

Blinded Review of Papanicolaou Smears

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In this issue of *Cancer Cytopathology*, Renshaw et al. examine the process of the blinded review of Papanicolaou (Pap) smears in the context of litigation and provide a detailed statistical analysis of this process.¹ Beginning in the early 1990s, pathologists increasingly became the target of malpractice litigation for misdiagnoses, both in surgical pathology and cytopathology.² In effect, plaintiff attorneys discovered who we are and what we do. Although not comprising the majority of claims for negligence lodged against pathologists, false-negative Pap smears quickly became the high-profile cases in the media, and even included the filing of criminal charges. The victims of allegedly false-negative Pap smears often were young and either badly injured or had died of cervical carcinoma after the Pap smear had been promoted as a fail-safe test for the detection of this malignancy. Both these elements provided the ingredients for sensational news coverage.

Deaths from cervical carcinoma have decreased dramatically since the early 1950s, when the Pap test was introduced for screening. Promoted as life-saving by the American Cancer Society and prominent medical organizations, and initially supported with federal funding for the screening and training of cytotechnologists and pathologists, the test came to be regarded in the public eye as an insurance policy against death from cervical carcinoma. The story that unfolded over the years, namely the exploitation of cytotechnologists, the loss leader status of the test in some laboratories, an expose published in *The Wall Street Journal*, and the Congressional investigation of laboratory practices and legislation to regulate laboratories (first in 1967 [The Clinical Laboratory Improvement Act of 1967] and later in 1988, which was directed more specifically at cytology [The Clinical Laboratory Improvement Amendments of 1988]), is well known to this readership and does not require review here. The responses of the laboratory community also are well known: promoting better laboratory quality control and quality assurance practices; continuing education; public awareness of the fallibility of the Pap test, even under the best of circumstances; new terminology for the standardized reporting of Pap smear interpretations; and new technology to improve the test and to test for the causative agent of cervical carcinoma, namely the human papillomavirus.

Ongoing throughout the past, current, and continuing litigation involving Pap smears has been the difficult and sometimes acrimonious debate over the definition of a standard of practice. Standard of

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practice generally is defined as *practice exercised with the degree of care used by a reasonably careful physician of like qualifications in the community in which he or she practices under the same or similar circumstances*.³ We have in effect two standards of practice for the interpretation of Pap smears: the cytotechnologist who screens the slide to detect abnormalities and, if the smear has questionable cells or other elements visible, the pathologist who makes the final interpretation of the case. The definition of standard of care need not be altered except to substitute the word *cytotechnologist* for *physician*. Determining the applicable standard in Pap smear cases is difficult and problematic.⁴ Although cytotechnologists have provided and continue to provide expert testimony in Pap smear litigation, in a majority of cases it is an expert pathologist who provides these opinions both for the plaintiff and the defense. Although I have rendered this type of opinion, one could challenge that it is not truly expert when the issue is that abnormal cells were not detected during the screening of the slide, in reality a standard that can be legitimately determined only by a cytotechnologist. The standard of care in medicine is not determined by juries and judges, but is opined by experts in the field. In the case of Pap smears, there are really two sets of experts: cytotechnologists who review the slide initially and pathologists who interpret their concerns (if there are any) on a particular case.

In an effort to develop a reasonable practitioner standard applicable to cytotechnologists for the screening of Pap smears, Holladay established a blinded review panel of experienced cytotechnologists. Briefly, the slide that was the subject of dispute was mixed with no less than 60–100 slides from the same (defendant) laboratory and from the same time period as the index case. Included in the minimum of 60–100 slides were examples of low-grade and high-grade intraepithelial lesions and/or carcinoma as a quality control check of the reviewing panel of cytotechnologists. A 10-member panel was used and each panel member screened all slides as they would under normal circumstances, indicating those cases that they would refer for further review and interpretation. The panel was told only that the review was part of a quality control program requested by a laboratory. The objective was to simulate the normal screening process of a Pap smear by cytotechnologists as closely as possible and hence to eliminate as much as possible the inherent bias in a retrospective review when the outcome is known or at least strongly inferred. After accumulating data from a significant number of blinded reviews, it appeared that this method returned favorable results to the defendant laboratory in

approximately 67–75% of cases and, conversely, a favorable result to the plaintiff in approximately 25–33% of cases. The process has been used to adjudicate cases prior to the filing of a lawsuit and has been presented as evidence in both deposition and trial testimony. The process has generally (but not universally) been embraced by the profession, as evidenced by the endorsement of state and national pathology societies and by defense attorneys, but not by the majority of plaintiff attorneys. Judges may or may not allow such evidence to be admitted in court.

In the current article, Renshaw et al. examine the sample size required to validate the blinded review statistically to detect various differences in case difficulty or ease of detection. They define ease of detection as the percentage of time that a case can be identified as abnormal in routine screening. Using large studies from the literature, the authors determined that the ease of detection of a routine case could be estimated to be as high as 80% whereas the ease of detection of cases that are missed (false-negative cases) on routine review is estimated to be 40%, with reported ranges in the literature of 27–43%. Although the mathematics are difficult for this writer, the conclusions verify that all Pap smears screened routinely by qualified cytotechnologists are not created equal. In their discussion Renshaw et al. examined 3 thresholds: cases almost always detected as abnormal (ease of detection of 99%), routine cases (ease of detection of 80%), and routinely false-negative cases (ease of detection of 40%). Data from the article indicate that increasing the number of reviews increases the statistical power of the blinded review. Comparing a 99% ease of detection case with an 80% ease of detection case may require 20 reviews whereas comparison of an 80% ease of detection case with a case with a 40% ease of detection may require only 15 reviews. The authors also note that blinded review is a labor-intensive and expensive process, with Holladay's procedure limited to 10 reviewers. However, the authors conclude that in the setting of 10 reviewers, using 2 different thresholds for comparing a 40% ease of detection case versus an 80% ease of detection case (5 of 10 reviewers will detect the case vs. 7 of 10 reviewers), there is only a 5% chance of misclassifying the case.

As the pathology and cytotechnology community strives to achieve a reasonable practitioner standard for the review of Pap smears in the context of litigation, blinded review as presented by Holladay and examined statistically in the article by Renshaw et al.¹ deserves support. Recent evidence appears to indicate that blinded review is becoming more widely accepted as both a prelitigation test and as testimony in court.

The profession should support these efforts. Currently, the determination of standard of care appears to rest on what event or events occurred at a given moment that ultimately led to injury to the patient. Simply stated, what did that pathologist or cytotechnologist do with that smear at a given point in time? In the past, expert testimony has focused only on the retrospective review of the cytology specimen. The inherent bias, context, and/or outcome cannot be eliminated from such a review, despite expert's testimony to the contrary. A review of negative Pap smears from my files with long follow-up, presented in workshop situations with context and outcome bias, was found to lead to significant numbers of abnormal interpretations. Blinded review determines how the

slide performs as closely as possible to how it was reviewed in the usual laboratory setting (i.e., how the test originally was conducted). The profession should support this standard of practice.

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