What's New with ER/PR and HER2?

Making standard of care tissue-based predictions in breast cancer

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Disclosures

- Advisory Board for Oncology Analytics, Inc.
- Consult for Novartis
- Research funding from Canon, Inc

Not related to topics in this talk

First Targeted Therapy for Cancer

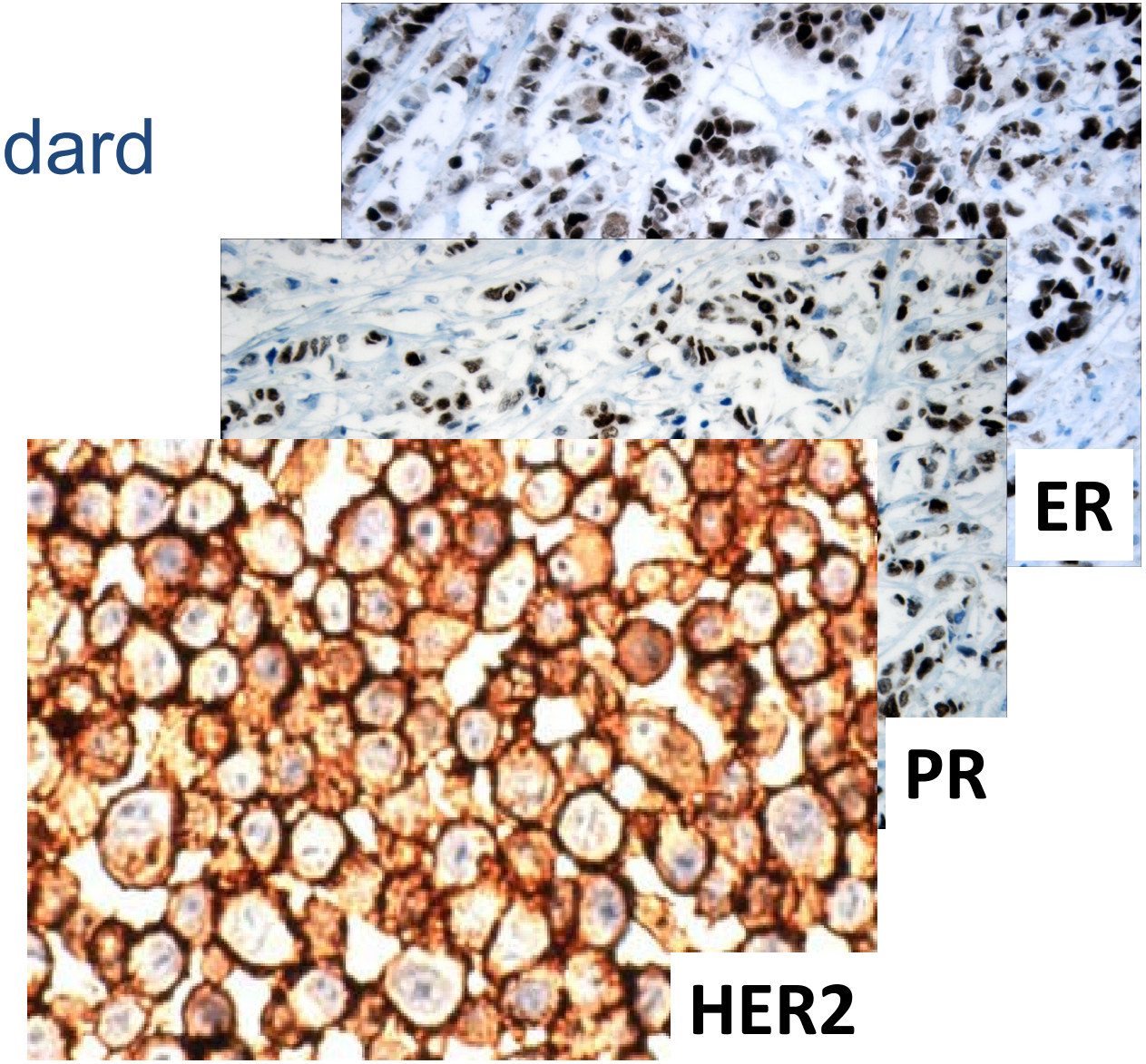
- Sir George Thomas Beatson
- Bilateral oophorectomy for treatment of advanced breast cancer
- Became the primary form of tx for premenopausal women with advanced breast cancer
- Targeting the ER pathway is still standard practice for hormone receptor positive (HR+) breast cancer
- In addition to oophorectomy, now use drugs include tamoxifen, aromatase inhibitors (AI), and fulvestrant
- Predictive marker ER (IHC)

Beatson GT. On Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions for a New Method of Treatment (Lancet, 1896)

Stockwell S. Cancer J for Clinicians 1983:33(2):105-107.

Where we are now with our standard of care assays for ER/PR/HER2

- recent changes in this area
- issues we are still struggling with



ER/PR/HER2

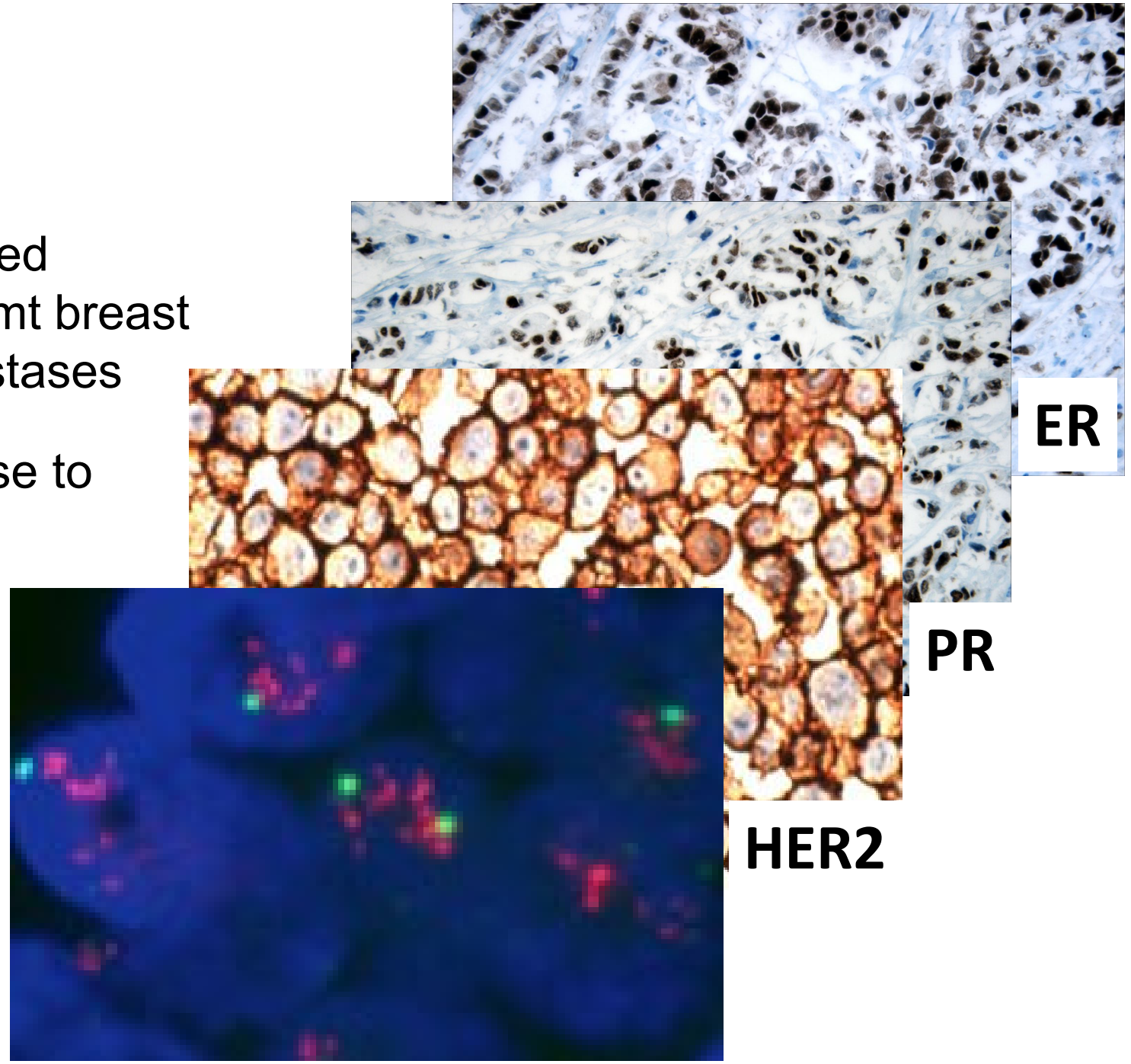
Testing done on all newly diagnosed invasive breast cancers, all post-tmt breast cancers, all recurrences, all metastases

ER/PR expression predict response to ER pathway targeting

- 80% response in ER+/PR+
- 40% response in ER+/PR-

HER2 overexpression and amplification predict response to HER2 targeting

- 65% pCR ER-/HER2+ monotx
- 40% pCR ER+/HER2+ monotx
- 80% with addition of chemotx



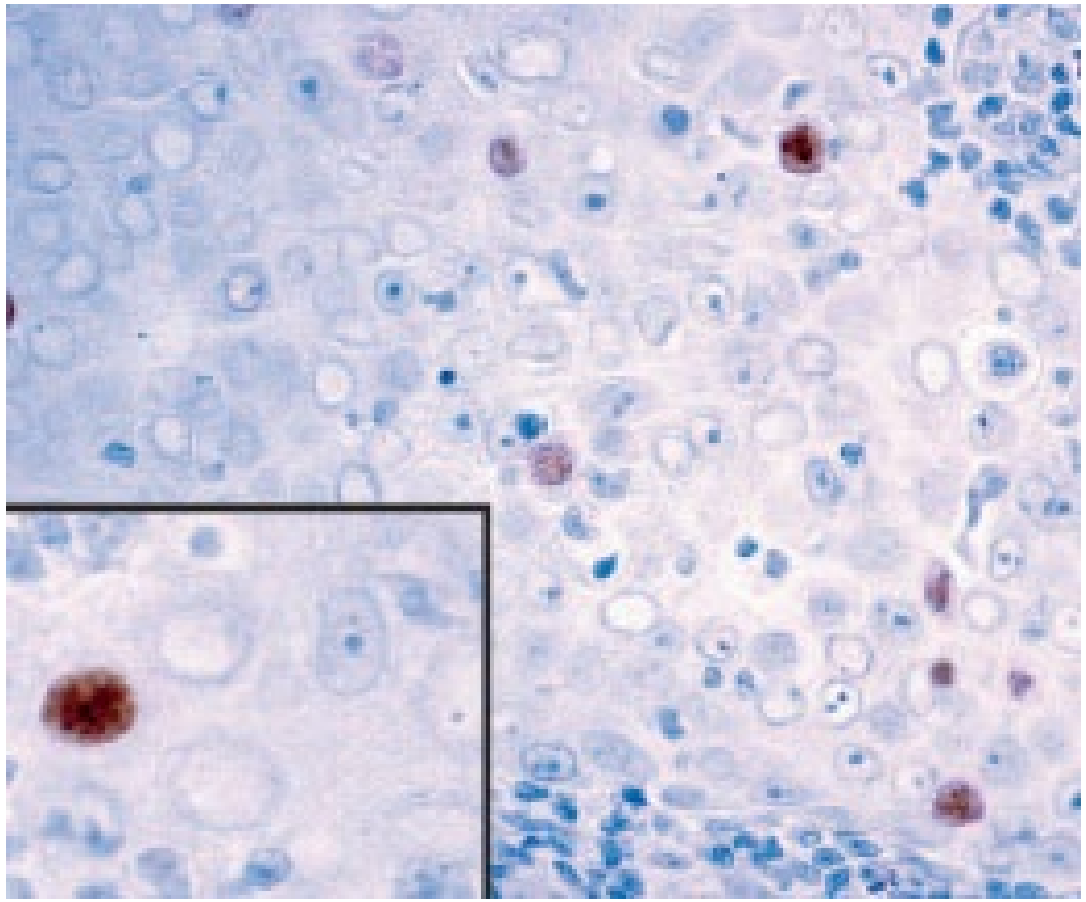
Current issues with ER/PR Testing:

Where should the cutoff point be for a positive result?

How can we avoid false negative results?

Is IHC the best way to do this?

Establishing Optimal Thresholds



Reisenbichler et al, Am J Clin Pathol 132:396-401, 2009.

A small number of cases show only rare positive cells.

Almost any cutoff point will identify groups with better and worse survival.

To predict response to tx for an **individual** pts, thresholds should be clinically validated according to outcome.

When IHC replaced LBAs, few studies were done for establishing optimal cutoff points

Variety of cutoff points used clinically and in literature (1%, 5%, 10%)

Failure to reach a consensus →discrepancies in interpretation and tmt recommendations

In some cases, patients may have been harmed by not receiving the tmt they should have received for their cancers.

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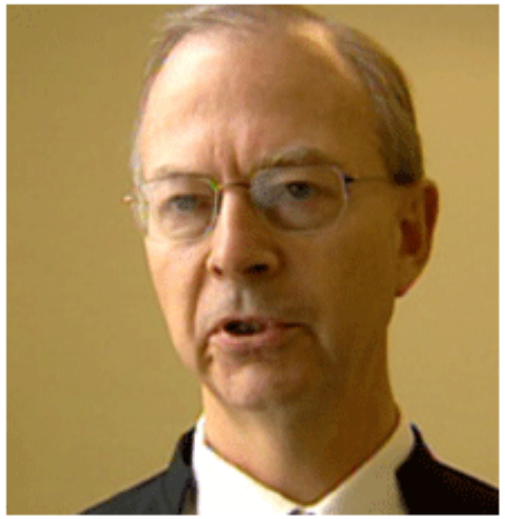
$17.5M settlement in flawed cancer tests

Last Updated: Monday, February 15, 2010 | 6:27 PM NT CBC News

A Supreme Court of Newfoundland and Labrador judge has approved a $17.5-million settlement in the class-action suit over errors in breast cancer testing conducted in the province between 1997 and 2005.

Estrogen receptor and progesterone receptor, or ER/PR, tests are used to determine what type of breast cancer — either hormone receptor negative or positive — a patient has.

The settlement was reached with the province's largest health authority, Eastern Health, in October and was presented to a Judge Carl Thompson on Feb. 2. He approved it Feb.12.



St. John's lawyer Ches Crosbie led the class-action suit over problems with cancer testing in Newfoundland and Labrador. (CBC)

Internal Links

- Controversial cancer tests still sent out of N.L.

External Links

- Judge Carl Thompson decision

(Note: CBC does not endorse and is not responsible for the content of external sites - links will open in new window)

Updated ASCO/CAP guidelines (2020)

Since 2010 have used a cutoff of 1%

POSITIVE	>10% positive cells
LOW POSITIVE	**1-10% positive cells for ER**
NEGATIVE	<1% positive cells (any intensity)

- acknowledge the more limited data on endocrine responsiveness in this group
- increasing evidence that at least some very low-expressors may be more like TNBC

→Many clinical trials for TNBC now set thresholds at 5% or 10%, to be able to enroll very low expressors

www.asco.org/guidelines/erpr

ER/PR: False positive and negative results

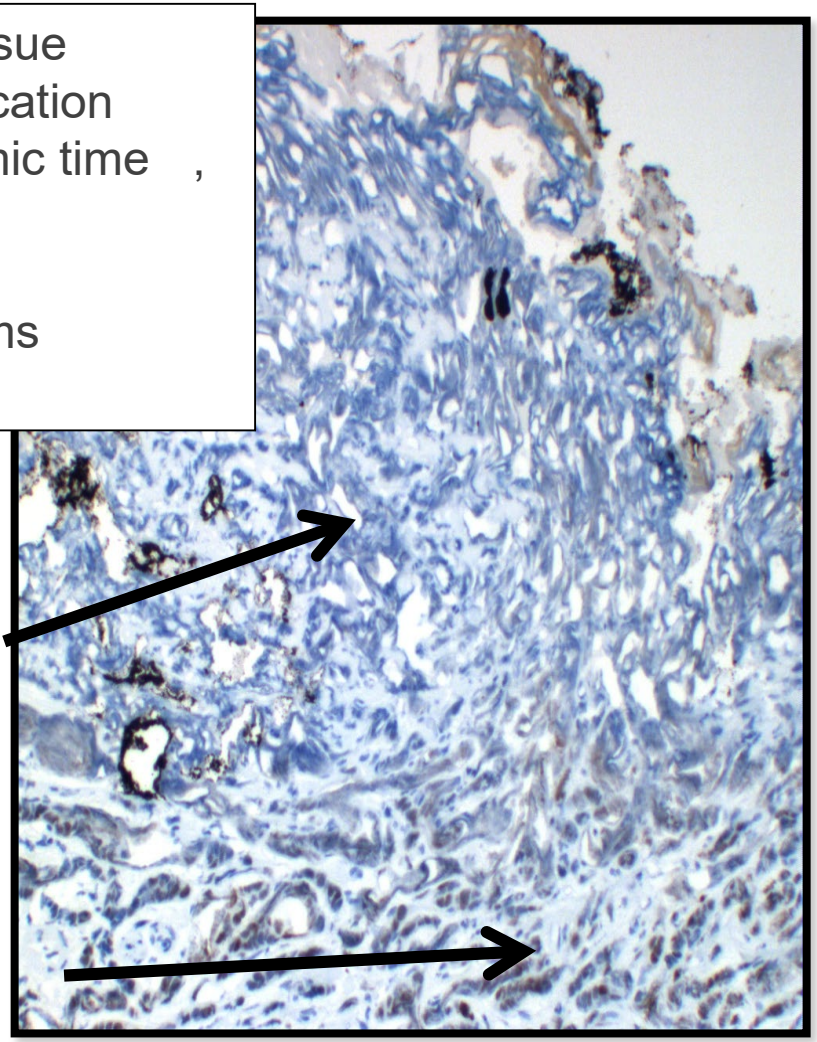
False negative results

--problems with the tissue
- -cautery, decalcification
- -prolonged ischemic time ,
- -poor fixation

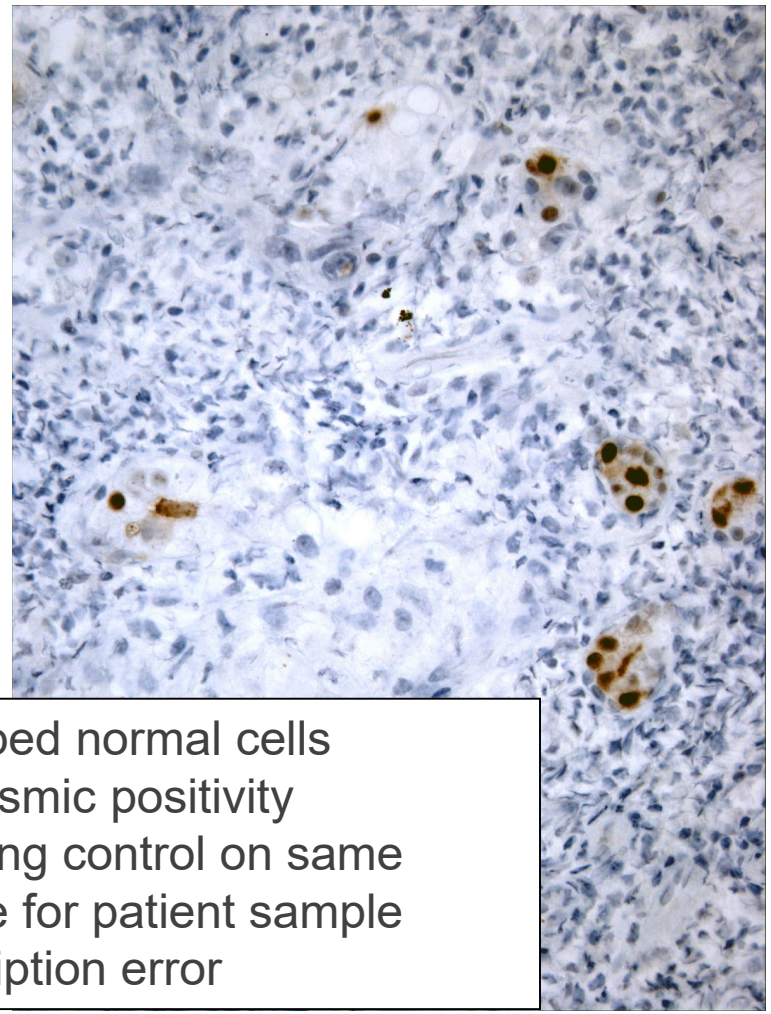
--technical problems
--interpretative problems
- -cut-off threshold

Negative ER, cauterized

Weak ER, non-cauterized



False positive results



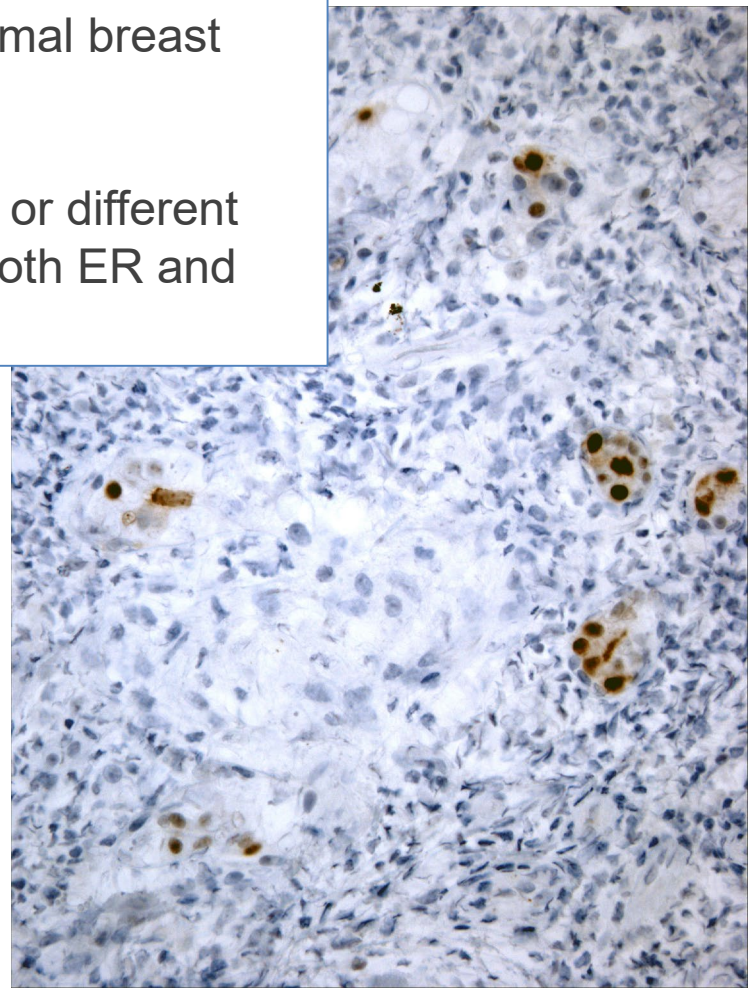
--entrapped normal cells
--cytoplasmic positivity
--mistaking control on same slide for patient sample
--transcription error

ER/PR: False positive and negative results

To avoid false negatives:

Always check that the normal breast epithelium is positive

If not, repeat on the same or different specimen – especially if both ER and PR are negative



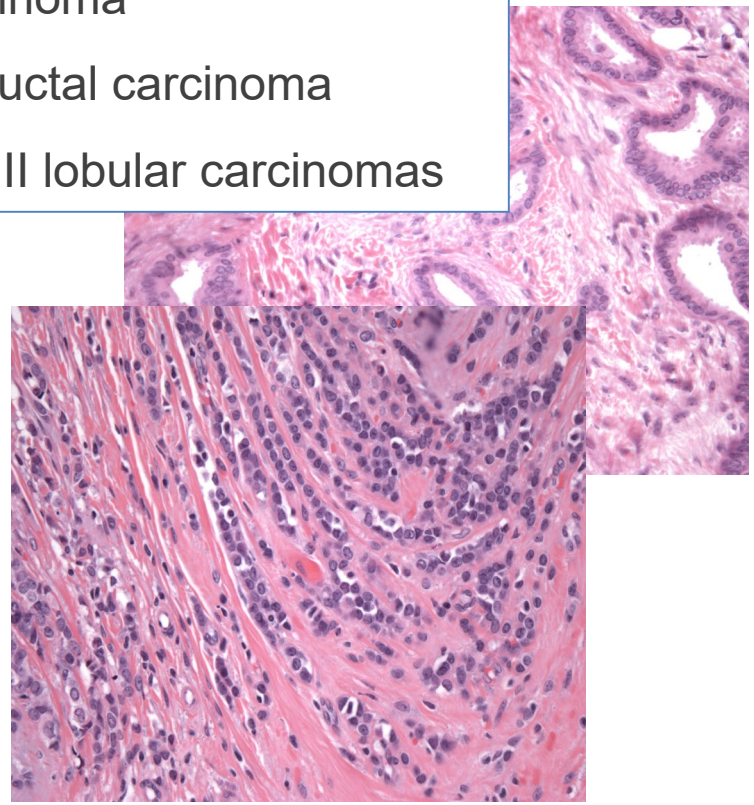
Correlate with histology. Some cancers are almost always ER-positive:

→mucinous carcinoma

→tubular carcinoma

→low-grade ductal carcinoma

→grade I and II lobular carcinomas



ER/PR: Avoiding false negative results

Problems with ER testing in Canada were discovered when 2 patients with **ER neg lobular carcinomas** were retested and found to be ER positive.

This resulted in r[illegible]f >1000 ER negative carcinomas from [illegible]ewfoundland, and Labrador from [illegible]

425 of the 1088 (39%) were found to be ER positive.

More than 100 of these pts died without receiving hormonal treatment.

<u>→Earlier attention to an unusual finding could have pointed to the problem earlier.</u>

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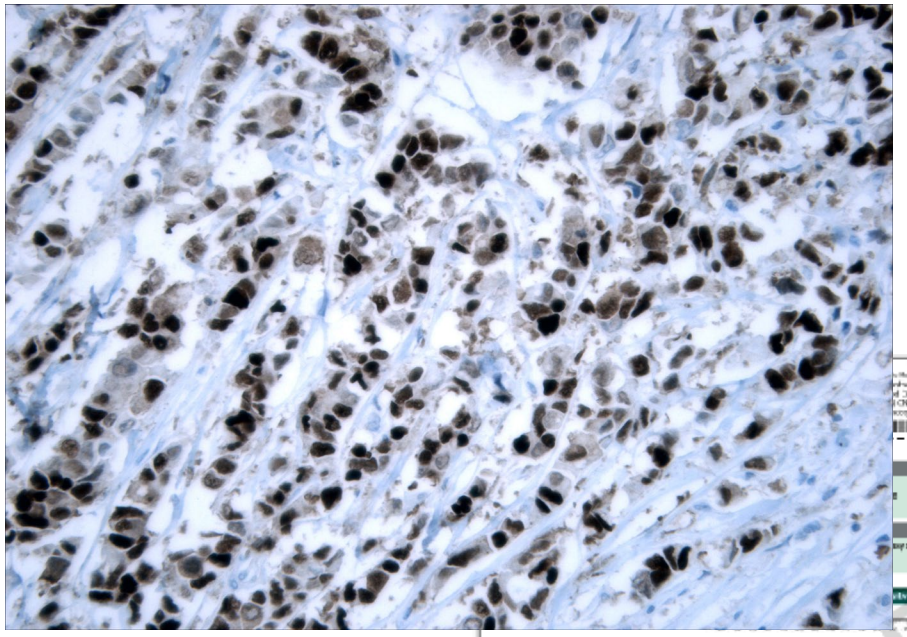
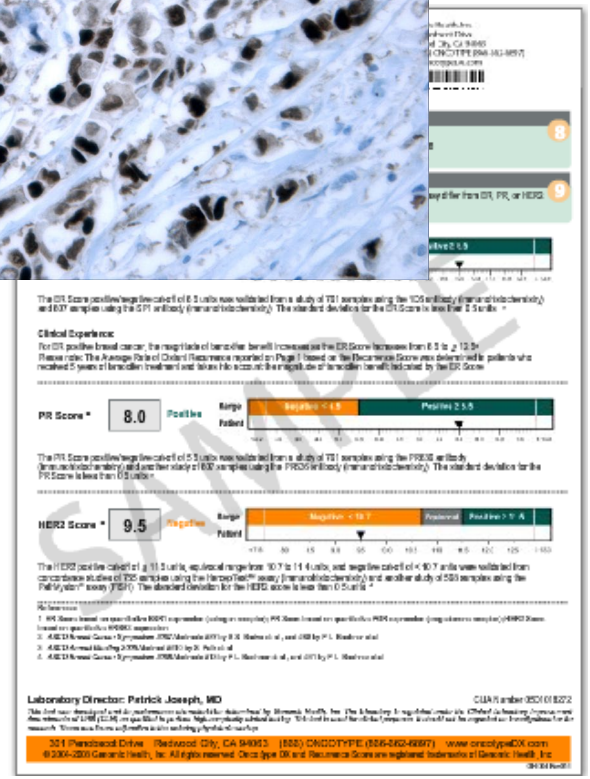
ER/PR: is IHC the best method?

IHC is cheap, fast and robust

What about other assays to detect ER/PR expression?

Are these acceptable for identifying patients likely to benefit from endocrine therapy?

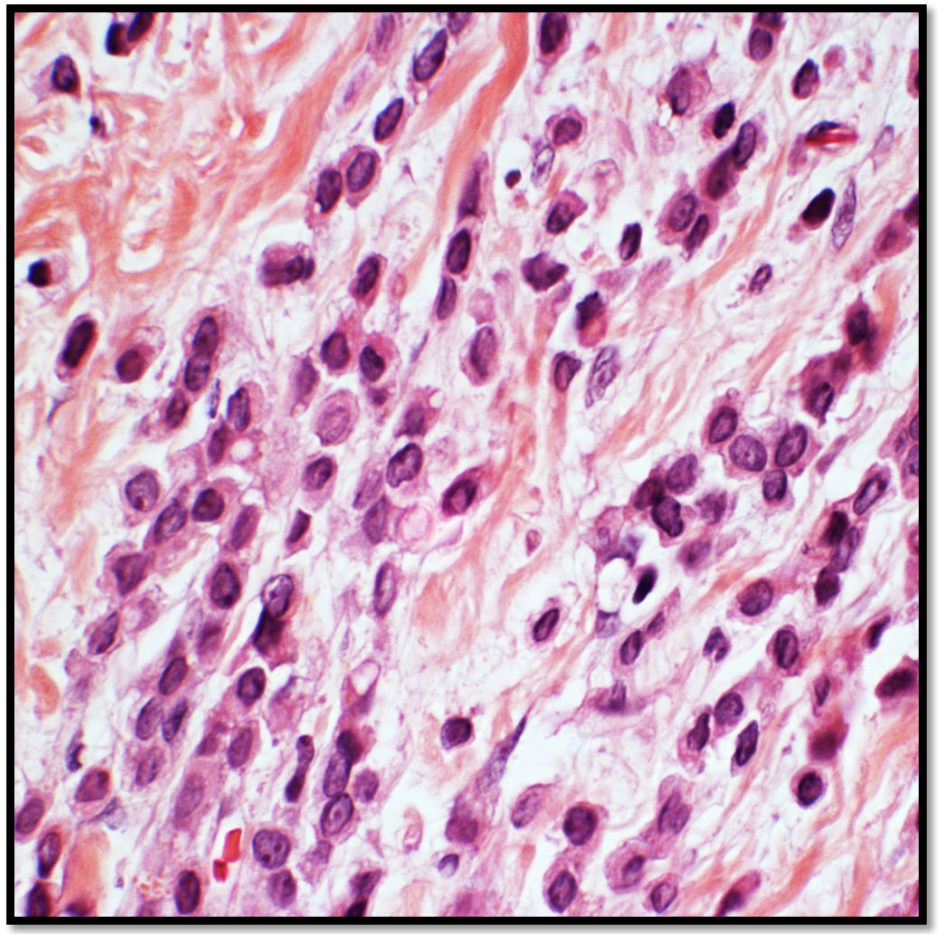




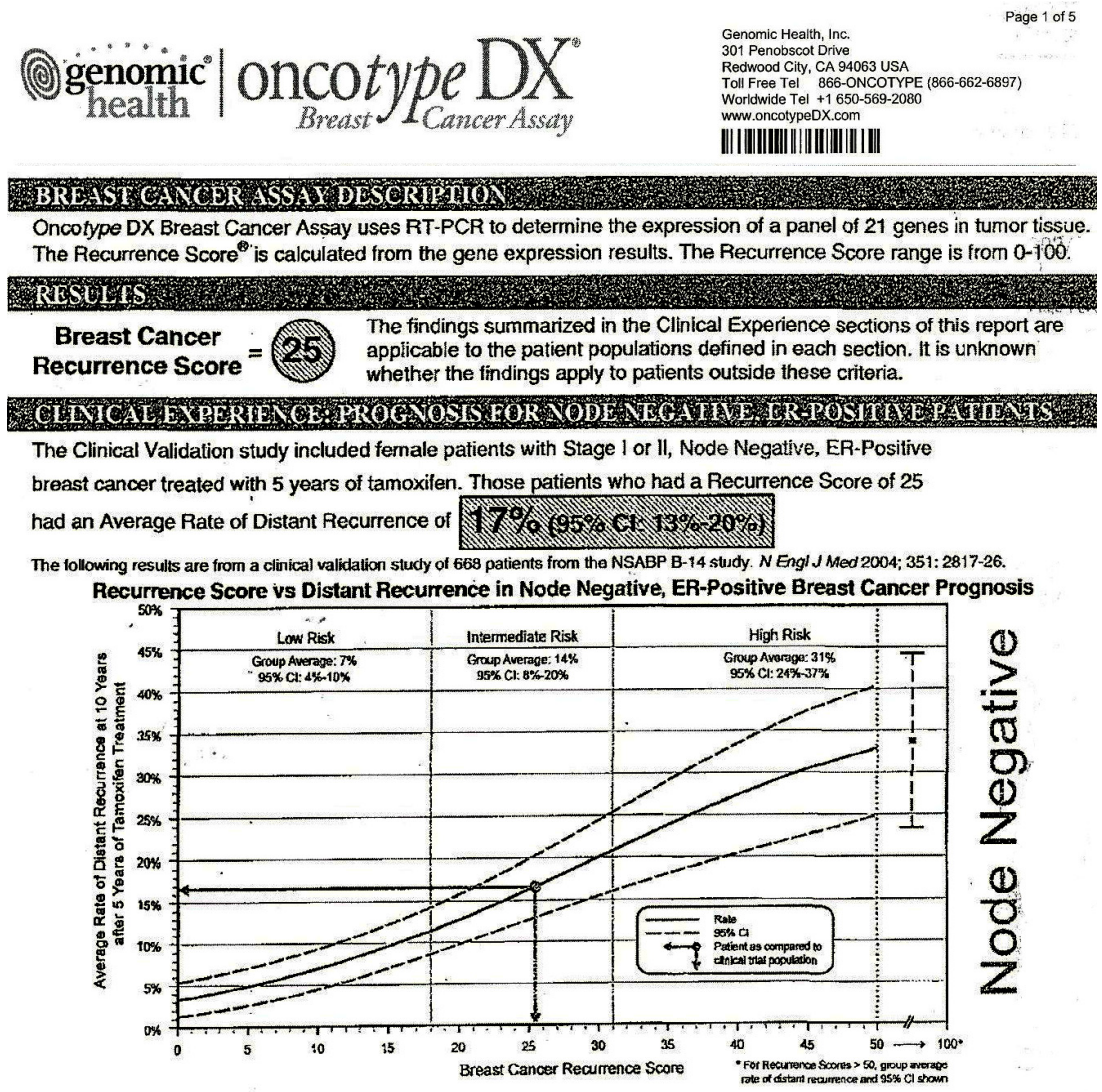
A Cautionary Tale

A 49 year old woman was diagnosed with a grade I invasive lobular carcinoma on core

Estrogen receptor	80%, strong
Progesterone receptor	70%, strong
HER2	0
Mitotic score:	1



Her oncologist requested Onco*type* DX on the core to help decide if she should consider neoadjuvant chemotherapy.



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genomic health | oncotype DX Breast Cancer Assay

Genomic Health, Inc.
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Toll Free Tel 866-ONCOTYPE (866-662-6897)
Worldwide Tel +1 650-569-2080
www.oncotypeDX.com

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.

RESULTS

Breast Cancer Recurrence Score = 25

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

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 25 had an Average Rate of Distant Recurrence of **17% (95% CI: 13%-20%)**

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

Surprisingly, the recurrence score was 25 (17% risk of recurrence on Tam)

This is in the range that chemotherapy might be considered.

Single gene scores

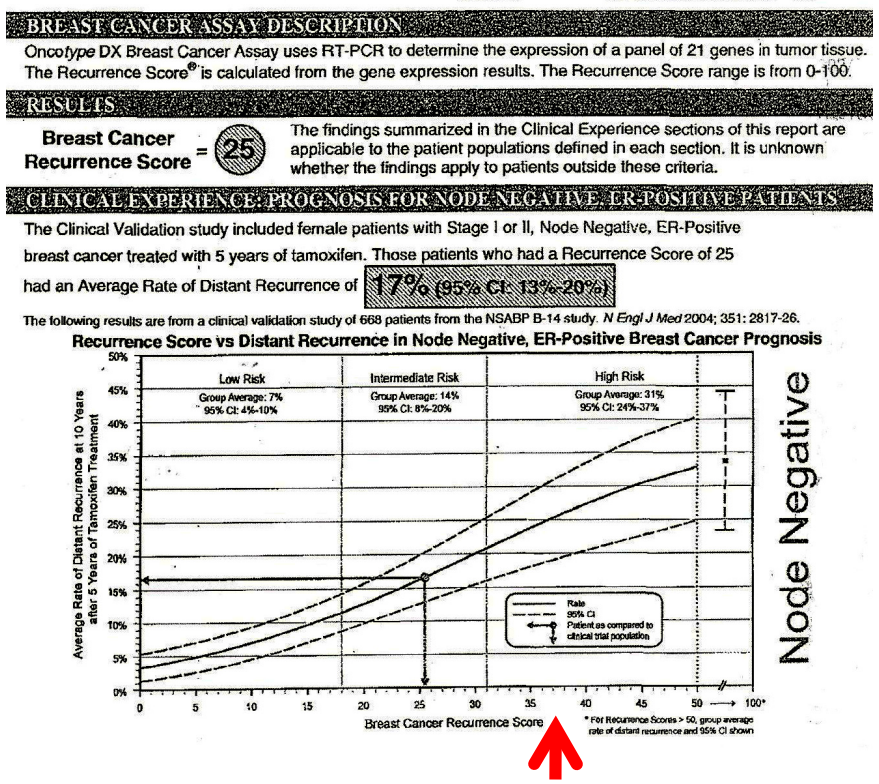
ER	Positive
PR	Negative
HER2	Negative

False negative PR elevated the RS.

Patient underwent surgery and a repeat study on the larger area of cancer in the excision.

Repeat testing on excisional specimen

First result



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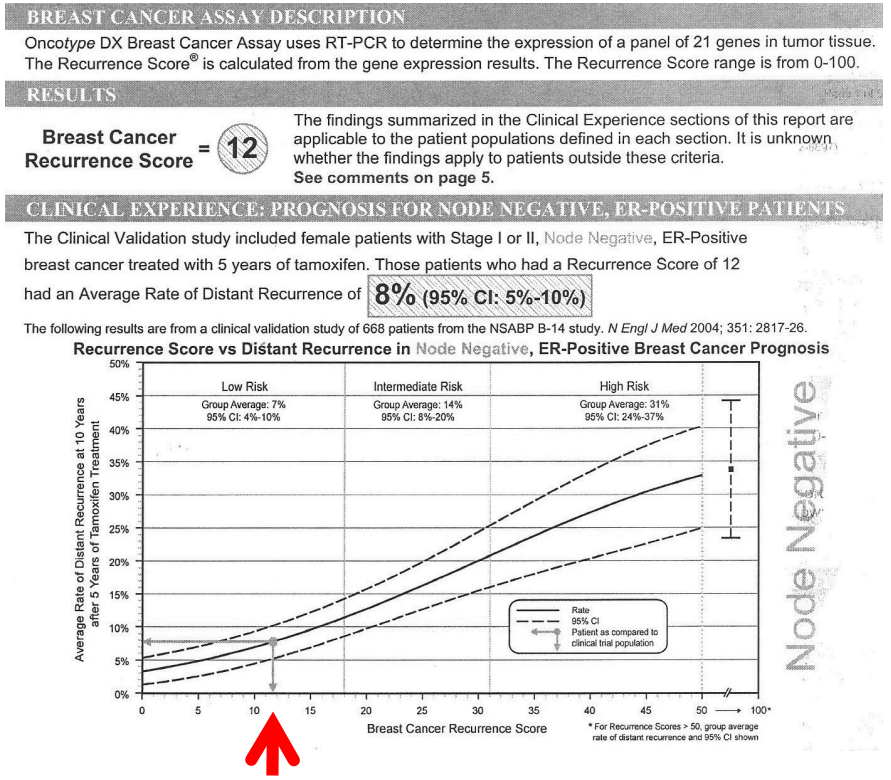
Second result



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RESULTS

Breast Cancer Recurrence Score = 12

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See comments on page 5.

CLINICAL EXPERIENCE: PROGNOSIS FOR NODE NEGATIVE, ER-POSITIVE PATIENTS

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 12 had an Average Rate of Distant Recurrence of 8% (95% CI: 5%-10%)

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

In the second test, the PR was positive and the RS much lower (12).
Pt was treated with hormonal therapy alone based on the second result.

→The pt received correct treatment because a discrepancy was detected and resolved.

ER/PR: other methods?

Molecular analysis of ER/PR from **scraped tissues**:

--ER concordant in 99%, PR concordant in 94%

Most common type of discrepancy: **false negative**

--low cellularity carcinomas (esp lobular)

--small cancers with large biopsy sites

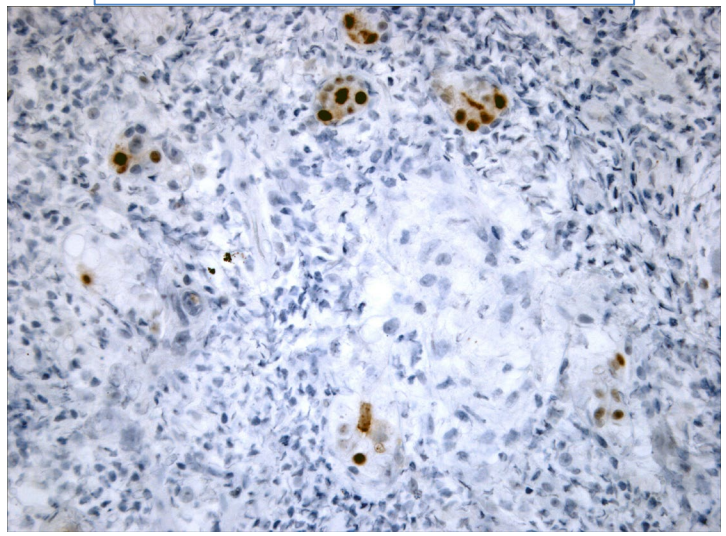
IHC is the correct result in 70% of discordant cases

Kraus JA et al. Semi-quantitative immunohistochemical assay versus oncotype DX qRT-PCR assay for estrogen and progesterone receptors: an independent quality assurance study. Mod Pathol 25:869, 2012.

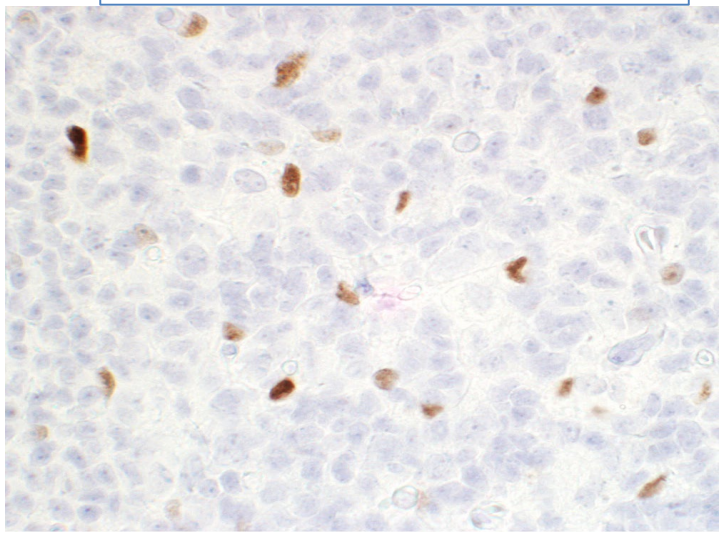
ER/PR: other methods?

Pitfalls in scoring **by image analysis**:
ER expression in

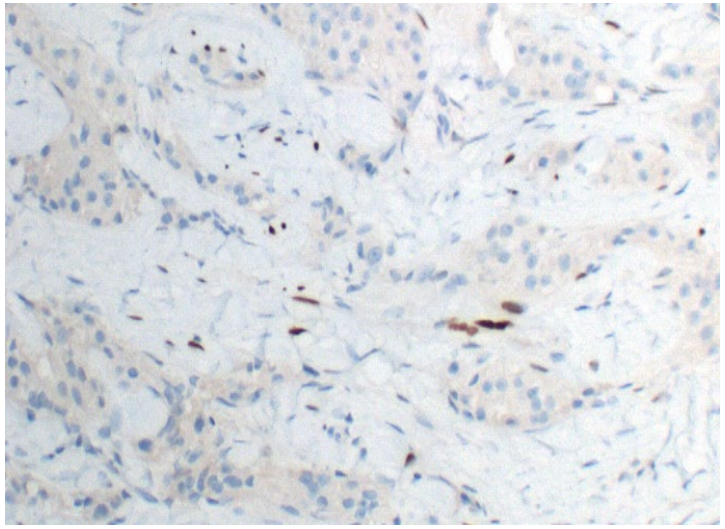
normal epithelium



normal lymphocytes



normal stroma



if you are using image analysis, set your thresholds so that you're not picking these up
2020 guidelines include recommendations for validation and monitoring QIA systems

ER/PR: Summary

Lower cutoff for + currently at 1%, except for clinical trials.

New category **ER LOW POSITIVE (1-10%)** acknowledges more limited information for these cases; may act more like TNBCs

Repeat testing in some cases may be helpful, especially if results are not concordant with previous results or if the histology doesn't seem to match.

Validated IHC is the only recommended test for predicting benefit from endocrine therapy at the current time.

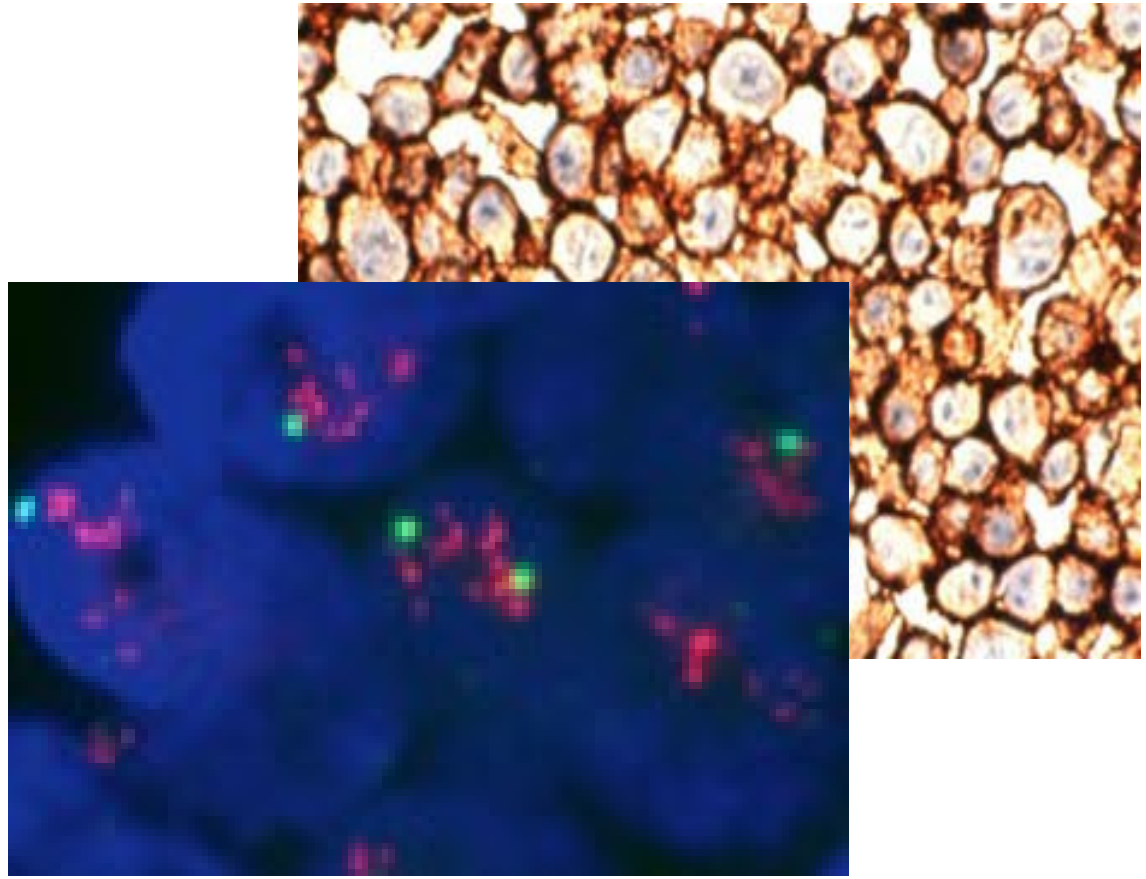
Allison KH et al. Estrogen and Progesterone Receptor Testing in Breast Cancer ASCO/CAP Guideline Update. Arch Pathol Lab Med 2020;144:545-563.

HER2 (ERBB2)

HER2 was the first cancer biomarker to be targeted by a therapeutic Ab (1998)

There are now a number of different HER2-targeted txs

trastuzumab(Herceptin)
lapatinib (Tykerb)
emtansine (Kadcyla)
pertuzumab (Perjeta)
trastuzumab-emtansine (T-DM1)
trastuzumab-deruxtecan (T-DXD)



Amplified and overexpressed in 15% of invasive breast cancers

Evaluated using IHC and/or FISH

Issues with HER2 Evaluation:

How to avoid false positive results (IHC)

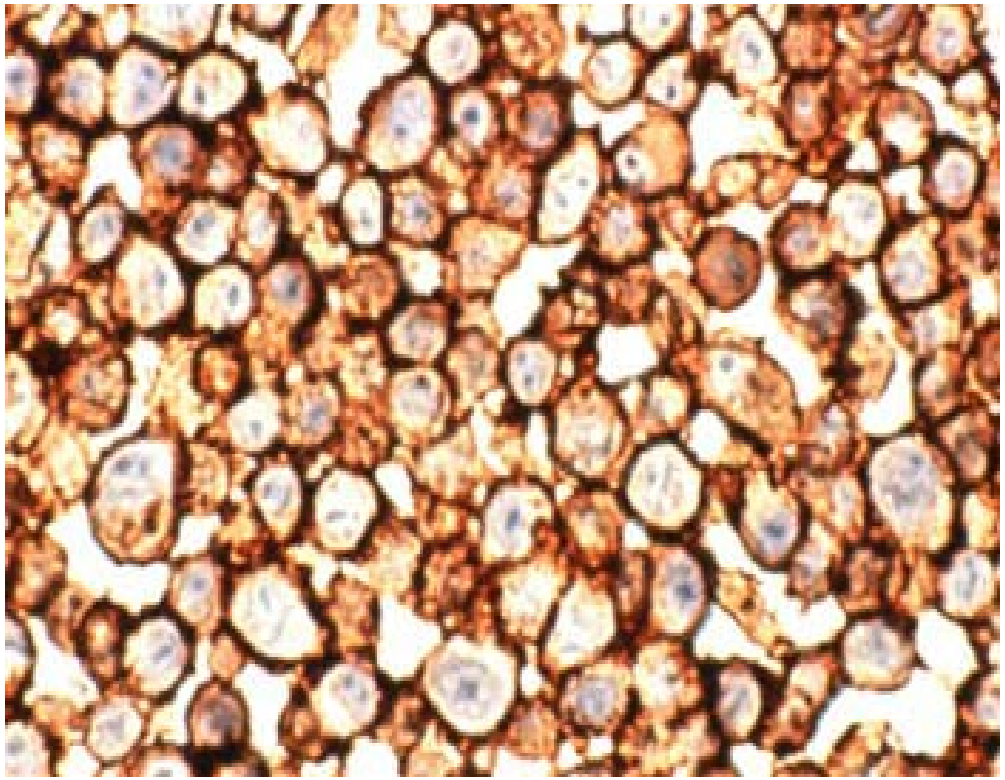
What is the best cutoff point for positive result (FISH)?

What do we do about heterogeneity?

What about HER2 low???

How to avoid false positive results

Immunohistochemical evaluation of HER2



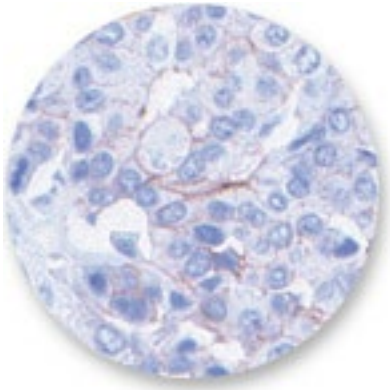
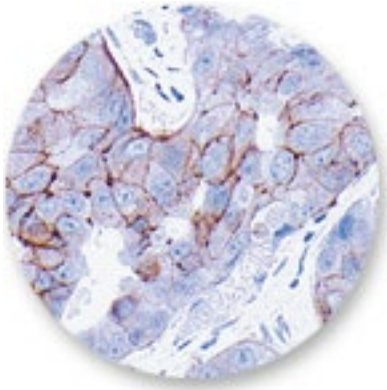
Many different antibodies to HER2

Strong 3+ positive staining with all HER2 antibodies is associated with amplification by FISH

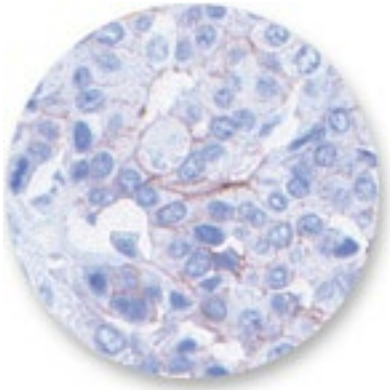
Differing sensitivities and specificities, especially in the intermediate ranges

IHC is subject to pre-analytical, analytical and interpretive variables

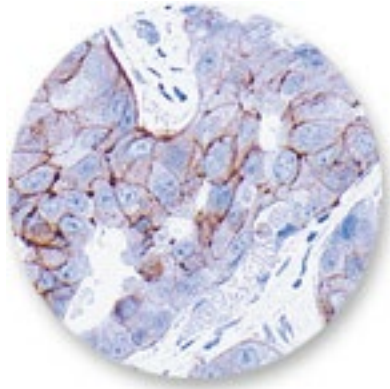
Standardization of Interpretive Criteria

0	1+	2+	3+
			
Staining in ≤10% cells	Faint partial >10% cells	Weak/moderate complete >10% cells	Strong complete >10% contiguous cells
NEGATIVE	NEGATIVE	EQUIVOCAL	POSITIVE

Haven’t been overly concerned about...

0	1+
	
Staining in ≤10% cells	Faint partial >10% cells
NEGATIVE	NEGATIVE

Very concerned about variability…

2+	3+
	
Weak/moderate complete >10% cells	Strong complete >10% contiguous cells
EQUIVOCAL	POSITIVE

HER2 IHC: False positive 3+

False positive HER2 IHC has significant consequences.

For individual patients, can lead to inappropriate treatment with HER2 targeted agents when other treatments would likely be more effective.

For clinical trials, incorrect classification of cancer can impede efforts to determine the effectiveness of HER2 targeted agents.

For society, HER2 targeted txs are costly (>$70,000/yr) vs the cost of confirmatory testing: IHC ~$90 or ISH ~$400

HER2 IHC: Causes of false positive 3+

Overstaining

normal breast tissue should be negative (except apocrine metaplasia which can be 1+ to 2+)

Edge artifact

lobular carcinomas can appear falsely positive in edges or between cells

Cytoplasmic positivity

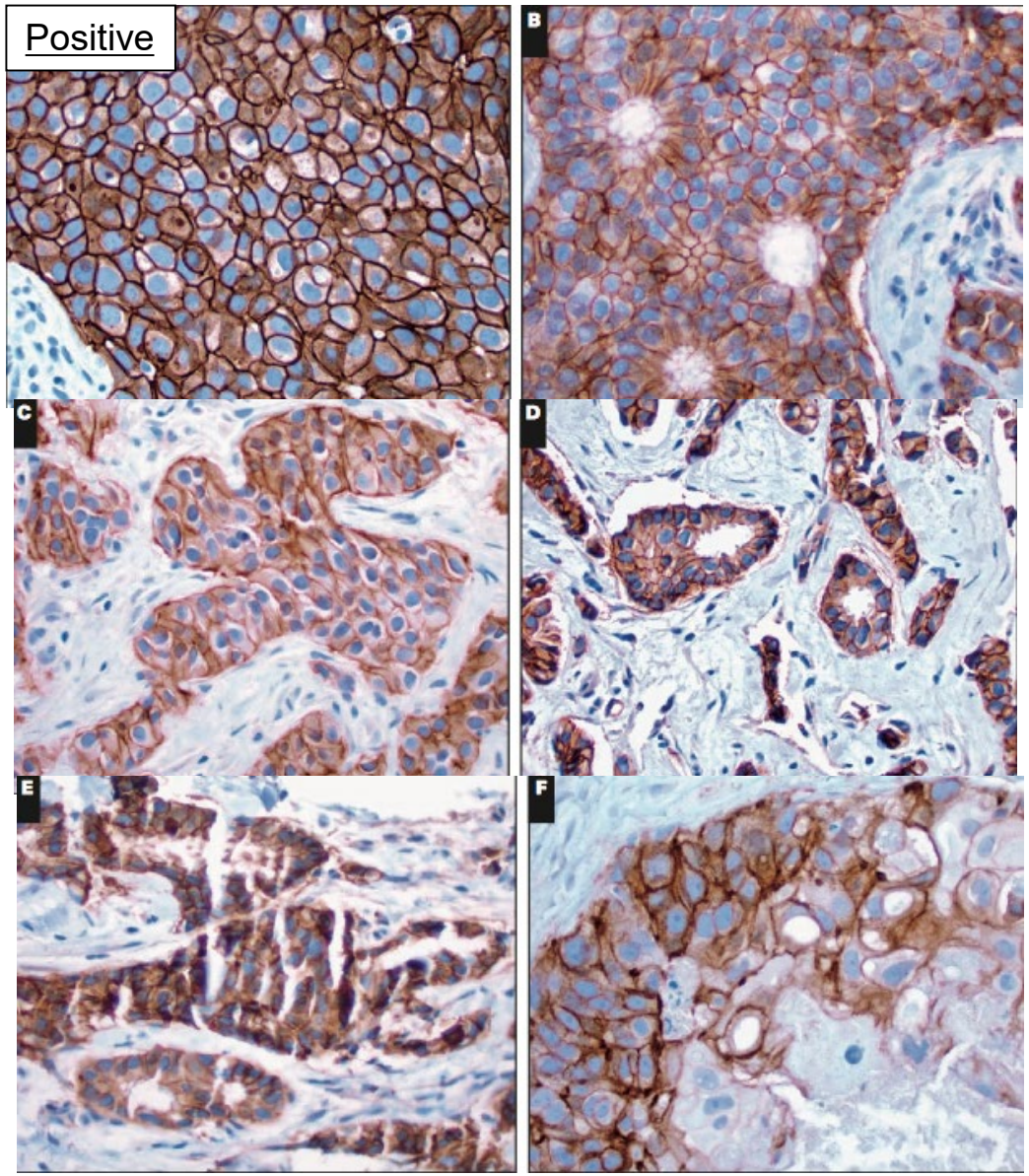
only membrane positivity should be scored

Overinterpretation

moderate complete or granular membrane expression

13 of 19 IHC/FISH discordant cases were from **overinterpretation** due to granular staining, crush artifact, and weak intensity.

Grimm EE et al. Am J Clin Pathol 134:284, 2010.

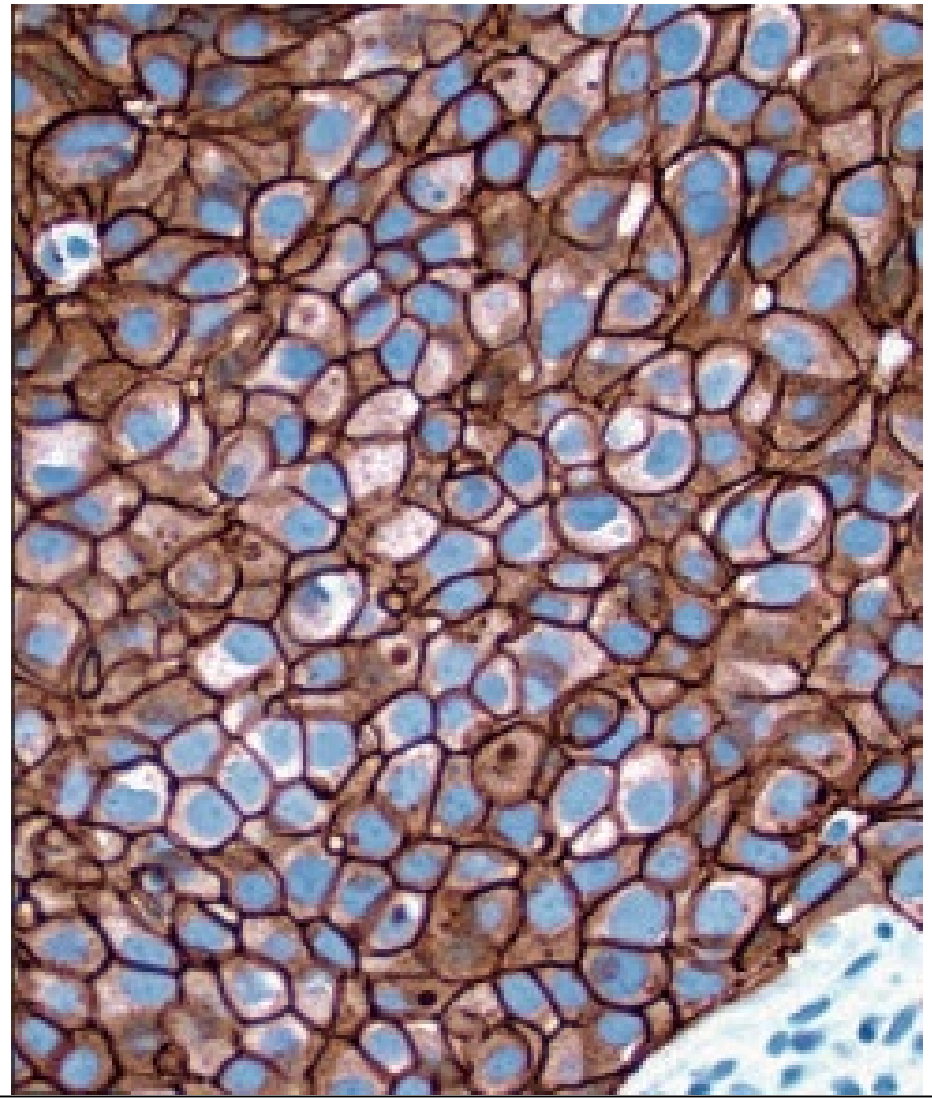


HER2 IHC: Avoiding false positive 3+

Have a very high threshold for interpreting a cancer as 3+.

There should be strong crisp complete membrane positivity throughout (>10% contiguous focus).

Have a low threshold for confirming by ISH in uncertain cases.



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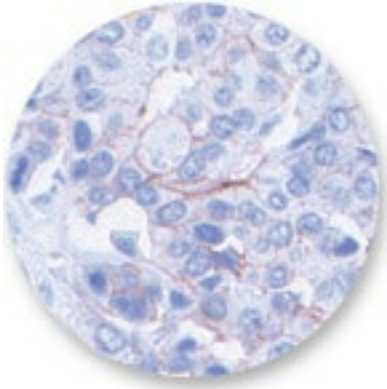
What is the best cutoff point for a positive result (FISH)?

Hybrid Testing Scheme: IHC with FISH

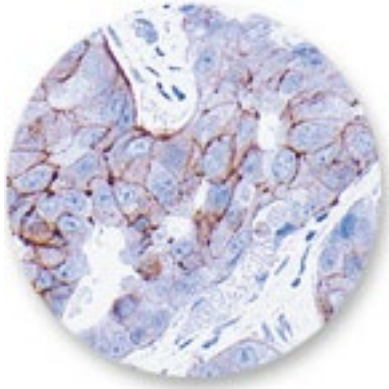
there is very high concordance between a IHC 3+ and amplification by FISH

0
negative

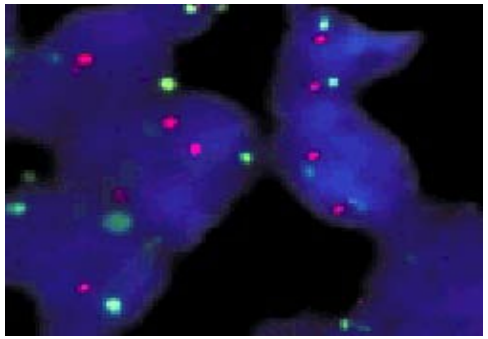
1+
negative



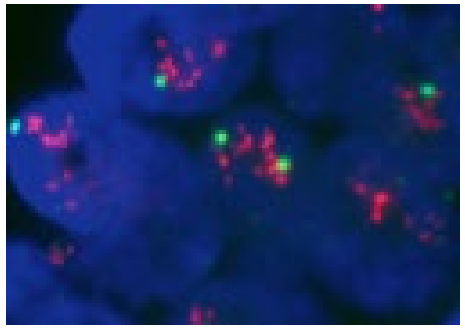
2+
equivocal



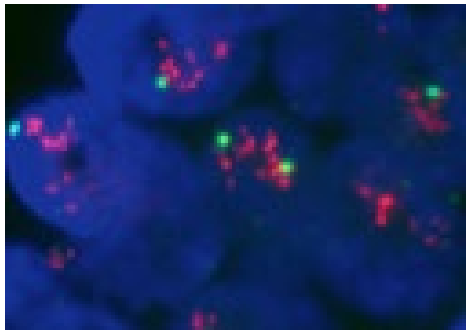
3+
positive



>95%

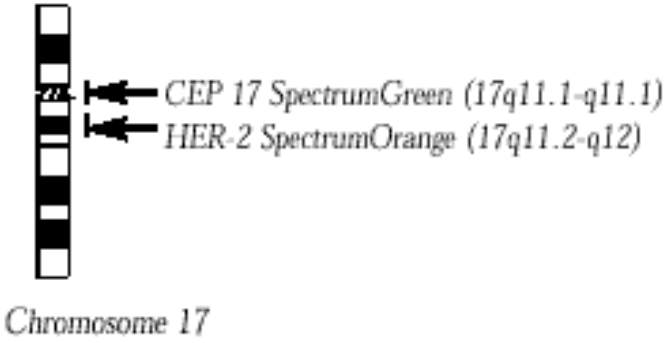


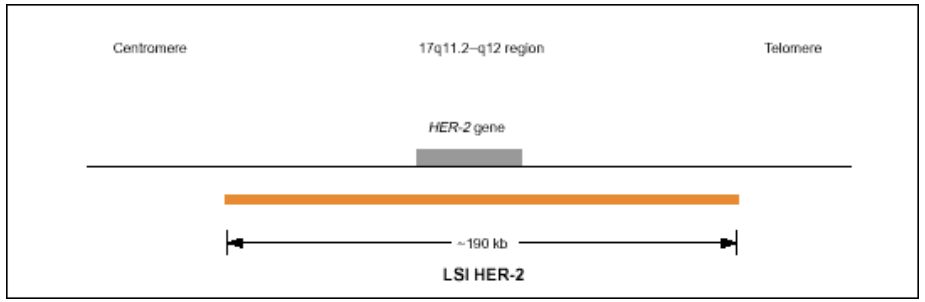
20-50%+



>95%

HER2 FISH





Two labelled DNA probes:

***HER2* probe**

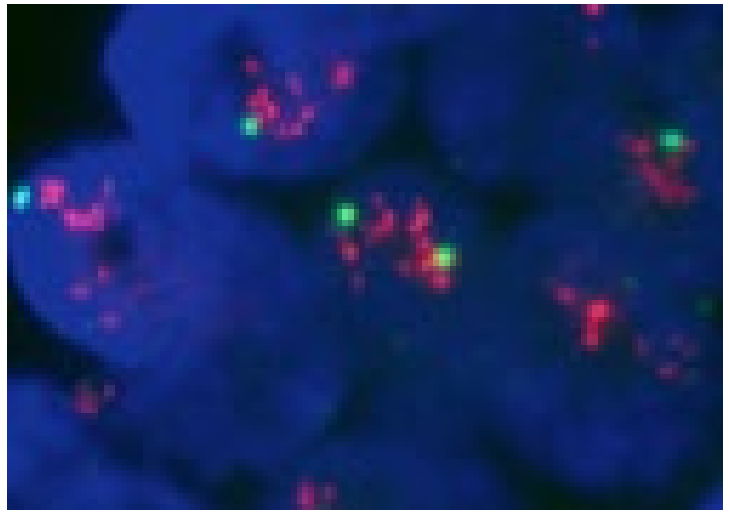
190 Kb; orange fluor

Hybridizes to entire length of HER2 gene

chromosome 17 probe (CEP17)

5.4 Kb; green fluor

pericentromere alpha satellite repeats



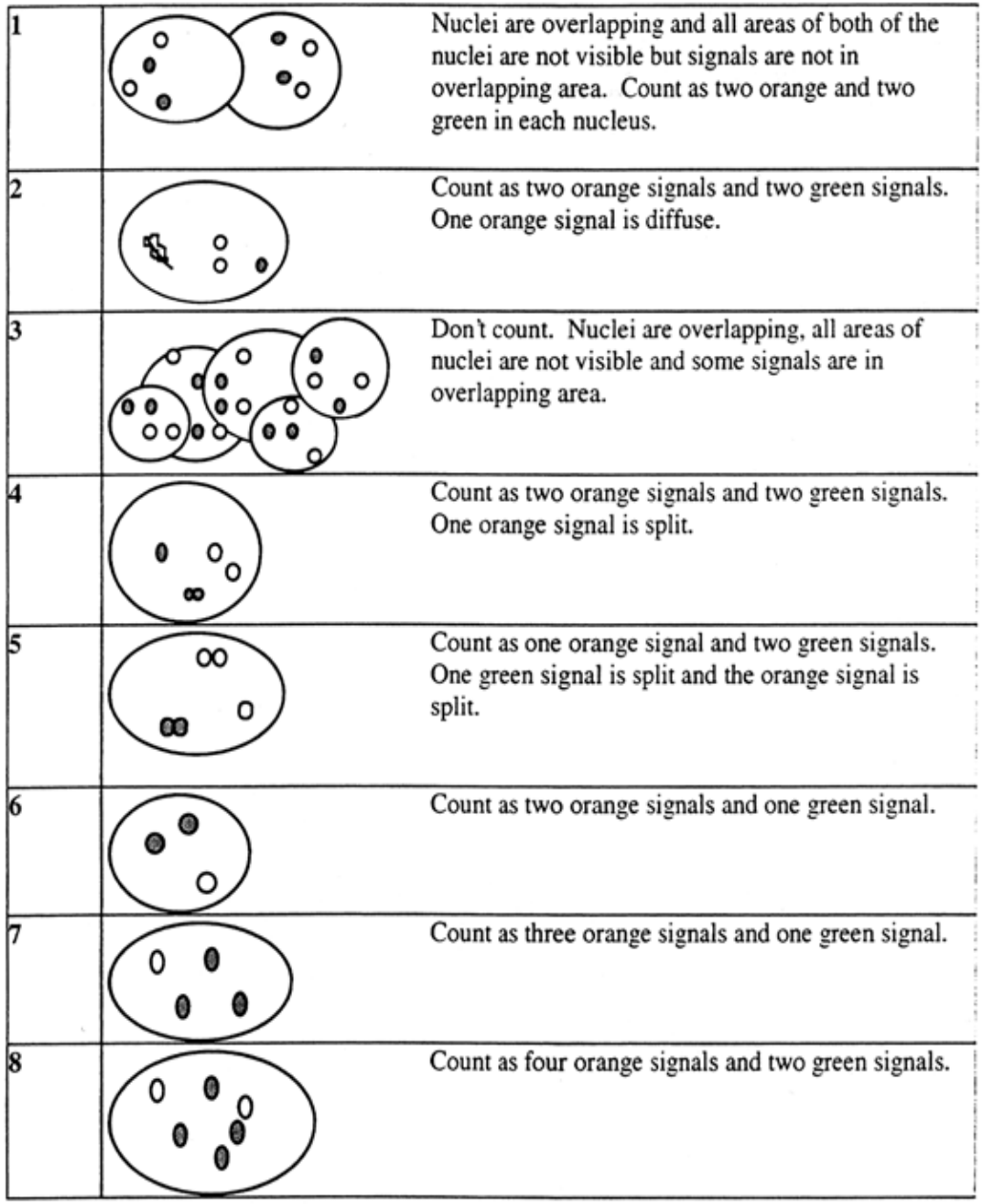
5 micron sections

Scoring

Standardized criteria

Count only cells with both orange and green signals present

Avoid counting overlapping cells → falsely elevate CN



1		Nuclei are overlapping and all areas of both of the nuclei are not visible but signals are not in overlapping area. Count as two orange and two green in each nucleus.
2		Count as two orange signals and two green signals. One orange signal is diffuse.
3		Don't count. Nuclei are overlapping, all areas of nuclei are not visible and some signals are in overlapping area.
4		Count as two orange signals and two green signals. One orange signal is split.
5		Count as one orange signal and two green signals. One green signal is split and the orange signal is split.
6		Count as two orange signals and one green signal.
7		Count as three orange signals and one green signal.
8		Count as four orange signals and two green signals.

FIGURE 1. Signal counting guide. Key: ○ = green probe; ● = orange probe.

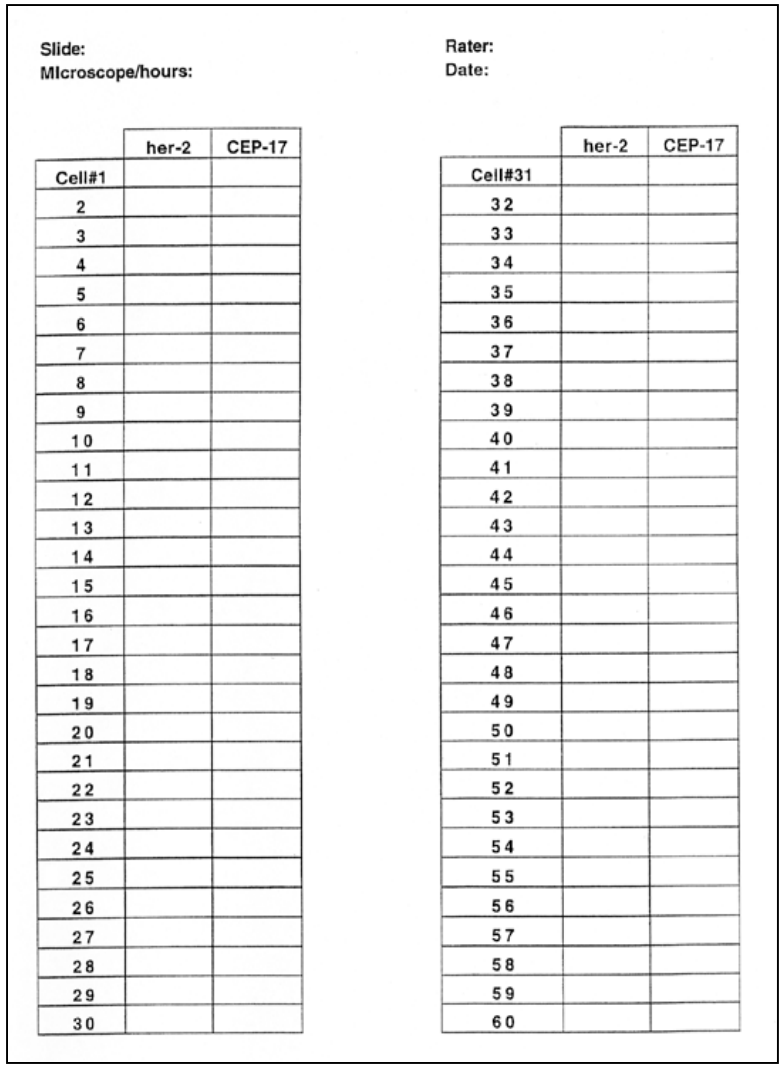
Scoring

Probe signals are counted in a minimum of 20 tumor cell nuclei

Exclude DCIS

Calculate:

- avg HER2 signals/cell
- avg CEP17 signals/cell
- ratio of *HER2* signals to chr17 centromere signals



Slide:
Microscope/hours:

Rater:
Date:

	her-2	CEP-17
Cell#1		
2		
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	her-2	CEP-17
Cell#31		
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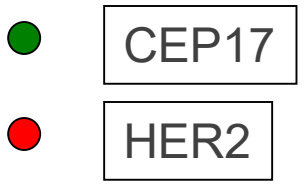
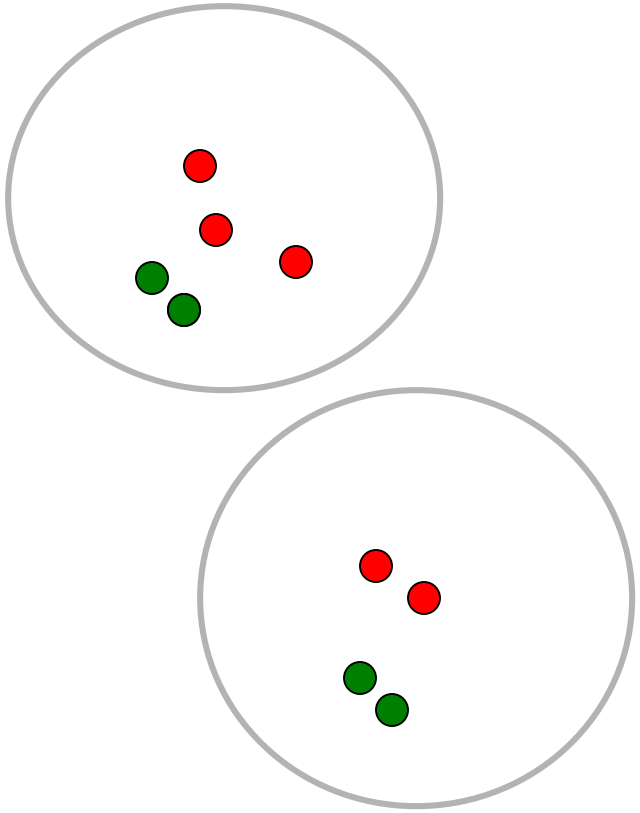
Classical FISH Results

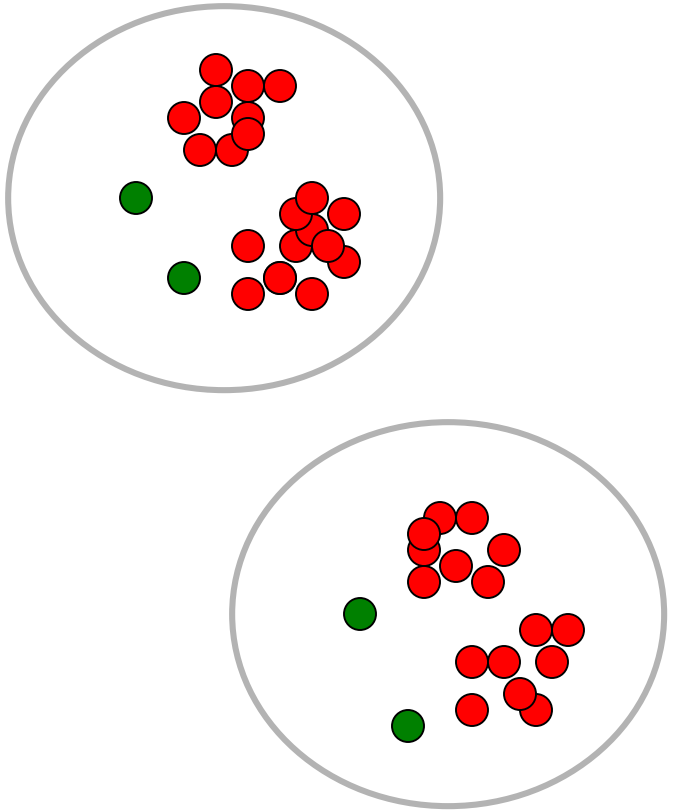


Not amplified



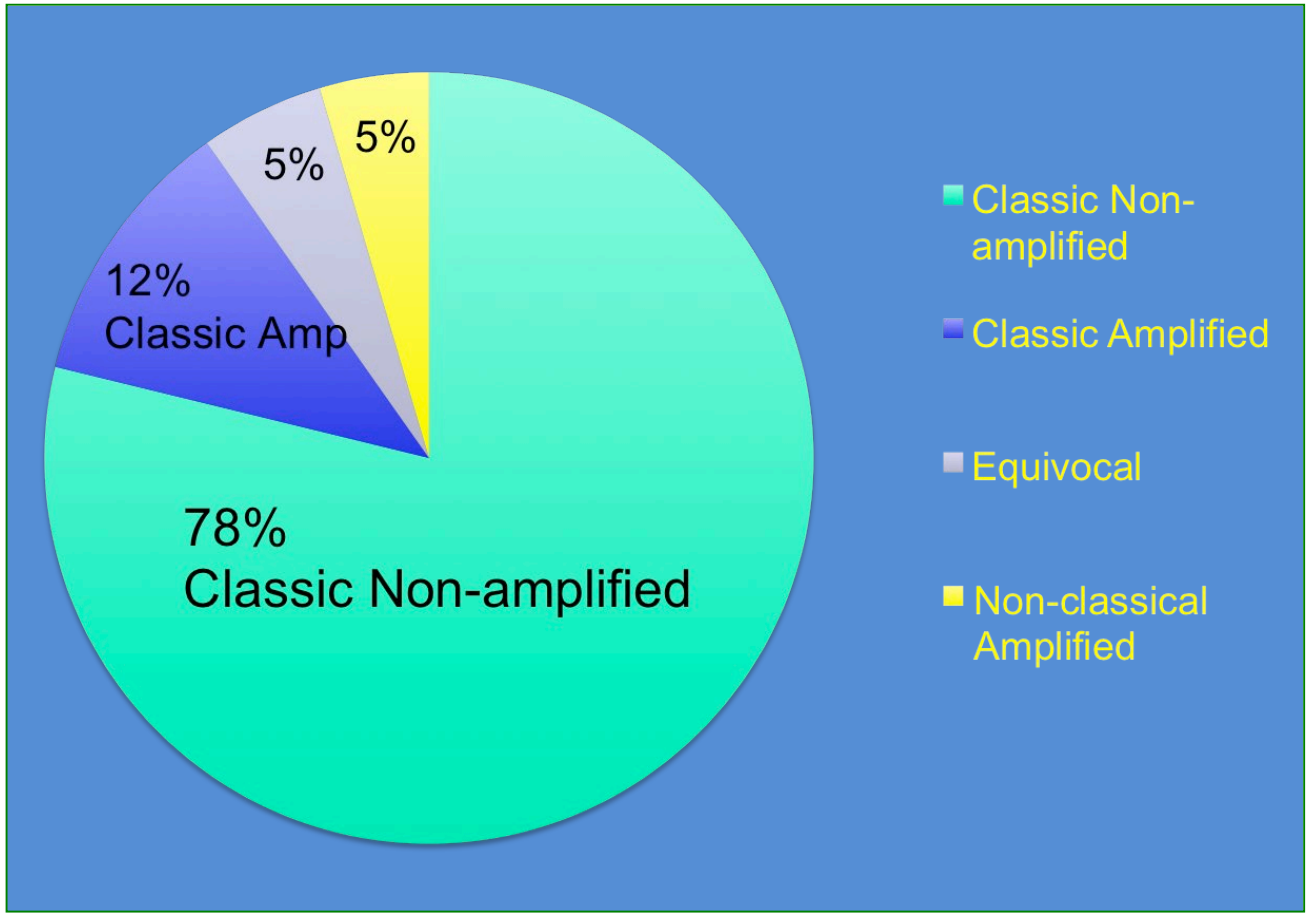
None respond to traditional HER2 directed therapy

Amplified



Many respond to traditional HER2 directed therapies

~90% of all breast cancers have classical results



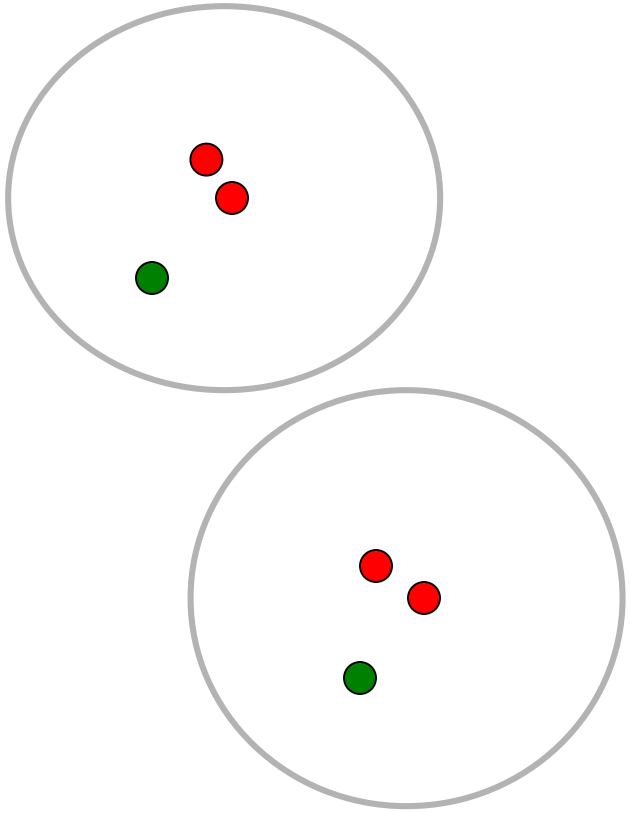
2018 update to ASCO/CAP HER2 guidelines addresses the remaining 10%

Equivocal and non-classical results
Groups 2, 3, 4

Ballard et al. Mod Pathol 30:227-235, 2017

Wolff A. et al. Archives of Path Lab Med. doi: 10.5858/arpa.2018-0902-SA, 2018.

Group 2: ratio ≥2.0 HER2 CN <4.0
previously classified as Positive (2013)



cases with loss of CEP17 ("monosomy")

→Ratio is ≥2 due to loss of CEP17

→no gain in HER2 CN

Now **NEGATIVE** (with IHC 0, 1+ or 2+)*

*Comment: evidence is limited on efficacy in this group

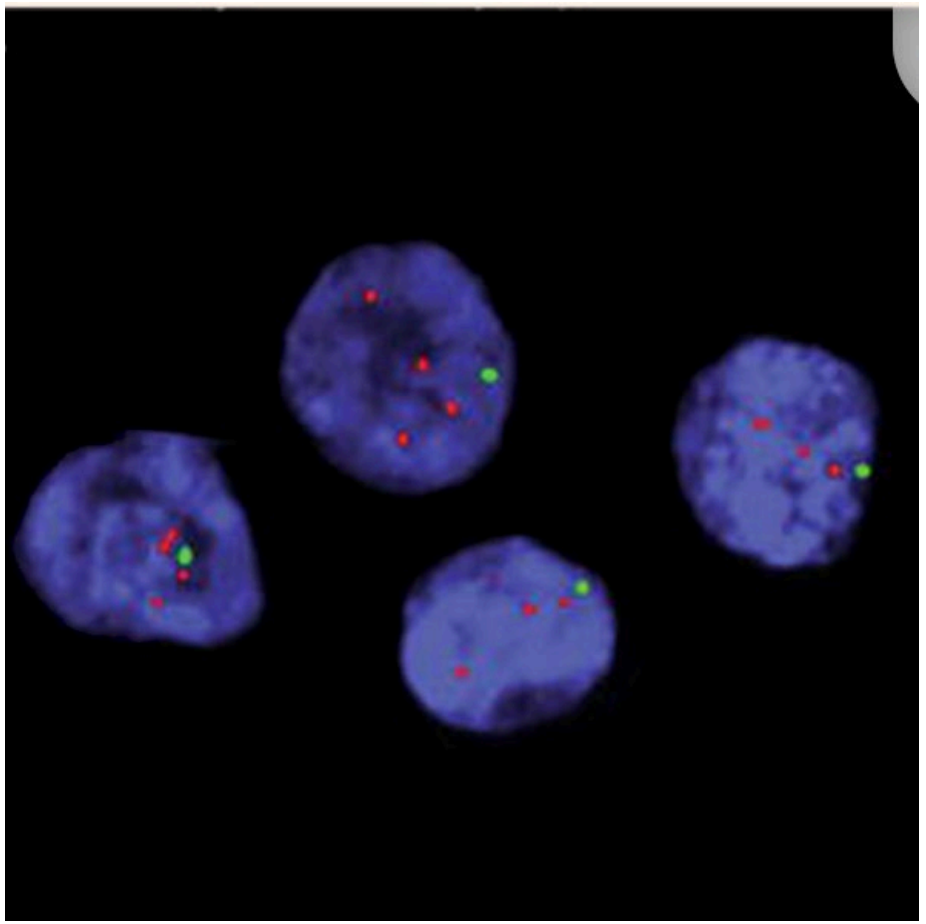
3+ IHC→ POS

>10,000 cases with central review testing for BCIRG there were NO Group 2 cases that were 3+

(Press MF et al, Archives Pathol and Lab Med, 2016)

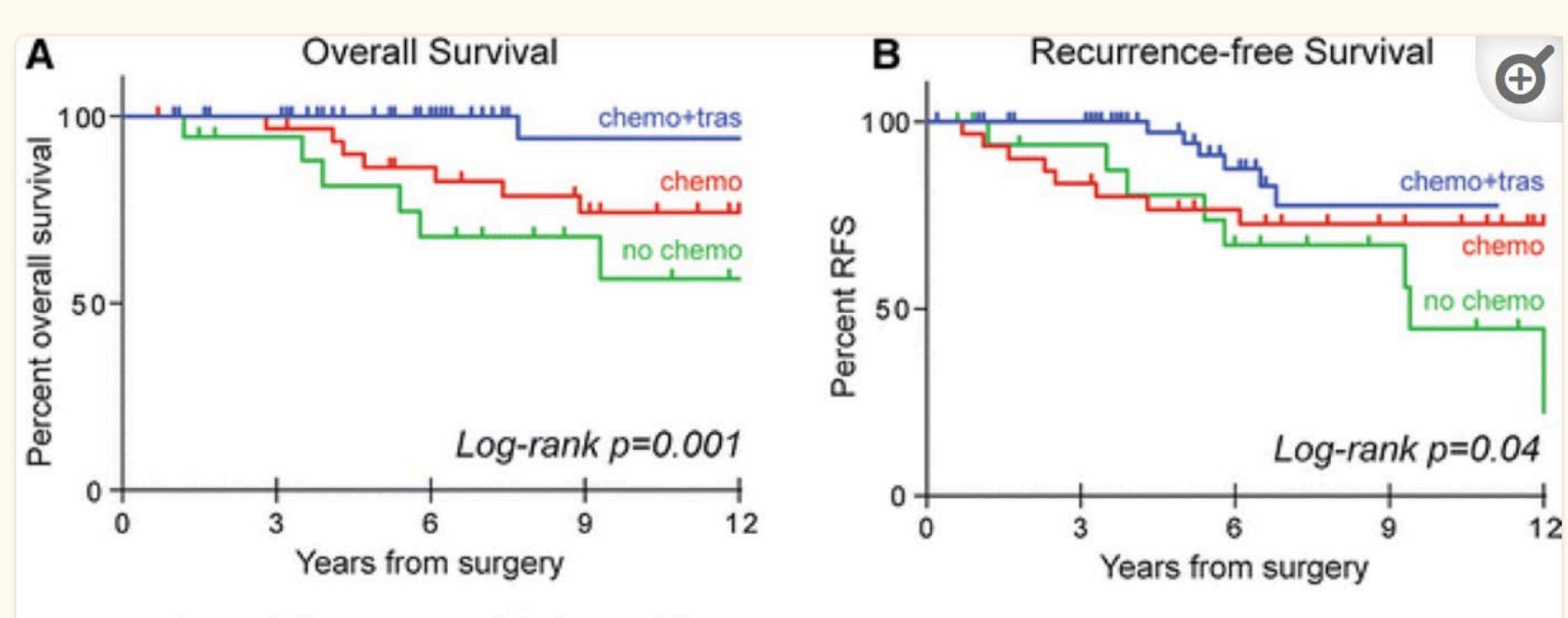
Controversy: Do Group 2 (m17) Respond to Targeted Tx?

- Reasonable question since the elevated ratio due to loss of CEP17 rather than gain of HER2
- These cases are rare so difficult to determine response to HER2-directed therapy.
- Retrospective review of 99 women with m17 to look at response to tx
  - CEP17 signal of <1.5 per nucleus and a *HER2*/CEP17 ratio of ≥2.0



Page DB, Wen H. et al. *Monosomy 17…*Breast Cancer Res Treat. 2018 Jan; 167(2): 547–554.

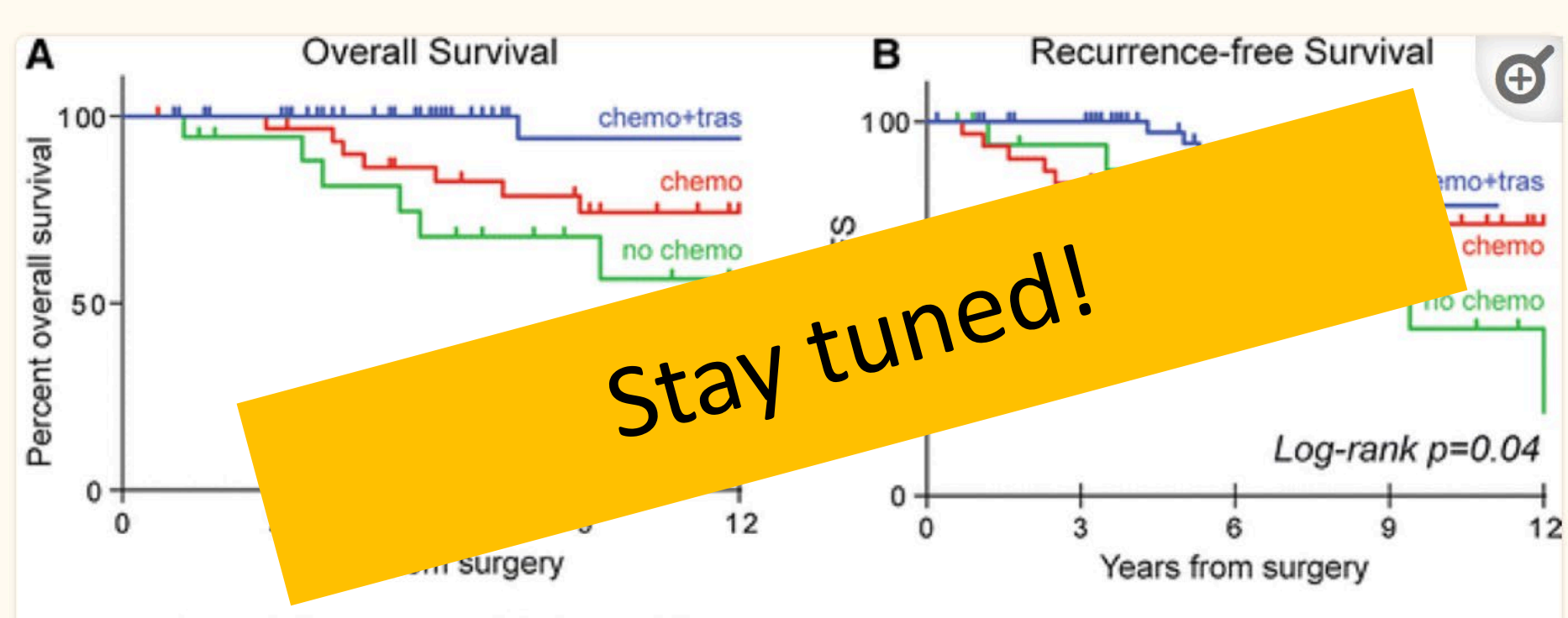
Monosomy 17 cases do appear to benefit from trastuzumab



51% trastuzumab plus chemotherapy
31% chemotherapy alone
8% got no chemotherapy

Difference held up in low stage and in just ER/PR pts as well
Similar survivals to those seen in large ph3 clinical trials for HER2+ BC

Monosomy 17 cases do appear to benefit from trastuzumab



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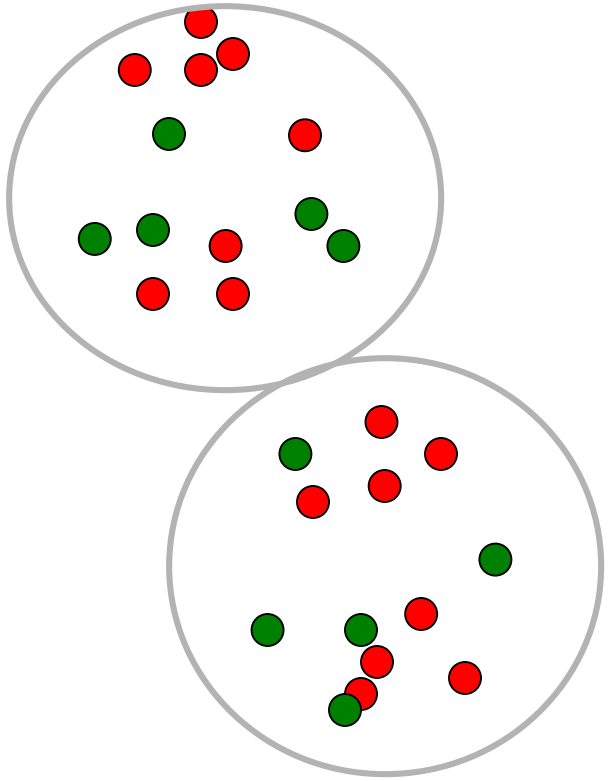
Difference held up in low stage and in just ER/PR pts as well
Similar survivals to those seen in large ph3 clinical trials for HER2+ BC

Group 3: HER2 CN ≥6 but ratio <2
previously classified as Positive (2013)



CEP17

HER2

CEP17 co-amplification (“polysomy”)

Positive by HER2 CN ≥6

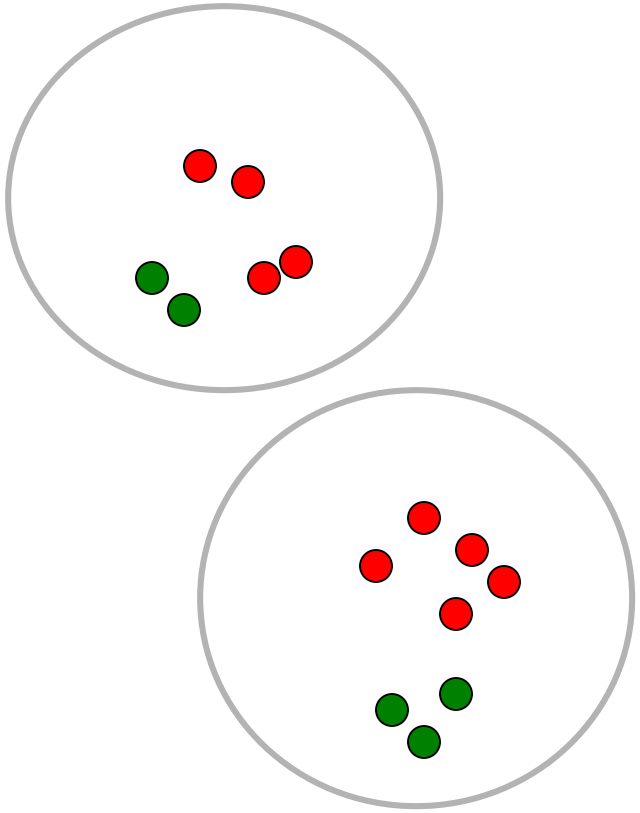
Ratio <2

Now **POSITIVE (with IHC 2+/3+)**

NEGATIVE (with IHC 0/1+)*

*Comment: There is insufficient data because these cases were not included in the initial clinical trials.

Group 4: ratio <2.0 with HER2 ≥4.0 and <6.0
previously classified as Equivocal (2013)



- CEP17
- HER2

Slightly elevated HER2 CN (4-6)

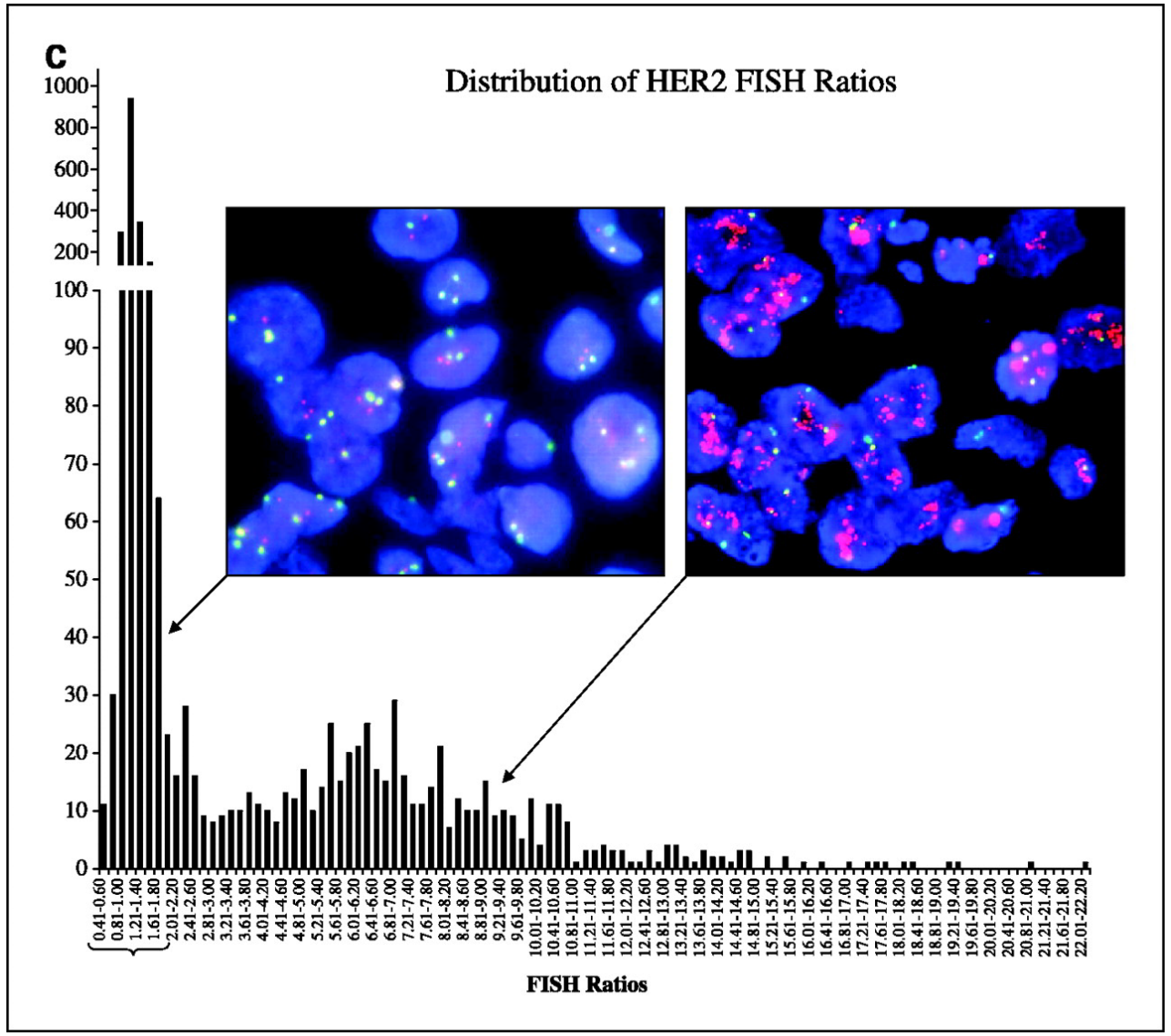
Ratio is <2

5% of all cases

NEGATIVE (with IHC 0/1+ or 2+)*

Comment: uncertain whether any benefit if not 3+.

Cutoff point for HER2 Positive FISH



Biology is a continuum.

Some breast cancers are at the threshold between clearly positive and clearly negative.

Retesting is likely to yield conflicting results

2018 Update is closing the gap

More tx response data needed for Groups 2-4

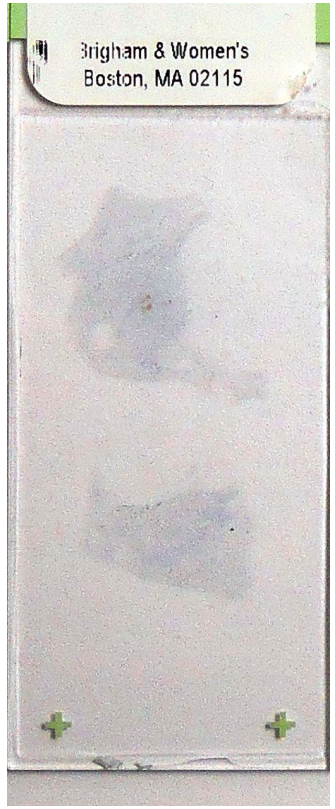
What do we do about heterogeneity?

How should we define and report HER2 heterogeneity?

Want to identify cases with distinct clustered subpopulations with different HER2 gene status.

Carcinomas are classified as HER2 positive if >10% of the cancer is positive (IHC/ISH).

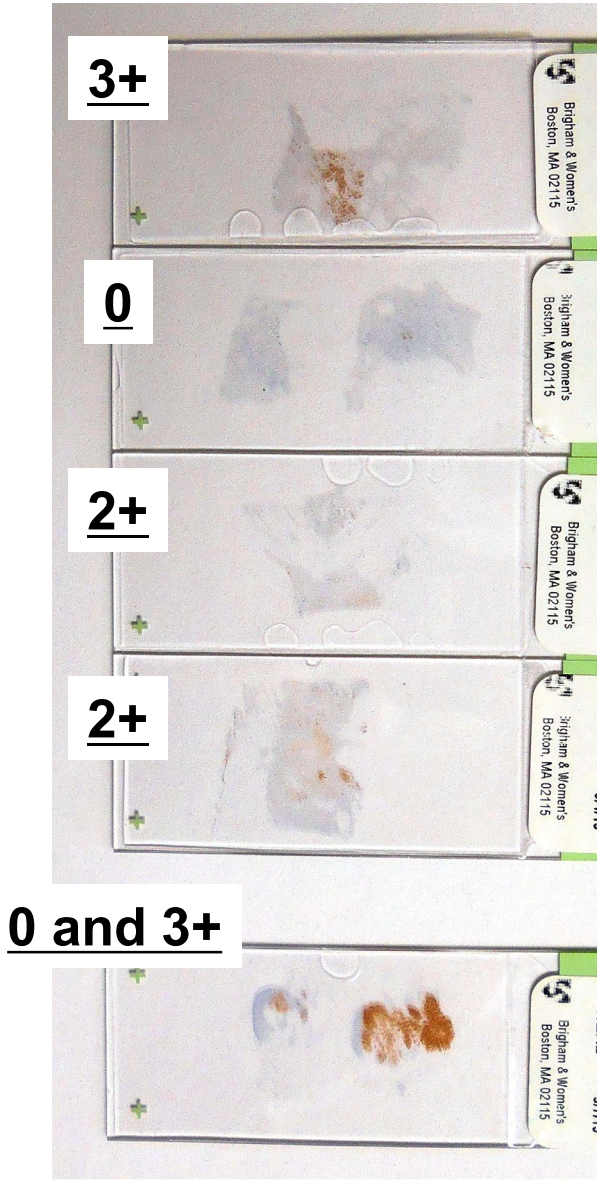
According to current guidelines, the cells must be “observed in a **homogeneous and contiguous** population” (i.e. not scattered)



breast

Lymph node

Discrete contiguous second population of cells with IHC 3+



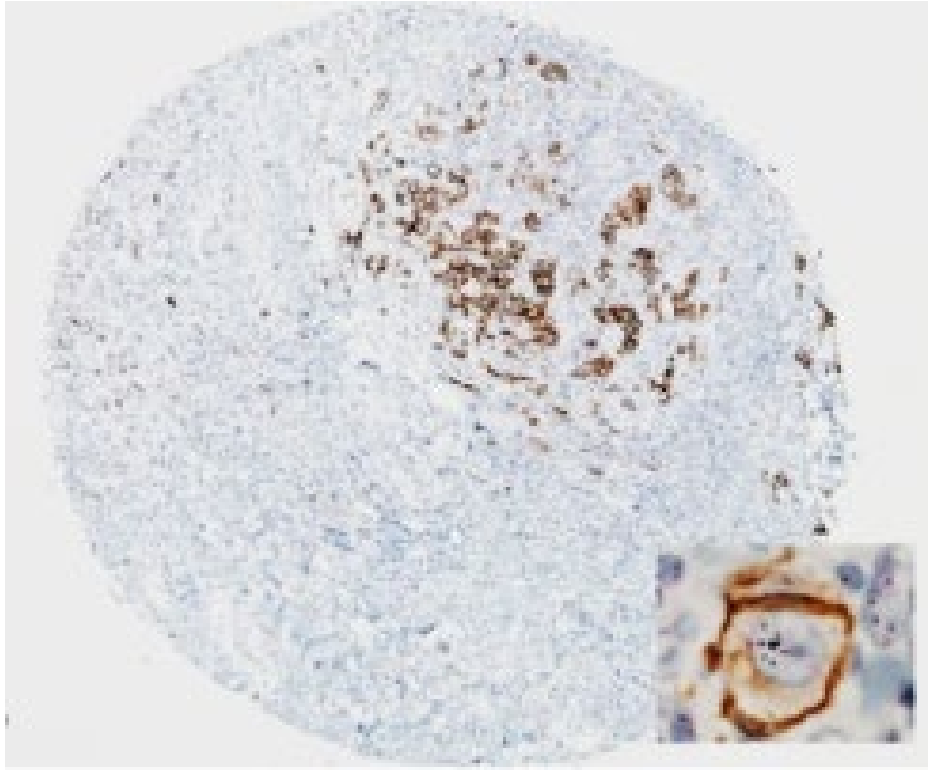
Four blocks of primary carcinoma

Lymph node metastases

Cancers with discrete identifiable subpopulations of HER2 positive cells are rare, <5% of total

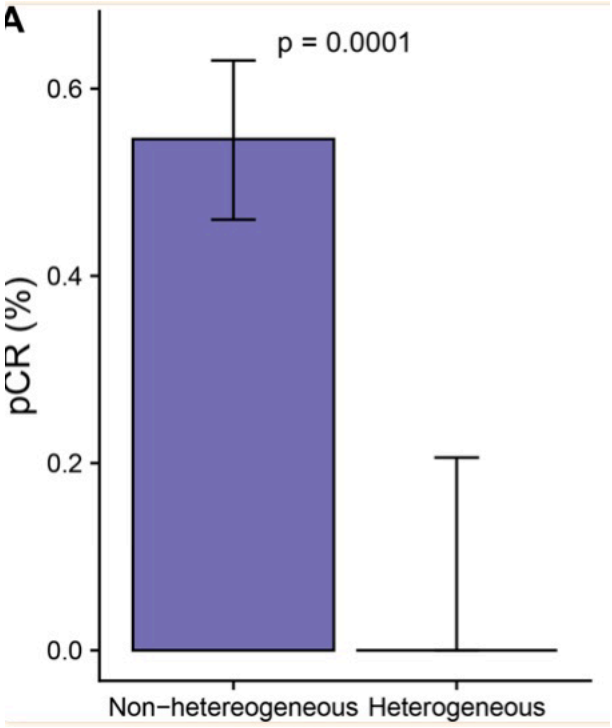
Discrete second population may be a source of “resistant” disease

Oncologists may wish to tailor therapy to include both the positive and negative areas, especially if triple negative.



Nitta et al. A gene-protein assay for HER2. Diag Pathol 7:60, 2012

HER2 heterogeneity predicts resistance to HER2 directed tx



Phase II study of HER2 monotx (TDM1 and pertuzumab) in HER2 positive cancers

Six cores two areas; 10% had ”heterogeneity” (16/157)

1)HER2 positivity by FISH in > 5% and < 50% of tumor cells (i.e., old CAP guideline)

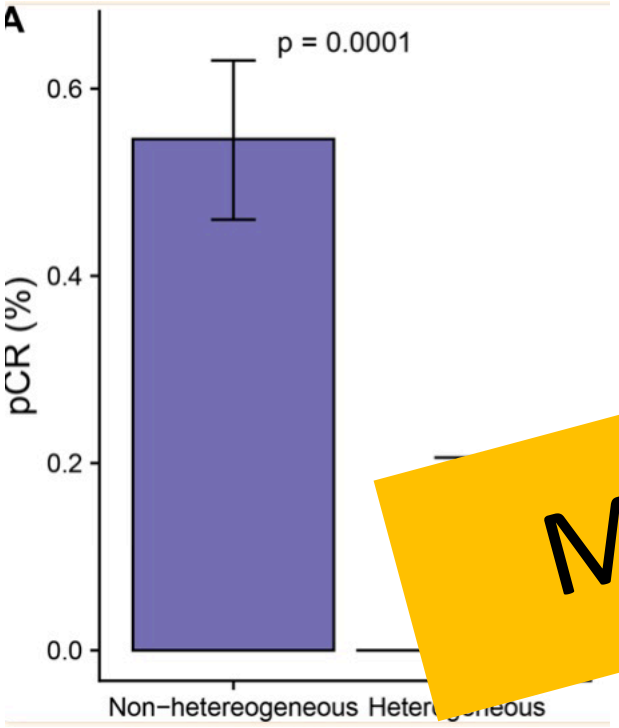
2) an area of tumor that tested HER2 negative.

49% of pts had a pCR

No pCR observed in patients with HER2 heterogeneity

*Metzger Filho et al. C*ancer Discov. 2021 Oct;11(10):2474-2487

HER2 heterogeneity predicts resistance to HER2 directed tx



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2)… …ative.

…a pCR

No pCR observed in patients with HER2 heterogeneity

More on this to come!

Metzger Filho et al. Cancer Discov. 2021 Oct;11(10):2474-2487

What about HER2 low??

Correlation between IHC/FISH and response to targeted tx?

Emerging evidence that pts with IHC 3+ tumors benefit more than those that are IHC 2+ and amplified.

IHC 3+ cases almost always show high level gene amplification, whereas the IHC 2+ cases often show low level amplification and/or heterogeneity

Response to NACT plus anti-HER2 targeted therapy is more often seen in tumors with higher *HER2/CEP17* ratios and higher *HER2* gene copy number

Krystel-Whittemore et al Breast Cancer Res. Treat. **177**, 61–66 (2019).
Meisel et al. Clin. Breast Cancer **20**, 19–24 (2020)
Veeraraghavan et al. *Ann. Oncol.* **30**, 927–933 (2019).

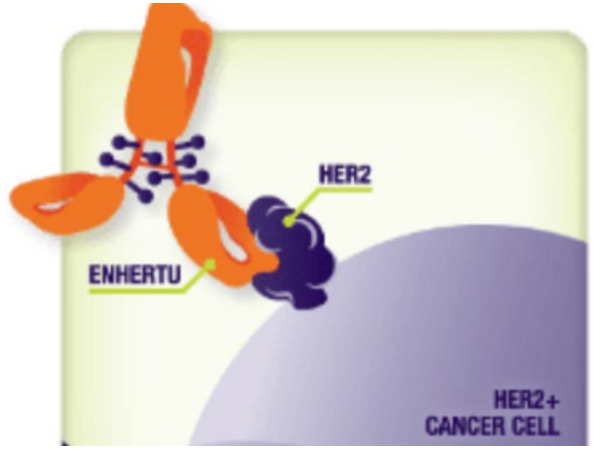
What about HER2 low expressing tumors?

HER2 low defined as 1+ or 2+ IHC with negative FISH

Some recent studies have shown that HER2 low cancers may still benefit from **antibody-drug conjugates**

trastuzumab-emtansine (T-DM1)
trastuzumab-deruxtecan (T-DXD)

enough to direct the drug to HER2 receptors in tumors that aren't HER2 driven/amplified

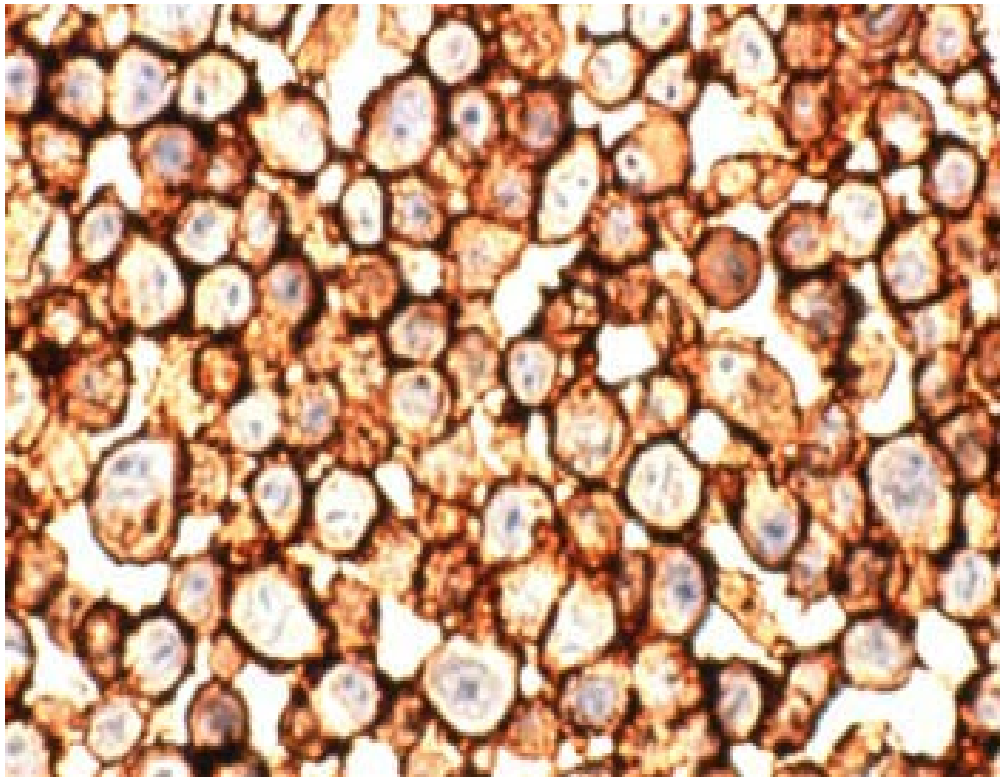


Enhertu.com

Antibody-drug conjugates are a class of drugs that consist of antibodies that carry a chemotherapy payload

Destiny-Breast04: phase 3 trial of ADC trastuzumab deruxtecan for HER2 low in adv/met BC. *Feb 2022*

Immunohistochemical evaluation of HER2



Many different antibodies to HER2

Strong 3+ positive staining with all HER2 antibodies is associated with amplification by FISH

Differing sensitivities and specificities, especially in the intermediate ranges

IHC is subject to pre-analytical, analytical and interpretive variables

Can pathologists even do this (distinguish 0 from 1+)?

- The distinction between HER2 IHC 0 and 1+ is arbitrary with high discordance rates among laboratories
- Some labs report these as **NEGATIVE 0 TO 1+**
- Recent study based on CAP surveys looked at current HER2 IHC assays
  - → pathologists cannot distinguish IHC scores 0 vs 1+
  - → only 26% of cases with 90% concordance

Fernandez et al (Rimm). JAMA Oncol. February 3, 2022

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  - →only 26% of cases with 90% concordance

NO!!

Fernandez et al (Rimm). JAMA Oncol. February 3, 2022

HER2: Summary

At least 90% of breast cancers can be easily classified into positive and negative groups corresponding to probability of tmt response.

False positive results on IHC have big consequences. Most often results from overstaining or overinterpretation of cases with moderate immunoreactivity. When in doubt, back down to 2+ and get ISH.

2018 Update reclassifies unusual types of FISH results incorporating corresponding IHC.

HER2: Summary

The only type of heterogeneity we are really concerned about is a discrete, contiguous population of HER2 positive tumor cells in a HER2 negative background.

→Rare: we report HER2 status for both populations with %

Pathologists cannot reliably distinguish HER2 low cases (1+ and 2+) from 0 with current assays.