High Risk Screening: A Multimodality Approach

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- Previously received research funds from Hologic
How to Do High Risk Screening

• Run the Tyrer-Cuzick model on each patient. (or maybe just those with some risk factors)
• If the lifetime result of the model is >20%, do an MRI on that patient.
• Plus, do mammography on everyone.
• Repeat.
Thank you.

Show of hands - How many people do this?
So you say...

But here is what is really happening...
How We Really Do High Risk Screening

• Run the Tyrer-Cuzick model on each patient.
• If the lifetime result of the model is >20%, *recommend* an MRI on that patient in addition to their mammography.
• Most patients decide not to get the MRI.
• Repeat.
Why don’t all patients choose to have the MRI?

• Out of pocket costs (deductible)
• Insurance denial
• Dislike of MRI scanner
  – Noise, Claustrophobia, General discomfort
• MRI contraindicated (e.g., pacemaker)
• Enough is enough - don’t want to do more medical stuff
Are they right? Cost/Benefit of screening MRI

- How good is the evidence for high-risk screening with MRI?
- Who is really at “high risk”?
- What is the risk of “financial toxicity”?

In the age of deductibles, cost vs benefit becomes *personal*
Outline

• Review the background of and evidence for high-risk screening with MRI
• Discuss the limitations of our current practice
• Discuss alternative contrast enhanced modalities to MRI for high risk screening
  – Molecular Breast Imaging
  – Contrast Enhanced Mammography
Background: 2007 ACS Consensus Panel

American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography
Debbie Saslow, Carla Boetes, Wylie Burke, Steven Harms, Martin O. Leach, Constance D. Lehman, Elizabeth Morris, Etta Pisano, Mitchell Schnall, Stephen Sener, Robert A. Smith, Ellen Warner, Martin Yaffe, Kimberly S. Andrews, Christy A. Russell and for the American Cancer Society Breast Cancer Advisory Group
CA Cancer J Clin 2007;57;75-89
2007 ACS Consensus Panel

“Screening MRI is recommended for women with an approximately 20–25% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin disease.”
2007 ACS Consensus Panel

• “There are several risk subgroups for which the available data are insufficient to recommend for or against screening, including women with a personal history of breast cancer, carcinoma in situ, atypical hyperplasia, and extremely dense breasts on mammography. “
2007 ACS Consensus Panel

Also insufficient evidence for women with lifetime risk of 15-20%.
2007 ACS Consensus Panel

Also insufficient evidence for women with lifetime risk of 15-20%.

- Lifetime risk “as defined by BRCAPRO or other models that are largely dependent on family history”
Screening MRI – Evidence 2007

- 6 screening studies of high-risk women
  - Netherlands: 50 CA / 1909 women = 2.6%
  - Canada: 22/236 = 9.3%
  - UK: 35/649 = 5.4%
  - Germany: 43/529 = 8.1%
  - US: 4/390 = 1.0%
  - Italy: 8/105 = 7.6%

CA Cancer J Clin 2007;57;75-89
Screening MRI – Evidence

• All showed sensitivities of MRI > mammo
  – MRI: 77 – 100%
  – Mammo: 16 – 40%
  – U/S: 16 – 40%
• No cancers seen by U/S not seen by MRI
• Some cancers seen by mammo but not MRI
  – Mostly DCIS
Limitations

• No mortality or survival outcome
  – Primary outcome is cancer detection rate or sensitivity

• But -- secondary outcomes are compelling
  – Decreased interval cancer rate
  – Inferred stage shift
Studies since 2007; eg: EVA

- > 20% lifetime risk by BRCAPRO
- 687 patients; 1679 rounds
  - So prevalence + incidence
  - 2 year follow-up
- Sensitivity of MRI = 93%; Mx = 33%; U/S = 37%
- No interval cancers
- DCIS better on MRI than mammo

Screening MRI for Additional Populations

• LCIS
  – Friedlander, et al. Radiol 2011 -- 5/307 (1.6%) CDR
  – Sung, et al. Radiol 2011 -- 12/670 (1.8%) CDR

• Personal History of Cancer
  – Giess, et al. Acad Radiol 2015 -- 12/1194 (1%) CDR
  – Lehman, et al. JNCI 2016 -- retrospective 1.7%

→ Similar to yield from familial high risk groups
Evidence Summary

• Level of evidence lower than for screening mammography
  – No RCTs
  – No mortality endpoints

• Still very compelling due to large effect
  – Decrease in mortality can be inferred
Who should be advising patients about high risk screening options?

• We should
  Most PCPs do not have the time nor expertise to deal with explaining high risk screening options.

• PCPs should
  We only see a subset of women, most of whom are over 40

Both PCPs and radiologists need to be involved
Next: Who is really at high risk?

• Is 20% the correct threshold?
• How was it chosen?
• Why lifetime risk and not 5y risk?
• Which models are appropriate?
• Is it fair to use multiple models?
• Does 20% risk have the same meaning as it did at the time of the consensus panel?
The 20% Threshold

• Meant to be about double the population risk
• Lifetime risk chosen to favor younger women
  – Yearly risk goes up with age
  – Lifetime risk goes down with age
• Gives choice of models
  – Didn’t say try all the models and pick the highest number
TABLE 4  Breast Cancer Risks for Hypothetical Patients, Based on 3 Risk Models

<table>
<thead>
<tr>
<th>Family History</th>
<th>BRCAPRO\textsuperscript{a,18}</th>
<th>Claust\textsuperscript{16}</th>
<th>Tyrer-Cuzick\textsuperscript{23}</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-year-old woman</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother BC 33</td>
<td>19%</td>
<td>36%</td>
<td>28%</td>
</tr>
<tr>
<td>Maternal aunt BC 42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-year-old woman</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paternal aunt BC 29, OC 49</td>
<td>23%</td>
<td>24%</td>
<td>32%</td>
</tr>
<tr>
<td>Paternal grandmother BC 35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-year-old woman</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paternal aunt BC 29</td>
<td>18%</td>
<td>24%</td>
<td>31%</td>
</tr>
<tr>
<td>Paternal grandmother BC 35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-year-old woman</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother BC 51</td>
<td>13%</td>
<td>18%</td>
<td>23%</td>
</tr>
<tr>
<td>Maternal aunt BC 60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-year-old woman of Jewish ancestry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother BC 51</td>
<td>18%</td>
<td>18%</td>
<td>28%</td>
</tr>
<tr>
<td>Maternal aunt BC 60</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Tyrer-Cuzick Model

• Freely available
• Uses both family history and other factors
  – Hormonal
    • Menarche, menopause ages
    • Parity (age at 1st birth)
  – Past biopsy results
• Not always straightforward
Example – effect of prior biopsy

- 40 yo; mat GM at age 80; first child at 24

<table>
<thead>
<tr>
<th>Bx Result</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No benign disease</td>
<td>14.6%</td>
</tr>
<tr>
<td>Hyperplasia (not atypia)</td>
<td>27.1%</td>
</tr>
<tr>
<td>Unknown benign</td>
<td>27.7%</td>
</tr>
<tr>
<td>Atypical Hyperplasia</td>
<td>42.8%</td>
</tr>
<tr>
<td>LCIS</td>
<td>67.3%</td>
</tr>
</tbody>
</table>
What is an “unknown” biopsy?
Need to fill in defaults – effect of parity

- 45 yo; mother with breast cancer at age 90

<table>
<thead>
<tr>
<th>Parity</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>19.5%</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>23.6%</td>
</tr>
<tr>
<td>1\textsuperscript{st} Child at 35</td>
<td>25.8%</td>
</tr>
<tr>
<td>1\textsuperscript{st} Child at 20</td>
<td>16.2%</td>
</tr>
</tbody>
</table>
Version 7 gives higher risks than version 6

40 yo; mother at age 70; 1st child at 25

Version 6
• 16.6%

Version 7
• 21.6%

Why?
1) Lifetime extended to age 85 in version 7 (from 80 in version 6)
2) Population risk adjusted to account for rising incidence in UK between 1994 and 2008 – 2010

Source: http://www.ems-trials.org/riskevaluator/
It is not hard to get over 20% if you are young

• Example:

35yo w mother at age 70; 1\textsuperscript{st} child at 29 –

Version 6: 20%
Version 7: 26%
So, back to our patient..

- Referring doctor gets a report suggesting “High risk screening with MRI may be appropriate.”
- Patient get a letter saying the same thing.
- Patient declines MRI because of cost.
- Ends up getting an ultrasound and/or tomo instead (esp if she also has dense breasts).
Are there better alternatives?
Tests for Breast Cancer Detection

- Mammography
- Tomosynthesis
- Ultrasound
- MRI
- MBI (BSGI)
- CEDM (CESM)

- Non-contrast
- Contrast-enhanced
Contrast-enhanced modalities find more cancers than non-contrast modalities

- Additional yield to mammography:
  - Tomosynthesis ~1.2 / 1000 (JAMA – all comers)
  - Ultrasound ~3.7 / 1000 (6666 – dense+HR)
  - MRI > 14.7 (ACRIN 6666)
  - MBI ----
  - CEDM (CESM) ----
Are there contrast studies we can do at a lower cost to the patient?

- Abbreviated MRI
- MBI
- CEDM
Molecular Breast Imaging

- IV Injection of 99mTc Sestamibi
  - 8 mCi (dual head); down from 20mCi
- Planar imaging of both breasts on a dedicated gamma camera
  - Dual headed or Single headed
  - Solid state CZT detectors or crystal scintillator
  - ~10 min acquisition per view
MBI for Dense Breast Screening

- Rhodes DJ, et al. 2015
  - 1585 women with dense breasts
    - 62% post-menopausal
  - Mammo + single round of MBI
  - Dual-headed solid state device
  - 8 mCi dose
  - Supplemental yield 8.8 cancers / 1000 screens
    - Note: inclusion criteria was dense tissue only
  - 6.5% false positives

AJR 2015 Feb;204(2):241-51
Example: Mammographically Occult Invasive Ductal Carcinoma in a 78 yo Woman

“Final pathology was multifocal node-negative grade I invasive ductal carcinoma, with largest mass (2 cm) visualized by MBI.”

AJR 2015 Feb;204(2):241-51
MBI Biopsy

- MBI biopsy add-ons available
  - Stereotactic or orthogonal view guidance
  - Similar to upright stereotactic (mammo) biopsy
  - Problem of Gad washout / hemorrhage avoided
  - Can verify sampling by imaging specimen on device
MBI vs MRI: Costs

• MBI
  – Machine cost: $300,000 – $550,000
  – 40 minute exam time
  – Radiopharmaceutical cost $50 - $75

• MRI
  – Machine cost: ~ $2,000,000 – $3,000,000
  – 20-40 minute exam time
  – Gadolinium cost $20-$50
At age 40...

Mammo: 3.7 mGy $\to$ 1.3 fatal cancers /100,000 studies

MBI: 20 mCi $\to$ 26 fatal cancers / 100,000 studies

Much lower for 8 mCi (~10 cancers)


O’Connor, et al, 2010 (cost/benefit ratio):

“If the primary use of MBI...is in women with dense breast tissue, then the administered doses need to be in the range 75–150 MBq”

Contrast-enhanced modalities find more cancers than non-contrast modalities

• Additional yield to mammography:
  – Tomosynthesis  ~1.2 / 1000  (JAMA – all comers)
  – Ultrasound      ~3.7 / 1000    (6666 – dense+HR)
  – MRI           > 14.7    (ACRIN 6666)
  – MBI           8.8     (Rhodes – dense)
  – CEDM (CESM)   ----
Contrast Enhanced Mammography (CEDM, CESM)

- IV injection of iodinated contrast with breast uncompressed

- Mammography acquired using dual-energy subtraction technique
  - Two images taken in rapid sequence under a single compression
  - kVp and filtration switched between images
Example – Unifocal IDCA
CEDM vs MRI: Literature

- Fallenberg, *et al.* European Radiology 2013;
  - Bilateral CEDM, MRI, mammo
  - 80 subjects with new CA at 1 site
  - Single reader of CEDM; clinical read of MRI
  - CEDM > MRI sensitivity for index lesion (100% vs. 97%)
- 80/80 vs 78/80
CEDM vs MRI: Literature (cont.)

  – Bilateral CEDM vs MRI
  – 52 subjects with new cancer
  – CEDM = MRI sensitivity for index lesion (96%)
    • 50/52
  – MRI > CEDM in detection rate for additional foci
    • 22/25 (88%) vs 14/25 (56%)
  – CEDM had fewer false positives than MRI
    • 2 vs 13
CEDM/CET vs MRI: Literature (cont.)

  - Mammo, DBT, CEDM, CE Tomo, MRI
  - 81 cancers; 144 benign lesions; 3 readers
  - ROC analysis – no difference between CEDM, CET, MRI
    - all 3 better than unenhanced DM, DBT
  - Sensitivities: 93-98% for CEDM; 86%-93% for MRI
CEDM/CET Case: Invasive Lobular CA

Mammo

CEDM

CE Tomo

MRI MIP
Same case -- CC Views

Mammo

CEDM

CE Tomo
Contrast-enhanced modalities find more cancers than non-contrast modalities

• Additional yield to mammography:
  – Tomosynthesis   ~1.2 / 1000 (JAMA – all comers)
  – Ultrasound     ~3.7 / 1000  (6666 – dense+HR)
  – MRI           > 14.7  (ACRIN 6666)
  – MBI           8.8 (Rhodes – dense only)
  – CEDM (CESM)   ??  No screening study!!
Relative Risks

• Contrast agent reaction risk
  – CEDM > MRI > MBI

• Radiation risk
  – MBI > CEDM > MRI

• Possible Risks
  – Gadolinium accumulation in the brain (MRI)
  – Renal risk (CEDM>MRI) (controversial)
Are MBI and CEDM really cheaper than standard MRI?

- **Yes**
  - Equipment is less expensive
  - Studies are faster (CEDM) or about as fast (MBI)

- **No**
  - Actual equipment cost may be small because MRI machine is already there and may be underutilized
What About Abbreviated MRI?

• Full protocol MRI (35 minutes):
  – Hospital facility charge $4000 - $6000
  – Negotiated rate $1800 - $3000

• Abbreviated MRI (6 minutes):
  – Hospital facility charge $4000 - $6000
  – Negotiated rate $1800 - $3000

“We don’t want to leave anything on the table.”
Hurdles to Adoption of MBI and CEDM

- CEDM: perceived risk of contrast reaction
- MBI: need to buy dedicated equipment
- CEDM: no billing code
- MBI & CEDM: not labeled for screening
  - But neither is MRI
Hurdles to Adoption (cont.)

• MRI is very profitable
  – Marginal revenue is high / marginal cost is low
  – High fixed costs need to be made up by revenue

• Institutions in the U.S. are hesitant to replace a high cost study with a low cost one

“We don’t want to leave anything on the table.”
Summary

• High risk screening is another opportunity for us to save lives

• Definition of high risk is imprecise
  – Multiple Models
  – Dependent on choice of parameters

• Cost/benefit is the issue on both a personal and societal basis

• MBI and CEDM seem to have similar performance to MRI, but other factors slow their adoption
Summary (cont.)

• A screening study is needed for CEDM/CESM to confirm comparable performance to MRI in that population