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EDITORIAL

Programmatic Assessments of the Clinical Effectiveness of Gynecologic Liquid-Based Cytology

The Ayes Have it

Terence J. Colgan, M.D.

Pathology and Laboratory Medicine, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada.

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In many areas of the United States, there has been a rapid adoption of gynecologic liquid-based cytology (LBC) for cervical screening. In some parts of the United States and in other countries, two challenging questions still are being asked by screening programs: 1) Is LBC better than the conventional Pap smear? and 2) Is LBC really worth it? In more precise medical terms: 1) Has the clinical effectiveness of LBC with respect to sensitivity and specificity really been proven? and 2) If effective, is implementation of LBC going to be cost-effective?

The answers to these two questions may seem self-evident to many American cytologists who have witnessed and participated in the significant shift to LBC in the last 2–3 years. From the perspective of the screening program director, however, it is essential that these questions be answered not using limited laboratory and clinical studies of special clinical populations, but rather using analyses that adopt a population-based approach and assess the value of LBC in a mass screening mode.

For these purposes, screening programs have turned to clinical epidemiologists to define the clinical and cost-effectiveness of LBC.[1–10] In addition to these clinical epidemiologic assessments, some programs have chosen to mount independent clinical studies of LBC. In the current issue of *Cancer Cytopathology,* Klinkhamer et al.[11] report the results of the first approach—a very rigorous clinical epidemiologic assessment of the published literature on the clinical effectiveness of LBC for cervical screening. By nature, epidemiologic assessments rapidly become outdated. The current study of LBC is no exception. Large prospective clinical studies that compare the sensitivity and specificity of LBC with the sensitivity and specificity of conventional cytology were reported after the completion of the current analysis, which terminated literature review in April 2000.[12,13]

There is a significant risk of a conflict of interest when clinical epidemiologic and technology assessment studies are sponsored by

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Address for reprints: Terence J. Colgan, M.D., Pathology and Laboratory Medicine, Suite 600, Mount Sinai Hospital, 600 University Avenue, Toronto, Ontario M5G 1X5, Canada; Fax: (416) 586-8628; E-mail: tcolgan@mtsinai.on.ca

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screening programs because understandably, these same programs seek to optimize resource allocation and minimize perturbations to existing systems. Concerns regarding costs and system disruption may render the proper evaluation of clinical effectiveness unfeasible. Optimally, studies of LBC should delineate clearly the two separate issues of clinical effectiveness and cost-effectiveness. Klinkhamer et al. have separated carefully these two issues and addressed the question of prime interest to women: Is LBC better than the conventional Pap smear? Cost-effectiveness is wisely set aside in this study.

Klinkhamer et al. reviewed published studies of LBC, but only accepted the cases that met strict inclusion criteria. For example, the inclusion criteria required that LBC was the primary screening test, the study cohort was well described, sensitivities and specificities for predefined diagnostic thresholds were known, and a reference test was used in the study to permit a comparison between the performance of conventional Pap smears and LBC. A variety of reference tests were accepted as external gold standards, including cytologic or histologic follow-up and panel diagnoses. Using these criteria, most of the LBC literature was excluded and did not contribute to the conclusions in the current study. After identifying 60 English-language, peer-reviewed, published studies on the performance of LBC, only 10 were found to fulfill these inclusion criteria. From each accepted study, a level of evidence and test performance characteristics was determined. Undoubtedly, some cytologists would object to either the selection of these criteria or to the application of them, and to the relevance of the conclusions drawn. For example, influential historical cohort studies, which have been important in the adoption of gynecologic LBC, were excluded using these criteria.[14,15] Furthermore, adequacy, the second criterion of clinical effectiveness, was not assessed.

Klinkhamer et al. concluded that LBC (ThinPrep; Cytec Corp., Boxborough, MA) is likely to be more sensitive to low-grade squamous intra-epithelial lesion (LSIL) or to more severe lesions than conventional screening, with almost unchanged specificity. They also found that the detection rate of LBC (ThinPrep) for atypical squamous cells of undetermined significance (ASCUS) and more severe lesions may be higher than that of conventional screening, with a slightly lower specificity. Some, perhaps many, cytologists will be surprised that an evidence-based analysis of LBC has resulted in such a tepid endorsement of the clinical effectiveness of LBC (ThinPrep). How do these conclusions from the cervical screening program in The Netherlands compare with technology assessments and pilot studies of LBC (ThinPrep) performed by screening programs in other countries? Is there a consensus emerging from clinical epidemiologic analyses and programmatic pilot studies regarding the value of LBC in cervical carcinoma screening?

Early clinical epidemiologic assessments of LBC (ThinPrep) did not find evidence of improved clinical effectiveness. A 1999 analysis by the Agency for Health Care Policy and Research (AHCPR) concluded that there was significant uncertainty associated with the sensitivity and specificity estimates for thin-layer cytology. The AHCPR recommended further study.[1] Subsequently, the U.S. Preventive Services Task Force reported that there was insufficient evidence to make any recommendations for adopting LBC.[9] Similarly, in October 2000, the New Zealand Clearing House for Health Outcomes and Health Technology Assessment concluded that there was insufficient evidence in the literature to reliably determine the test sensitivity and specificity of LBC and strongly recommended against the implementation of LBC at that time.[3] (It is noteworthy that the Broadstock study[3] evaluated the published literature from the same time period as the study performed by Klinkhamer et al.) A 1997 Canadian health technology assessment focused exclusively on automated rescreening strategies and neglected any evaluation of LBC.[5]

An accumulation of other and more recent American, British, and Australian studies have recognized the improved clinical effectiveness of LBC (ThinPrep) compared with the conventional Pap smear. Although noting that existing studies of LBC (ThinPrep) frequently did not provide external adjudication, a 1999 study by Brown and Garber[10] concluded that the mean proportional increase in the detection of LSIL and more severe lesions for LBC (ThinPrep) compared with the conventional smear was 14.9%. The American Cancer Society (ACS) completed an extensive literature review and assessment and issued revised guidelines in 2002 on the early detection of cervical carcinoma. The ACS concluded that LBC (ThinPrep) was more sensitive but less specific for high-grade lesions, but the ACS also expressed concerns regarding specificity, because of increased ASCUS detection.[7]

A 1998 Australian technology assessment concluded that LBC (ThinPrep) would improve the clinical efficacy of the Pap test but cautioned that the increased costs could not be justified from a public health perspective.[2]

Major support for the claim of improved clinical effectiveness of LBC (ThinPrep) has been forthcoming from the United Kingdom. In 2000, a health technology assessment of the U.K. National Health Service reported that LBC did offer a reduction in inadequate

specimens and had improved sensitivity.[6] Subsequently, pilot studies were conducted in both Scotland and England. The 2001 Scottish Cervical Screening Programme pilot study identified an improved detection rate of high-grade squamous intra-epithelial lesion (HSIL) by LBC (ThinPrep) combined with markedly reduced unsatisfactory tests compared with the corresponding conventional smear.[8] The interim clinical evaluation of a three-site pilot study of LBC in England performed by the U.K. National Cancer Screening Program found a significant increase in the detection of HSIL for the two sites using LBC (ThinPrep). These Scottish and English data and a new metaanalysis of 14 studies comparing the sensitivities of LBC and conventional smears concluded that LBC had superior sensitivity. This finding led the National Institute for Clinical Excellence, U.K. (NICE) to recommend this year (2003) that LBC be used as the primary means of screening in England and Wales.[4]

A recent evaluation study in France comparing conventional and monolayer cytology has limited applicability to programmatic planning. The reasons are that the study included many nonscreening patients within its study cohort, used a split-sample method, and had relatively few numbers.[16]

The Klinkhamer et al. study, then, joined a growing list of clinical epidemiologic studies that concluded that LBC (ThinPrep) is clinically effective. They take great care to point out that acceptance of clinical effectiveness must be followed by an assessment of cost-effectiveness before programmatic implementation. A number of variables affect cost-effectiveness, including the reduction of inadequacy rates with associated repeat testing, screening interval(s), colposcopy referral policies, use of oncogenic human papillomavirus (HPV) testing for triage, introduction of HPV testing in the older age groups to attenuate screening intervals, and implementation of automated and location-guided screening devices.

Another LBC technique—SurePath (TriPath Imaging, Burlington, NC)—is available for gynecologic cytology. There are fewer data available on the clinical effectiveness of LBC (SurePath). Klinkhamer et al. reported that there is insufficient evidence to support the hypothesis that LBC (SurePath) has a higher detection rate of cervical abnormalities compared with the conventional Pap smear. Before implementation of the LBC (SurePath) method, they suggested that further evaluation is necessary. In contrast, the 2003 NICE report concluded that there is insufficient evidence to recommend one LBC product over another.[4] Recently, TriPath received approval from the U.S. Food and Drug Administration (FDA) for its expanded claim that SurePath together with the PrepStain slide processor demonstrated superiority in sensitivity to HSIL and more serious lesions compared with the conventional smear technique.[17] These FDA study data have not yet been published in the peer-reviewed literature. It is likely that the clinical effectiveness of LBC (SurePath) will still need to be confirmed in larger studies and clinical epidemiologic analyses.

In summary, the clinical epidemiologic analysis of LBC from The Netherlands is a significant addition in the peer-reviewed literature of programmatic assessments of the clinical effectiveness of LBC. Although there may be concerns regarding the methodology of Klinkhamer et al., the current study, as well as previous studies, lead to the conclusion that with respect to programmatic assessments of the clinical effectiveness of LBC—the ayes have it.

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