# 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?

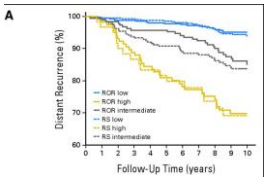
## Features of gene expression tests

| 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<br>Node negative<br>Node positive | <4 lymph nodes | ER-positive<br><br>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 | |

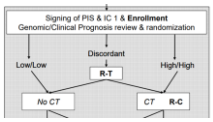



N Engl J Med. 2006 Aug 10;355(6):560-9.

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

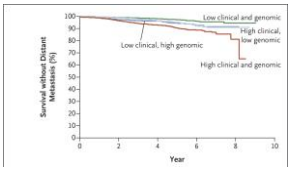



| ER status | HER2 status | Grade | Nodal status | Tumor Size | Clinical Risk in Mindact |
|---|---|---|---|---|---|
| ER positive | HER2 negative | well differentiated | N- | ≤ 3 cm | C-low |
| | | | | 3.1-5 cm | C-high |
| | | | 1-3 positive nodes | ≤ 2 cm | C-low |
| | | | | 2.1-5 cm | C-high |
| | | 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

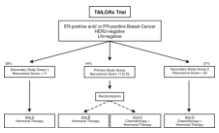
- MINDACT
  - Chemo only benefits people with high clinical and genomic risk
  - People with clinical low risk cancers don't need gene expression profiling




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

N Engl J Med 2019; 380:2395-2405

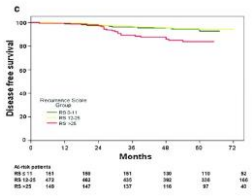
**Table 3. Event Rates at 5 Years, According to Histologic Grade.***

| 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

## 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?

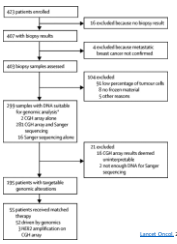
## Case 1 continues

- 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

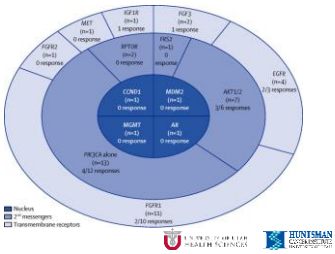
- SAFIR01/UNICANCER trial
- Feasibility study to see how often targeted treatments could be identified for women with metastatic breast cancer




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

## SAFIR01: A mixed success

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



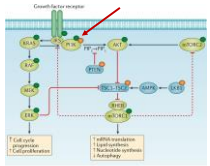

## Targetable mutations in breast cancer

- 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



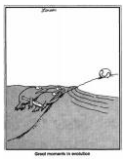
Nature Reviews Clinical Oncology **volume 15**, pages273–291(2018

## 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

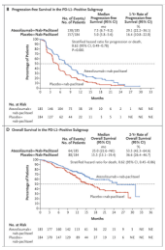


## Case 2

- 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

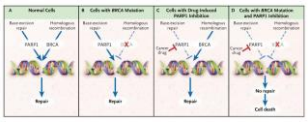
"Now! ..... That should clear up a few things around here!"

## 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

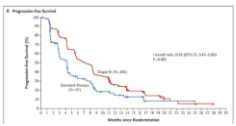
- PARP inhibitors target cells with defects in homologous recombination
  - Particularly germline BRCA1/2 pathogenic variants
- Approved in ovarian cancer
  - Olaparib, rucaparib, niraparib, talozoparib



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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- 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

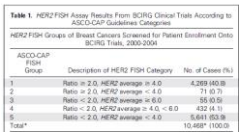
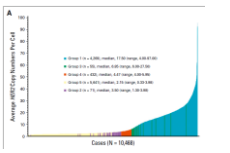


**Table 1.** *HER2* FISH Assay Results From BCIRG Clinical Trials According to ASCO-CAP Guidelines Categories

*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 (40.9) |
| 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**

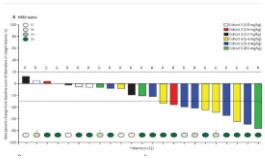
## What will not save us: Circulating Tumor Cells

- 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?