Discrepant Diagnoses: Where’s the Harm?

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Error Reduction: pre-analytical

- inadequate sample size
- crush/cauterized artifact
- non-representative sample
- mislabeling of a specimen
- poor technical quality
- loss of the tissue

Error reduction: post-analytical

- typographical errors
  - ‘no malignancy seen’
  - ‘malignancy not identified’
- misidentification of site or patient
- failure to transmit the report to the clinician
Analytical Step

Does the resulting report generate appropriate therapy for the patient?

Discrepant Diagnosis
‘being at variance’

Significant discrepancy
• Results in inappropriate treatment or non-treatment

Insignificant discrepancy
• No treatment consequences

Diagnostic concordance among pathologists interpreting breast biopsy specimens

Elmore JG, Longton GM, Carney PA, Geiler BM, Onega T, Tosteson AN, Nelson HD, Pepe MS, Allison KH, Schnitt SJ, O’Malley FP, Weaver DL

JAMA 2015 313:1122-1132
JAMA

OBJECTIVE
To quantify the magnitude of diagnostic disagreement among pathologists compared with a consensus panel reference diagnosis and to evaluate associated patient and pathologist characteristics

Methods
• 240 cases
• 3 expert breast pathologists
• 115 participants (practicing pathologists)
• Participants diagnoses compared with expert consensus diagnosis

Methods (con’t)
• Single H & E slide
• Core biopsy or excision
• 4 diagnostic categories
  – Benign, no atypia
  – Atypia
  – DCIS
  – Invasive carcinoma
Methods

- Single H&E slide
- No recuts
- No special studies
- No standardized diagnostic definitions were provided
- No consultation
- No time constraints
- No clinical or imaging information other than age and mammographic density

Results

- Experts agreed in 75% of cases, Following consensus review, 90%
- Participants agreed with consensus diagnosis in 75% of cases

<table>
<thead>
<tr>
<th>Consensus DX</th>
<th>Pathologist DX vs Consensus DX, % (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>Benign, no atypia</td>
<td>2070</td>
</tr>
<tr>
<td>Atypia</td>
<td>2070</td>
</tr>
<tr>
<td>DCIS</td>
<td>2097</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>663</td>
</tr>
</tbody>
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JAMA 2015 313:1122-1132
Case Difficult Rating

- Very easy
- Very challenging

Level of Confidence

- Very confident
- Not at all confident

Ask for a Second Opinion?
Borderline between 2 dx?

Pathologists’ Characteristics

• Low volume
• Small group
• Non-academic

Expertise vs Evidence in Assessment of Breast Biopsies: An Atypical Science

“well-designed, conducted, and analyzed study suggest improvements need to be made”

Limitations pointed out

“nevertheless, ….should be a call to action”

Davidson N and Rimm D, JAMA 2015; 313:1109
Expertise vs Evidence in Assessment of Breast Biopsies: An Atypical Science

4% miss in the dx of invasive cancer
- mostly DCIS with small area of micro-invasive
16% discordance in DCIS
- ?low grade DCIS vs ADH? Core biopsy or excision?

Davidson N and Rimm D, JAMA 2015; 313:1109
Expertise vs Evidence in Assessment of Breast Biopsies: An Atypical Science

Davidson N and Rimm D, JAMA 2015, 313:1109
Relative risk confirmation

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</thead>
<tbody>
<tr>
<td>Proliferative disease without atypia</td>
<td>1.5-2X</td>
<td>1.6X</td>
<td>1.3X</td>
<td>1.9X</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>4-5X</td>
<td>3.7X</td>
<td>4.3X</td>
<td>4.24X</td>
</tr>
</tbody>
</table>

Expertise vs Evidence in Assessment of Breast Biopsies: An Atypical Science

“alert breast cancer scientists to define atypia using some objective molecular criteria”

“daunting task, but a better and more reproducible histologic and molecular classification of atypia could emerge”

Davidson N and Rimm D, JAMA 2015, 313:1109

Consensus/discrepancy of high recurrence score and poor seventy gene profile from NKI-295 dataset (courtesy Dr. Les Dalton)

Fan C, et al. NEJM 2006
Molecular analysis of ADH

- LOH & CGH show common patterns of genetic alteration in ADH, low grade DCIS, and invasive carcinoma
- Frequent sites of LOH in ADH and invasive carcinoma: chromosomes 16q, 17p, and 11q13
- Studies of ADH are from cases of established cancer, both invasive and in situ
- Few studies of ADH as the most advanced lesion
- No studies have established significance of these changes through large, clinically validated patient cohorts.

Biomarkers of ADH?

- ADH is typically negative for HMW keratins (CK 5/6) and diffusely positive for ER
- Usual hyperplasia shows variable expression of HMW keratins and ER
- Expression of these markers is similar in ADH and low-grade DCIS
- None is sufficiently validated for routine clinical use
Editorial: Are all ductal proliferations of the breast premalignant?

“The evidence for ductal proliferations of the breast being associated with the development of breast carcinoma originally came from epidemiological studies. There have now been a variety of genetic analyses of such lesions, which have shown a range of alterations from none to 37% of hyperplasias. Alterations in growth regulatory factors can also be found in a proportion of hyperplasias. The findings to date indicate that not all hyperplasias are premalignant and that the early events in breast carcinogenesis remain elusive.

Rosemary Walker, J Pathol 2001; 195:401-03

Expertise vs Evidence in Assessment of Breast Biopsies: An Atypical Science

“undesirable short-term outcome…heightened anxiety among women undergoing biopsy”

Davidson N and Rimm D, JAMA 2015; 313:1109

New York Times

Breast Biopsies Leave Room for Doubt, Study Finds

“The new findings, reported Tuesday in JAMA, challenge the common belief that a biopsy is the gold standard and will resolve any questions that might arise from an unclear mammogram or ultrasound”

...Denise Grady, March 15, 2015
Wall Street Journal

New Ways Doctors Reach Agreement on Patient Diagnoses: studies show many breast biopsies are misdiagnosed; some hospitals use digital images

“as many as one in four breast biopsies are initially misdiagnosed”

Laura Landro, June 9, 2015

Interpretive diagnosis error reduction in surgical pathology and cytology: guidelines from CAP and ADASP


CAP and ADASP Guidelines

• Additional review has been shown to detect discrepancies
• Objective: create recommendations for the review of anatomic pathology cases
• Expert panel, literature search

**CAP and ADASP Guidelines**

- Should develop procedures for review of selected cases
- Review should be timely
- Review should be relevant to practice
- Procedures should monitor and document
- If poor agreement, take steps to improve agreement


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**CAP and ADASP Guidelines**

_87% of responders, during open comment period, agreed with guidelines_


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**CAP and ADASP Guidelines**

_Only 87% of responders, during open comment period, agreed with guidelines_


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CAP and ADASP Guidelines

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Medicolegal Aspects of Neoplastic Dermatology

- May 2000- Oct 2004
- 100% review by second pathologist
- 35,756 cases
- Significant error detected in 25 cases (0.07%)

A.N. Crowson, Mod Pathol 2006

Consensus Conference

- Most vocal participant?
- Democracy? 3 against 1
- Most experienced pathologist?
How to reduce clinically significant discrepancies?

- Education
- Communication
- Clinical setting including imaging
- Attention to morphology
Sclerosed Papilloma

How to reduce clinically significant discrepancies?

- Education
- Communication
- Clinical setting including imaging
- Attention to morphology
- Choose words wisely
  - “cannot exclude....”
Where’s the Harm?

- Inappropriate treatment
- Patient anxiety
- $$ $$ $$ cost
  - Excisional biopsy cost estimates $3000 - $10,000
- Erosion of clinician and patient confidence in pathologist