or laboratory errors may be associated with a specific cytotechnologist or anatomic pathologist. However, if errors are associated with inaccurate interpretation throughout the laboratory, the rescreening can be broadened, or switching to the prospective approach may be indicated. A complete rescreening of all of a laboratory's slide specimens is rarely productive. For example, in 1993, a HCFA specialized survey found substantial deficiencies in a Rhode Island hospital cytology laboratory. The hospital voluntarily and temporarily closed its laboratory and initiated review of almost 30,000 Pap smear slides; the massive rescreening effort found the laboratory to have been correct in 99.4% of the cases (*14*).

The rescreening required by the retrospective method will overlap or extend the rescreening initiated by HCFA for a specialized survey. HCFA usually does not become involved in rescreening efforts once it has determined whether and what sanctions are appropriate for that cytology laboratory. Thus, if public health officials determine that a HCFA report on a specialized survey is not specific enough for determining the best approach to responding to a regulatory closure of a laboratory, the officials must decide the standards for and extent of the additional rescreening and who will perform and pay for the rescreening.

A false-negative cytology smear is identified when positive cells are found on rescreening of a smear initially reported to be negative. For external review, a minimum diagnosis of SIL on rescreening serves as the threshold for identifying a false negative. (For a laboratory's internal review, the threshold is often set at ACUS; the ACUS threshold includes SIL false negatives.)

Public health officials should consult with statisticians and pathologists to determine how many specimens need to be rescreened to reliably estimate a laboratory's FNR. These officials will also need to determine what an acceptable laboratory FNR is and be able to communicate to the public that a very low FNR is unrealistic. The National Cancer Institute emphasizes that "none of the screening, diagnostic, or therapeutic techniques developed in medicine are perfect. Accordingly, a few women will develop cervical cancer despite adherence to accepted screening protocols" (*7*). Nonetheless, women concerned about their cervical cytology status should be encouraged to have another Pap smear test or to request their Pap smear slide be re-evaluated.

Before rescreening begins, public health officials will need to ensure that slides and medical records as well as funds for the rescreening are secured. Although the sanctioned laboratory could be held accountable for the cost of rescreening, the laboratory may not be generating income, particularly if it has been closed. Therefore, alternative sources should be considered. Other issues officials will need to address include determining who will be involved in selecting the laboratory or laboratories where the rescreening will be performed, who will coordinate the selection, and how the deadline for rescreening will be established. The rescreening facility must be certified by HCFA, practice sound quality control and quality assurance methods, and employ sufficient qualified personnel to complete the rescreening and report the results by the established deadline.

Provide Accurate, Timely Information to the Public

During their review of laboratory problems identified by HCFA, public health officials must decide how the public should be notified. These officials must consider the public's right to know as well as the risk of causing undue concern or panic. If HCFA determines that closure of a cytology laboratory is warranted, the agency will announce the closure in local newspapers. When this situation occurs, public health officials should initiate a public education campaign. The HCFA notice may not be evident to the laboratory's clients (i.e., the health-care providers who submitted Pap smear samples to the laboratory for analysis) or the clients' patients; conversely, the notice may trigger media interest and lead to public anxiety. Public health officials can provide timely, accurate, and educational information so that the public will respond calmly and that women will take the initiative to have routine, periodic Pap smear tests.

For HCFA sanctions other than closure, determining how to inform the public or key groups or individuals (e.g., health-care insurers, managed-care organizations, and other purchasers of health-care services; the laboratory's clients; or women whose Pap smears were evaluated by the laboratory) can be more complex. Public health officials should consider the following issues:

- The right of the public to be informed
- The laboratory's right to challenge HCFA survey findings and to present its position accurately
- Whether HCFA has already notified the laboratory's clients and the general public of the sanction
- Whether the confidentiality of test results or of health-care provider–patient relationships will be compromised.

Regardless of the type of sanction, three components of the public warrant special consideration—the laboratory's clients (i.e., health-care providers), the women whose Pap smears were evaluated by a laboratory, and the media.

Health-Care Providers

A form letter can be mailed to health-care providers who submitted Pap smear samples to the laboratory for analysis during the time of concern. Both health-care providers who work in public clinics and those who work in private settings should be notified. This letter can briefly explain the HCFA regulatory process and reason for closure of the laboratory, outline the planned response of public health officials (e.g., notifying women that they should have a repeat Pap smear test or conducting a retrospective slide rescreening), and ask each provider's help in contacting their patients.

If a retrospective slide rescreening has been initiated by the public health department, health-care providers should be notified if any of the Pap smear slides they had submitted to the laboratory were identified as false negatives. The providers are obligated to notify patients having false-negative Pap smear results and to follow up with further cervical cytology testing.

Women Whose Pap Smears Were Evaluated by a Sanctioned Laboratory

Communication targeting women whose Pap smears were assessed by a sanctioned laboratory should emphasize that most women have negative Pap smears and that when Pap smear specimens initially diagnosed as negative or within normal limits are rescreened, >99% will be found to be truly negative. Public health officials should also stress the importance of routine, periodic Pap smear tests. Cervical cancer develops slowly, and most precancerous or cancerous conditions will be detected during routine screening over several years (*15*). The American Cancer Society consensus recommendations for cervical cancer screening take into account the possibility of abnormal cells not being detected on a single Pap smear slide (*13*).

If a prospective approach is taken, public health officials should be prepared to inform women how to arrange for a Pap smear resampling. For example, women can make an appointment with a public health clinic or with their regular health-care provider. The state public health department could also distribute a list of health-care providers who have volunteered to resample patients.

Women should be informed that their Pap smear slide can be rescreened on request and how to make such a request. If more than 5 years have passed since the last Pap smear test, however, the specimen may no longer be available for rescreening. Patients who receive a rescreening diagnosis of ACUS or a TBS diagnosis of atypical squamous cells (or glandular cells) of undetermined significance need to be told that these diagnoses do not constitute a false negative. However, the National Cancer Institute recommends that these patients have follow-up Pap smear tests (*7*).

The Media

Through the media, public health officials can present their views and educate the public about the need for regular cervical cytology screening, the irreducible FNR, and other issues. The public health department can designate a media spokesperson to clarify technical terms, describe the HCFA regulatory process, and put the laboratory closure in context. A fact sheet or backgrounder can be distributed to the press to foster accurate, balanced reporting of the laboratory closure and the actions of the public health department.

CONCLUSION

Public health departments can effect a coordinated response to regulatory closure of a cervical cytology laboratory in their jurisdictions. Collaboration with the state survey agency and the HCFA regional office is important to ensure a measured and appropriate response. Specific decisions regarding notification and rescreening will reflect the circumstances of each laboratory closure. The health and safety of the public should guide all actions.

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Appendix A. False Negatives and False Negative Rates (FNRs): A Review

The literature cites an astounding range of laboratory FNRs, from <1% to 93%. In some studies, however, the reported FNR was actually the percentage of negative smears found to be positive or abnormal on review. In other studies, false-negative cases were based on a review diagnosis of ACUS rather than SIL when the initial diagnosis was negative; although the former is often used for a laboratory's internal review, only the latter is appropriately used for external evaluation of a laboratory. In addition, although an accurate laboratory FNR is based on random rescreening of a laboratory's cases, some published Pap smear rescreening studies focused on specimens collected from patients at high risk for developing cervical cancer or patients who were subsequently clinically diagnosed with SIL or carcinoma. Any reported laboratory FNR must be analyzed carefully to determine whether the value was accurately determined (Table 2).

TABLE 2. Study results on rescreening of Pap smears initially diagnosed as negative

Reference	Setting	No. of Pap smears rescreened	Description of samples*	Threshold†	Smears found to be false negative	False negative rate
Yobs et al. (*16*)	2 University-based medical centers	19,474	Consecutive smears, excluding cases with original diagnosis of unsatisfactory or diagnoses associated with glandular abnormalities	SIL	2.0%	30%
Allen et al. (*17*)	2 University teaching hospital laboratories	80	Smears from patients who had had all negative smears within 5 years of diagnosis of high-grade SIL or carcinoma	SIL ACUS Unsatisfactory	7.5% 15.0% 17.5%	
Sherman & Kelly (*18*)	University teaching hospital laboratory	123	All available smears from 20 women with ≥3 negative smears preceding a diagnosis of high-grade SIL or carcinoma	SIL ACUS Unsatisfactory	22.7% 52.7% 66.7%	
Nick et al. (*19*)	University teaching hospital laboratory	351	All available negative smears from 143 women within 5 years of diagnosis of high-grade SIL	Unsatisfactory	70.7%	
Gatscha et al. (*20*)	University teaching hospital	3,962	From 1 year, random sample and targeted rescreen of smears of high-risk patients	Not stated	0.28%	
		422	All available smears in the 5 years preceding histologically confirmed high-grade SIL or carcinoma	ACUS Unsatisfactory	25.8% 28.7%	
Tabbara & Sidawy (*21*)	University teaching laboratory	2,124	Random sample; rescreening was performed by a cytopathology fellow	ACUS	0.2%	1.6%
Slagel et al. (*22*)	University laboratory	435	Consecutive smears from a high-risk patient population; automation-assisted rescreening	SIL ACUS	0.7% 3.4%	9.4% 25.0%
Dean (*23*)	Teaching laboratory		All available negative smears in the 5 years preceding diagnosis of high-grade SIL or carcinoma	Unsatisfactory	18%–29%	

Hatem & Wilbur (*24*)	2 Teaching centers	17	Smears from patients who had had a negative smear in the 2 years preceding a diagnosis of high-grade SIL or carcinoma	SIL ACUS	64.7% 94.1%	
Wang (*25*)	Community hospital laboratory	~200	Combination of random smears and smears in the 5 years preceding a cytologic diagnosis of high-grade SIL or carcinoma	SIL	3.4%	
		19,623	Both random samples and consecutive smears	SIL	0.48%	
Personal communication, SE Wang to ML Nielsen	Community hospital laboratory		All smears from 1 year	SIL		<12.5%
Krieger & Naryshkin (*10*)	Community hospital		Quarterly random sampling	ACUS	0%–17%	
Inhorn & Shalkham (*26*)	State laboratory		Random sample from 1 year	ACUS	0.7%	9.0%–11.7%[§]
			All smears from 1 year from a high-risk patient population	ACUS	1.5%	
			All available smears in the 5 years preceding cytologic diagnosis of high-grade SIL or carcinoma	ACUS	13.6%	
Colgan et al. (*27*)	Independent laboratory	3,477	Consecutive smears	SIL ACUS	0.4% 2.4%	12.7%
Krieger & Naryshkin (*10*)	Independent laboratory	>1,000,000	Random sample from 15 years	ACUS	0.3%–0.7%[§]	4%–11%
Jones (*28*)	312 Laboratories	3,762	From responding laboratories, all available smears in the 5 years preceding cytologic diagnosis of high-grade SIL or carcinoma	SIL ACUS Unsatisfactory	10.1% 19.9% 20.4%	

*All smears rescreened were initially diagnosed as negative.
†A false-negative cytology smear is identified when positive cells are found on rescreening of a smear initially reported to be negative. For external review, a minimum diagnosis of squamous intraepithelial lesions (SIL) on rescreening serves as the threshold for identifying a false negative. For a laboratory's internal review, the threshold is often set at atypical cells of undetermined significance (ACUS). The ACUS threshold includes SIL false negatives, and the Unsatisfactory threshold includes ACUS and SIL thresholds.
§Approximated from study data.

Appendix B. Automated Rescreening of Pap Smear Slides

As of December 1997, the U.S. Food and Drug Administration (FDA) had approved two techniques for automated computer-assisted evaluation of cervical cytology smears. These instruments are marketed as PAPNET Testing System (Neuromedical Systems, Inc., Suffern, NY) and AutoPap 300 QC System (Neopath, Inc., Redmond, WA). Neither is approved for use in initial interpretation of Pap smears; the FDA limits use of these instruments to rescreening of smears previously interpreted as negative. These automated screening methods, intended for quality control and adjunctive testing, could reduce laboratory false negatives due to human error, but they will not eliminate false negatives. Their drawbacks are limited availability, higher cost, and operators' limited experience using them in clinical settings. A laboratory that uses these instruments is not necessarily less likely to have a serious problem, since laboratory personnel still provide interpretation of Pap smear specimens. If computer-assisted methods are being considered for rescreening slides when a laboratory is closed, public health officials should obtain current FDA labeling of the equipment, current HCFA policies, and the views of relevant professional organizations regarding use of the equipment.

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