Characteristics of a Breast Pathology Consultation Practice

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Context.—Intradepartmental consultation is a routine practice commonly used for new diagnoses. Expert interinstitutional case review provides insight into particularly challenging cases.

Objective.—To investigate the practice of breast pathology consultation at a large tertiary care center.

Design.—We reviewed breast pathology cases sent for private consultation and internal cases reviewed by multiple pathologists at a tertiary center. Requisitions and reports were evaluated for diagnostic reason for consultation, rate of multiple pathologist review at the tertiary center, use of immunohistochemistry, and, for private consultation cases, type of sender and concordance with the outside diagnosis.

Results.—In the 985 private consultation cases, the most frequent reasons for review were borderline atypia (292 of 878; 33.3%), papillary lesion classification (151 of 878; 17.2%), evaluating invasion (123 of 878; 14%), subtyping carcinoma (75 of 878; 8.5%), and spindle cell (67 of 878; 7.6%) and fibroepithelial (65 of 878; 7.4%) lesion classification. Of 4981 consecutive internal cases, 358 (7.2%) were reviewed, most frequently for borderline atypia (90 of 358; 25.1%), subtyping carcinoma (63 of 358; 17.6%), staging/prognostic features (59 of 358; 16.5%), fibroepithelial lesion classification (45 of 358; 12.6%), evaluating invasion (37 of 358; 10.3%), and papillary (20 of 358; 5.6%) and spindle cell (18 of 358; 5.0%) lesion classification. Of all internal cases, those with a final diagnosis of atypia had a significantly higher rate of review (58 of 241; 24.1%) than those with benign (119 of 2933; 4.1%) or carcinoma (182 of 1807; 10.1%) diagnoses. Immunohistochemistry aided in diagnosis of 39.7% (391 of 985) and 21.2% (76 of 359) of consultation and internally reviewed cases, respectively.

Conclusions.—This study confirms areas of breast pathology that represent diagnostic challenge and supports that pathologists are appropriately using expert consultation.

METHODS

Patient Selection

Intradepartmental consultation is a common practice that acts as a second review in the setting of new malignant diagnoses or in challenging diagnoses in routine practice.1,2 For particularly challenging cases, interinstitutional consultation is a valuable service that allows cases to be reviewed by specialists with expert knowledge. In breast pathology, second review is a particularly valuable practice because diagnostic discordance that alters patient management may be seen in up to 11% of cases.3,4 Recent reports have suggested poor concordance among pathologists for certain breast pathology diagnoses, including atypias, in situ carcinomas, fibroepithelial lesions, low-grade cancers, and papillary lesions.5–11 In atypical and in situ lesions, the use of ancillary studies such as additional levels improved diagnostic accuracy when compared with a reference panel of expert pathologists.12 Immunohistochemical (IHC) stains, second review, and changes in processing can be useful, especially in preventing overdiagnosis of atypias, such as atypical ductal hyperplasia (ADH) (ie, false positives).13–15

The accurate diagnosis of ADH on core biopsy is important because of the current recommendations for excision given the relatively high incidence of upgrade to invasive or ductal carcinoma in situ (DCIS) on excision.16,17 However, there are limited data for the long-term risk of invasive carcinoma or DCIS posed by ADH.18,19 As a common question in interinstitutional consultation, confirming or refuting a diagnosis of ADH has significant impact on the patient’s subsequent management.

In our practice, we observed some cases to be inherently challenging, requiring IHC, additional levels, or multiple expert consulting pathologists. In this study, we sought to investigate the practices of intradepartmental and interdepartmental breast pathology consultation at a large tertiary care center.

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For external cases sent for consultation, requisitions and reports were evaluated by 3 authors for the type of sender, diagnostic reason for consultation, rate of multiple pathologist review at the tertiary center, use of IHC to support a diagnosis, and, when available, rate of concordance with the given or favored outside diagnosis.

For internal cases, the pathology reports and, when necessary, slides from the case were reviewed by 2 authors; features assessed were review by second pathologist, diagnostic reason for review, IHC use to support a diagnosis, and general diagnostic category of benign, atypia, or carcinoma. The atypia category included ADH, apocrine atypia, atypical lobular hyperplasia, and classic lobular carcinoma in situ. The carcinoma category included pleomorphic lobular carcinoma in situ, DCIS, and invasive breast carcinoma.

For all patients, additional information including sex, age, and procedure type was recorded. When the diagnostic question was borderline atypia, the differential diagnosis of benign versus atypia and atypia versus carcinoma in situ was also recorded. Example cases of borderline atypia were shown in the Figure, A through D.

Of note, at our institution, all cases of invasive breast carcinoma and DCIS are reviewed for multidisciplinary discussion. Internally reviewed cases included in this study were those that were reviewed prior to diagnosis and not for multidisciplinary review. Cases were chosen for review at the discretion of the signing pathologist.

**Statistical Analysis**

Descriptive statistics (ie, frequencies and percentages for categorical variables, and mean and range for continuous variables) were calculated. We used $\chi^2$ tests or Fisher exact tests to test the difference in consultation case features between patient/clinician- and pathologist-requested review. The same tests were used to evaluate the association of IHC use with diagnostic questions. Significance was determined if $P < .05$. All analyses were conducted using SAS (version 9.4, SAS Institute, Cary, North Carolina).

**RESULTS**

**Consultation Cases**

Nine hundred ninety consecutive breast pathology consultation cases were reviewed. Five cases were excluded that had been previously signed out at their contributing institutions and had no diagnostic question; these cases were sent with the sole request of performing IHC for estrogen receptor, progesterone receptor, and/or HER-2/neu as the indication for consultation.
Of the remaining 985 cases, 972 patients (98.7%) were female and the mean patient age was 57 years (range, 12–93 years). Of the 985 cases, 816 (82.8%) had clear indication of a diagnostic question as the reason for consultation, with 754 (92.4%) having 1 and 62 (7.6%) having 2 main diagnostic questions (for a total of 878 diagnostic questions). Eight hundred seventy-five of 985 (88.8%) consultations were pathologist requested and 110 of 985 (11.2%) were clinician or patient requested.

The most common indications for review were borderline atypia (292 of 878; 33.3%), classification of papillary lesions (151 of 878; 17.2%), evaluation for possible invasion (123 of 878; 14%), subtyping of in situ or invasive carcinoma (75 of 878; 8.5%), and classification of spindle cell (67 of 878; 7.6%) and fibroepithelial (65 of 878; 7.4%) lesions (Table 1).

Immunohistochemistry aided in diagnosis in 391 of 985 cases (39.7%). Use of IHC was significantly associated with and most frequently aided in differentiating breast primary from other carcinomas (22 of 23; 95.7%), diagnosis of spindle cell lesions (49 of 67; 73.1%), assessing possible invasion (82 of 123; 66.7%), subtyping of carcinoma in situ or invasive breast carcinoma (49 of 75; 65.3%), and diagnosis of papillary lesions (85 of 151; 56.3%) (\(P < .001\)). Infrequent IHC use was significantly associated with diagnostic questions of classification of fibroepithelial lesions (5 of 65; 7.7%) and borderline atypia (62 of 292; 21.2%) (\(P < .001\)). Review by more than one consultant

### Table 1. Characteristics of Breast Pathology Consultation Cases From Outside Institutions (N = 985)

| Characteristic                                      | Value       |
|----------------------------------------------------|-------------|
| **Sex, No. (%)**                                   |             |
| Female                                             | 972 (98.7)  |
| Male                                               | 13 (1.3)    |
| **Age, mean (range), y**                           |             |
| 57 (12–93)                                         |             |
| **Requestor, No. (%)**                             |             |
| Patient/clinician                                  | 110 (11.2)  |
| Pathologist                                        | 875 (88.8)  |
| **Procedure, No. (%)**                             |             |
| Core/punch biopsy or FNA                           | 546 (55.4)  |
| Excision                                           | 422 (42.9)  |
| Both                                               | 17 (1.7)    |
| **Reason for consult was provided, No. (%)**       |             |
| No                                                 | 169 (17.2)  |
| Yes (1 main question)                              | 754 (76.5)  |
| Yes (2 main questions)                             | 62 (6.3)    |
| **Diagnostic questions, No. (%) (n = 878)**        |             |
| Borderline atypia                                  | 292 (33.3)  |
| Classification of papillary lesion                 | 151 (17.2)  |
| Possible invasion                                  | 123 (14.0)  |
| Subclassification of carcinoma in situ or invasive cancer | 75 (8.5) |
| Classification of spindle cell lesion              | 67 (7.6)    |
| Classification of fibroepithelial lesion           | 65 (7.4)    |
| Classification as primary breast carcinoma or other neoplasm | 23 (2.6) |
| Classification of other proliferative and/or sclerosing lesion | 20 (2.3) |
| Interpretation for other prognostic features (ie, margins, grade, lymph node involvement, size) | 14 (1.6) |
| Classification of lymphoid or other inflammatory lesion | 11 (1.3) |
| Possible discordance with clinical impression (ie, no residual neoplasm, lesion does not explain mass) | 10 (1.1) |
| Interpretation of ER, PgR, and/or HER-2            | 9 (1.0)     |
| Classification in the setting of prior therapy     | 6 (0.7)     |
| Classification of vascular lesion                  | 5 (0.6)     |
| Third opinion for discordance between 2 outside hospitals | 4 (0.5) |
| Possible Paget disease                             | 3 (0.3)     |
| **Differential diagnosis considered if diagnostic question of borderline atypia, No. (%) (n = 292)** |             |
| Benign versus atypia                               | 134 (45.9)  |
| Atypia versus carcinoma in situ                    | 158 (54.1)  |
| **Immunohistochemistry aided in diagnosis, No. (%)** |             |
| No                                                 | 594 (60.3)  |
| Yes                                                | 391 (39.7)  |
| **Reviewed by >1 consultant pathologist, No. (%)** |             |
| No                                                 | 608 (61.7)  |
| Yes                                                | 377 (38.3)  |
| **Agreed with outside favored/given diagnosis, No. (%)** |         |
| None given                                         | 323 (32.8)  |
| No                                                 | 138 (14.0)  |
| Yes                                                | 518 (52.6)  |
| Partial (in multipart case)                        | 6 (0.6)     |

Abbreviations: ER, estrogen receptor; FNA, fine needle aspiration; HER-2, HER-2/neu; PgR, progesterone receptor.

Of the remaining 985 cases, 972 patients (98.7%) were female and the mean patient age was 57 years (range, 12–93 years). Of the 985 cases, 816 (82.8%) had clear indication of a diagnostic question as the reason for consultation, with 754 (92.4%) having 1 and 62 (7.6%) having 2 main diagnostic questions (for a total of 878 diagnostic questions). Eight hundred seventy-five of 985 (88.8%) consultations were pathologist requested and 110 of 985 (11.2%) were clinician or patient requested.

The most common indications for review were borderline atypia (292 of 878; 33.3%), classification of papillary lesions (151 of 878; 17.2%), evaluation for possible invasion (123 of 878; 14%), subtyping of in situ or invasive carcinoma (75 of 878; 8.5%), and classification of spindle cell (67 of 878; 7.6%) and fibroepithelial (65 of 878; 7.4%) lesions (Table 1).

Immunohistochemistry aided in diagnosis in 391 of 985 cases (39.7%). Use of IHC was significantly associated with and most frequently aided in differentiating breast primary from other carcinomas (22 of 23; 95.7%), diagnosis of spindle cell lesions (49 of 67; 73.1%), assessing possible invasion (82 of 123; 66.7%), subtyping of carcinoma in situ or invasive breast carcinoma (49 of 75; 65.3%), and diagnosis of papillary lesions (85 of 151; 56.3%) (\(P < .001\)). Infrequent IHC use was significantly associated with diagnostic questions of classification of fibroepithelial lesions (5 of 65; 7.7%) and borderline atypia (62 of 292; 21.2%) (\(P < .001\)). Review by more than one consultant.
pathologist was not significantly associated with any specific diagnostic question.

Clinician/patient–requested review was significantly associated with less frequent indication of reason for consultation, use of IHC, and review by more than one consultant pathologist as compared with cases that were sent by an outside pathologist for review (P < .001). When provided, there was high concordance with the original/favored diagnosis, especially when the review was clinician/patient requested (Table 2).

**Internally Reviewed Cases**

Four thousand nine hundred eighty-one consecutive internal breast pathology cases were reviewed, of which 359 (7.2%) had documentation of at least 1 additional pathologist review. Review was significantly associated with excision procedure and diagnostic categories of atypia or DCIS/carcinoma (P < .001) (Table 3).

Of the 359 internally reviewed cases, 358 patients (99.7%) were female and the mean patient age was 51 years (range, 11–88 years). Three hundred (83.6%) and 29 (8.1%) patients had 1 and 2 diagnostic questions, respectively (for a total of 358 diagnostic questions).

The most common reasons for review were borderline atypia (90 of 358; 25.1%), subtyping of in situ or invasive carcinoma (63 of 358; 17.6%), staging/prognostic features (59 of 358; 16.5%), classification of fibroepithelial lesions (45 of 358; 12.6%), assessing possible invasion (37 of 358; 10.3%), and classification of papillary (20 of 358; 5.6%) and spindle cell (18 of 358; 5.0%) lesions (Table 4).

Immunohistochemistry aided in diagnosis in 76 of 359 cases (21.2%). Use of IHC was significantly associated with and most frequently aided in assessing possible invasion (24 of 37; 64.9%) and not using IHC was significantly associated with classification of fibroepithelial lesions (0 of 45; 0%) (P < .001).

**DISCUSSION**

Numerous studies have shown pathology case review to decrease interpretive diagnostic error and, when done in a timely manner, to improve patient care. However, guidelines for case review are general, allowing for the system of review to be tailored to the needs of the individual pathology practice. Thus, surgical pathology review practices vary and difficult cases for which interobserver variability is highest may be managed differently from institution to institution, potentially resulting in higher rates of underinterpretation or overinterpretation and inappropriate patient management.

Breast pathology diagnoses of atypia and low-grade DCIS have long been known to have lower rates of diagnostic concordance as compared with most benign and invasive carcinoma diagnoses. A recent publication by Elmore et al showed significant discordance in the interpretation of breast atypias, with rates of 17% overinterpretation and 35% underinterpretation by a group of 115 participating pathologists when compared with an expert panel. Additional areas of diagnostic challenge include in situ lesions, fibroepithelial lesions, low-grade cancers, and papillary lesions.

In many situations diagnostic accuracy for challenging breast pathology diagnoses can be improved by the use of ancillary studies. For example, deeper levels aid in establishing margin status, and myoepithelial IHC markers may be helpful in establishing microinvasion or in the subclassification of papillary lesions. In another example is the use of cytokeratin 5/6 IHC, which is helpful in establishing the diagnosis of atypia when the differential diagnosis is...

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**Table 2. Consultation Case Features Significantly Associated With Patient/Clinician–Versus Pathologist-Requested Review**

| Feature                                             | Patient/Clinician–Requested (n = 110) | Pathologist-Requested (n = 875) | P     |
|-----------------------------------------------------|-------------------------------------|-------------------------------|-------|
| Reason for review was provided, No. (%)             | 17 (15.5)                           | 769 (87.9)                    | <.001 |
| Immunohistochemistry aided in diagnosis, No. (%)    | 19 (17.3)                           | 372 (42.5)                    | <.001 |
| Reviewed by >1 consultant pathologist, No. (%)      | 17 (15.5)                           | 360 (41.1)                    | <.001 |
| Agreed with outside pathologist, No. (%)            | 5 (4.6)                             | 318 (36.3)                    | <.001 |
| Unknown                                             |                                     |                               |       |
| No                                                  | 15 (13.6)                           | 123 (14.0)                    |       |
| Yes                                                 | 87 (79.1)                           | 431 (49.3)                    |       |
| Partial (in multipart case)                         | 3 (2.7)                             | 3 (0.4)                       |       |

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**Table 3. Features Significantly Associated With Internally Reviewed Breast Pathology Cases**

| Feature                                             | Not Reviewed (n = 4622) | Reviewed (n = 359) | P     |
|-----------------------------------------------------|-------------------------|--------------------|-------|
| Procedure, No. (%)                                  |                         |                    | <.001 |
| Breast core/punch biopsy                            | 1603 (34.7)             | 131 (36.5)         |       |
| Breast excision<sup>a</sup>                          | 2283 (49.4)             | 219 (61.0)         |       |
| Axillary                                            | 249 (5.4)               | 7 (1.9)            |       |
| Plastics<sup>b</sup>                                | 487 (10.5)              | 2 (0.6)            |       |
| Diagnostic category, No. (%)                        |                         |                    | <.001 |
| Benign                                              | 2814 (60.9)             | 119 (33.1)         |       |
| Atypia or LCIS                                      | 183 (4.0)               | 58 (16.2)          |       |
| DCIS/invasive carcinoma                             | 1623 (35.1)             | 182 (50.7)         |       |

Abbreviations: DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ.

<sup>a</sup> Includes excisional biopsy, lumpectomy, and mastectomy procedures.

<sup>b</sup> Includes reconstructive breast, capsule, and skin excisions.
benign hyperplasia, as ADH is cytokeratin 5/6 negative and usual ductal hyperplasia is cytokeratin 5/6 positive. However, the pattern of cytokeratin 5/6 negativity in ADH is also observed in low-grade DCIS and thus is not helpful in this differential diagnosis.23,24 Intradepartmental and interdepartmental consultation may be of greater benefit for challenging diagnoses in situations in which ancillary studies cannot be obtained (eg, because of small sample and/or loss of tissue) or are less helpful, such as in the differential diagnosis of ADH and low-grade DCIS.

A criticism of studies reporting poor pathology concordance for certain breast pathology diagnoses is the artificial nature of many of these studies, with selection bias for more challenging/borderline cases.23,24 Intradepartmental and interdepartmental consultation may be of greater benefit for challenging diagnoses in situations in which ancillary studies cannot be obtained (eg, because of small sample and/or loss of tissue) or are less helpful, such as in the differential diagnosis of ADH and low-grade DCIS.

A criticism of studies reporting poor pathology concordance for certain breast pathology diagnoses is the artificial nature of many of these studies, with selection bias for more challenging/borderline cases. Additionally, review is often limited to evaluation of only one representative slide and there is typically lack of ability to obtain ancillary studies or second opinion, measures commonly performed to aid in diagnosis of challenging cases in routine practice. Furthermore, there is no gold standard for these diagnoses such as a confirmatory molecular assay, just the diagnostic criteria established by Page et al.17 Because of greater training and experience, expert diagnosis is thus typically used as the reference. However, there can be disagreement even among experts, with final diagnosis sometimes requiring multiple opinions to (hopefully) reach consensus agreement and the most appropriate diagnosis.5,12

This study highlights the significant use of consultation for more challenging diagnoses. Specifically, borderline atypias were the most common indication for review in both consultation and internally reviewed cases. Additionally, when comparing all breast pathology cases evaluated at our institution, those with a final diagnosis of atypia had a significantly higher rate of review (58 of 241; 24.1%) than those with benign (119 of 2933; 4.1%) or carcinoma (182 of 1807; 10.1%) diagnoses ($P < .001$). These findings support pathologist understanding of the challenging nature of the diagnosis of atypia and thus the more common use of second opinion to help avoid underinterpretation or overinterpretation.

Following borderline atypia, the more common reasons for review were similar among consult and in-house cases in this study, with subtyping, ruling out invasion, and

| Table 4. Characteristics of Internally Reviewed Breast Pathology Cases (n = 359) |
|-----------------|-----------------|
| **Characteristic** | **Value** |
| Age, mean (range), y | 51.4 (11–88) |
| Sex, No. (%) | |
| Female | 358 (99.7) |
| Male | 1 (0.3) |
| Procedure, No. (%) | |
| Breast core/punch biopsy | 131 (36.5) |
| Breast excisiona | 219 (61.0) |
| Axillary | 7 (1.9) |
| Plasticsb | 2 (0.6) |
| Diagnostic category, No. (%) | |
| Benign | 119 (33.1) |
| Atypia or LCIS | 58 (16.2) |
| DCIS/invasive carcinoma | 182 (50.7) |
| Reason for review was provided, No. (%) | |
| No | 30 (8.4) |
| Yes (1) | 300 (83.6) |
| Yes (>1) | 29 (8.1) |
| Diagnostic questions, No. (%) (n = 358) | |
| Borderline atypia | 90 (25.1) |
| Subclassification of carcinoma in situ or invasive cancer | 63 (17.6) |
| Interpretation for other prognostic features (eg, margins, grade, lymph node involvement, size) | 59 (16.5) |
| Classification of fibroepithelial lesion | 45 (12.6) |
| Possible invasion | 37 (10.3) |
| Classification of papillary lesion | 20 (5.6) |
| Classification of spindle cell lesion | 18 (5.0) |
| Classification of other proliferative and/or sclerosing lesion | 8 (2.2) |
| Classification as primary breast carcinoma or other neoplasm | 4 (1.1) |
| Possible discordance with clinical impression (ie, no residual neoplasm, lesion does not explain mass) | 5 (1.4) |
| Classification in the setting of prior therapy | 3 (0.8) |
| Classification of vascular lesion | 3 (0.8) |
| Classification of lymphoid or other inflammatory lesion | 3 (0.8) |
| Differential diagnosis considered if diagnostic question of borderline atypia, No. (%) (n = 90) | |
| Benign versus atypia | 61 (67.8) |
| Atypia versus carcinoma in situ | 29 (32.2) |
| Immunohistochemistry aided in diagnosis, No. (%) | |
| No | 283 (78.8) |
| Yes | 76 (21.2) |

Abbreviations: DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ.

a Includes excisional biopsy, lumpectomy, and mastectomy procedures.
b Includes reconstructive breast, capsule, and skin excisions.
classification of papillary, spindle cell, and fibroepithelial lesions contributing to the majority of the remaining indications for review, highlighting the challenging nature of these diagnoses. Currently there is a lack of helpful IHC to aid in the differential diagnosis of fibroadenoma and phyllodes tumor, and pathologist interobserver agreement has been described as only fair with limited core biopsy sampling. Additionally, currently available IHC may be, but is not always, helpful in the differential diagnoses for the remaining above-listed reasons for review. The higher proportion of these diagnostic questions further highlights pathologist knowledge of their challenging nature and higher likelihood of seeking expert consultation, despite flexible published guidelines for consultation.

One difference in reason for review between internal and external consult cases was the higher proportion of internal cases that were reviewed for staging measures such as evaluation of tumor size, grade, lymph node involvement, and margin status. It is likely that cases with these reasons for review, which are more for staging rather than diagnosis, are reviewed internally as well and are not deemed to require expert external pathologist consultation.

It is difficult to establish specific standard guidelines for pathology review, as cases vary in their inherent difficulty, amount of lesion able to be assessed, and slide quality. Additionally, expertise of signing pathologists varies based on level of training/experience. Thus, second review of a suspected atypical breast lesion may be of great benefit for one pathologist but unnecessary for another. In the recent publication by Elmore et al., they saw statistically significant discordance with reference diagnoses among participating pathologists who had lower weekly breast pathology case volumes or worked in smaller practices (<10 versus ≥10 pathologists) or nonacademic settings. Their findings support that pathologists’ experience also needs to be taken into account in selection of cases for expert opinion. However, they also saw higher discordance when the participating pathologist indicated the case was difficult or borderline or when the pathologist desired a second opinion, again supporting the ability of many to recognize cases for which expert opinion would be beneficial.

In this study we saw relatively high concordance between the contributing pathologist’s favored or given diagnosis and the final diagnosis for consultation cases, with at least partial agreement in 524 of 662 cases (79.2%). However, nearly a third (323 of 985; 32.8%) did not submit a favored/given diagnosis. Additionally, a favored diagnosis may not have represented the final diagnosis rendered by the contributing pathologist. Therefore, it is difficult to calculate overall concordance and this study cannot be equally compared with studies examining concordance with a reference standard with a review of test set of breast cases with benign, atypical, DCIS, and invasive carcinoma diagnoses, which is similar to our cohort. However, they also surveyed participants about perceived agreement (ie, how well they thought their diagnosis agreed with the reference diagnosis) and found that pathologists overall “do a good job of estimating their diagnostic agreement.” However, there was 5.5% overestimation of agreement. Moreover, overestimation of performance was greatest in the diagnosis of atypias. Following a Web-based educational program there was improvement in the gap between actual and perceived agreement, highlighting one method to help pathologists better identify cases for which expert consultation may be of greatest benefit.25

CONCLUSIONS

This study highlights that breast pathology cases for which a second expert opinion was obtained disproportionately represent areas of known diagnostic challenge, supporting that many pathologists are appropriately using consultation. Continuing medical education is one method that may further improve case selection for expert review.

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