Diagnostic Uncertainty Expressed in Prostate Needle Biopsies

A College of American Pathologists Q-Probes Study of 15 753 Prostate Needle Biopsies in 332 Institutions

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Objective.—To determine the rate of diagnostic uncertainty in rendering diagnoses on prostate needle biopsy and to examine pathology practice variables that influence that rate.

Design.—Anatomic pathology departments participating in the College of American Pathologists Q-Probes laboratory quality improvement program retrospectively reviewed their last 50 consecutive prostate needle biopsy diagnoses. For each diagnosis, participants provided information concerning patients’ prostate-specific antigen levels; number, locations, and laterality of biopsy specimens; number of tissue levels examined; performance of high-molecular-weight cytokeratin immunoperoxidase staining; and acquisition of consultations from general pathologists or experts in prostate pathology. Characteristics of pathology practices included yearly surgical and prostate needle biopsy caseloads, number of pathologists rendering biopsy diagnoses, use of standard descriptive checklists, access to patients’ prostate-specific antigen and digital rectal examination results, percentages of prostate needle biopsies routinely submitted for internal consultations, and presence of departmental experts in prostate pathology.

Setting and Participants.—Three hundred thirty-two public and private institutions located in the United States (n = 318), Canada (n = 6), Australia (n = 5), United Kingdom (n = 2), and Guam (n = 1).

Main Outcome Measure.—The rate of diagnostic uncertainty in prostate needle biopsy diagnoses.

Biopsy specimens for which the histologic findings fail to meet the minimum criteria needed to establish definitive diagnoses, or at least establish diagnoses that advance patient management, may compel surgeons to alter their management plans and perhaps repeat the biopsy procedures. Clinicians may feel that pathologists’ expressions of diagnostic uncertainty undermine the efficiency of the biopsies. What pathologists view as caution, surgeons may see as ambivalence. Finding the statistical fulcrum upon which these two attitudes balance provides both pathologists and surgeons with a realistic sense of the limitations of biopsy analysis. One measure of this statistical fulcrum is the normative rate of diagnostic uncertainty that exists in the general pathology community. Estimations of diagnostic uncertainty in clinical practice have generally been derived from eyeballing series of studies performed in the relatively controlled environments of individual institutions.

Since 1989, the College of American Pathologists Q-Probes program has conducted multi-institutional studies that have determined a wide range of performance benchmarks in both anatomic pathology and laboratory medicine.1 Laboratories participating in these studies have been able to compare their individual performances on a wide variety of laboratory procedures with those of their peers. Participants have also had access to the sizable, multi-in-
stitional reference database of practice variables that Q-Probes studies have, over the past decade, shown to influence laboratory performance. There are now more than 1200 Q-Probes subscribers throughout North America, the United Kingdom, and Australia, representing the gamut of practice environments. The College of American Pathologists maintains a listing of Q-Probes benchmarks from anatomic and clinical pathology studies on the Internet at www.cap.org.

In this Q-Probes study, we attempted to establish a model to allow participants to quantify diagnostic uncertainty in their practices of anatomic pathology. As a substrate for this model, we chose to examine the frequency with which the histologic evaluations of prostate needle biopsies (PNBs) were unable to establish unequivocally or exclude the presence of adenocarcinoma of the prostate in patients suspected of harboring that disease. We elected to study PNBs because we believed that they are performed frequently enough in modern practice to provide us with ample case material, and that they are performed for indications narrow enough, namely, to rule out one disease (adenocarcinoma), to facilitate analysis of the data. We evaluated the effects of various conditions concerning the PNB specimens and of various pathology practice characteristics on the rates of diagnostic uncertainty.

MATERIALS AND METHODS

Definitions of Terms

Case—A single patient episode (accession case number) for which tissue was submitted for examination. One case may have included more than one specimen, and each specimen may have been evaluated by one or more blocks.

Uncertainty Case Rate—The number of cases in which diagnoses implied uncertainty (see “Diagnoses Implying Uncertainty”) divided by the total number of cases examined.

Positive Diagnoses—Diagnoses indicating the presence of adenocarcinoma in at least 1 biopsy specimen associated with a case.

Negative Diagnoses—Diagnoses indicating no evidence of adenocarcinoma and implying no element of uncertainty in any of the biopsy specimens associated with a case (see “Diagnoses Implying Uncertainty”). This category included, but was not limited to, diagnoses of benign, no evidence of malignancy, atrophy, etc (ie, follow-up diagnostic biopsy is not necessarily indicated).

Diagnoses Implying Uncertainty—Diagnoses that are neither clearly positive nor clearly negative for adenocarcinoma, but which may require the urologist to perform another biopsy to definitively establish or rule out the presence of malignancy and, hence, plan treatment. Uncertain diagnoses include, but are not limited to, suspicious for malignancy, consistent with malignancy, consistent with but not diagnostic of malignancy, probable malignancy, cannot rule out malignancy, and rule out malignancy. For purposes of recording the data, the category of uncertain diagnoses included diagnoses of prostatic intraepithelial neoplasia (PIN) and carcinoma in situ (CIS); however, these diagnoses were tabulated and analyzed separately and were not included in the tabulation of uncertain diagnoses.

Design

Institutions enrolled in the College of American Pathologists Q-Probes program for the first quarter of 1998 participated in this study. On their enrollment in the Q-Probes program, each participating institution submitted certain demographic information, including their geographic location, community classification (urban, suburban, rural), teaching status, residency program status, occupied bed size, and accreditation status.

For a period spanning no more than 2 years previous, participants culled from their surgical pathology files their last 50 consecutive PNB surgical pathology reports, excluding any consultation cases that may have been referred to them from other institutions. Participants indicated the number of consecutive surgical pathology reports that they scanned to glean the 50 PNB cases required for this study. If they could not produce the required 50 cases, participants tallied all surgical case accessions in the preceding 2 years and reported on all PNB cases accessioned during this interval. Diagnoses and information concerning the PNB specimens were entered onto standardized input forms. For cases in which none of the diagnoses were positive for invasive adenocarcinoma, participants indicated whether the final diagnosis for the entire case was CIS/PIN, negative for malignancy, or whether the final diagnosis implied uncertainty (ie, was neither clearly positive nor clearly negative for malignancy; see “Definitions”). From these aggregate data, we calculated the overall rates of positive, negative, CIS/PIN, and uncertain PNB diagnoses. We did not attempt to determine whether the diagnoses submitted for this study were accurate. We did not ask participants to obtain clinical correlation or follow-up.

We evaluated the effects of variables concerning PNB cases and of variables concerning institutional pathology practices on the rates of diagnostic uncertainty. For each case, participants responded to specific inquiries concerning the specimen and the manner in which it was processed by making check marks on input forms. Participants described specific conditions occurring during the preanalytic phase of testing (the period of the time leading up to the pathologist's examination of the specimen) and specific conditions occurring during the analytic phase of testing (the period of time during which the pathologist examined the specimen). The preanalytic variables included whether pathologists had the results of patients’ prostate-specific antigen (PSA) levels at the time of case sign-out, and if so, whether those levels were elevated; the number, the locations, and the laterality of the biopsy specimens; and the number of levels and/or recuts that pathologists examined. The analytic variables included whether pathologists performed high-molecular-weight cytokeratin (HMWK) immunoperoxidase staining on any of the specimens; whether pathologists obtained intranstitutional consultations from general pathologists or intranstitutional consultations from designated experts in prostate pathology on any of the specimens; and whether pathologists obtained extranstitutional consultations on any of the specimens. We compared the aggregate rates of diagnostic uncertainty occurring in the presence and in the absence of each of these conditions. We excluded from this analysis cases for which practice conditions were listed as “unknown” or for which the inquiries were not answered. If a participant failed to answer a question, that response was excluded from the database for that question only. In evaluating the associations between these conditions and diagnostic uncertainty, we used χ² goodness-of-fit tests to test differences between groups and considered a P value of .05 or less to be statistically significant.

We determined each participating institution's specific rate of diagnostic uncertainty and then organized those rates into a percentile distribution. Each participant responded to specific inquiries concerning their pathology department's practice characteristics by making check marks on input forms. For those institutions performing at least 10 biopsy examinations during the study period, we compared the frequencies of these practice variables occurring in the lowest and in the highest 10th percentiles. The specific practice variables that participants described included the number of total surgical pathology cases and PNB cases accessioned in the previous 12 months; the total number of surgical pathologists responsible for rendering diagnoses on those accessioned cases; whether pathologists routinely performed high- or low-molecular-weight cytokeratin immunoperoxidase staining; whether pathologists systematically used standard descriptive or diagnostic checklists when examining PNBs; whether pathologists routinely reviewed biopsy cases; and whether institutions relied upon experts in prostate pathology; and the percentage of PNBs they routinely
submitted for internal consultation regardless of the initial assessment or diagnosis. If a participant failed to answer a question, that response was excluded from the database for that question only. In evaluating the associations between practice characteristics and diagnostic uncertainty, we used Wilcoxon and Kruskal-Wallis tests to assess differences between groups and considered a P value of .05 or less to be statistically significant.

RESULTS

A total of 332 institutions subscribing to the Q-Probes program for the first quarter of 1998 participated in this study. These institutions were located in 47 states in the United States (n = 318) and in Canada (n = 6), Australia (n = 5), the United Kingdom (n = 2), and Guam (n = 1). The median participating institution contained 189 beds (range, 0–1520). Most (62%) participants practiced in private nonprofit hospitals, 14.7% in governmental facilities, 6.7% in private for-profit hospitals, 6.7% in private laboratories or clinics, 3.7% in university hospitals, and 6.1% in other types of facilities. Most (56.9%) participating institutions listed their location as urban, 22.5% as suburban, 19.7% as rural, and 0.9% as federal or other. Most (90.7%) participating institutions were accredited by the Joint Commission for Accreditation of Healthcare Organizations, and most (86.7%) participating laboratories were accredited by the College of American Pathologists. A third (33.5%) of the institutions had or were affiliated with teaching programs, and 17.8% had residency programs.

In the 12 months prior to performing this study, the 332 participants accessioned a total of 4238 180 surgical cases, of which 122 495 (2.9%) were PNBs. During that 12 months, the median participating institution accessioned 9542 surgical cases (range, 714–178 490), of which 176 (range, 0–45 108) were prostate biopsies, and employed 4 (range 4–104) surgical pathologists.

For this study, the 330 participating institutions submitted diagnoses on a total of 15 753 PNB cases, S746 (55.5%) of which indicated the absence of adenocarcinoma, 5267 (33.4%) of which indicated the presence of adenocarcinoma, and 619 (3.9%) of which indicated the presence of CIS, PIN, or both. A total of 1740 (11.0%) of all diagnosis were uncertain, including those that indicated a diagnosis of CIS or PIN, and 1121 (7.1%) of all diagnoses were uncertain, excluding those that indicated a diagnosis of CIS and PIN.

Table 1 shows the rates of diagnostic uncertainty by specimen variables occurring during the preanalytic phase of testing. For 90.9% of 15 793 PNB cases for which participants supplied information concerning access to patients' PSA results, the diagnoses of 36.5% of which were uncertain, and did not have access to 36.5% of patients' PSA results, the diagnoses of 6.5% of which were uncertain. The 1.2% higher rate of diagnostic uncertainty associated with cases with access to PSA results was statistically significant (P = .005). Similarly, the 1.4% higher rate of diagnostic uncertainty associated with cases consisting of multiple specimens was also statistically significant (P = .005).

Table 2 shows rates of final diagnostic certainty and diagnostic uncertainty by specimen variables occurring during the analytic phase of testing. Of the 14 753 cases for which participants indicated whether diagnosing pathologists performed HMWK staining, participants indicated that pathologists ordered HMWK staining on 417 (2.8%) cases. Following HMWK staining, the diagnostic status of 264 (68.1%) of these cases became certain (ie, positive or negative for adenocarcinoma), and the diagnostic status of 133 (31.9%) remained uncertain.

Table 1. The Rates of Diagnostic Uncertainty by Specimen Variables Occurring During the Preanalytic Phase of Testing

<table>
<thead>
<tr>
<th>Specimen Condition</th>
<th>No. (%)</th>
<th>Percent Uncertain</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge of prostate-specific antigen results at time of case sign-out (n = 14 355)*</td>
<td>Yes 9117 (63.5)</td>
<td>7.7</td>
<td>.005</td>
</tr>
<tr>
<td>No 5238 (36.5)</td>
<td>6.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of biopsy samples submitted by urologist (n = 14 829)</td>
<td>1 biopsy 3134 (21.1)</td>
<td>6.3</td>
<td>.005</td>
</tr>
<tr>
<td>&gt;1 biopsy 11 695 (78.9)</td>
<td>7.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location of biopsy within prostate (n = 14 327)</td>
<td>Unilateral 2619 (18.3)</td>
<td>6.5</td>
<td>.045</td>
</tr>
<tr>
<td>Bilateral (right and left lobes, quadrant, sextant) 11 708 (81.7)</td>
<td>7.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of levels within the tissue block examined by pathologist (n = 14 968)</td>
<td>1 level only 596 (4.0)</td>
<td>8.1</td>
<td>.544</td>
</tr>
<tr>
<td>Multiple levels 14 372 (96.0)</td>
<td>7.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* n indicates number of cases for which participants supplied information.

Table 2. Rates of Final Diagnostic Certainty and Uncertainty by Specimen Variables Occurring During the Analytic Phase of Testing

<table>
<thead>
<tr>
<th>Specimen Condition</th>
<th>No. (%)</th>
<th>No. (%) Certain Diagnoses</th>
<th>No. (%) Uncertain Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-molecular-weight keratin stain ordered (n = 14 753)*</td>
<td>417 (2.8)</td>
<td>284 (68.1)</td>
<td>133 (31.9)</td>
</tr>
<tr>
<td>Internal consult obtained by general pathologist (n = 14 186)</td>
<td>3782 (26.7)</td>
<td>3287 (86.9)</td>
<td>495 (13.1)</td>
</tr>
<tr>
<td>Internal consult obtained by expert in prostate pathology (n = 14 616)</td>
<td>402 (2.8)</td>
<td>332 (82.6)</td>
<td>70 (17.4)</td>
</tr>
<tr>
<td>External consult obtained (n = 14 827)</td>
<td>323 (2.2)</td>
<td>226 (70.0)</td>
<td>97 (30.0)</td>
</tr>
</tbody>
</table>

* n indicates number of cases for which participants supplied information.
Table 3. Percentile Distribution of Institutional Rates of Prostate Needle Biopsy Diagnoses (n = 330 Institutions)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percentile, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10th</td>
</tr>
<tr>
<td>Positive for adenocarcinoma</td>
<td>20</td>
</tr>
<tr>
<td>Negative for adenocarcinoma</td>
<td>38</td>
</tr>
<tr>
<td>CIS/PIN*</td>
<td>0</td>
</tr>
<tr>
<td>Uncertain</td>
<td>0</td>
</tr>
</tbody>
</table>

* CIS indicates carcinoma in situ; PIN, prostatic intraepithelial neoplasia.

Table 4. Surgical Pathology Departmental Policies and Practice Characteristics

<table>
<thead>
<tr>
<th>Departmental Policies and Practice Characteristics*</th>
<th>No. (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologists usually have access to patients’ PSA results when they sign out the case</td>
<td>226 (68.7)</td>
</tr>
<tr>
<td>Pathologists usually have access to results of patients’ DRE when they sign out the case</td>
<td>31 (9.4)</td>
</tr>
<tr>
<td>Routine protocol for examining prostate biopsy cores</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Use a standard descriptive or diagnostic checklist when examining or arriving at diagnoses on prostate needle biopsy specimens</td>
<td>63 (19.1)</td>
</tr>
<tr>
<td>Pathologist on staff designated as expert in prostate pathology</td>
<td>50 (15.2)</td>
</tr>
<tr>
<td>Percentage of prostate needle biopsies routinely submitted by department protocol for internal consultations</td>
<td>134 (40.9)</td>
</tr>
</tbody>
</table>

* PSA indicates prostate-specific antigen; DRE, digital rectal examination.
† Number of institutions supplying information.

The element of uncertainty is inescapable in the practice of medicine. Pathologists experience this uncertainty when histologic findings of biopsy specimens fall just short of providing the diagnostic criteria needed to establish definitive diagnoses. This uncertainty commonly leads to tension between the need to advance patient management and the level of caution needed to avoid therapeutic misadventure. The purpose of this study was to measure the ambient rate of uncertainty for a commonly performed task in the current practice of anatomic pathology. As a model for this task, we chose to measure the rate of uncertainty in rendering diagnoses on prostate needle biopsies. The College of American Pathologists Q-Probes program provided an excellent vehicle by which to gather this sort of data because it afforded ready access to a large number of pathology practices and to a variety of practice environments widely distributed throughout the United States and elsewhere.

The overall case rate of diagnostic uncertainty for the aggregate of 15753 PNBs performed in this study, excluding those cases diagnosed as showing CIS and PIN, was 7.1%. The median pathology department rate of diagnostic uncertainty for 332 institutions participating in this study was 6%, ranging from 0 at the 10th percentile to 14% at the 90th percentile. These rates of diagnostic un-
certainty are similar to the 1.5% to 8.3% range of “atypical” or “suspicious” PNB diagnoses cited in recently reported unselected series.9±14 However, the conditions of those published studies differ from those of our study in that they reflect the experience of individual or small groups or institutions, many of which are academic and in which the practice environments are presumably homogeneous. Some of these groups are staffed by recognized experts in the field of prostate pathology, some process a high percentage of consult cases, some are based in community hospitals, and some are based in major teaching institutions. In contrast, this study reflects the daily experience of a large heterogeneous population of pathologists practicing in a variety of geographic and community locations. Pathologists participating in this study may have varied widely in their expertise, in their definitions and use of diagnostic criteria, and in their practice characteristics. Given the variables that contribute to uncertainty in pathologic diagnoses, not the least of which are the unpredictability of biological behavior and the frequencies of diseases in various populations, we do not present these rates of diagnostic uncertainty as representing performance benchmarks. Rather, they provide a snapshot of current practice.

In addition to establishing the range of diagnostic uncertainty, we studied the association of preanalytic and analytic practices with the aggregate rate of diagnostic uncertainty. Two thirds of participants had access to patients’ PSA results at the time of diagnosis. The 1.2% higher rate of diagnostic uncertainty associated with access to patients’ PSA results may have reflected the unwillingness of some pathologists to sign out a normal PNB diagnosis if they knew that the patient had an elevated PSA level. Even though this 1.2% difference is statistically significant, it is doubtful that it has clinical relevance in daily practice. Cheville and coworkers9 reported that in patients with suspicious findings on PNB, the initial mean PSA values were higher in those patients whose subsequent PNBs demonstrated adenocarcinoma than in those patients whose subsequent PNBs did not. However, several other studies have shown that the PSA results in patients with suspicious findings on PNB did not predict whether their subsequent PNBs demonstrated adenocarcinoma.15–18 In about 80% of the cases reported for this study, urologists sampled both sides of the prostate and submitted more than 1 biopsy sample. Although the 1.4% higher rate of diagnostic uncertainty that was associated with submitting multiple rather than single PNB specimens was statistically significant, it is doubtful that this small difference would be clinically significant in daily practice. The rate of diagnostic uncertainty was not associated with unilateral or bilateral prostate sampling.

The number of tissue levels that the pathologist examined was not associated with higher or lower rates of diagnostic uncertainty. We did not ask participants to specify whether pathologists ordered multiple levels initially (preanalytic testing variable), or whether they ordered deeper levels after their initial examination (analytic testing variable). We arbitrarily considered the number of levels examined to be a preanalytic testing variable. Ickowski and coworkers14 found that in patients diagnosed as having suspicious findings on PNB, the number of tissue levels examined did not influence whether adenocarcinoma was demonstrated on subsequent biopsies. Other studies, however, have shown that examining multiple tissue levels uncovers additional increments of both neoplastic and suspicious lesions that were not present on the initial cuts.19–22 As a preanalytic variable, examining multiple tissue levels may not influence outcome, but as an analytic testing variable, it probably does. We agree with Manivel23 in recommending that pathologists cut deeper levels on problem cases.

In this study, the location within the testing process at which the testing variable was manipulated affected the rate of diagnostic uncertainty. Variations in conditions of specimen management occurring during the preanalytic testing phase had no effect on the rate of suspicious diagnoses. Unlike those variables of specimen management occurring during the preanalytic phase of testing, over which pathologists might be expected to exert very little influence, pathologists are likely to exert near complete control over those variables of specimen management occurring during the analytic phase of testing. Indeed, in this study, manipulations of specimen management during the analytic testing phase, although not always frequently exercised, had a profound effect on rates of diagnostic uncertainty. For instance, participants performed HMWK staining on only 2.8% of cases. Assuming that the diagnostic status of all these cases was uncertain prior to staining, performing HMWK staining resolved the diagnostic status of more than two thirds of these cases. Several authors have shown that performing HMWK staining resolves, or at least assists in resolving, 64% to 75% of problem PNB diagnoses.24,25 We did not ask participants to specify the number of atypical glands that were present on the biopsy cores.

More than 90% of participating pathology departments stated that they routinely submit all or some fraction of their PNB cases to their colleagues for internal consultation. In this study, pathologists consulted their peers on slightly more than a quarter of the cases. Assuming that all diagnoses were uncertain prior to internal consultation, obtaining internal consultations from intradepartmental general pathologists resolved 87% of diagnostically uncertain cases. Obtaining consultations from intradepartmental experts in prostate pathology resolved diagnostic uncertainty in 83% of those cases, and obtaining extradepartmental consultation from experts in prostate pathology resolved diagnostic uncertainty in 70% of those submitted cases. The lower percentage of diagnostic resolution occurring when specimens were sent for extradepartmental consultations compared with that occurring when specimens were sent for intradepartmental consultation may have reflected higher degrees of diagnostic challenge in those cases selected for external consultation.

We studied the effects that certain departmental practice characteristics may have exerted on the institutional rates of diagnostic uncertainty. Although certain practices may have assisted in resolving diagnostic uncertainty on individual cases, none of the variations in pathology departmental practices and policies that we examined was associated with higher or lower institutional rates of diagnostic uncertainty. For instance, institutional rates of diagnostic uncertainty were not associated with whether pathologists routinely had access to the results of patients’ PSA or digital rectal examinations. Bostwick and his coworkers5 have shown that there is no correlation between digital rectal examination findings and biopsy diagnoses. Several authors have shown that in patients with suspicious findings on PNB, the results of their rectal exami-
nations at the time of diagnosis did not predict whether adenocarcinoma was demonstrated on subsequent biopsies.\textsuperscript{15,16,18,20} Institutional diagnostic uncertainty was not associated with departmental use of diagnostic checklists in signing out cases, routinely cutting multiple tissue levels, or with routinely obtaining intradepartmental consultations. Neither aggregate nor institutional rates of diagnostic uncertainty were associated with the geographical locations of hospitals, types of communities in which hospitals were located, hospitals’ teaching status, laboratories’ or hospitals’ accreditation status, yearly surgical pathology caseloads, or with yearly PNB caseloads.

Uncertainty in attempting to establish a diagnosis on a PNB specimen is a rare but expected occurrence. This 1998 Q-Probes study has defined the ambient rate of PNB diagnostic uncertainty as it is currently practiced in participating laboratories, the majority of which were located in the United States. This rate of diagnostic uncertainty is likely to change over time with the advent of newer diagnostic equipment and technologies.

Molly Walsh, PhD, College of American Pathologists, Northfield, Ill, provided statistical support for this study. The authors thank College of American Pathologists staff members Tari Vaughn and Kim O’Donnell for their invaluable assistance in conducting this study and preparing this manuscript.

References