ATHENA WISDOM INITIATIVE:
RISK-BASED SCREENING FOR BREAST CANCER
The Screening Debate in the US?

• ACS vs. USPSTF
  – When to start, when to stop, screening intervals, modality]

• Little guidance around operationalizing risk assessment
  – Some may be under-screened, some over-screened

• Preventive services are not reaching women who most need them

• Many women are confused and frustrated
Women Are Caught in the Middle

Rethink The Word 'Cancer'
Aim Is To Reduce Aggressive Treatment

Long-term study questions benefits of mammogram screening

Scientists Seek to Rein In Diagnoses of Cancer
By TARA PARKER-POPE JULY 29, 2013 11:00 AM

Breast Cancer Confusion Widespread,
By KATIE MOISSE via GOOD MORNING AMERICA

Breast cancer screening guidelines confuse doctors

Vast Study Casts Doubts on Value of Mammograms
By GINA KOLATA FEB. 11, 2014

Mammograms Save Lives
Criticism of breast-cancer screenings is more about rationing than improving care
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And many are choosing not to screen at all...

Mammograms Save Lives
Criticism of breast-cancer screenings is more about rationing than cancer screenings
Breast Cancer Screening: What It Can Be

• Based on advances in:
  – Risk-assessment
  – Biology
• More effective at finding “relevant” cancers
• Integrated with prevention
• More cost-effective (better health care value)
• Personalized
Merging research and innovation with care improvement

A New Approach to Screening

LEARN who gets what kind of cancer

CONTINUOUS IMPROVEMENT

ADAPT/TAILORE Prevention Biopsy Treatment Screening

A partnership between the UCLA Institute for Precision Health, Clinical & Translational Science Institute, and the Garrick Institute for the Risk Sciences
WISDOM Study Design: Precision Medicine
WISDOM Study Design: Precision Medicine

Eligible Patients

Consent

Randomized Cohort

Observational Cohort

Randomize

Annual Screening

Risk-based Screening

Annual Screening
WISDOM Study

Risk-based Screening Arm

Mammogram - breast density

Athena Health Questionnaire
- family history, comorbidities, previous biopsies, age, race/ethnicity

Genomic profiling
- BRCA, BROCA, SNPs
- saliva collection

Mammogram + MRI
Annual Mammogram
Biennial Mammogram
No screening until age 50

Screening Recommendation Notification and Education

Breast Health Specialist counseling

Portal enrollment and consent

RBS Consumer Engagement

Risk Model

UCLA | Center for SMART Health
A partnership between the UCLA Institute for Precision Health, Clinical & Translational Science Institute, and the Garrick Institute for the Risk Sciences
BREAST DENSITY
Breast Density

- The amount of fibro glandular parenchyma on a mammogram
- Mammogram reports describe density
  1. The breast is almost entirely fat
  2. There are scattered fibro glandular densities
  3. The breast tissue is heterogeneously dense. This may lower the sensitivity of mammography
  4. The breast tissue is extremely dense, which could obscure a lesion on mammography
Breast Density

- Breast cancer and breast parenchyma are both white
- Fat is nearly black
- The greater amount of fat, the easier it is to recognize a cancer
- Heterogeneously dense and extremely dense breasts can obscure a cancer, even a large cancer
Cancer in Fatty Breasts
Cancer in Dense Breasts
Breast Density
Breast Density

• Sensitivity and specificity reduced
Breast Density

• Sensitivity and specificity reduced
  – Sensitivity 33 to 81%
Breast Density

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  – Sensitivity 33 to 81%
  – False positives increased
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• Breast density is a significant independent risk factor for breast cancer
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  – 4-5x relative risk
Breast Density

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• Breast density is a significant independent risk factor for breast cancer
  – 4-5x relative risk
• California law mandates patient notification
GENOMICS
Genetic “Architecture” of Breast Cancer

Familial Cancer Syndromes
BRCA1/2

Intermediate Penetrance (CHEK2)

Common SNPs (GWAS)
Seven Years of GWAS

76 SNPs genome wide significant, nearly all from European GWAS/replication
All have odds ratios <1.4 or >0.8
Loci include known candidates and novel genes/pathways
9 Key Genes

BRCA 1
BRCA 2
TP53
PTEN
STK11

• PALB2
• CHEK 2
• CDH1
• ATM
81 SNPs

• Known/Accepted Risk Variants
  – Evidence from GWAS and COGS validation studies

• Discovery Variants
  – Coding variants in breast cancer pathways
  – Coding variants in 10-12 key cancer signaling pathways

• Disease/Treatment Modifying Variants
  – Key variants associated with ASME genes for pharmacogenetic studies

COGS= Collaborative ovarian, prostate, and breast gene-environment study
GWAS= Genome Wide Association Studies
Population Medicine → Precision Medicine

Tailored screening recommendation for individual woman
Trial Inclusion:
- Receiving care within UC/Athena
- No prior breast cancer diagnosis

Risk Assignment Notification and Education
Assigned screening frequency and modality (if applicable)

Follow-Up
Cancer detected: Molecular profiling
Screening Frequency
<table>
<thead>
<tr>
<th>Screening interval</th>
<th>6 months: Highest Risk</th>
<th>Annual: Elevated Risk</th>
<th>Biennial: Average Risk</th>
<th>Not screened: Lowest Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 40-50</td>
<td>≥ 2% overall risk</td>
<td>≥ 1% risk of ER- or BIRADS 4</td>
<td>≥ 1% risk of ER+</td>
<td>&lt; 2% overall risk &lt; 1% risk of ER- &lt; 1% risk of ER+ Not screened again until 50</td>
</tr>
<tr>
<td>Age 50-65</td>
<td>≥ 7% overall risk</td>
<td>≥ 1.5% ER-risk</td>
<td>&lt; 7% overall risk &lt; 1.5% risk of ER- &lt; 2.5% risk of ER+</td>
<td>NA</td>
</tr>
<tr>
<td>Age &gt;65</td>
<td>≥ 7% overall risk and low comorbidity</td>
<td>≥ 1.5% ER-risk and low comorbidity</td>
<td>&lt; 7% overall risk &lt; 1.5% risk of ER- &lt; 2.5% risk of ER+</td>
<td>High comorbidity</td>
</tr>
</tbody>
</table>
How does risk-based screening compare?

**Safety:** Clinically detected cancer

**Efficacy:** False positive recalls
Risk Based Screening: Higher Value/

TRANSFORMATIVE AND INNOVATIVE POSSIBILITIES
High Risk Patient and Genetic Testing

Current Paradigm

- Identified As High Risk
- Genetic Counseling
- Genetic Testing

Possible Future Paradigm

- Risk Stratification
  - Patient Data
  - Clinical Data
  - Imaging Data
- Genomic Screening
  - Genetic Counseling
  - Whole exome analysis

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Screening and Imaging

Current Paradigm

Screening
Mammogram

Other
Imaging
Procedures

Biopsy

Possible Future Paradigm

Circulating
Tumor
Cells

Search for
Tumor
(imaging)

Biopsy/Surgery
Improving utilization of invasive

Current Paradigm

Abnormal Mammogram (4a, 4b, 4c) → Biopsy → Outcome

Possible Future Paradigm

Abnormal Mammogram + Additional clinical/path data → Biopsy Versus Watchful Waiting → Outcome
• Quantitative Breast Density

• Automated image interpretation and computer assisted diagnostics