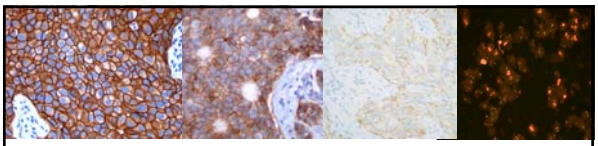

Challenges in Breast Cancer Predictive Marker Interpretation

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Roadmap

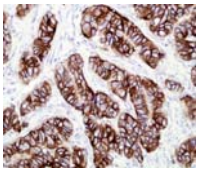
1. Mini-course on HER2 testing (2013 CAP/ASCO Guidelines Update) with test cases
2. Using a series of cases work through challenging cases involving hormone receptor, HER2, Ki67 and Oncotype results :
   -- Recognizing and explaining discordant results

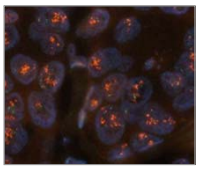
Why Test for HER2?

- HER2 positive cancers have:
  - Aggressive biology/worse prognosis (without therapy)
  - Frequent need for chemotherapy (often includes anthracyclines)
  - Frequent benefit from HER2 targeted therapies
    - Reduces recurrences by 50% and mortalilty by 33%
- Testing is required by CAP/ASCO on all newly diagnosed breast cancers and recurrences/mets
- Clinical trials eligibility can be dependent on HER2 status (including 1+ or 2+ results)

How do we test for HER2?

- Protein Over-Expression: Immunohistochemistry (IHC)
- Gene Amplification: In Situ Hybridization
  - Fluorescence In Situ Hybridization (FISH)
  - Other ISH bright field tests (CISH, SISH, DISH, etc)





Bright-field ISH

- For SISH/CISH/DISH – compare with normal cells and for borderline cases seek expert opinion
- Preferentially use an FDA approved assay or document validation
- Will NOT be covered

ASCO/CAP HER2 Testing Guideline Update—Wolff et al

How do we test for HER2?

How does your practice test for HER2?

A. IHC first with reflex FISH testing on equivocal cases only
B. Dual testing (IHC and FISH on all cases)
C. FISH testing first with reflex IHC on FISH equivocal cases only
D. Other ISH testing (CISH, DISH or SISH, etc)
E. Other

Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer

American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update

Antonio C. Wolff*, M. Elizabeth H. Hammond*, David G. Hicks*, Mitch Dowsett*, Lisa M. McShane*, Kimberly H. Allison, Donald C. Allred, John M.S. Bartlett, Michael Bilous, Patrick Fitzgibbons, Wedad Hanna, Robert B. Jenkins, Pamela B. Mangu, Soonmyung Paik, Edith A. Perez, Michael F. Press, Patricia A. Spears, Gail H. Vance, Giuseppe Viale, and Daniel F. Hayes*

- New CAP/ASCO HER2 testing guidelines published in Oct 2013

What's New??

ASCO/CAP HER2 Testing Guideline Update—Wolff et al

2013 Guidelines: Who to test

Topic	2007 Recommendations	2013 Recommendations
Specimens to be tested	All primary breast cancers and metastases should have at least one HER2 test performed	All newly diagnosed patients with breast cancer must have a HER2 test performed. Patients who then develop metastatic disease must have a HER2 test performed in a metastatic site if available.

Emphasis on retesting new metastases = estimated that 10-15% change HER2 status

ASCO/CAP HER2 Testing Guideline Update—Wolff et al

2013 Guidelines: What is a HER2 IHC positive result?

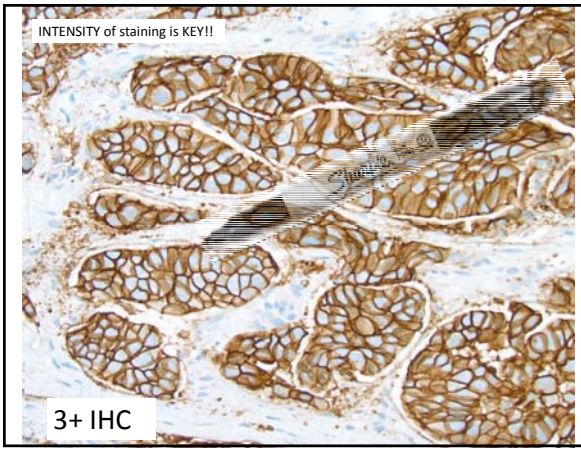
2007 Recommendations	2013 Recommendations
IHC Positive: 3+ by IHC (uniform intense membrane staining of >30%)	IHC Positive: 3+ by IHC (circumferential membrane staining that is complete, intense*+)

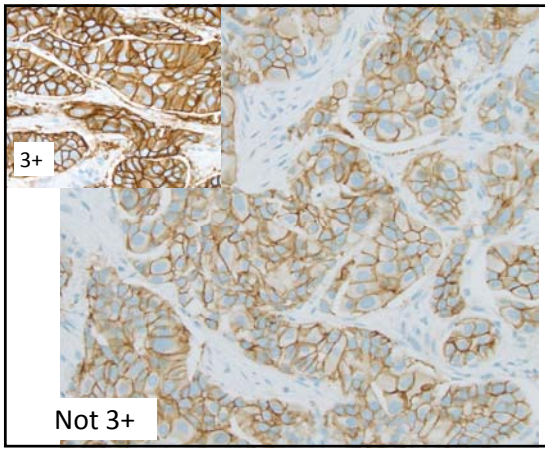
Change in % cells

*observed in a homogeneous and contiguous population and within >10% of the invasive tumor cells
+Readily appreciated using a low power objective

NEW: Guidelines recommend reporting what % of cells are 3+ positive in cases reported as positive
Classically HER2 positive cancers are UNIFORMLY 3+ (>95% of cells)
Advice: Don't perseverate on percentage – usually all or none! If in doubt, call it 2+

ASCO/CAP HER2 Testing Guideline Update—Wolff et al





2013 Guidelines: What is IHC Equivocal?

2007 Recommendations	2013 Recommendations
IHC Equivocal: 2+ by IHC	IHC Positive: 2+ by IHC based on: Circumferential membrane staining that is incomplete and/or weak/moderate* and within >10% of the invasive tumor cells+ or Complete and circumferential membrane staining that is intense and within ≤10% of the invasive tumor cells+

*observed in a homogeneous and contiguous population and within >10% of the invasive tumor cells
+Readily appreciated using a low power objective

ASCO/CAP HER2 Testing Guideline Update—Wolff et al

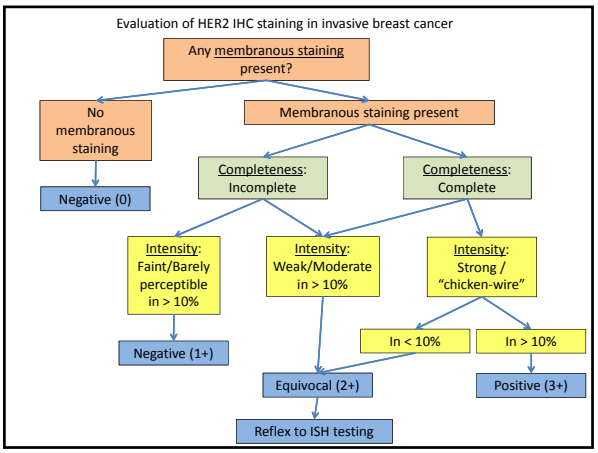
2013 Guidelines: What is IHC Negative?

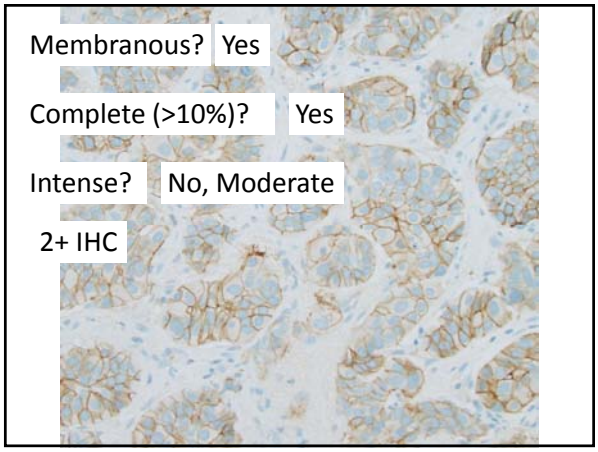
2007 Recommendations	2013 Recommendations
IHC Negative: 0 : No staining 1+: Weak incomplete membrane staining in any proportion of tumor cells or weak, complete membrane staining in <10% of cells	IHC Negative: 0 : No staining+ or membrane staining that is incomplete and is faint/barely perceptible and within ≤10% of the invasive tumor cells+ 1+: incomplete membrane staining that is faint/barely perceptible and within > 10% of the invasive tumor cells

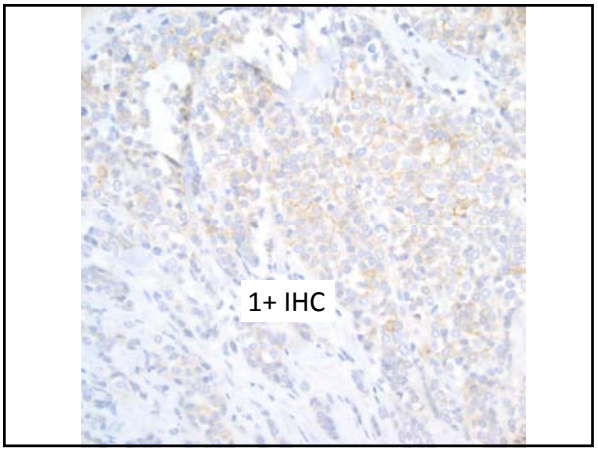
More detailed definitions for 0 and 1+ staining

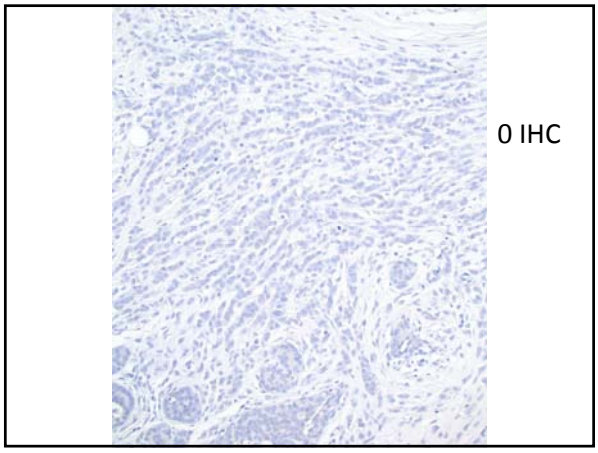
+Readily appreciated using a low power objective

ASCO/CAP HER2 Testing Guideline Update—Wolff et al







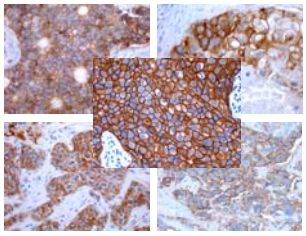


Achieving 95% Cross-Methodological Concordance in HER2 Testing

Causes and Implications of Discordant Cases

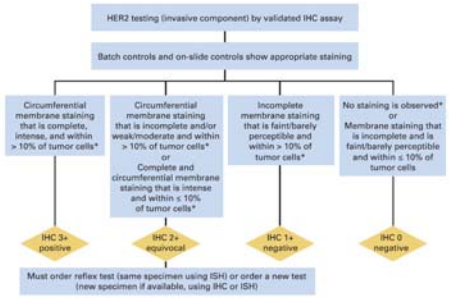
Erin E. Grimm, MD, Rodney A. Schmidt, MD, PhD, Paul E. Swanson, MD, Suzanne M. Dintzis, MD, PhD, and Kimberly H. Allison, MD

- 697 cases with both IHC and FISH results
- 96% overall concordance
- Most common reason for discordant on review: Over-interpretation of IHC stain intensity



Am J Clin Pathol 2010;134:284-292
DOI: 10.1309/AJCPUQB18XZOHHBJ

IHC Summary

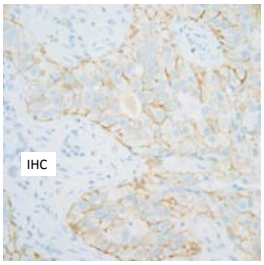


ASCO/CAP HER2 Testing Guideline Update—Wolff et al

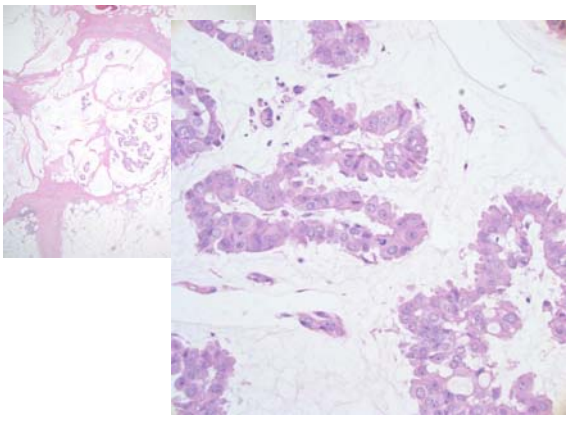
Test Case 1

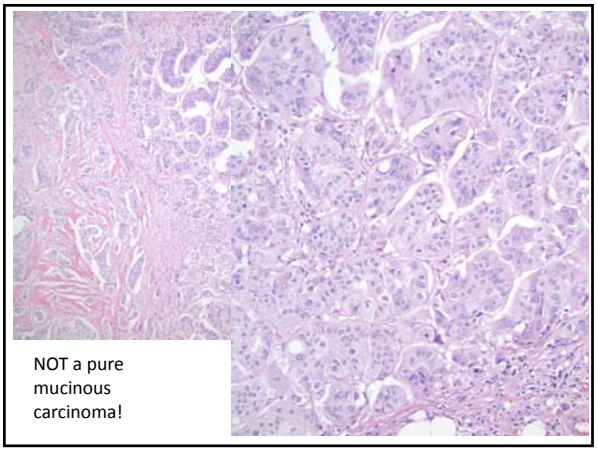
42 year old with a diagnosis of invasive mucinous carcinoma. You receive the HER2 IHC and FISH for interpretation. How do you report the case?

A. IHC 2+ (equivocal), FISH amplified
B. IHC 3+ (positive), FISH amplified
C. IHC 2+ (equivocal), FISH equivocal
D. IHC 1+ (negative), FISH amplified
E. Repeat the test and review the histology



FISH results:
Mean HER2 signals/cell = 8.0
Mean CEP17 signals/cell = 2.2
HER2:CEP17 Ratio = 3.6





NOT a pure mucinous carcinoma!

Recognizing Possible Discordant HER2 Testing

Discordant if HER2 positive and Grade 1 invasive carcinoma of any of the following types:

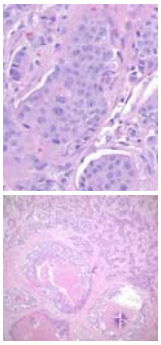
- Ductal or lobular and ER and PR positive
- Pure Tubular, Mucinous, Cribriform or Adenoid Cystic

Table 2. Histopathologic Features Suggestive of Possible HER2 Test Discordance

Criteria to Consider*
New HER2 test should not be ordered if the following histopathologic findings occur and the initial HER2 test was negative:
Histologic grade 1 carcinoma of the following types:
Infiltrating ductal or lobular carcinoma, ER and PgR positive
Tubular (at least 90% pure)
Mucinous (at least 90% pure)
Cribriform (at least 90% pure)
Adenoid cystic carcinoma (90% pure) and other triple negative
Similarly, a new HER2 test should be ordered if the following histopathologic findings occur and the initial HER2 test was positive:
Histologic grade 1 carcinoma of the following types:
Infiltrating ductal or lobular carcinoma, ER and PgR positive
Tubular (at least 90% pure)
Mucinous (at least 90% pure)
Cribriform (at least 90% pure)
Adenoid cystic carcinoma (90% pure) and other triple negative
If the initial HER2 test result is a core needle biopsy specimen of a primary breast cancer is negative, a new HER2 test must be ordered on the excision specimen if one of the following is observed:
Tumor is grade 3
Amount of invasive tumor in the core biopsy is small
Resection specimen contains lymphovascular carcinoma that is morphologically distinct from that in the core
A new HER2 result is equivocal for HER2 after testing by both ISH and IHC
There is doubt about the specimen handling of the core biopsy (long ischemic time, short time in fixative, different fixatives or the test is suspected by the pathologist to be negative on the basis of testing error

ASCO/CAP HER2 Testing Guideline Update—Wolff et al

Classic HER2 Positive Cancer Features



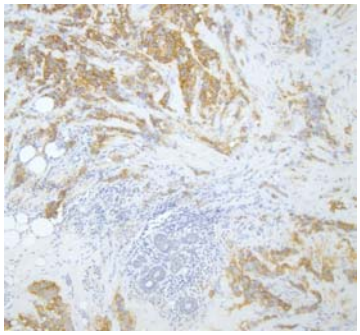
- High grade
- Apocrine-like features (abundant cytoplasm, nucleoli)
- Comedo DCIS
- Frequently ER/PR negative (not always)
- Younger patients
- Higher stage at diagnosis

HER2 Negative on Core Biopsy; When to Retest in the Excision?

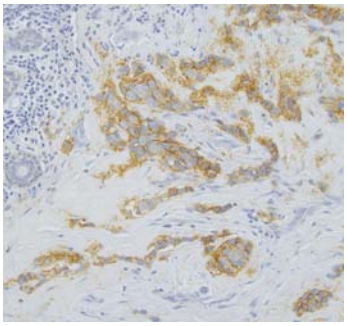
- Tumor is Grade 3
- Amount of invasion in core was small
- Resection has high grade carcinoma that is morphologically distinct from that in core
- Core biopsy result is equivocal for HER2 after both IHC and ISH
- Doubt about specimen handling of core
- Pathologist suspects testing error

Test Case 2

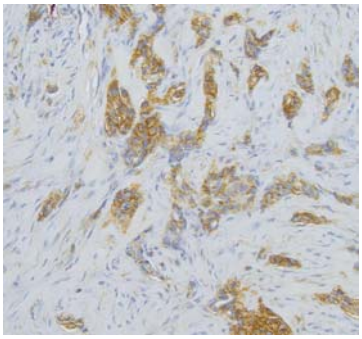
- Nottingham grade 2 invasive ductal carcinoma
- 50 year old woman
- You receive the HER2 IHC stain to interpret



Test Case 2



Test Case 2



A. 0
B. 1+
C. 2+
D. 3+
E. Other

2013 Guidelines: What is HER2 Indeterminate?

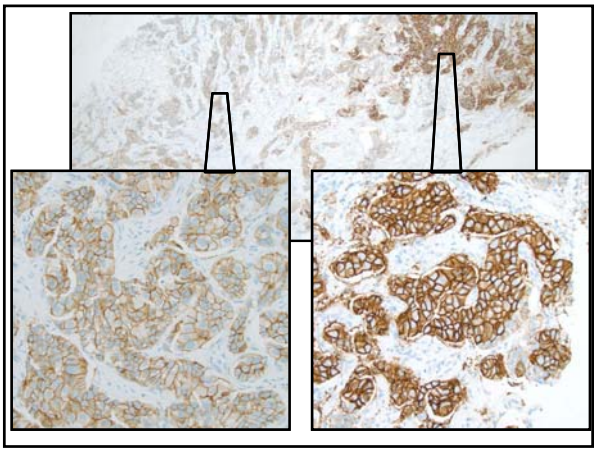
- Inadequate specimen handling
- Artifacts (crush or edge)
- Analytical testing failure
- Controls not as expected
- Unstained slide cut > 6 weeks prior
- For ISH:
  - Not at least 2 areas to count, >25% of signals unscorable/weak, > 10% of signals occur over cytoplasm, nuclear resolution poor, auto-fluorescence strong
- Reason for indeterminate result should be reported
- Another method of testing can be attempted or another sample requested

Cold ischemic time < 1 hour
Formalin fix 6-72 hours

ASCO/CAP HER2 Testing Guideline Update—Wolff et al

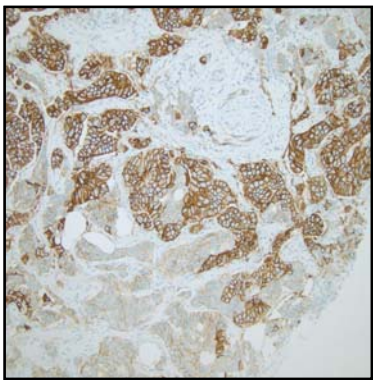
Test Case 3

- Nottingham grade 3 invasive ductal carcinoma
- 45 year old woman
- You receive the HER2 IHC to interpret

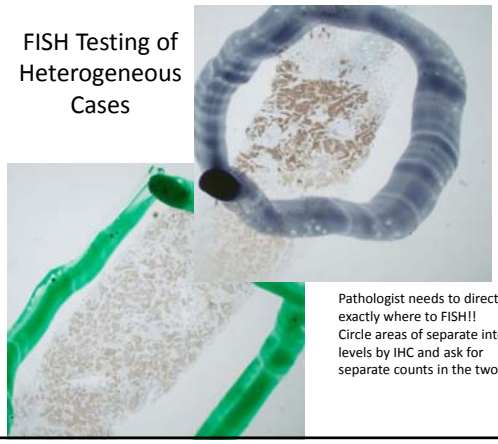


Your Interpretation:

A. 0
B. 1+
C. 2+
D. 3+
E. Other



FISH Testing of Heterogeneous Cases



Pathologist needs to direct exactly where to FISH!!
Circle areas of separate intensity levels by IHC and ask for separate counts in the two areas

2013 Guidelines: HER2 Heterogeneity by FISH

- Must <u>score separately</u> an aggregated positive population that is > 10% of total tumor population
- Report must include:
  - HER2 status as positive with the percentage of the total tumor that is amplified
  - Ratio and signals/cell of both populations

See Table 1 "ISH Interpretation" and Data Supplement 8: ISH Interpretation Criteria *ASCO/CAP HER2 Testing Guideline Update*—Wolff et al

2013 Guidelines: ISH Interpretation

- <u>Pathologist</u> should either scan ISH slide prior to counting OR use IHC to define the areas of potential HER2 amplification
  - Implies Dual Testing by IHC and FISH if the pathologist cannot be at the fluorescence scope
  - Reason: To rule out heterogeneity

See Table 1 "ISH Interpretation" and Data Supplement 8: ISH Interpretation Criteria *ASCO/CAP HER2 Testing Guideline Update*—Wolff et al

Example report of heterogeneous case

FINAL DIAGNOSIS: Heterogeneous for HER2 gene amplification with the following features:

a. Positive for HER2 gene amplification in 20% of the invasive carcinoma (ratio = 4.5, mean HER2 signals/cell = 8.5)

b. Negative for HER2 gene amplification in 80% of the invasive carcinoma (ratio = 1.0, mean HER2 signals/cell = 2.0)

COMMENT:
This sample is heterogeneous for HER2 gene amplification. A distinct, clustered subpopulation, representing 20% of the invasive carcinoma is positive for HER2 gene amplification. The same area is also positive for HER2 over-expression. The remainder of the invasive cancer in this sample is HER2 negative. The 2013 CAP/ASCO HER2 testing guidelines would consider this a HER2 positive result and the patient should be considered a candidate for HER2 targeted therapy.

Unusual HER2 IHC staining:

- Strong cytoplasmic staining only → Recommend calling Equivocal (2+) and sending to ISH testing
- Heterogeneous staining (distinct separate areas with different staining patterns) → Recommend evaluating as separate areas if going to perform ISH. An amplified result in >10% in a clustered pattern is considered a positive result (document percent positive and note heterogeneity).
- Discordant result with histology (grade 1 or pure tubular or mucinous carcinoma that is HER2 3+) → Recommend re-evaluating grade/histologic subtype as well as HER2 test. Additional testing on subsequent specimens may be required to resolve.

2013 Guidelines: What is a HER2 FISH/ISH positive result?

2007 Recommendations	2013 Recommendations
Positive: FISH ratio > 2.2 or > 6 average HER2 signals/cell	Positive: Single probe ISH with average HER2 copy number ≥ 6.0 or Dual probe ISH with ratio ≥ 2.0*; with an average HER2 copy number ≥ 4 signal/cell or Dual probe ISH with ratio ≥ 2.0*; with an average HER2 copy number < 4 signal/cell^ or Dual probe ISH with ratio < 2.0*; with an average HER2 copy number ≥ 6.0 signals/cell*

Positive Ratio returned to 2.0

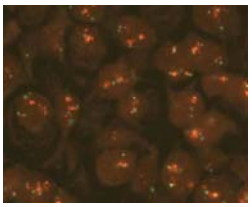
*observed in a homogeneous and contiguous population and within >10% of the invasive tumor cells
^See Data Supplement 2e for additional information

ASCO/CAP HER2 Testing Guideline Update—Wolff et al

HER2 FISH

Cell	HER2	CEP17
1	15	2
2	9	2
3	7	1
4	12	2
5	10	2
6	10	1
7	8	3
8	2	2
9	2	2
10	8	2
11	15	1
12	12	3
13	8	2
14	2	2
15	7	2
16	9	2
17	12	1
18	12	2
19	15	2
20	10	3
Mean	9.25	1.95
Ratio	4.74	

- Positive for HER2 gene amplification



Must include both mean signals/cell and ratio on report!

Co-amplification / "Polysomy"

Cell	HER2	CEP17
Mean	7.85	6.9
Ratio	1.14	

- Data Supplement 2B and 2E:
  - True polysomy is rare (more common = co-amplfication of peri-centromeric regions)
  - May result in protein over-expression
  - Evidence is mixed on if cancers with this profile respond to HER2 targeted therapy
  - Considered a positive result (treatable)

Hanna WM, Ruschoff J, Bilous M, et al: HER2 in situ hybridization in breast cancer: clinical implications of polysomy 17 and genetic heterogeneity. Mod Pathol, 2013

Example report: Coordinate Amplification

FINAL DIAGNOSIS:

Positive for HER2 gene amplification with coordinately increased HER2 and CEP17 signals (ratio = 1.14, mean HER2 signals/cell = 7.85, mean CEP17 = 6.9); See comment

COMMENT:

This cancer has ≥ 6.0 mean HER2 signals/cell but coordinately increased centromertic control signals resulting in a HER2:CEP17 ratio < 2.0. Because array-based comparative genomic hybridization (aCGH) studies have shown that true polysomy (duplication of the entire chromosome) is actually rare, while gain of the pericentromeric region of chromosome 17 is more commonly observed, the 2013 CAP/ASCO HER2 Testing Guidelines Update recommends considering these cases positive. However, there is limited data to indicate if patients receive benefit from HER2 targeted therapy in this setting without over-expression of the HER2 protein by IHC. This sample was 2+ by IHC.

Monosomy example

	HER2	CEP17
Mean	3.4	1.2
Ratio	2.8	

FINAL DIAGNOSIS:

Positive for HER2 gene amplification by ratio with loss of CEP17 signal (ratio = 2.8, mean HER2 signals/cell = 3.4, mean CEP17 = 1.2); See comment

COMMENT:

This cancer has an average CEP17 signal of <2.0 resulting in a HER2/CEP17 ratio ≥ 2.0 by ISH, despite a low average HER2 copy number < 4.0. There is limited data on how these patients respond to HER2 targeted therapy. However, the 2013 CAP/ASCO HER2 Testing Guidelines Update recommended considering these cases HER2 positive based on limited data on a similar group of patients included in the HERA trials that did not show reduced benefit for trastuzumab. However, the guidelines panel also recommended consideration of further HER2 testing in this setting. This case was HER2 __ by IHC.

2013 Guidelines: What is FISH/ISH Equivocal?

2007 Recommendations	2013 Recommendations
ISH Equivocal: FISH ratio 1.8-2.2 or 4-6 average HER2 signals/cell	ISH Equivocal: Single probe ISH with average HER2 copy number ≥ 4.0 and < 6.0 signals/cell* Or Dual probe ISH with ratio < 2.0; with an average HER2 copy number ≥ 4.0 and < 6.0 signals/cell*

*observed in a homogeneous and contiguous population and within >10% of the invasive tumor cells

No more equivocal category based on ratio!

Per Data Supplement 8: ISH Interpretation Criteria
If *HER2/CEP17* ratio between 1.8 and 2.2, have an additional person count an additional 20 non-overlapping cells

ASCO/CAP HER2 Testing Guideline Update—Wolff et al

Example report: Equivocal FISH

	HER2	CEP17
Mean	4.85	2.7
Ratio	1.79	

FINAL DIAGNOSIS:

Equivocal for HER2 gene amplification (ratio = 1.79, mean HER2 signals/cell = 4.85, mean CEP17 = 2.7); See comment

COMMENT:

This cancer has a negative ratio (< 2.0) and an equivocal mean HER2 signals/cell between (≥ 4 and < 6). The case was notable for scattered, intermixed cells with increased HER2 signal, the significance of which is unclear. The 2013 CAP/ASCO HER2 Testing Guidelines Update recommends reporting cases with these results as equivocal for HER2 gene amplification. There is limited data to indicate if patients receive benefit from HER2 targeted therapy in this setting without over-expression of the HER2 protein by IHC. This sample was ___ by IHC. Additional HER2 testing is recommended on additional samples if/when available.

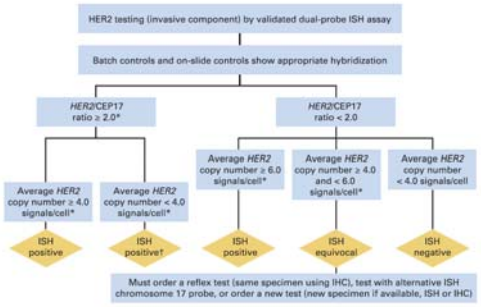
2013 Guidelines: What is FISH/ISH Negative?

2007 Recommendations	2013 Recommendations
ISH Negative: FISH ratio < 1.8 or < 4 average HER2 signals/cell	ISH Negative: Single probe ISH with average HER2 copy number < 4.0 signals/cell or Dual probe ISH with ratio < 2.0; with an average HER2 copy number < 4.0 signals/cell*

*observed in a homogeneous and contiguous population and within >10% of the invasive tumor cells

ASCO/CAP HER2 Testing Guideline Update—Wolff et al

ISH Summary



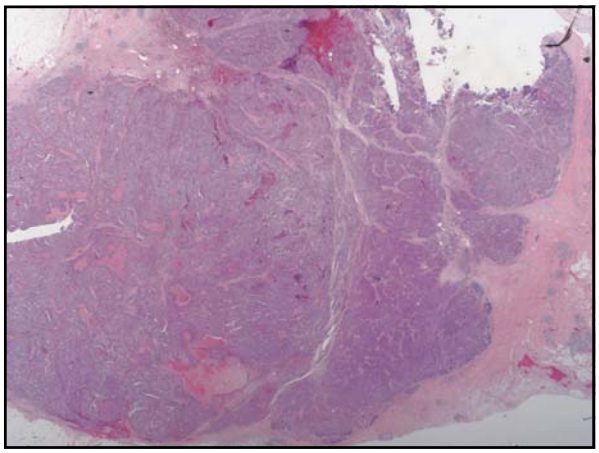
ASCO/CAP HER2 Testing Guideline Update—Wolff et al

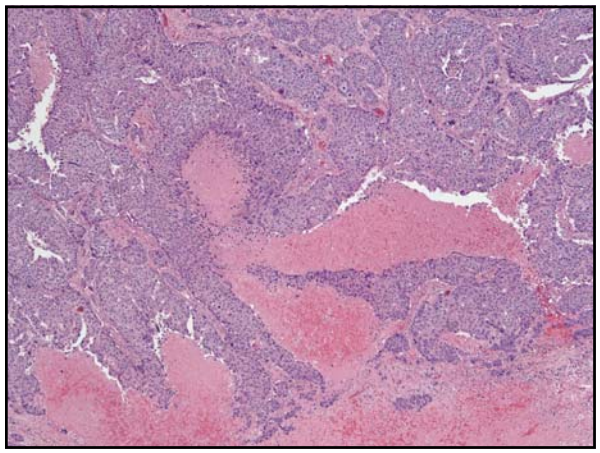
Take-Home Points for HER2 Testing

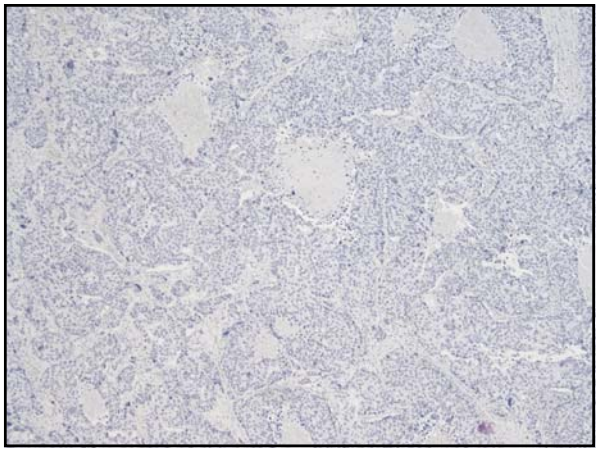
- Know new thresholds for HER2 positive, equivocal, negative by IHC and ISH
  - IHC: 30%→10% change for 3+
  - FISH: Return to 2.0 ratio but use HER2 signals/cell as well
    - Still recount cases close to positive threshold
- Have strict criteria for a HER2 3+ result by IHC
  - Keep your threshold for strong intensity of staining high!
- Correlate HER2 status with histology/biology
  - Work-up discordant cases!
- Screen for heterogeneity by IHC or FISH
  - Direct where to FISH appropriately!

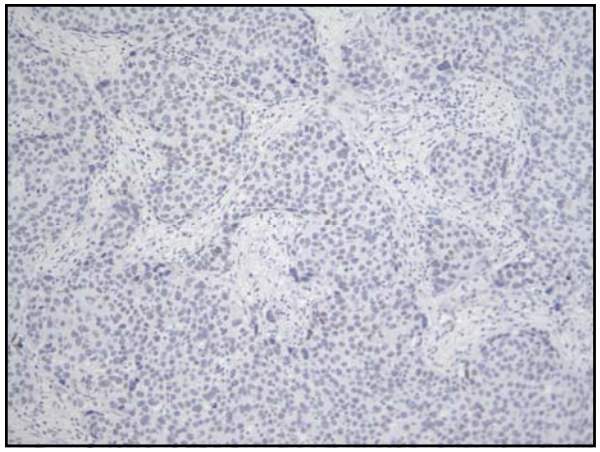
Test Case 4

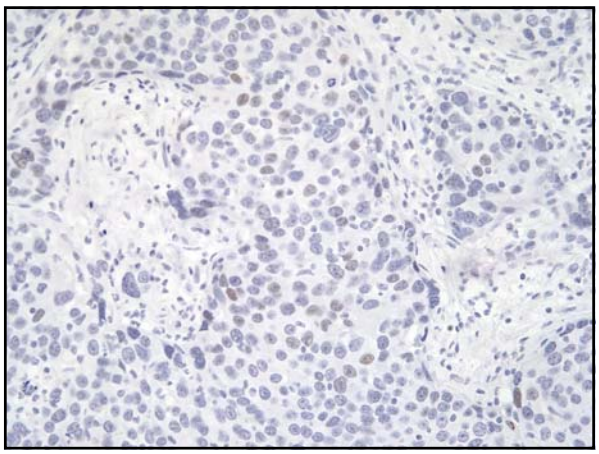
37 year old with invasive breast cancer

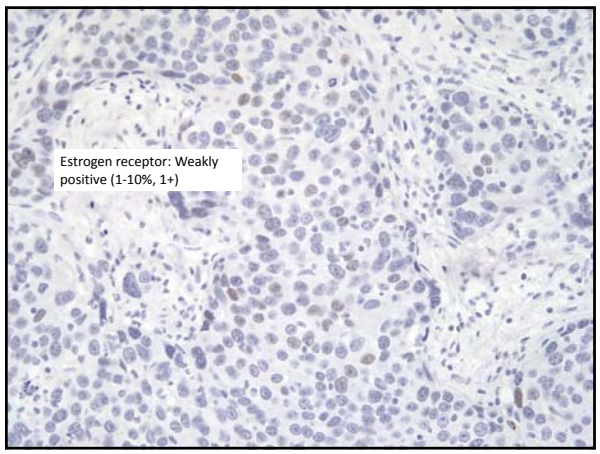


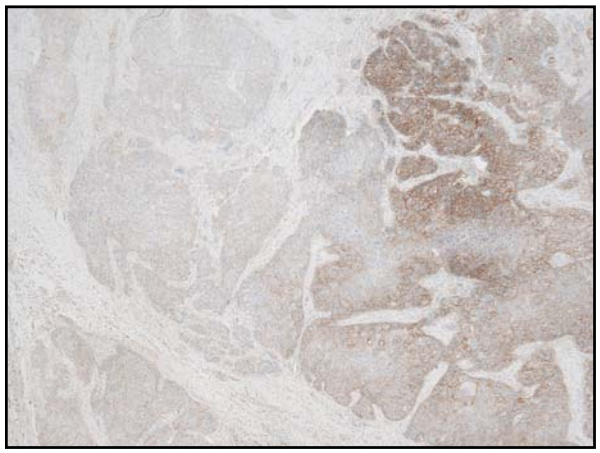


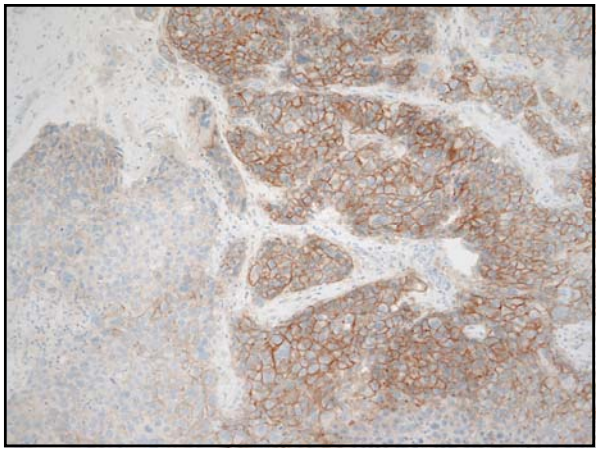


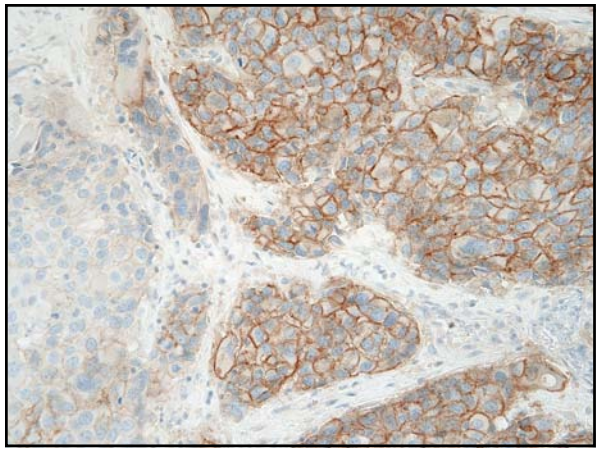


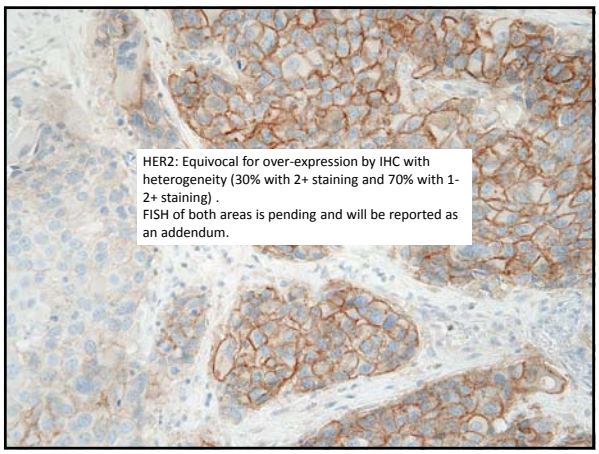


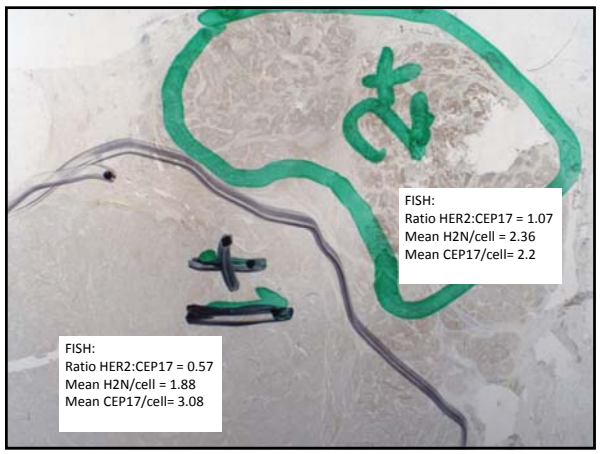

Estrogen receptor: Weakly positive (1-10%, 1+)

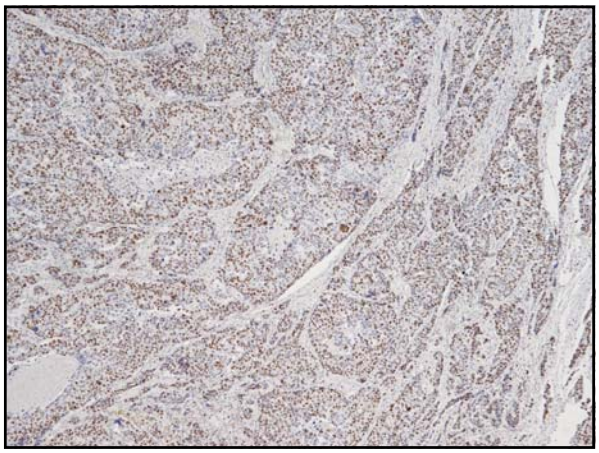


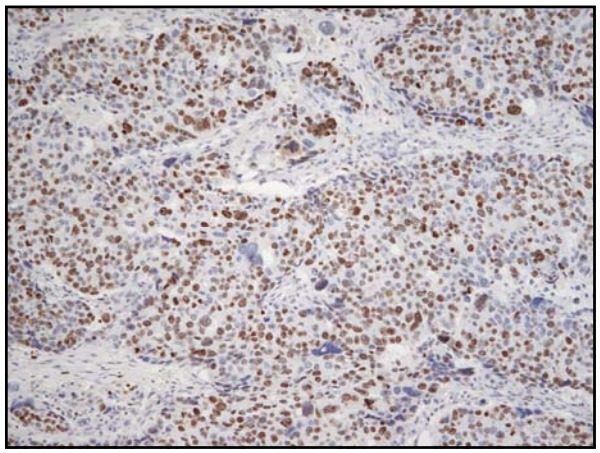


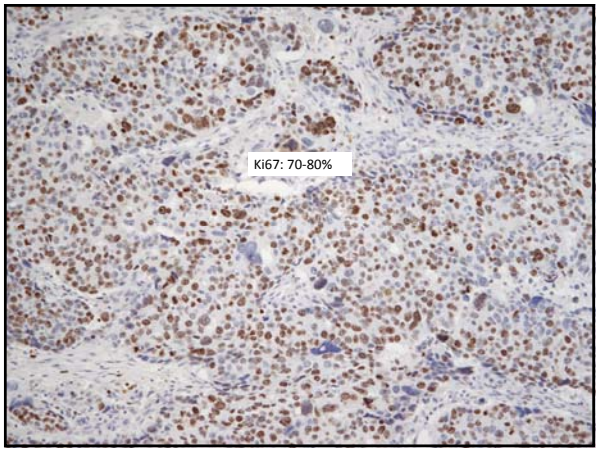



HER2: Equivocal for over-expression by IHC with heterogeneity (30% with 2+ staining and 70% with 1-2+ staining) .
FISH of both areas is pending and will be reported as an addendum.


FISH:
Ratio HER2:CEP17 = 1.07
Mean H2N/cell = 2.36
Mean CEP17/cell= 2.2
FISH:
Ratio HER2:CEP17 = 0.57
Mean H2N/cell = 1.88
Mean CEP17/cell= 3.08





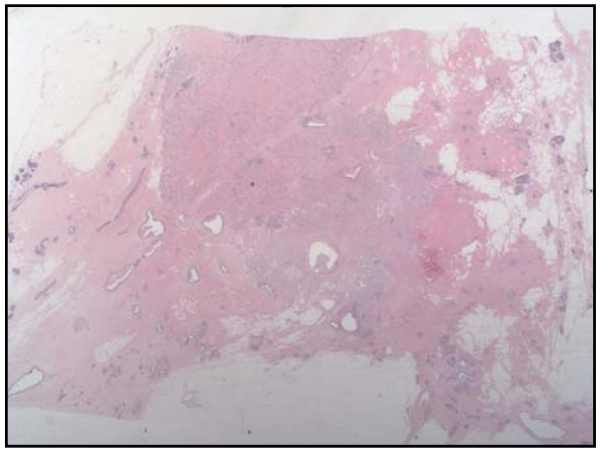


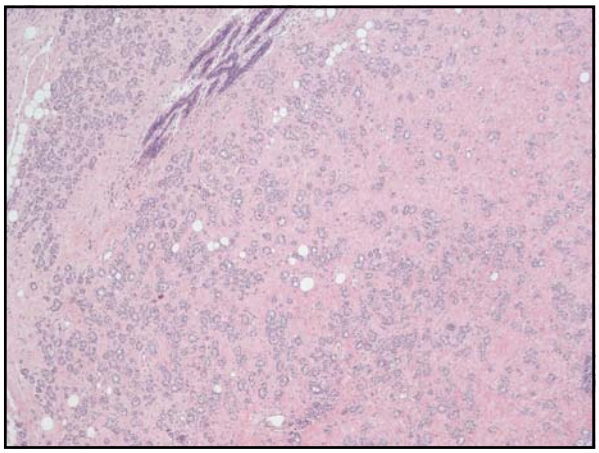
Take home points Case 4:

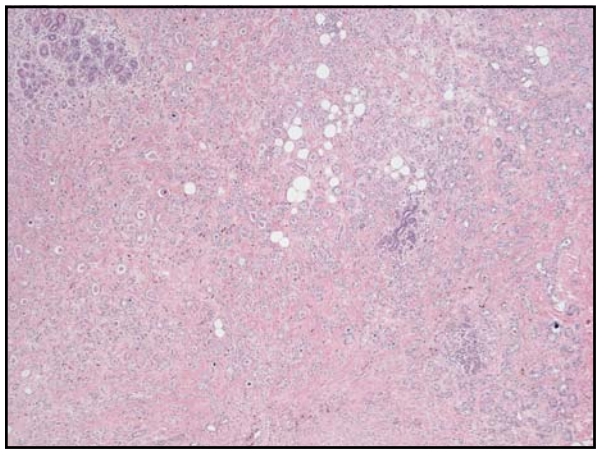
- Weak ER staining counts! CAP/ASCO threshold for positive is 1% weak staining
- Note HER2 heterogeneity on IHC and FISH different areas of expression separately
- Ki67 high in this case (more critical range is 10-15%)
- Mention basal-like features on histology in this case

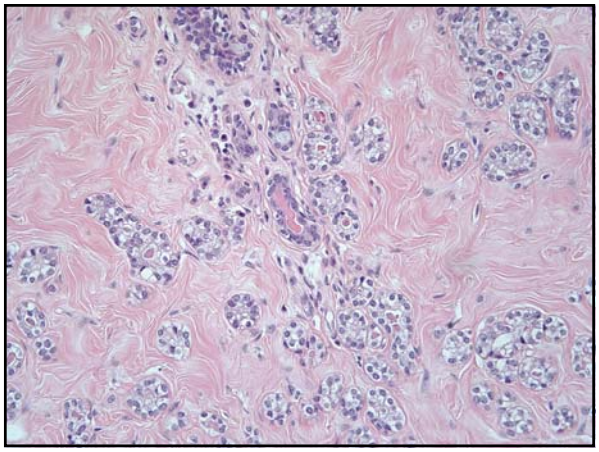
Case 5

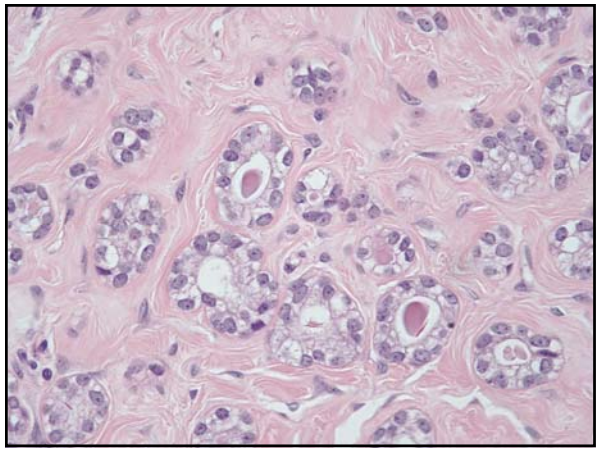
59 year old with excision for IDC on core

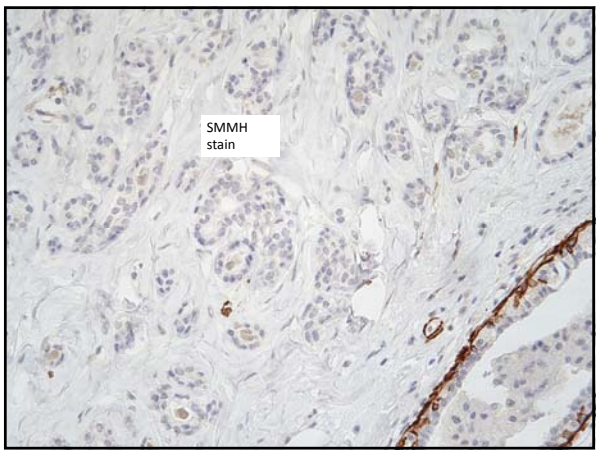


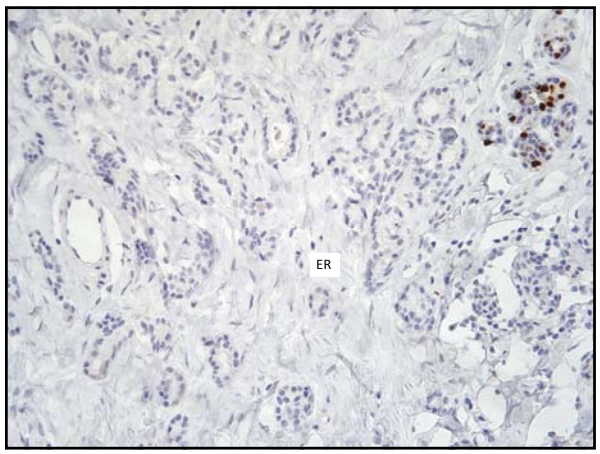









SMMH
stain

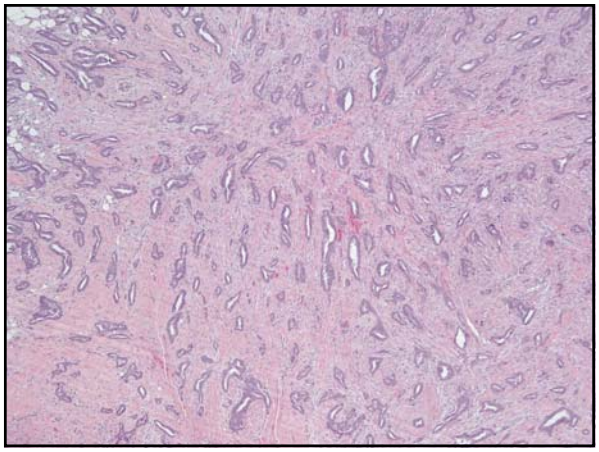

ER

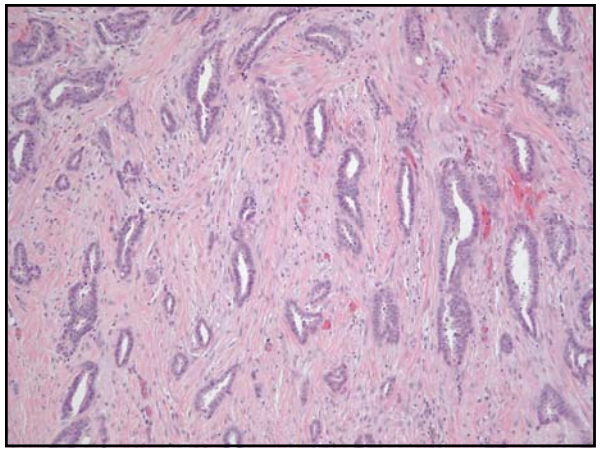
Take-home points:

- Correlate panel with histology!
- Low grade processes that are ER/HER2 negative:
  - Adenoid cystic carcinoma
  - Low grade metaplastic carcinomas (adenosquamous carcinomas, fibromatosis-like, etc)
  - Well differentiated apocrine carcinomas
  - Microglandular adenosis (not "invasion"?)
- Worth a comment in reports! Clinicians often treat all triple negative cancers the same

Case 6

65 year old with invasive breast cancer





Pathology findings:

- Nottingham grade 1 invasive ductal/tubular carcinoma
- ER: Strong positive (>95%, 3+)
- PR: Positive (50-60%, 2+)
- HER2: Negative by IHC and FISH
- Ki67: 5-10%

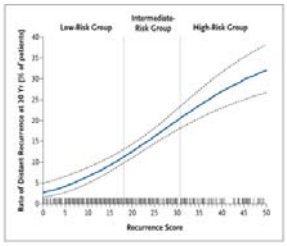
Oncologist requests a block be sent for OncotypeDX testing

Oncotype DX recurrence score: 34 (High)!!!

Why???

OncotypeDX Recurrence Score

- RT-PCR using 21 genes
- Predicts recurrence rates in ER+, lymph node negative patients
- Now also report quantitative ER, PR and Her2 mRNA levels



oncotype DX Breast Cancer Assay

Calculating the RS

16 Cancer and 5 Reference Genes

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1 **BAG1**

CD68

INVASION
Stromelysin 3
Cathepsin L2

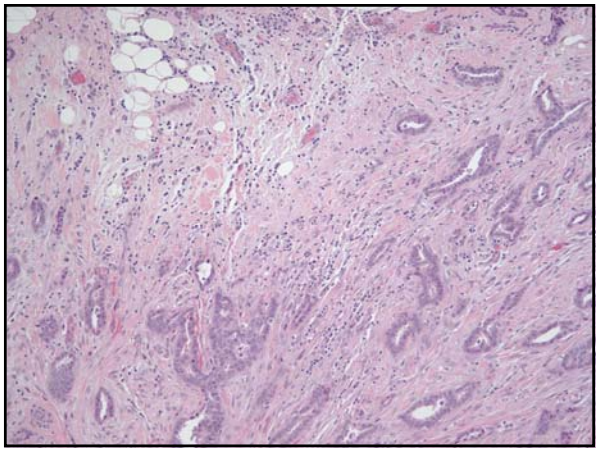
HER2
GRB7
HER2

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

RS = + 0.47 x HER2 Group Score
- 0.34 x ER Group Score
+ 1.04 x Proliferation Group Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

Category	RS (0-100)
Low risk	RS <18
Int risk	RS ≥18 and <31
High risk	RS ≥31

Paik et al. *N Engl J Med.* 2004;351:2817-2826.



Take home points:

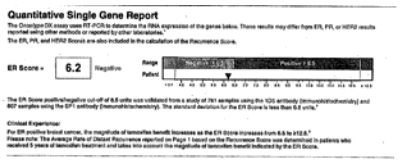
- The pathologist needs to correlate Oncotype DX results with rest of the features of the case and be able to explain unexpected results or advise on testing
- When selecting blocks for testing try to avoid blocks with intermixed inflammation

Case 7

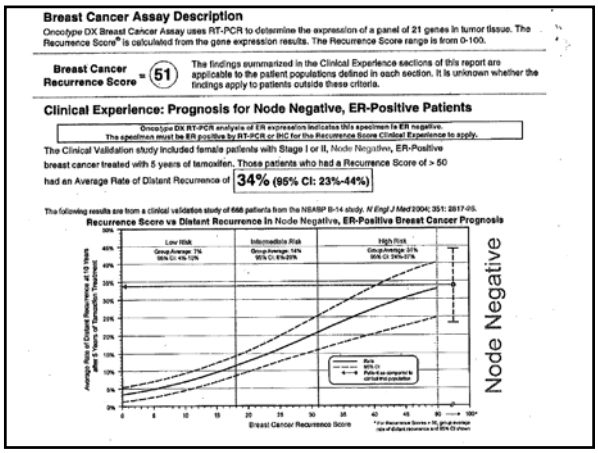
54 year old woman with a Grade 3 invasive ductal carcinoma. Her oncologist asks you to explain differences in reported ER results.

Summary of ER Results on Grade 3 IDC

- Core Biopsy outside read by image analysis : ER 2%
- Core biopsy by our review: 20%, 1+
- Excision at Stanford: 30%, 1-2+
- Oncotype DX: High RS (54; 34% recur)


Quantitative Single Gene Report

ER Score = 6.2 Negative



Breast Cancer Assay Description

Oncotype DX Breast Cancer Assay uses RT-PCR to determine the expression of a panel of 21 genes in tumor tissue. The Recurrence Score® is calculated from the gene expression results. The Recurrence Score range is from 0-100.

Breast Cancer Recurrence Score = (51)

The findings summarized in the Clinical Experience sections of this report are applicable to the patient populations defined in each section. It is unknown whether the findings apply to patients outside these criteria.

Clinical Experience: Prognosis for Node Negative, ER-Positive Patients

Oncotype DX RT-PCR analysis of ER expression indicates this specimen is ER negative. The specimen must be ER positive by RT-PCR or IHC for the Recurrence Score Clinical Experience to apply.

The Clinical Validation study included female patients with Stage I or II, Node Negative, ER-Positive breast cancer treated with 5 years of tamoxifen. Those patients who had a Recurrence Score of > 50 had an Average Rate of Distant Recurrence of **34% (95% CI: 23%-44%)**

The following results are from a clinical validation study of 668 patients from the NSABP B-14 study. *N Engl J Med* 2004; 351: 2817-26.

Recurrence Score vs Distant Recurrence in Node Negative, ER-Positive Breast Cancer Prognosis

Node Negative

How do you explain the different results?

1. Heterogeneity for ER expression/different samples used
2. Differences in assay techniques
3. Differences in interpretation techniques
4. Error
5. Other

Final Take-Home Points

- Know your guidelines
- Know something about ancillary testing techniques even if you don't perform them yourself
- Recognizing discordant ancillary test results and when to repeat or offer additional testing
- Be able to explaining apparent discrepant results to clinical teams and advise on management decisions relating to ancillary test results