Are We Ready to Predict Who is at Risk For What Kind of Breast Cancer?

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NOT YET

But soon . . . .

NO DISCLOSURES

Breast Cancer Gene Expression Profiling Prognostic Tests

1. OncotypeDX Recurrence Score (Paik et al., NEJM, 2004)
2. MammaPrint (van de Vijver et al., NEJM, 2002)
3. The PAM50 Intrinsic Subtypes: LumA, LumB, Basal-like, HER2-enriched, Normal-like (Parker et al., JCO 2009)
4. The PAM50 Risk of Recurrence (ROR) (Parker et al., JCO 2009)
5. IHC4 (ER, PR HER2, Ki-67 + clinical features) (Dowsett et al JCO )
6. Genomic Grade Index (Sotiriou et al. JNCI 2006)
7. Breast Cancer Index: 2-gene ratio plus 5-gene proliferation (Ma et al., CCR 2008)
8. EndoPredict (Filipi et al., CCR)
Risk factors for breast cancer are evolving

<table>
<thead>
<tr>
<th>Components</th>
<th>Data Source for modelling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical risk factors (family history, atypia, previous biopsies, hormone exposure)</td>
<td>Breast Cancer Surveillance Consortium (BCSC)</td>
</tr>
<tr>
<td>Breast density</td>
<td>Breast Cancer Surveillance Consortium</td>
</tr>
<tr>
<td>Susceptibility SNPs</td>
<td>Collaborative Oncological Gene-Environment Study (COGS); Breast Cancer Association Consortium (BCAC)</td>
</tr>
<tr>
<td>BRCA/BROCA</td>
<td>Literature</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Surveillance Epidemiology and End Results (SEER)-Medicare</td>
</tr>
<tr>
<td>Breast cancer biology</td>
<td>COGS / Literature</td>
</tr>
<tr>
<td>Qualifying Markers of Breast Cancer Risk-pro Neurotensin/pro-Enkephalin</td>
<td>Malmo Diet and Cancer Study Malmo Prevention Project</td>
</tr>
</tbody>
</table>

Figure 1: An example of the distribution of visually assessed percentage density of the breast. The sample consists of 50,831 women between 46 and 75 years of age. Density was estimated in two views of each breast on a visual analogue scale and the four readings were combined to give a single value per woman [34].

Genetic “Architecture” of Breast Cancer

- Familial Cancer Syndromes
  - BRCA1/2
- Intermediate Penetrance (CHEK2)
- Common SNPs (GWAS)

70% density compared to 5% density increases risk 4.6 fold.

Highest Density is where the risk is...
Explained heritability of breast, and ovarian cancer – what’s the status after iCOGS?

<table>
<thead>
<tr>
<th>Cancer</th>
<th>New loci</th>
<th>Total loci</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>49</td>
<td>76</td>
</tr>
<tr>
<td>Breast HR-</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Ovarian</td>
<td>8</td>
<td>12</td>
</tr>
</tbody>
</table>

iCOGs (Collaborative Oncological Gene-environment Study) consortium, PI: Easton, 13 papers in Nature April 2013

What in the landscape has changed?

Opportunities in our evolving policy and technology landscape

- Supreme Court Decision June 2013
  - Cannot patent the genome
  - Enables emerging technologies to compete and for the market to drive down price
- Next Generation Risk Assessment
  - Risk: BRCA, BROCA, SNPs at high volume: inexpensive
  - Tumor profiling
  - 2D/3D mammography, MRI, breast density
- Affordable Care Act
  - Everyone is covered, no pre-existing conditions
  - Enables the provision of information that would have previously rendered a person "uninsurable"

What in the landscape has not changed?
Screening Recommendations – Other Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Start age</th>
<th>Stop age</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>40</td>
<td>NA</td>
<td>Annually</td>
</tr>
<tr>
<td>Sweden</td>
<td>45</td>
<td>74</td>
<td>Biennially</td>
</tr>
<tr>
<td>UK</td>
<td>50</td>
<td>70</td>
<td>Triennially</td>
</tr>
<tr>
<td>Netherlands</td>
<td>50</td>
<td>70</td>
<td>Biennially</td>
</tr>
<tr>
<td>France</td>
<td>50</td>
<td>74</td>
<td>Biennially</td>
</tr>
<tr>
<td>Italy</td>
<td>50</td>
<td>70</td>
<td>Biennially</td>
</tr>
<tr>
<td>Germany</td>
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<td>70</td>
<td>Biennially</td>
</tr>
</tbody>
</table>

Switzerland recently considering ending mammography screening altogether because of lack of evidence that the benefits outweighs the harms. Bilier-Andorno and Jüni, NEJM, 2014.

Breast Cancer Screening Today

- Based on trials from the 1980’s
- Mired in controversy
- Resource intensive
  - $8-10 billion/year in U.S.
- Unintended consequences:
  - False positives (75% of biopsies \(\rightarrow\) benign)
  - Over-diagnosis and Overtreatment
- Impacts everyone...
- Opportunity for improvement

Women are caught in the middle

Long-term study questions benefits of mammogram screening

Breast Cancer Confusion Widespread Survey Finds

Rethink The Word 'Cancer,' Panel Says

Breast cancer screening guidelines confuse doctors and patients

Vast Study Casts Doubts on Value of Mammograms

Breast cancer screenings is more about rationing than rationality.

Screening: What Do We Need?

More Light

Less Heat
What Can be Done?

- Undress the Breast Cancer Screening Controversy
- Advance the State of the Art of Risk Assessment, Screening, and Prevention
- Develop model that is transparent, evolves, and results in seamless clinical adoption

"One Size Does NOT Fit All"

Cancer Screening

Is There a Better Option?

- Personalized
- Based on advances
  - Risk-assessment
  - Biology
  - USPSTF framework
- More cost effective
- Integrated with prevention
- Evidence-based, adaptive, evidence-generating
- More effective at finding “relevant” cancers

ASSIGN: Age to Start, Frequency
PROFILE: Tumors at Diagnosis ➔ LEARN
ADAPT: Refine risk, screening assignments
WISDOM STUDY: **WOMEN INFORMED TO SCREEN DEPENDING ON MEASURES OF RISK**

Risk Based Screening Hypothesis

- Clinical trial comparing annual screening (usual care) with personalized (risk-based) approach to breast cancer screening
  - Test if:
    - Safe
    - Less morbid
    - Readily accepted by women
    - Enables prevention
    - Cost effective
- Implemented by Athena
- Funded by multiple stakeholders who stand to benefit from results — payers, providers, government, public grants, private grants

WISDOM Study Pragmatic Design

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Annual Screening Arm

- Athena standard of care
  - Includes standard risk assessment and referral for prevention counseling if at very high risk
- Patients will return for a screening mammogram on a yearly basis
Personalized Screening Arm

Risk Model

- Mammogram (Breast Density)
- Athena Health Questionnaire
- Genetic testing

- Mammogram + MRI
- Annual Mammogram
- Biennial Mammogram
- No screening until the age of 50

Breast Health Specialist counseling

The Athena Breast Health Network

- Established network with a large community referral base
  - 10 University of California Campuses
  - 13 Mid-west hospitals (Sanford Health)
- >100 providers committed to modernization & improvement
  - Pathologists, radiologists, primary care providers, oncologists, surgeons, radiation oncologists
- Anticipated participation of 150,000 women over 10 years
  - Screening and Prevention, Diagnosis and Treatment, Survivorship speciality areas
  - Over 75,000 women enrolled to date

Study Aims

Determine if personalized screening (as compared to annual screening):

1. **Is as safe**
   - Minimal or no increase in > stage 2B (node positive)
   - No increase in the rate of systemic therapy
2. **Is readily accepted**
   - Greater choice of personalized over annual screening in the self-assigned cohort;
   - Willingness to be randomized, greater adherence to recommended screening;
   - No overall increase in anxiety in the personalized screening arm;
   - No decisional regret
3. **Is less morbid**
   - Fewer recalls and biopsies;
   - Less low grade DCIS (less over-diagnosis).
4. **Enables prevention** as measured by
   - Greater uptake of risk reducing interventions

5. **Greater Health Care Value**
Trial Funding

- RWJF Planning Grant
- PCORI

**Pragmatic Trial Award**
February 2015

Payer Participation

- Payers will be part of the solution from the inception
- Cover clinical service provided for the trial through Athena network
  - UC Care
  - Blue Shield has developed a “coverage with evidence development”
- In conversations with all commercial plans (including Medicare/Noridian) who cover our populations

Key Questions

- Who needs to start screening at 40 vs. 50?
- Who needs screening every 6 months, every one year, every 2 years (or less frequently?)
- When do you stop screening? After 70, who will not realize survival benefit from screening?
- Are there groups of patients at low risk for breast cancer, or only at risk for low risk curable cancer that will not benefit from screening?

Profile all Tumors that Arise, and Continue to Optimize Screening Using an Adaptive Learning Engine

FOCUS RESOURCES ON THOSE WITH MOST TO GAIN
Avoid harm in those least likely to benefit
Risk Based Screening Can Be More Than just an improved screening strategy!

LEARN who gets what kind of cancer

CONTINUOUS IMPROVEMENT

ADAPT/TAILORED Strategy
Prevention
Biopsy
Treatment
Screening

PRACTICE GENERATING EVIDENCE

UNDERSTANDING THE EVIDENCE . . .
The POWER TO CATALYZE CHANGE

WISDOM Study Value Chain

WISDOM
Knowledge
Learn and Improve
Data ➔ Information