Application of Advances in Molecular Testing in the Clinical Management of Breast Cancer Patients

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Disclosures

- I have no relevant conflicts of interest to disclose.
- I run clinical trials with many pharmaceutical companies
- The views expressed here are mine alone and may not represent the views of the University of Utah, the State of Utah, or the Huntsman Cancer Institute

Objectives

- Recognize predictive and prognostic molecular markers in breast cancer
- Choose appropriate patients for gene expression profiling of breast tumors
- Understand the impact of the definition of tumor subtype on treatment decisions

Case 1

- A 55 year-old woman has a screening mammogram, which shows a suspicious speculated asymmetry in the right breast.
- Biopsy shows a grade 1, ER 95%, PR 90%, HER2 1+ invasive ductal carcinoma
- She has a bilateral mastectomy (for no good reason) and has a 1.8cm tumor that is grade 1 and 1 of 4 sentinel lymph nodes has a micrometastasis.
- An Oncotype was sent.
- Was the Oncotype appropriate?

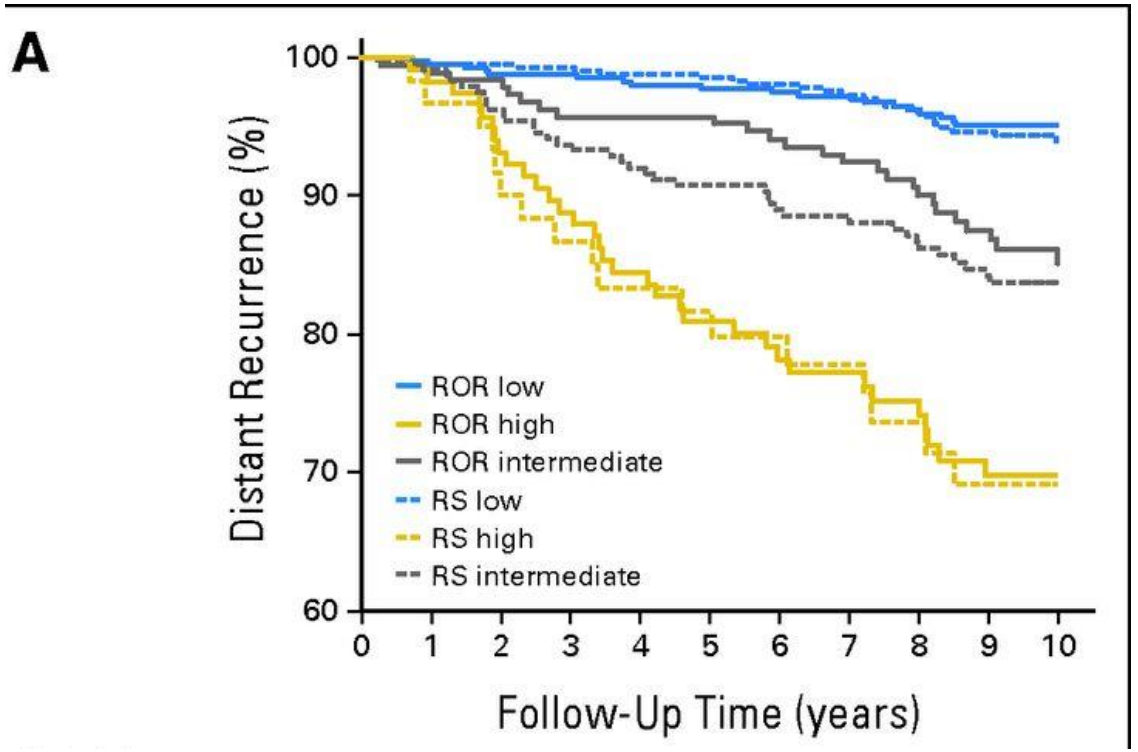
Features of gene expression tests

Feature	Oncotype	MammaPrint	Prosigna/ROR	Breast Cancer Index
Number of Genes	21	70	50	7
Able to be done on FFPE	Yes	Yes	Yes	Yes
Output	Score (0-100)	Binary (High/Low)	Score (0-100)	Score (0-10)
Population	ER-positive, HER2-negative Node negative Node positive	<4 lymph nodes	ER-positive Node negative or node positive	ER-positive, node negative
Incorporates clinical variables	Calculator on website integrates age, size, and grade	No	Score incorporates tumor size	No
Predictive of chemotherapy benefit	Yes	Yes	Unknown	Unknown

Gene expression tests give similar data

B.

Two-way contingency table	**Recurrence Score**	
	Low or Int. (# of patients)	High
70-gene predictor		
Good	81	34
Poor	22	158
Statistics for two-way contingency table analysis		
p-value†	<0.001	
Cramer's V††	0.60	



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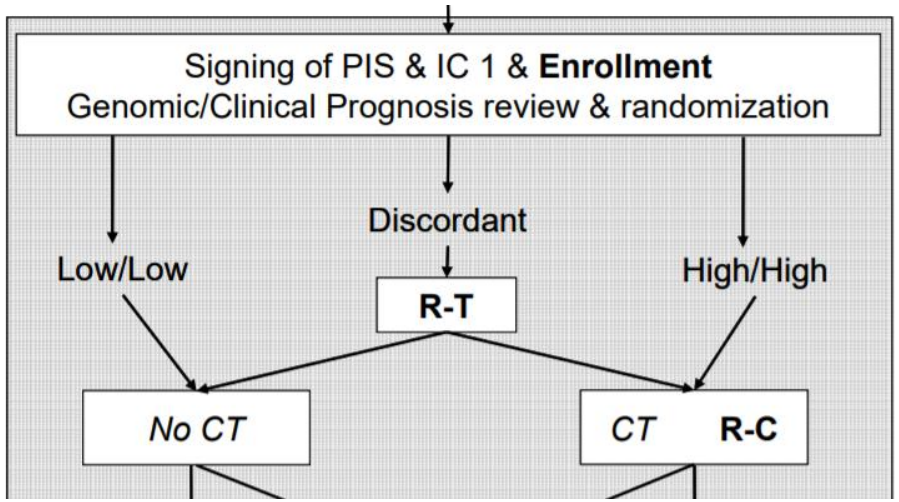
N Engl J Med. 2006 Aug 10;355(6):560-9.

JCO **August 1, 2013** vol. 31 no. 22 **2783-2790**

Prospective Validations

- MINDACT
  - Validation of Mammoprint
  - Randomized trial of chemotherapy vs no chemo for people with high clinical risk but low genomic risk OR low clinical risk but high clinical risk

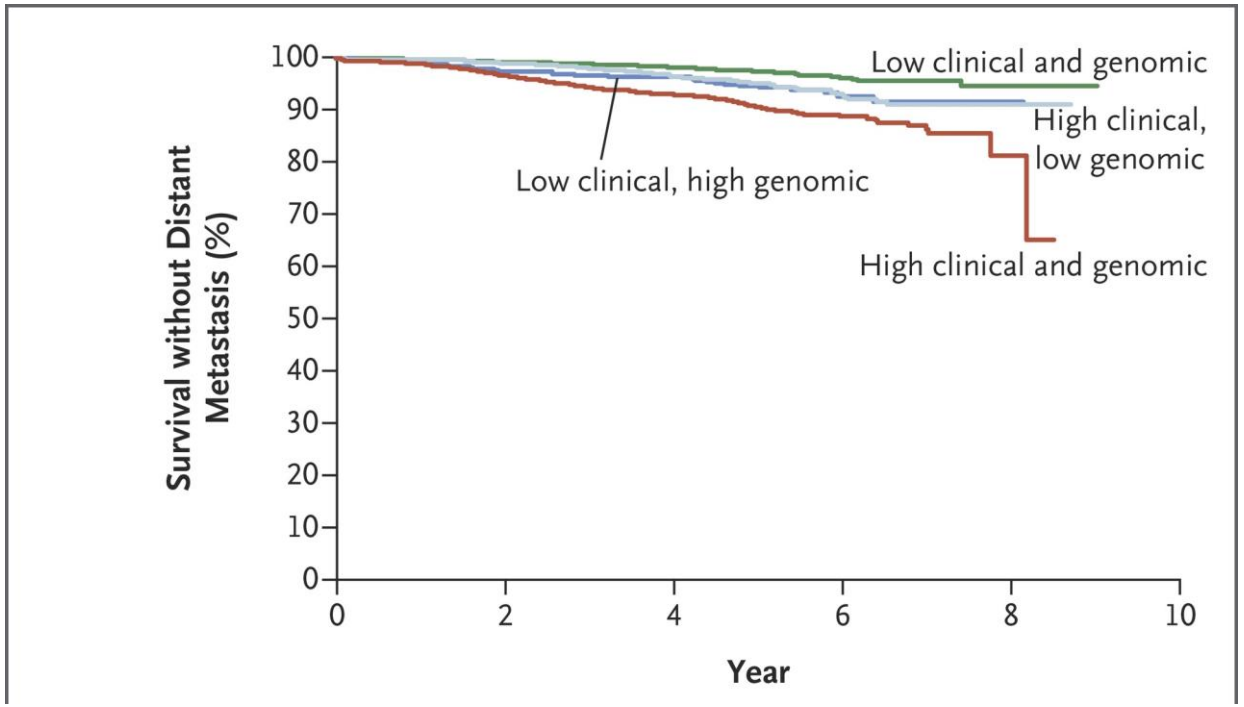


ER status	HER2 status	Grade	Nodal status	Tumor Size	Clinical Risk in Mindact
ER positive	HER2 negative	well differentiated	N-	≤ 3 cm	C-low
				3.1-5 cm	C-high
			1-3 positive nodes	≤ 2 cm	C-low
				2.1-5 cm	C-high
		moderately differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high

Cardoso F et al. N Engl J Med 2016;375:717-729

Prospective Validations

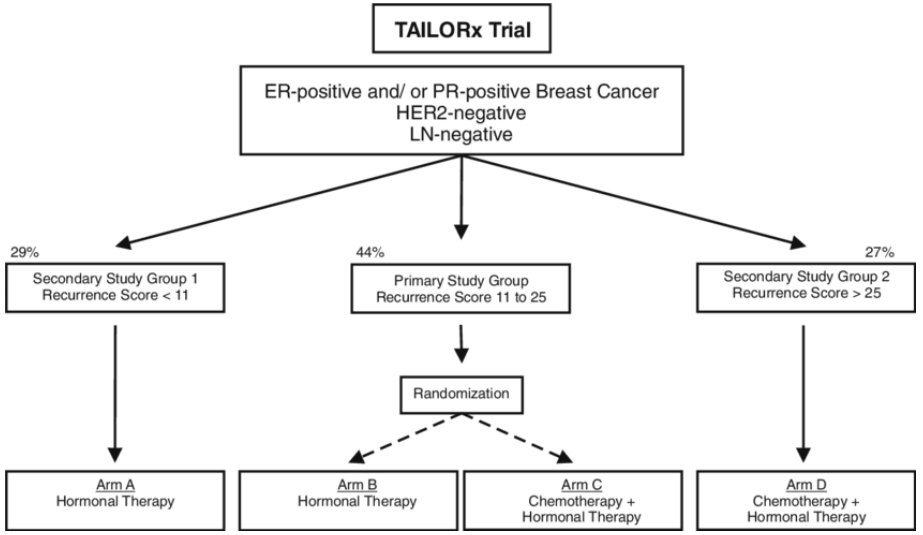
- MINDACT
  - Chemo only benefits people with high clinical and genomic risk
  - People with clinical low risk cancers don't need gene expression profiling



Cardoso F et al. N Engl J Med 2016;375:717-729

Prospective validations

- TAILORx
  - Validation of Oncotype for node negative cancers
  - No chemotherapy if Oncotype Recurrence Score < 11
  - Randomized to chemo or no chemo if Oncotype Recurrence Score 11-25



Prospective Validations

- TAILORx
  - Oncotype RS < 11
    - <1% distant recurrence at five years without chemo
  - Oncotype RS 11-25
    - No benefit from adjuvant chemotherapy in entire population
    - Benefit seen in some subgroups:
      - High clinical risk by MINDACT criteria
      - Low clinical risk but age <50 and Oncotype recurrence score 21-25

Table 3. Event Rates at 5 Years, According to Histologic Grade.*

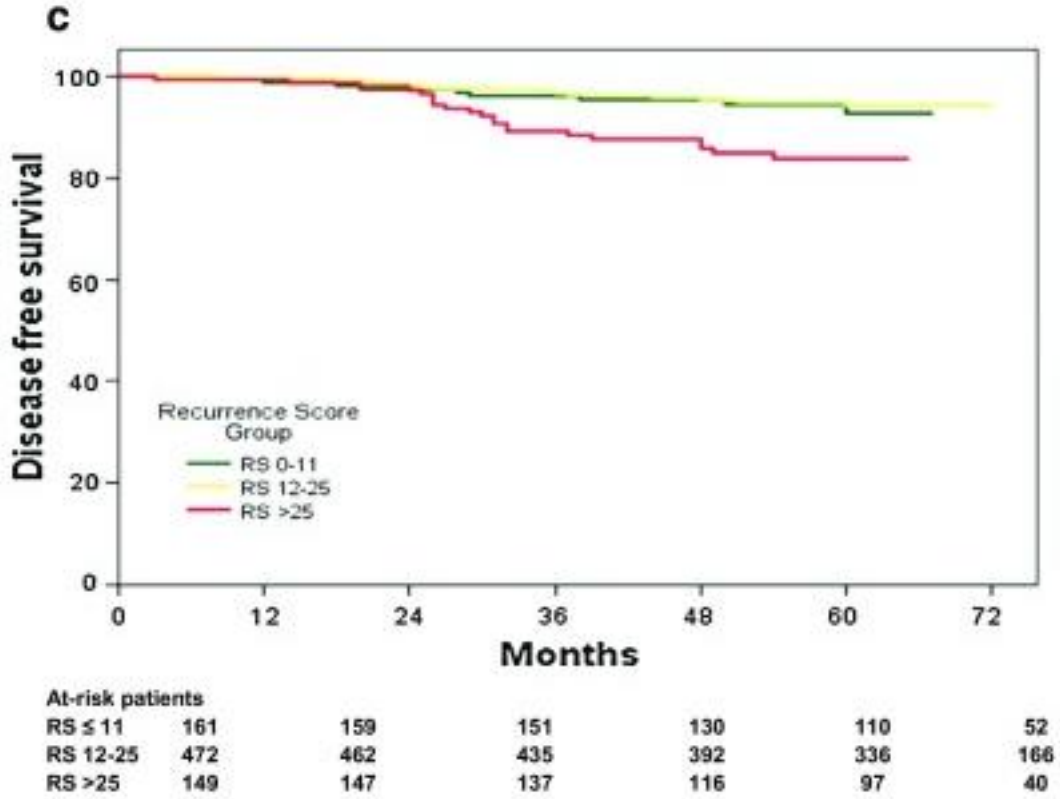
Tumor Grade	Invasive Disease–free Survival (95% CI)	Freedom from Distant Recurrence (95% CI)
All grades	93.8 (92.4–94.9)	99.3 (98.7–99.6)
Low grade	95.8 (93.5–97.3)	99.8 (98.3–100)
Intermediate grade	93.6 (91.7–95.1)	99.0 (98.0–99.5)
High grade	91.3 (83.9–95.4)	100 (NC–NC)

N Engl J Med 2015; 373:2005-2014

N Engl J Med 2019; 380:2395-2405

Prospective Validations

- German PlanB
  - Validation of Oncotype for node positive breast cancers
  - Recurrence score <11 treated without chemotherapy even if N1
  - 95% disease free survival at 5 years
- RxPonder
  - US validation of Oncotype for node positive cancers
  - Results pending



Breast Cancer Res Treat. 2017; 165(3): 573–583.

Bottom line

- Gene expression profiling is not needed if:
  - Low clinical risk by MINDACT criteria
  - N2-3
  - T3-4
  - Comorbidities preclude chemotherapy

Case 1

- A 55 year-old woman has a screening mammogram, which shows a suspicious speculated asymmetry in the right breast.
- Biopsy shows a grade 1, ER 95%, PR 90%, HER2 1+ invasive ductal carcinoma
- She has a bilateral mastectomy (for no good reason) an has a 1.8cm tumor that is grade 1 and 1 of 4 sentinel lymph nodes has a micrometastasis.
- An Oncotype was sent.
- Was the Oncotype appropriate?

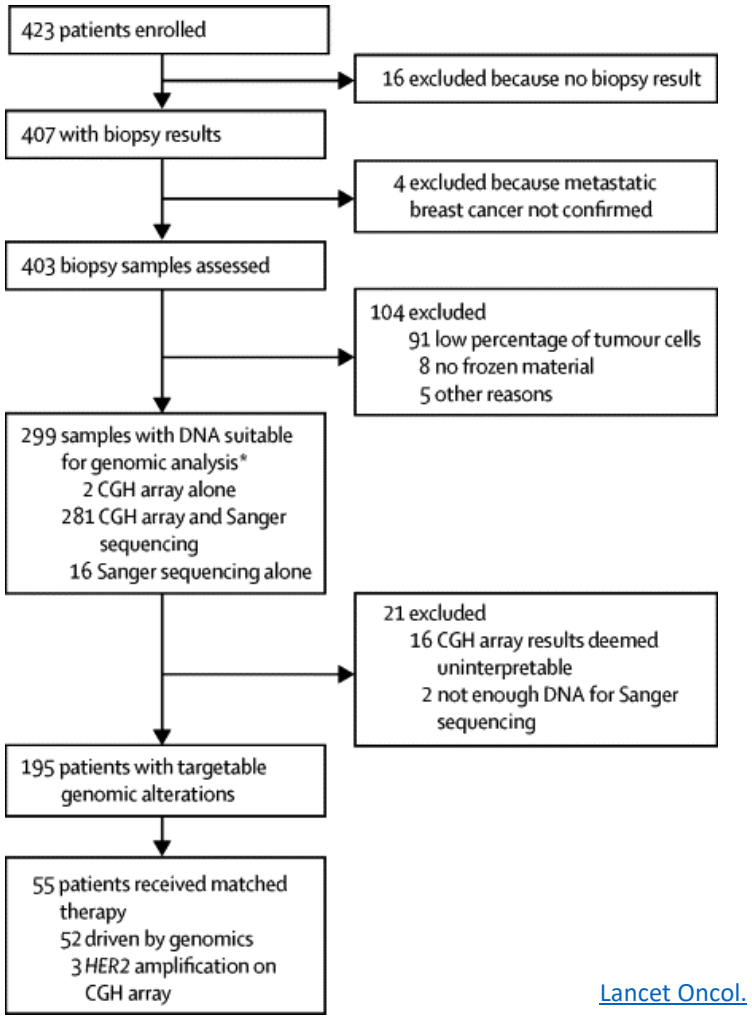
Case 1 continues

- It is 5 years later and the patient is now 60 years old and presents with abdominal pain. CT scans show lytic bone lesions and two liver lesions. Biopsy of a liver lesion shows metastatic ductal carcinoma that is still ER 95%, PR 90%. She is started on anastrozole and palbociclib. Her cancer remains stable for 22 months and she then has enlargement of both liver lesions. The oncologist requests a new liver biopsy to be sent for next-generation sequencing.

- What is the chance that the next-generation sequencing result will change the next step in therapy?

Molecular Profiling to Determine Treatment

- SAFIR01/UNICANCER trial
- Feasibility study to see how often targeted treatments could be identified for women with metastatic breast cancer



Lancet Oncol. 2014 Mar;15(3):267-74.

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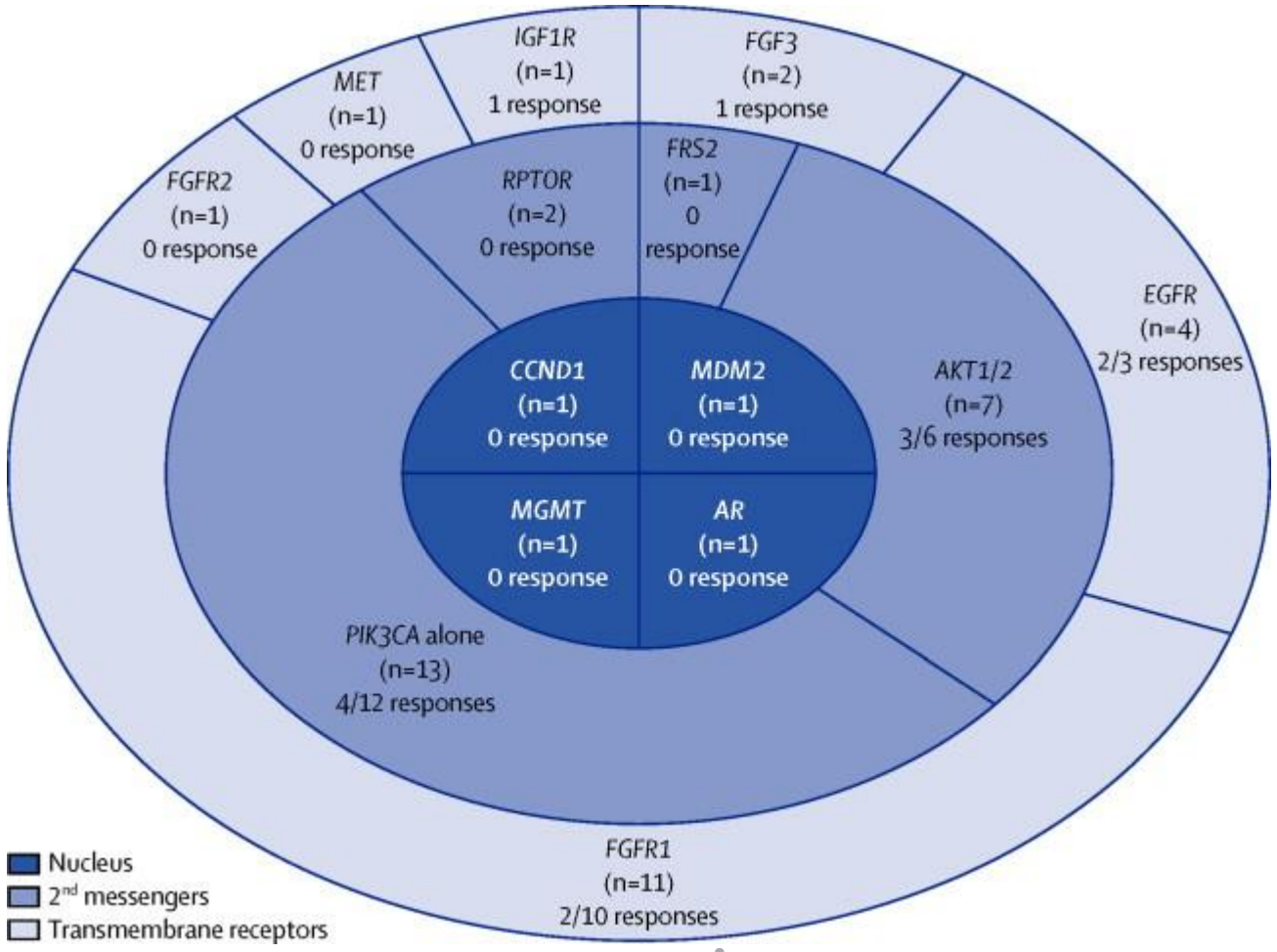
SAFIR01: A mixed success

- Issues with targeting somatic genetic alterations
  - Context matters
  - Current drugs are suboptimal
  - 50% of women don't have targetable alterations



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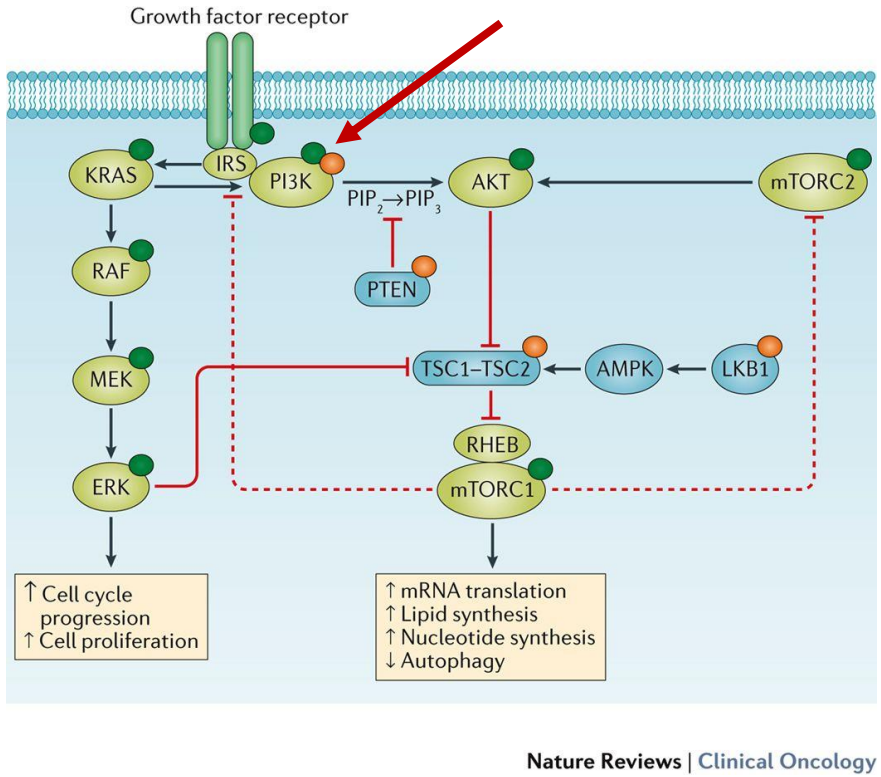
Targetable mutations in breast cancer

- PREDICT
  - UCSD cohort of metastatic cancer patients sequenced using NGS
  - 60 breast cancer patients
  - 45 were matched to treatments based on NGS
    - 33% DCR at 6 months compared to 21% for unmatched patients
  - However,
    - 20 of the matched patients were based on:
      - HER2 amplification
      - PIK3CA mutation
      - ESR1 mutation
    - Every breast patient with disease control at 6 months received anti-HER2 therapy, everolimus, or tamoxifen
      - All drugs already approved for breast cancer

Mol Cancer Ther. 2016 Apr;15(4):743-52. doi: 10.1158/1535-7163.MCT-15-0795. Epub 2016 Feb 12.

PIK3CA in breast cancer

- Mutated in ~40% of ER-positive primary breast cancers
- Alpelisib is an inhibitor of the alpha isoform of PI3K
- SOLAR-1 randomized trial
  - Addition of alpelisib to fulvestrant led in metastatic, ER-positive, HER2-negative, PIK3CA mutated breast cancer led to:
  - Median PFS 11 months vs 5.7 months
  - Minimal to no benefit if PIK3CA wild-type



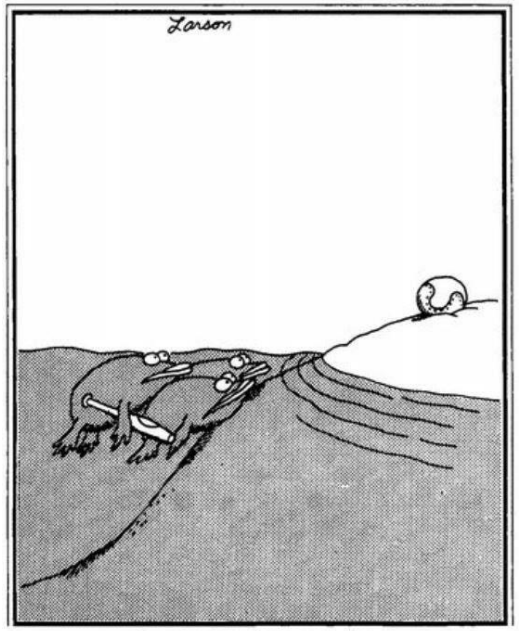
Nature Reviews Clinical Oncology **volume 15**, pages273–291(2018

Detecting PIK3CA mutations

- FDA approved companion diagnostic
  - Neogenomics
  - PCR based
- Tumor based NGS panels
- ctDNA or cfDNA
  - Sensitivity ranges 25-80%
    - Lower in bone only disease
  - Specificity > 95%

ESR1 mutations in breast cancer

- Activating mutations in the estrogen receptor
- Rare (1-10%) in primary breast cancers
- Decreases PFS with aromatase inhibitor but not SERD (fulvestrant)
- However,
  - Unknown effect when AI is combined with targeted agent
  - 40% of women treated with AI still have PFS over 1 year
  - Determination of effect of mutations is immature



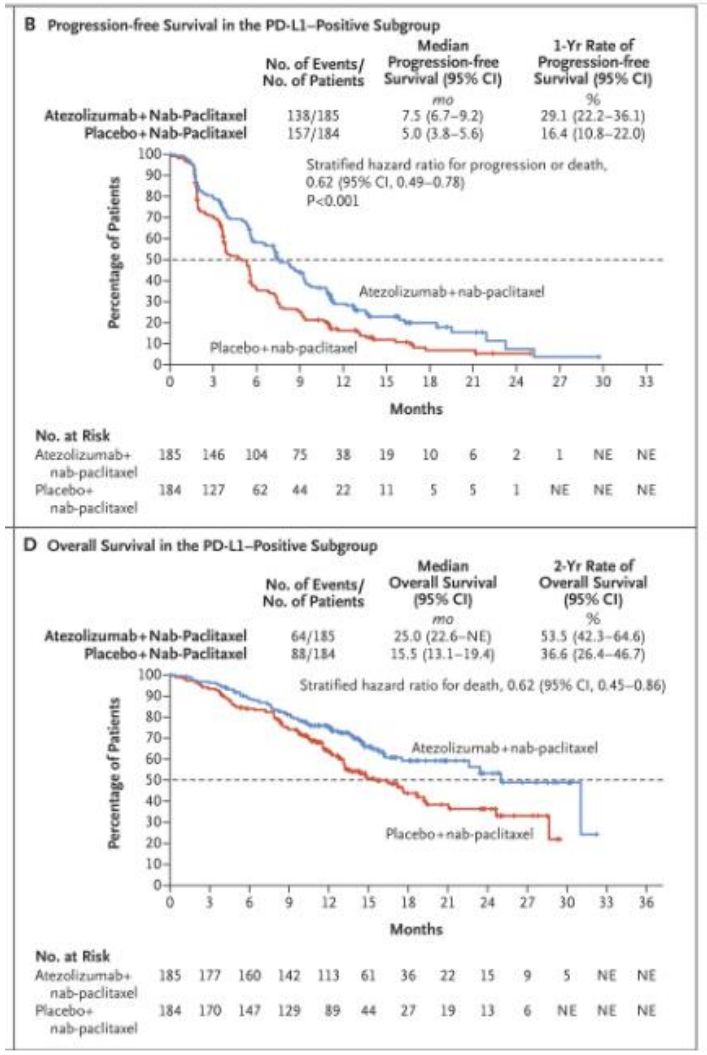
Great moments in evolution

Case 2

- A 57 year-old woman presents with a progressive right chest wall/breast mass and right arm swelling. PET/CT shows the chest wall mass, mediastinal adenopathy, and a mass in her deltoid muscle. Biopsy shows invasive ductal carcinoma, ER 0, PR 0, HER2 1+ (negative)
- What other immunohistochemistry is needed?

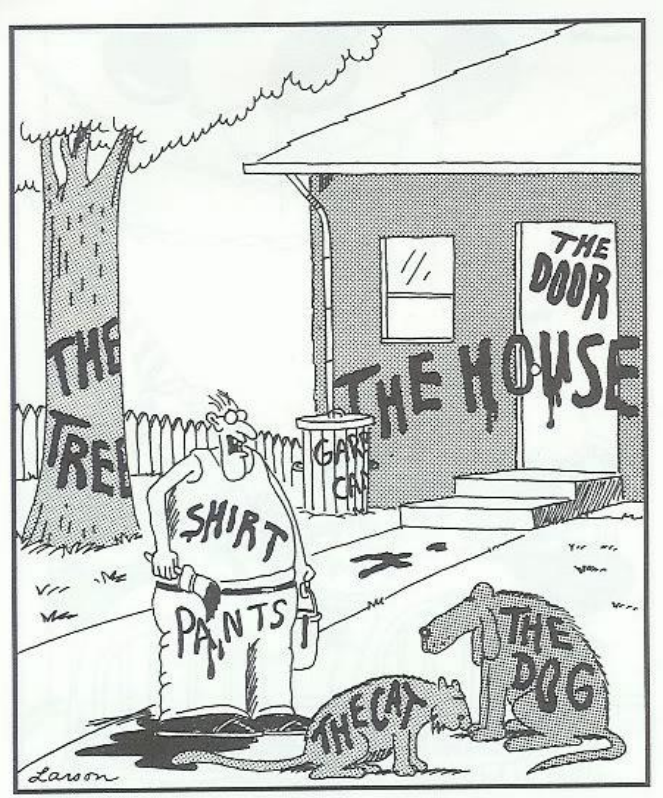
Immunotherapy in breast cancer

- IMpassion130
  - Metastatic triple negative breast cancer with no prior treatment for metastatic disease. (Systemic treatment for early stage disease allowed >12 months prior)
  - Atezolizumab (anti-PD-L1 antibody) +nab-paclitaxel vs nab-paclitaxel
  - In women with PD-L1 positive tumors, atezolizumab:
    - Increased PFS (HR 0.62, median 7.5 months vs 5 months)
    - May increase OS (HR 0.62, median 25 months vs 15.5 months)



PD-L1 positivity

- Assay and cutoff depend on tumor type and PD-L1 inhibitor
- For atezolizumab for TNBC
  - Ventana assay using SP142
  - TPS = Tumor infiltrating cells
  - Positive if >=1%
- Note:
  - Cutoff with this assay is different for urothelial cancer or NSCLC
  - Not validated on bone biopsies



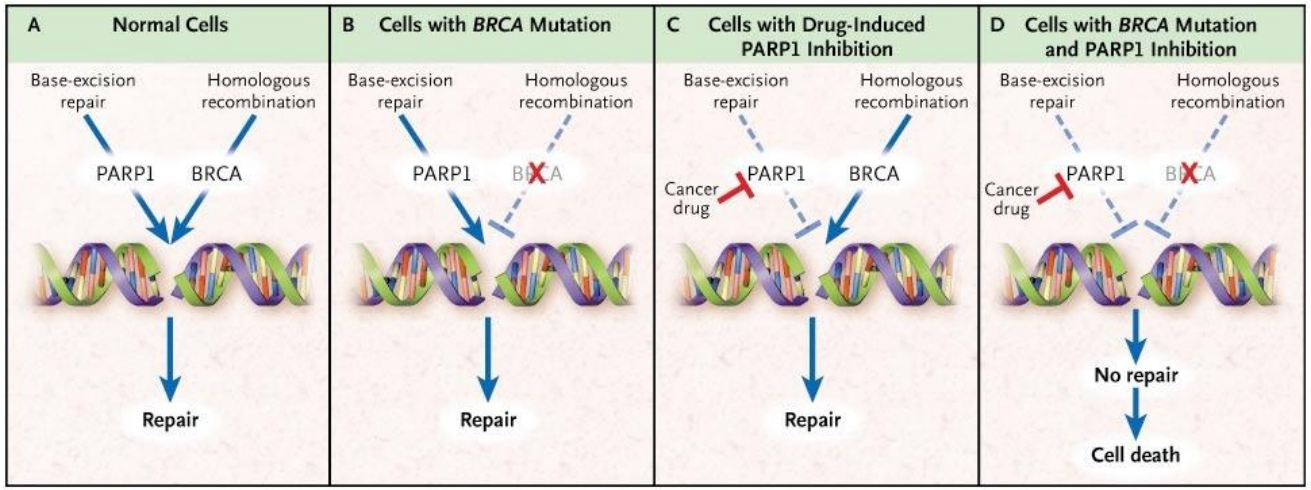
"Now! … *That* should clear up a few things around here!"

Case 2 continued

- A 57 year-old woman presents with a progressive right chest wall/breast mass and right arm swelling. PET/CT shows the chest wall mass, mediastinal adenopathy, and a mass in her deltoid muscle. Biopsy shows invasive ductal carcinoma, ER 0, PR 0, HER2 1+ (negative)
- Her tumor is PD-L1 positive, so she is treated with nab-paclitaxel and atezolizumab for 12 months.
- Although the tumors in the chest wall and deltoid originally shrank, they are now growing again.
- The oncologist is considering using olaparib rather than chemotherapy.
- What biomarker needs to be tested for olaparib?

PARP inhibitors

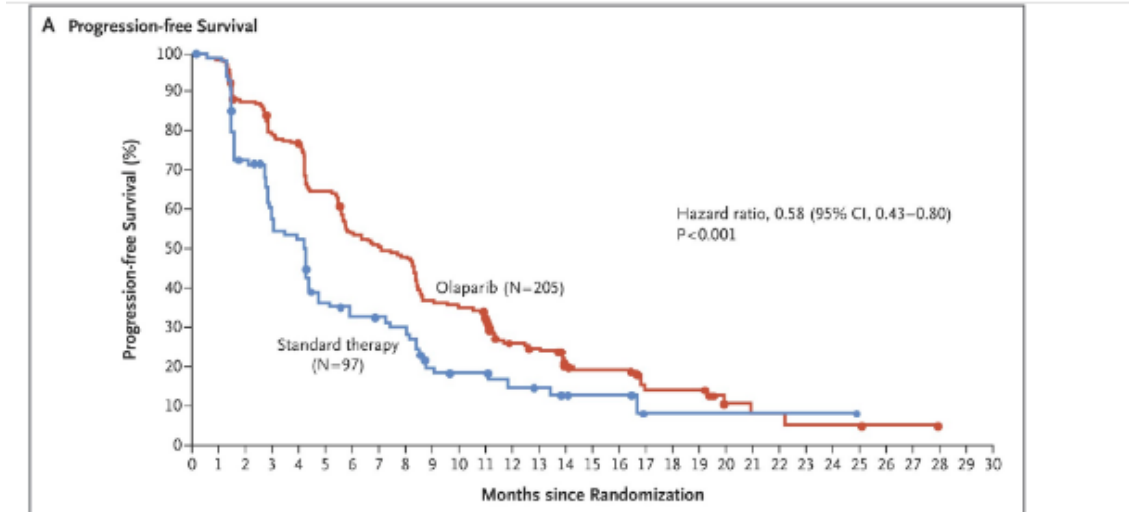
- PARP inhibitors target cells with defects in homologous recombination
  - Particularly germline BRCA1/2 pathogenic variants
- Approved in ovarian cancer
  - Olaparib, rucaparib, niraparib, talozoparib



N Engl J Med 2009; 361:123-134

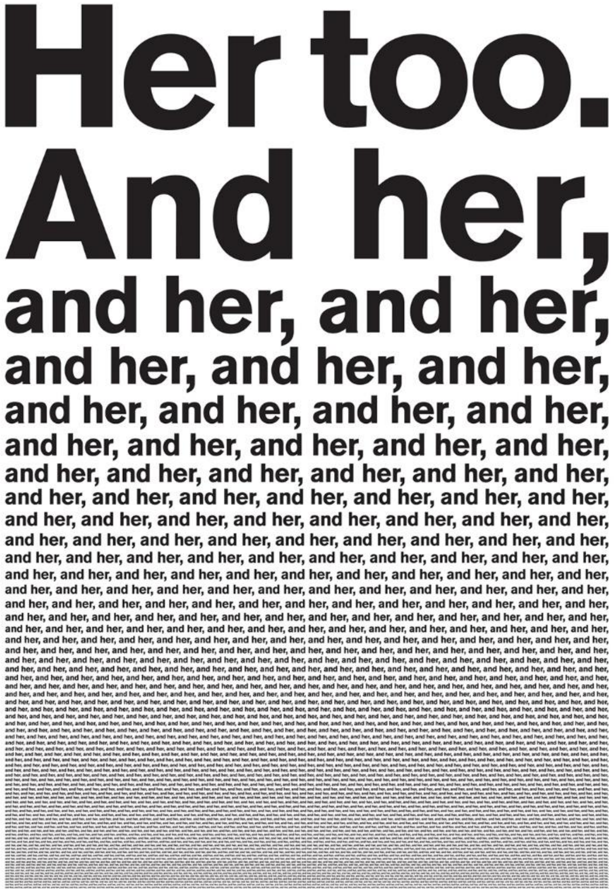
PARP inhibitors in breast cancer

- OlympiAD
  - Randomized trial of olaparib vs chemotherapy
  - Metastatic breast cancer
  - Germline BRCA1 or BRCA2 pathogenic variant
  - Response rate 60% with olaparib vs 29% with chemotherapy
- Open questions
  - Treatment of early stage disease?
  - Somatic BRCA1/2 mutations
  - Germline variants in other homologous recombination pathway genes



Case 3

- 37 yo woman palpates a mass in her right breast and notes pain and skin changes.
- Imaging shows a 10 cm mass that on biopsy is grade III, ER 0, PR 0, HER2 2+, FISH HER2 signals/nucleus 2.8, HER2/CEN17 1.8. Axillary node contains carcinoma on biopsy.
- Is the HER2 positive or negative?



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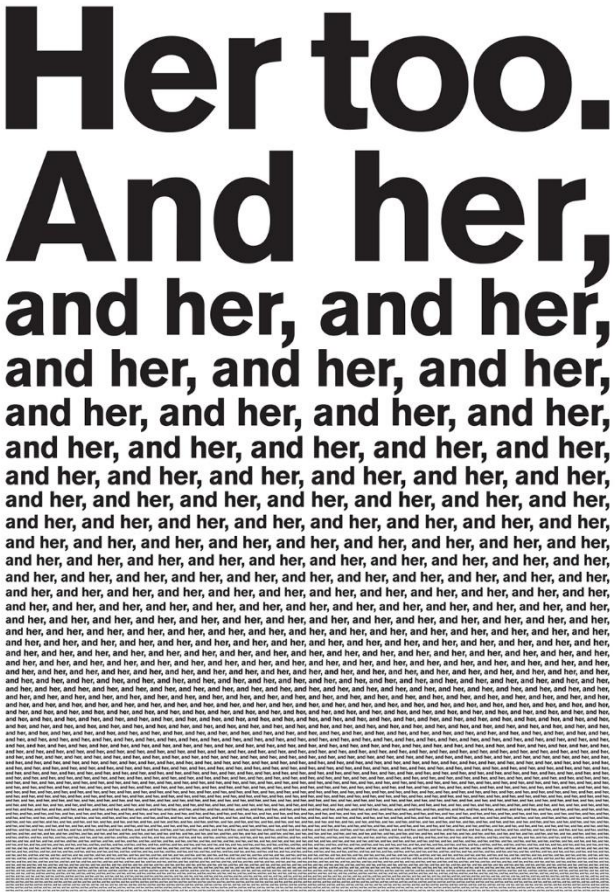
- Imaging shows a 10 cm mass that on biopsy is grade III, ER 0, PR 0, HER2 2+, FISH HER2 signals/nucleus 2.8, HER2/CEN17 1.8. Axillary node contains carcinoma on biopsy.
- Receives neoadjuvant chemotherapy without HER2-targeting drugs
- Mastectomy shows 1cm of residual cancer with dermal involvement, LVI, 1/16 positive nodes.
- Started on adjuvant capecitabine.
- 4 months later relapses on chest wall. HER2 2+ IHC with FISH on relapse has HER2 copy number 4.1 and HER2/CEN17 ratio 2.1
- Is HER2 positive or negative?



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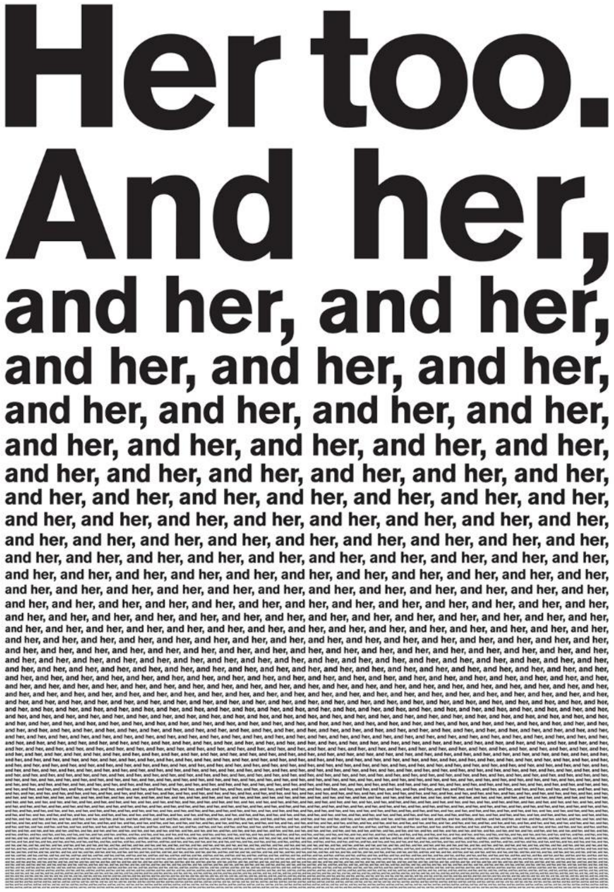
- Started on adjuvant capecitabine.
- 4 months later relapses on chest wall. HER2 2+ with FISH on relapse has HER2 signal number 4.1 and HER2/CEN17 ratio 2.1
- Recheck of HER2 FISH on the mastectomy specimen shows HER2 signal number 4.1 and HER2/CEN17 ratio 2.5
- Treated with vinorelbine, trastuzumab, pertuzumab with progression within two months



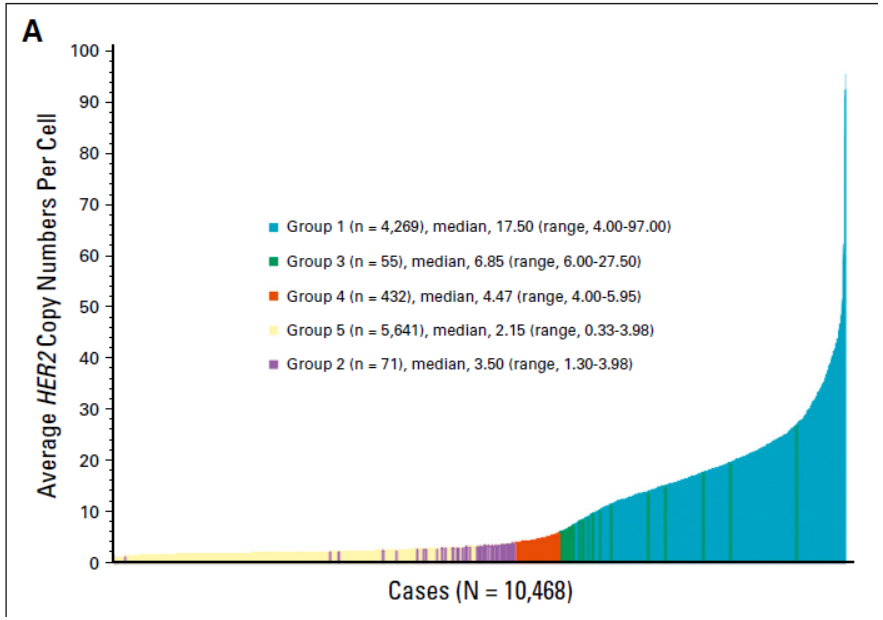
HER2 testing

- Not a complete review of ASCO-CAP guidelines
- Medical Oncologist take
  - Most people are obvious (group 1 of group 5) but 5-10% are borderline
  - Clear benefit of anti-HER2 therapy in group 1
  - Clearly no benefit in group 5
  - Group 4 seems to act like HER2-negative
  - Groups 2 and 3 are too rare to tell

Table 1. *HER2* FISH Assay Results From BCIRG Clinical Trials According to ASCO-CAP Guidelines Categories

HER2 FISH Groups of Breast Cancers Screened for Patient Enrollment Onto BCIRG Trials, 2000-2004

ASCO-CAP FISH Group	Description of HER2 FISH Category	No. of Cases (%)
1	Ratio ≥ 2.0, *HER2* average ≥ 4.0	4,269 (40.8)
2	Ratio ≥ 2.0, *HER2* average < 4.0	71 (0.7)
3	Ratio < 2.0, *HER2* average ≥ 6.0	55 (0.5)
4	Ratio < 2.0, *HER2* average ≥ 4.0, < 6.0	432 (4.1)
5	Ratio < 2.0, *HER2* average < 4.0	5,641 (53.9)
Total*		10,468* (100.0)



Problem with HER2 uncertainty

- Treatment paradigms are now completely different for HER2-positive and HER2-negative breast cancers
  - Whether to do neoadjuvant therapy
  - Whether to do gene expression profiling
  - What drugs to give after surgery
  - Sequence of metastatic therapies
  - Eligibility for clinical trials

What will not save us: Gene expression

		RT-PCR in OncotypeDx			
		Equivocal	Negative	Positive	Total
IHC/FISH	Equivocal	0	23	0	23
	Negative	5	779	0	784
	Positive	12	14	10	36
	Total	17	816	10	843

JCO **November 10, 2011** vol. 29 no. 32 **4279-4285**

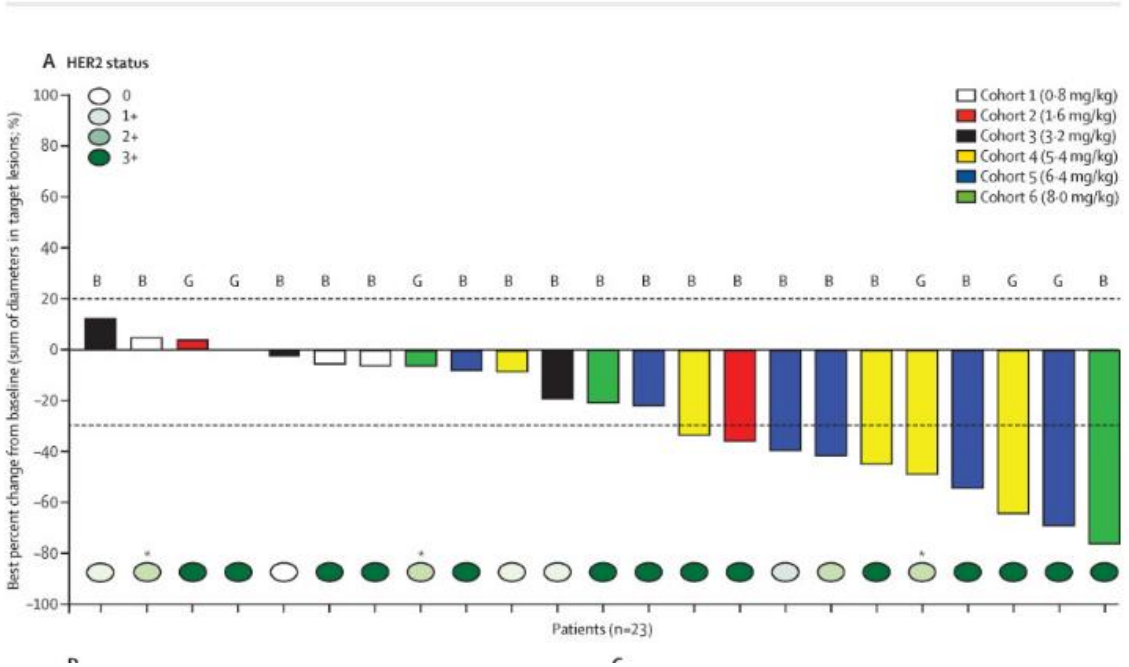
What will not save us: Circulating Tumor Cells

- Targets in CTCs may not reflect the full biology
  - Phase 2 trial of lapatinib in women with HER2-positive CTCs but HER2-negative tumors
  - 7 of 96 women screened
  - No responses, 1 stable disease

Breast Cancer Res Treat. 2012 Jul;134(1):283-9

What might help

- Drugs targeting low HER2 expression
  - Trastuzumab deruxtecan (DS-8201)
  - Antibody drug conjugate
  - Approved 12/2019 for HER2-positive metastatic breast cancer
  - May have activity if IHC is 1+ or 2+ regardless of gene amplification

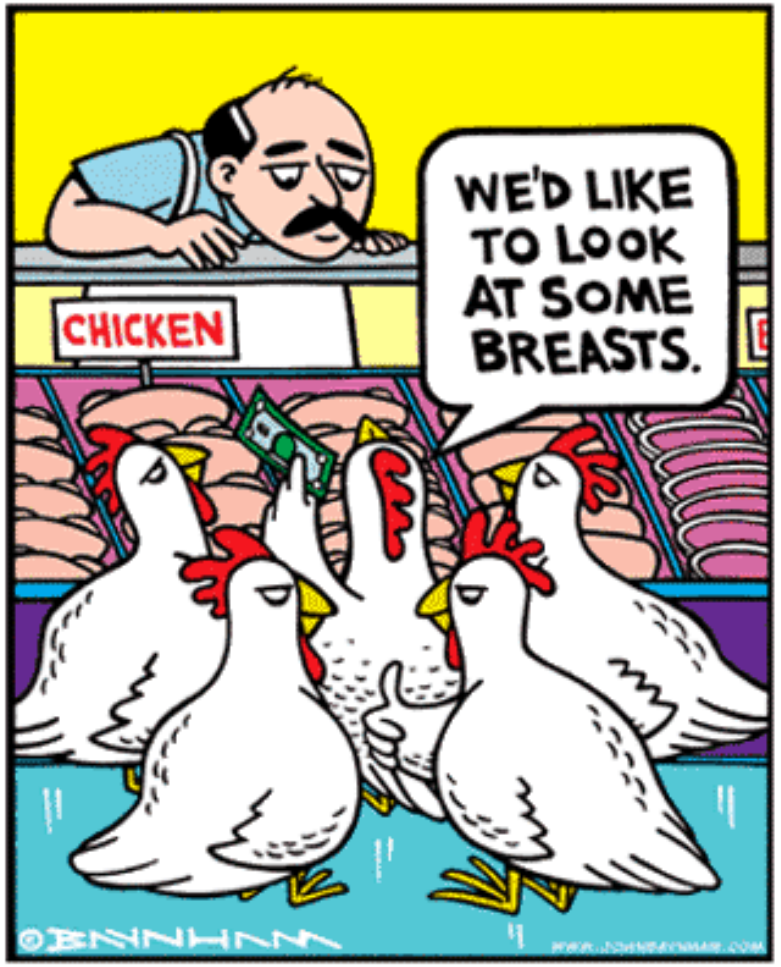


Conclusion

- Gene expression profiling is appropriate for stage 1-2, ER-positive, HER2-negative breast cancer that is high clinical risk to determine the need for adjuvant chemotherapy
- There are predictive molecular alterations for determining therapy in some metastatic breast cancers
  - PIK3CA mutation
  - PD-L1
  - BRCA1/2
- Large NGS panels remain to be proven useful in metastatic breast cancer
- Borderline HER2 results are frustrating for patients, providers, and pathologists

Thank you

- Questions?



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