MOLECULAR PROFILING IN METASTATIC BREAST CANCER, GUIDING TREATMENT CHOICE IN 2019
OUTLINE OF TODAY’S TALK

- Define the problem
- Molecular profiling, how does it work?
- Examples in ER positive and triple negative metastatic breast cancer of how molecular profiling is utilized to guide treatment choice
- Discuss barriers to molecular profiling
The Problem...
Figure 8. Trends in Female Breast Cancer Death Rates by Race/Ethnicity, US, 1975-2017

- NH white
- American Indian/Alaska Native
- NH black
- Hispanic
- Asian/Pacific Islander

Incidence

Death

American Cancer Society, www.cancer.org
5 year breast cancer specific survival rates, 2009 - 2015

American Cancer Society, www.cancer.org
**Current Medicine**
One Treatment Fits All

- Cancer patients with e.g. colon cancer

**Future Medicine**
More Personalized Diagnostics

- Cancer patients with e.g. colon cancer
- Blood, DNA, Urine and Tissue Analysis
“Variability is the law of life, and as now no two bodies are alike and behave alike under abnormal conditions, which we know as disease.”

- Sir William Osler
EARLY TARGETS, CAN WE FIND MORE TARGETS?

Figure 1. Distribution of Female Breast Cancer Subtypes, US, 2012-2016

- HR+/HER2+: 4%
- HR-/HER2-: 12%
- HR+/HER2+: 11%
- HR-/HER2+: 73%

American Cancer Society, www.cancer.org
One potential solution...
Molecular Profiling
The power of DNA…
**HotSpot Profiling**
HotSpot profiling analyzes specific well-known regions (blue) ("hot spots") of a gene without looking at the rest of the gene (white) and often misses potentially actionable alterations.

**Comprehensive Profiling**
Comprehensive profiling enables analysis of the entire gene and pinpoints alterations that other tests might miss.
SOURCES OF DNA – TISSUE VS LIQUID BIOPSY

- Tissue biopsy
- Circulating tumor cells = cells that have shed into the vasculature of lymphatics from a primary tumor
- ctDNA = tumor-derived fragmented DNA in the bloodstream that is not associated with cells
- cfDNA = DNA freely circulating in the bloodstream but not necessarily of tumor origin.
- There is general concordance between tissue and liquid results.
- If going to use a ctDNA liquid biopsy, must be taken at time of tumor progression, because they can be false negative while a tumor is responding to treatment

ADVANTAGES OF LIQUID BIOPSY

Fig. 1. Genome sequencing vs “a priori” techniques: comparison and application summary.

<table>
<thead>
<tr>
<th>Tissue biopsy</th>
<th>Liquid biopsy</th>
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<tbody>
<tr>
<td>Does not allow early detection</td>
<td>Diagnose cancer earlier through screening</td>
</tr>
<tr>
<td>Allows histological diagnosis and staging</td>
<td>Determine the risk of recurrence</td>
</tr>
<tr>
<td>Allows metastasis characterization</td>
<td>Determine treatment selection through biomarkers</td>
</tr>
<tr>
<td>Does not allow monitoring disease</td>
<td>Determine mechanisms of resistance</td>
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</tbody>
</table>

- Often difficult, invasive and multiple sampling are not always feasible
- Not always representative of tumor heterogeneity
- Single snapshot over time and space

- Non-invasive procedure, easily repeatable and highly reproducible
- Representative of tumor heterogeneity
- Real-time monitoring of disease
GERMLINE VS SOMATIC MUTATIONS

Somatic mutations
- Occur in non-germline tissues
- Cannot be inherited

Germline mutations
- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome

Mutation in tumor only
(for example, breast)

Mutation in egg or sperm

All cells affected in offspring

Parent

Heritable

Child
OLAPARIB FOR METASTATIC BREAST CANCER WITH GERMLINE BRCA MUTATION

Progression Free Survival (PFS): 7 months vs 4.2 months

Robson et al. NEJM 2017
FDA Approves Foundation Medicine's FoundationOne CDx™, the First and Only Comprehensive Genomic Profiling Test for All Solid Tumors Incorporating Multiple Companion Diagnostics

1. A single test that analyzes all guideline-recommended genes in solid tumors, including companion diagnostic indications with a direct path to therapy.

2. National coverage for qualifying Medicare and Medicare Advantage patients across all solid tumors.†

3. Results include MSI and TMB with the option to add PD-L1† testing to help inform immunotherapy decisions.

4. Comprehensive platform that can be updated regularly as more genes and biomarkers are indicated for use with FDA-approved therapies.
ESR1 MUTATED HORMONE RECEPTOR POSITIVE BREAST CANCER

Acquired through prior aromatase inhibitor therapy

Toy et al. Nat Genet 2013
Frequency of targetable mutations are low.
ALPELISIB IN PI3KCA MUTATED METASTATIC BREAST CANCER

Gene mutation that predicts for response to therapy

PFS = 11 months

Cohort with PIK3CA-Mutated Cancer

<table>
<thead>
<tr>
<th>Survival Duration</th>
<th>Placebo-Fulvestrant (N = 172)</th>
<th>Alpelisib-Fulvestrant (N = 169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>5.7 months</td>
<td>11 months</td>
</tr>
</tbody>
</table>

PFS = 5.7 months

Cohort without PIK3CA-Mutated Cancer

<table>
<thead>
<tr>
<th>Survival Duration</th>
<th>Placebo-Fulvestrant (N = 116)</th>
<th>Alpelisib-Fulvestrant (N = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>6.9 months</td>
<td>8.9 months</td>
</tr>
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</table>

Hazard ratio for progression or death, 0.65 (95% CI, 0.50–0.85) P < 0.001

Gene mutation that predicts for response to therapy

Ciruelos et al. NEJM 2019
ESR1 MUTATION HORMONE RECEPTOR POSITIVE BREAST CANCER

Gene mutation that predicts resistance to therapy

Fribbens et al. JCO 2016
GENES TO PREDICT RESPONSE TO CDK 4/6 INHIBITORS

Gene mutation that predicts resistance to therapy

Li et al Cancer Cell 2018
Genomic Predictors of response to PD-L1 inhibitors:

- PD-L1 expression on tumor cells
- PD-1 expression on tumor infiltrating lymphocytes
- Mismatch repair deficiency
- High tumor mutation burden
Atezolizumab in PD-L1 positive breast cancer

*Approximately 50% of patients with prior Taxane therapy.

Adams et al. NEJM 2018
TUMOR MUTATIONAL BURDEN AND RESPONSE TO IMMUNOTHERAPY

A. Subtype and Mutational Burden

<table>
<thead>
<tr>
<th>Subtype</th>
<th>TMB-Lo</th>
<th>TMB-Hi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>0.60</td>
<td>0.40</td>
</tr>
<tr>
<td>HER2E</td>
<td>0.55</td>
<td>0.45</td>
</tr>
<tr>
<td>LumA</td>
<td>0.90</td>
<td>0.10</td>
</tr>
<tr>
<td>LumB</td>
<td>0.80</td>
<td>0.20</td>
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Thomas et al. Oncoimmunology 2018
Yarchoan et al. NEJM 2017
Only approximately 1.7% of breast cancers are mismatch repair deficient
Why aren’t we profiling every cancer – barriers to molecular profiling.
THE MAJORITY OF MUTATIONS FOUND ARE RARE OR NOT ACTIONABLE

- Simply having a mutation doesn’t mean you have a good chance of responding to drug because there is a mass amount of context biology at play.
- Not all mutations have a corresponding drug.
- Many cancers have more than 1 driver mutation and are able to develop compensatory resistance.
- There is tumor heterogeneity amongst cancer cells.
PHYSICIAN CITED BARRIERS TO MOLECULAR PROFILING

CITY OF HOPE, SINGLE CENTER EXPERIENCE

Yuan et al. Oncotarget 2017
COST OF SEQUENCING A CANCER

2008: $1,000,000
2018: $5,000
## COST OF MOLECULAR PROFILING

### Selected commercially available targeted next-generation sequencing platforms and specifications

<table>
<thead>
<tr>
<th>Platform</th>
<th>Sample reqs</th>
<th>Sequencer</th>
<th>Genes covered and mutation types (if specified)</th>
<th>Additional analyses</th>
<th>Cost (USD)</th>
<th>Time</th>
<th>Year released</th>
</tr>
</thead>
</table>
| FoundationOne (Foundation Medicine) | - FFPE  
- Prefer no decalcification, but may use EDTA | Illumina | 315 genes (+28 introns) fusions, copy number variations | MSI TMB | $5800 | 14 days | 2011 |
| Caris Molecular Intelligence (Caris Life Sciences) | - FFPE  
- Fresh specimen in 10% neutral buffered formalin  
- Malignant fluid up to 120 cc  
- No decalcified specimens | Illumina | >600 genes fusions, copy number variations | IHC MSI TMB TISH | $6500 | 10–14 days | 2014 |
| OncoDEEP (OncoDNA) | - FFPE  
- Prefer no decalcification, but may use EDTA | Ion Torrent | 75 genes fusions, methylation, splice variants | IHC MSI TMB | ~$3500 (2990 Euros) | 7 days | 2014 |
| OncoSTRAT& GO (OncoDNA) | - FFPE and 2 mL blood samples (for ct DNA) | Ion Torrent | > 500 genes (solid portion) + 40 genes (liquid portion) fusions, methylation, splice variants | IHC MSI TMB | ~$5800 (4990 Euros) | 10 days | 2016 |
| Tempus xT/xO (Tempus Labs) | - FFPE and matched blood (solid tumors) or saliva (lymphoma) sample for normal DNA  
- Prefer no decalcification, but may use EDTA | Illumina | 595 genes (xT); 1711 genes (xO) fusions, copy number variations, splice variants | MSI TMB | $4800 (Tempus xO) | 14–21 days | 2017 |
INCREASING NUMBER OF DRUGS FOR RARE TUMORS – LAROTRECTINIB FOR TRK FUSION-POSITIVE CANCERS

NTRK fusions are present in up to 9% of breast cancers

Drilon et al. NEJM 2018
I-PREDICT CLINICAL TRIAL

Sicklick et al. Nature Medicine 2019
Molecular profiling of metastatic breast cancer can be used to identify targetable mutations to guide treatment of breast cancer. Current actionable genetic identifiers include:

- PIK3CA – Alpelisib
- ESR1 – Fulvestrant
- Mismatch repair deficiency, tumor mutation burden, PD-L1 expression – Pembrolizumab

Mutation does not always equal response

Using combinations of drugs that target different mutations may increase response by overcoming the “driver” effect or compensatory resistance mechanisms.

Further development of liquid biopsies will allow us to be able to monitor how tumor mutations change over time and with serial treatments.