Benefits and Risks of Breast Cancer Screening – Opportunities for Precision Medicine

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DISCLOSURE

• Martin Yaffe:
  – holds shares in Volpara Health Technologies, a manufacturer of software for breast cancer imaging
  – lab has a research collaboration on breast tomosynthesis and contrast-enhanced digital mammography with GE Healthcare
    • receives no remuneration or other personal considerations related to that collaboration
  – principal of Mammographic Physics Inc which provides QC services for mammography

Learning Objectives

• To discuss the benefits and risks of breast cancer screening, and to understand how this discussion drives and is impacted by technological developments, communications, politics and guidelines
Screening for Earlier Detection of Breast Cancer

- Communications, politics and Guidelines
- Performance Characteristics
- Evidence for Benefit
- Limitations and Harms
  - Missed cancers
  - “False Positives” - Abnormal recalls, no cancer
  - Negative biopsies
  - Overdetection/overdiagnosis/overtreatment
  - Radiation risk
- Cost effectiveness – will not discuss today
- How to improve screening – new techniques
- Stratified screening

Recommendations On Breast Cancer Screening

- **American Cancer Society**
  - Individual woman's decision with guidance from primary healthcare provider
  - Screening should be available from age 40
  - and is strongly recommended from age 45
  - Performed premenopausally, should be annual (fewer deaths)
  - Switch to two years after menopause if no major risk factors
  - Recommendations were based on RCTs, modern observational studies and modeling

Canadian Task Force on Preventive Health Care

- **CTFPHC (Similar to US Preventive Services Task Force)**
  - Did not accept evidence from other than old RCTs
  - Recommend against routine mammogram screening before 50
    - Consult with physician re risk factors. Little info provided to physicians on such risk factors
    - No recommendations for high-risk women (should ideally receive MRI)
  - Biennial or triennial (no supporting evidence) screening for women over 50
  - Recommend against routine clinical exams
The Media

The New York Times

Vast Study Casts Doubt on Value of Mammograms

[Image of a cartoon with a doctor and patient discussing mammograms]
Why is there controversy about breast cancer screening?

- Intense philosophical differences regarding preventive measures vs acute care
  - Screening is expensive — many women must be screened to save a few lives
  - Money is spent now — benefit, if it occurs, comes later
  - Only 3% of women die of breast cancer
    - Screening potentially reduces mortality by 40% (when delivered ideally), so would reduce to 1.8%
    - But viewed another way screening would avert 10,000 breast cancer deaths in US each year as well as avoidance of some mastectomy and chemo
- Without question, screening has limitations. Individuals put different emphasis on their importance to support their position

Why is there controversy about breast cancer screening?

- Despite solid scientific evidence to the contrary, some authors suggest that screening doesn’t work
- These publications are covered widely by the media while careful meta-analyses are largely ignored
- News media prefer stories that disrupt the prevailing wisdom. It makes better headlines: “NEW STUDY SHOWS THAT MAMMOGRAPHY SCREENING DOESN’T SAVE LIVES!”
How Media Works

Reporters are busy, have short deadlines and do not have time to read the relevant underlying scientific literature. Instead they attempt to get balance by interviewing “the usual suspects”, i.e. one person who supports the findings of a study and one who does not. Give equal weight to both regardless of evidence.

Principles of Screening

Properties of an Ideal Screening Technique

- Sensitive – finds small “early” cancers
  - Prognostic – finds the bad cancers
- Specific – accurate in identifying when cancer is not present
- Safe
- Innocuous
- Cost effective
Performance of Modern Screening Mammography

• Cancer detection rate – 2-5 per 1000 screens
• Sensitivity – 80-85%
  – 60% in very dense breasts
• Specificity 93% on recurring screens
  – 85% on initial screens (15% of women called back)
  – 96% in Europe
• Biopsy rate – 1-1.5%
• Efficiency - 86 women needed to screen per death averted
  – 4.1 per life-year gained

Limitations of Modern Screening Mammography

• Misses 15% - 40% of cancers
  – Greatest problem in dense breasts and women at high risk (lack of sensitivity)
• 7% - 15% of women without cancer are called back after screening for “false positives” (lack of specificity)
• 2 out of 3 biopsies are negative for cancer (unnecessary biopsies?)
• 86 women needed to screen per death averted (inefficient)
• Some of the cancers are indolent and could probably have been ignored (overdetection)

The Lancet · Saturday 13 April 1985

REDUCTION IN MORTALITY FROM BREAST CANCER AFTER MASS SCREENING WITH MAMMOGRAPHY

Randomised Trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare

L. Tabar  C. J. G. Fagerberg
A. Gao  L. Balderorp
L. H. Holmberg  O. Gruenifix
U. Ljunquist  B. Lundstrom
Kupparberg Country Project  Stockholm County Project
Group*  Group*
G. Erikson  N. E. Day
F. Pettersson
The Evidence for Screening (Intent to Screen Analysis)

<table>
<thead>
<tr>
<th>Trial</th>
<th># of women</th>
<th>Age range</th>
<th>Follow-up interval (years)</th>
<th>RR for breast CA mortality</th>
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</thead>
<tbody>
<tr>
<td>New York</td>
<td>60,580</td>
<td>40-64</td>
<td>10</td>
<td>0.77</td>
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<tr>
<td>Malmö</td>
<td>42,283</td>
<td>45-69</td>
<td>8.8</td>
<td>0.96</td>
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<tr>
<td>Two-county</td>
<td>133,065</td>
<td>40-74</td>
<td>13</td>
<td>0.70</td>
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<tr>
<td>Edinburgh</td>
<td>54,054</td>
<td>45-69</td>
<td>7 and 10</td>
<td>0.72</td>
</tr>
<tr>
<td>Canada (UBC)</td>
<td>89,635</td>
<td>40-69</td>
<td>13</td>
<td>1.04</td>
</tr>
<tr>
<td>Stockholm</td>
<td>60,784</td>
<td>40-69</td>
<td>11</td>
<td>0.74</td>
</tr>
<tr>
<td>Upland</td>
<td>11,705</td>
<td>49-69</td>
<td>11</td>
<td>0.86</td>
</tr>
<tr>
<td>Age (UK)</td>
<td>160,921</td>
<td>39-41</td>
<td>10.7</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Slide courtesy Dr. Jean Seely, Ottawa

Screening - By detecting cancers earlier we reduce the incidence of the lethal cancers

- Are we accomplishing this?
More recent data: women who actually got screened
Pan-Canadian Study of Mammography Screening and Mortality from Breast Cancer

<table>
<thead>
<tr>
<th>Region</th>
<th>SMR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Columbia</td>
<td>0.58</td>
<td>0.54-0.62</td>
</tr>
<tr>
<td>Manitoba</td>
<td>0.60</td>
<td>0.52-0.68</td>
</tr>
<tr>
<td>Ontario</td>
<td>0.73</td>
<td>0.68-0.76</td>
</tr>
<tr>
<td>Quebec</td>
<td>0.59</td>
<td>0.55-0.64</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>0.41</td>
<td>0.33-0.48</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>0.64</td>
<td>0.54-0.74</td>
</tr>
<tr>
<td>Newfoundland and Labrador</td>
<td>0.67</td>
<td>0.42-0.91</td>
</tr>
</tbody>
</table>

Summary (random): 0.60 (0.52-0.67)


40% fewer breast cancer deaths

Women first participating at age 40-49

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<tr>
<td>British Columbia</td>
<td>0.58</td>
<td>0.51-0.65</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>0.42</td>
<td>0.26-0.59</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>0.66</td>
<td>0.47-0.85</td>
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</tbody>
</table>

Summary (random): 0.56 (0.45-0.67)

44% fewer breast cancer deaths

Modern Observational Studies from Screened Populations

<table>
<thead>
<tr>
<th>Study Location, age of women</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall et al 1966 (Italy, 60-75 y)</td>
<td>0.51 (0.39-0.68)</td>
</tr>
<tr>
<td>Milterberg et al 1966 (Netherlands, 50-64 y)</td>
<td>0.54 (0.37-0.79)</td>
</tr>
<tr>
<td>Fieder et al 2004 (Wales, 50-75 y)</td>
<td>0.49 (0.36-0.68)</td>
</tr>
<tr>
<td>Gable et al 2007 (Scotland, 40-)</td>
<td>0.95 (0.91-0.99)</td>
</tr>
<tr>
<td>Adgaidal et al 2008 (U.S., 50-79 y)</td>
<td>0.95 (0.23-3.51)</td>
</tr>
<tr>
<td>Poole et al 2008 (U.K., 50-74 y)</td>
<td>0.59 (0.49-0.73)</td>
</tr>
<tr>
<td>Robus et al 2008 (Australia, 50-69 y)</td>
<td>0.93 (0.63-1.38)</td>
</tr>
<tr>
<td>van Schorren et al 2011 (Netherlands, 50-69 y)</td>
<td>0.65 (0.49-0.87)</td>
</tr>
<tr>
<td>Holmström et al 2012 (Sweden, 50-69 y)</td>
<td>0.46 (0.39-0.54)</td>
</tr>
<tr>
<td>Otto et al 2012 (Netherlands; 50-69)</td>
<td>0.53 (0.40-0.66)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.51 (0.46-0.58)</td>
</tr>
</tbody>
</table>

NOTES: Weights are from random effects analyses

For women in their 40s, mortality reduction about 24%
To Benefit from Screening One Must Be Screened

Breast cancer mortality reduction in women invited versus not invited
25% reduction in mortality

Breast cancer mortality reduction in women screened versus not screened
38% reduction in mortality

TT = intention to treat  PP = per protocol

Slide = courtesy, Dr. Solveig Hofvind - Oslo


Conclusions of IARC working group

- Women 50 to 69 years of age who were invited to attend mammographic screening had, on average, a 23% reduction in the risk of death from breast cancer; women who attended mammographic screening had a higher reduction in risk, estimated at about 40%
Reduced Morbidity for Screen-Detected Cancers

- Earlier Diagnosis = More easily tolerated treatment
- Tumours < 2 cm less likely to require more surgery
  - Lumpectomy vs mastectomy
  - Sentinel node bx vs axillary dissection: less chance of lymphedema
- Tumours < 2 cm less likely to require chemotherapy
- Smaller tumours: < $$$ spent on treatment and less time off work

Slide courtesy Dr. Jean Seely, Ottawa

Earlier Detection vs Improved Therapy

- It has been suggested that with newer therapies there is no benefit in detecting breast cancers early.
  - Little evidence for this
- Rather than a tension there is actually a synergy between earlier detection and therapy
  - Easier to treat earlier disease – reduced mortality and morbidity
  - Reduction of treatment costs:
    - Stage 1 breast cancer $30,000
    - Stage 4 - $66,000


The Quality of Mammography Screening Available in the Early 1980s Does Not Reflect that of Today

Also, major advances in therapies – Trastuzumab, Aromatase inhibitors
DMIST TRIAL 2005
Pisano, Gatsonis, Hendrick, Yaffe et al.
• Compared digital mammography to SF Mammography for screening
• For women who were pre- or –peri-menopausal and/or had dense breasts
  – DM was more sensitive in detecting cancers than SFM with no loss in specificity

Improvements in mammography

Modelling
• Because no new randomized trial data available the best way to estimate benefits (and harms) of modern screening is by modelling
Modelling Health Outcomes in Screening Mammography


Work used a modified WISCONSIN breast cancer model, developed under CISNET, an NCI consortium

Outcomes

- Burden
  - Deaths due to bc
  - Life-years lost
  - QALYs lost
- Benefits
  - Deaths averted, LY gained, QALYs gained
- Harms
  - Additional deaths and LY lost, QALYs lost

How Should We Compare Benefits and Harms?

- Need a common currency
- QALYs (quality-adjusted years of life)
- Assign a utility factor (0-1 scale) that is multiplied by each year of life to describe its quality (eg reduced due to a biopsy or having chemo)
- For perfect quality of life 1 QALY = 1 life-year
### Table 1

<table>
<thead>
<tr>
<th>Screening strategy</th>
<th>Breast cancer deaths averted per 1,000 women alive at age 40</th>
<th>Mortality reduction (%) with 15 years follow-up</th>
<th>LY gained per 1,000 women alive at age 40</th>
<th>Screening examinations per woman</th>
<th>Screened per death averted</th>
<th>Screened per LY gained</th>
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<tbody>
<tr>
<td>Annual 40 to 69</td>
<td>9.1</td>
<td>50.2</td>
<td>201.1</td>
<td>30</td>
<td>2,984</td>
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<td>Annual 40 to 74</td>
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<td>53.4</td>
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<td>Annual 50 to 69</td>
<td>7.4</td>
<td>45.5</td>
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<td>160.9</td>
<td>25</td>
<td>2,484</td>
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<td>Biennial 40 to 74</td>
<td>7.3</td>
<td>38.5</td>
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<td>18</td>
<td>2,165</td>
<td>138</td>
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<td>Biennial 50 to 69</td>
<td>5.2</td>
<td>32.3</td>
<td>105.2</td>
<td>10</td>
<td>1,696</td>
<td>170</td>
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<td>Biennial 50 to 74</td>
<td>6.1</td>
<td>35.9</td>
<td>116.3</td>
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<td>1,783</td>
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<td>Triennial 50 to 69</td>
<td>4.0</td>
<td>24.6</td>
<td>80.0</td>
<td>7</td>
<td>1,557</td>
<td>222</td>
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<td>Triennial 50 to 74</td>
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<td>27.9</td>
<td>89.2</td>
<td>9</td>
<td>1,589</td>
<td>177</td>
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<td>Annual 40 to 49,Biennial 50 to 69</td>
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<td>38.7</td>
<td>158.2</td>
<td>20</td>
<td>2,651</td>
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<tr>
<td>Annual 40 to 49,Biennial 50 to 74</td>
<td>7.9</td>
<td>42.0</td>
<td>170.3</td>
<td>22</td>
<td>2,593</td>
<td>118</td>
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<tr>
<td>Annual 40 to 49</td>
<td>2.0</td>
<td>18.6</td>
<td>58.0</td>
<td>10</td>
<td>5,152</td>
<td>526</td>
</tr>
</tbody>
</table>


### Lives vs Life-Years

Both burden of breast cancer and potential value of screening shifts to younger age when life-years are considered.

### NCI Wisconsin CISNET Model

Yaffe, Mittmannt et al Health Reports 2015.
What are the “harms” of screening?

• Missed cancers – false reassurance
• Missed screens
• Radiation
• “False positives”?
• Additional negative biopsies
• Overtreatment due to overdiagnosis and/or overdetection
• Could have spent time and money on something more important?

Missed Cancers

• Sensitivity can be as high as 90% in fatty breasts when prior mammograms are available for comparison
• Can fall to 60% or lower in very dense breasts
  – Probably other techniques should be considered for screening such women
    • Ultrasound
    • Tomosynthesis
    • Breast MRI
• Missed opportunities for detection also occur if women do not attend screening at recommended intervals

False Positive

• A better name would be “Abnormal recall/ no cancer” (false alarm)
• Most women called back after screening do not have cancer
  – North America
    • After first screen recall rate is 12-14%
    • After subsequent screens ~7% related to skill, experience
  – Europe 4-5%
• Most of the recalls are to rule out the very small chance of a cancer being present. They are not “errors”
• It would be helpful if this process were made more clear to patients
Overdiagnosis

- Cancers that never would have surfaced in a woman’s lifetime if they had not been detected by screening
- Correct term is overdetection – diagnosis takes place in the path lab
- Tests used in pathology cannot fully determine if the cancer will be aggressive or indolent – thus overdiagnosis
- This leads to overtreatment (or undertreatment)

How big a problem is overdetection?

- Some have claimed 50%!
- Bleyer and Welch (2012) estimated that 22% of cancers were overdetected
- But there were large errors in their methodology - no apparent correction for lead time due to screening or temporal changes in incidence
- Pulitti has shown that if proper correction is made for these effects the estimates reduce to the range 1-10%
  - Most of the overdetection is likely in the form of DCIS
  - But DCIS can also be undertreated

Overdetection

- The question is, should we forgo the opportunity to save lives and reducing morbidity by detecting some cancers, when other cancers probably don’t need to be detected? This has been suggested.
- Perhaps a more rational approach is to use existing biomarkers (and seek new ones) that predict aggressiveness and use these to guide treatment.
  - Some cancers may receive minimal treatment or watchful waiting (as in prostate cancer)
How do Benefits and Harms of Screening Compare?

• My analysis using QALYs (caution preliminary work) Annual screening 40-74 vs biennial 50-74
• For 1000 women, followed from age 40-89
  – Benefit = 50 QALYs
  – Harm of FPs – 7.1 QALYs
  – Harm of Overdetection/overtreatment – 0.5 QALYs
  – Benefit:Harm 50/(7.6) = 6.6:1

Values for harms from work of Dr. Craig Earle - J Clin Oncol 2000 18:3302-3317

The truth is that screening is inefficient

• Must screen many women (200*) to detect a cancer and many more (2600*) to save a life.
• But, depends how you look at it:
  – If screening is carried out over an appropriate period at an appropriate interval, about one breast cancer death will be averted per 90 women screened
  – A year of life gained for every 4 women screened

* One time

Can We Do Better? - The Opportunities

• Improved sensitivity and specificity
  – Digital breast tomosynthesis
  – Ultrasound
  – Contrast imaging based on angiogenesis
  • MRI
  • CEDM
• Stratified screening
  – Breast MRI for High-Risk Women
  – Identifying other groups who should be screened differently (very low risk, intermediate risk)
Tomosynthesis – should it replace DM for breast cancer screening?

Cancer was occult on 2D mammography.

Preliminary Performance Data for Tomosynthesis

- Better imaging of the moderately dense breast
- Reduced abnormal recall rate when no cancer present – fewer false positives/greater specificity
- Improved detection of small invasive cancers
- Better characterization of cancers

TMIST (ECOG-ACRIN)

- Randomized trial in 165,000 women will compare the number of advanced/aggressive cancers detected using Tomosynthesis vs Digital Mammography
- Study Chair Etta Pisano, MD, Canadian PI Martin Yaffe, PhD

With advanced or aggressive cancers defined as:
1) All invasive cancers over 2.0 cm. in size.
2) All invasive tumors that are over 1 cm. in size and which have prognostic markers that suggest aggressive behavior (i.e. triple negative or Her2+).
3) All tumors that have positive nodes or metastases at the time of diagnosis.
Breast Ultrasound

- Detects small invasive cancers not seen on mammography
- Reduced specificity
- Handheld ultrasound is user-dependent and very labour intensive
- Performance of automated ultrasound historically not as good - improving

60F, 5-yr risk 2.5%, 24-mo US: 12 mm grade 1 IDC-DCIS, N0

ACRIN 6666

10% dx with ≥ stage IIB
Angiogenesis

- Tumour induces angiogenesis
- Resulting vessels are of poor quality & leaky

Vascularized tumour penetrated by capillaries

Leaky Angiogenic Vessels

Choyke and McDonald – Nature Medicine

Breast MRI for High-Risk Women

- Studies in Canada, Germany, The Netherlands, UK demonstrated that this method was highly accurate in detecting breast cancer in these women.
Performance of MRI vs Mammog. For High Risk Women

- Ontario High Risk Breast Screening Program
- 8,782 women ages 30-69 undergoing annual mammography and MRI (20,053 exams)

Stage Distribution of Cancers

<table>
<thead>
<tr>
<th></th>
<th>MRI Cohort N=41</th>
<th>Controls N=77</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>DCIS</td>
<td>24%</td>
<td>12%</td>
</tr>
<tr>
<td>Invasive, mean</td>
<td>0.9 cm</td>
<td>1.8 cm</td>
</tr>
<tr>
<td>≤ 1 cm</td>
<td>74%</td>
<td>35%</td>
</tr>
<tr>
<td>&gt; 2 cm</td>
<td>3%</td>
<td>29%</td>
</tr>
<tr>
<td>Node +</td>
<td>13%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Warner, E. et al. JCO 2011;29:1664-9
Abbreviated Breast MRI - Reduced Imaging Time

56-year old woman, dense breast

Images courtesy of Dr. Christiane Kuhl, Aachen, Germany

Reading MIP images

abnormal L breast

9 mm invasive cancer NST
MRI detects cancers that are occult on mammography

Images courtesy of Dr. Christiane Kuhl, Aachen, Germany

Contrast-Enhanced Digital Mammography (IV Iodine Contrast)

Relative mammography images
Standard mammography images (P & A view) showed very dense and mammographic breast with left cancer.

Axial contrast-enhanced images
Marginal sign does not correspond to the specified area on the index image. Lesion is in right breast with enhancement seen in the left breast consistent with LC.
CEDM vs MRI
• Both have superior sensitivity to mammo
• No claustrophobia
• More accessible
• More specific?
• Patient preference
• May be useful for imaging women with dense breasts and for screening those at intermediate risk

Breast Density

Non-Dense

Fibroglandular Tissue

Dense

Mammography Sensitivity

Risk of Developing Cancer

Early Matters

What’s New

Are you DENSE?
Stratified Screening: Precision medicine for detection

- What if we provided alternative screening for all women with dense or poor detectability breasts?

Stratified Screening Strategy based on Masking

- First mammogram
- Masking score: Low → Continue in mammolo screening
- Masking score: High → Alternative screening (tomo, MRI, US, ...)

Impact: fewer missed cancers, fewer call-backs?

Detectability Map (brighter = easy to see lesion)
Radiomic Masking Index

- A measure of the masking probability or risk caused by density and its arrangement in a given mammogram
- Based on image texture and "detectability"

Stratified Screening by Masking

Mainprize JG, Alonzo-Proulx O, Yaffe MJ

<table>
<thead>
<tr>
<th>Model</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI-RADS</td>
<td>0.67 [0.57-0.76]</td>
</tr>
<tr>
<td>DET-mask</td>
<td>0.79 [0.69-0.87]</td>
</tr>
<tr>
<td>CNN-mask</td>
<td>0.79 [0.70-0.89]</td>
</tr>
<tr>
<td>DET + CNN</td>
<td>0.82 [0.72-0.90]</td>
</tr>
</tbody>
</table>

We need better tools in the pathology lab to distinguish killer cancers from indolent ones.
Example of MxIF in breast cancer – validation vs IHC4

Multiplex Immunofluorescence (MxIF) - Bartlett Group/ GE GRC

IHC4

ER, PgR, HER2, Ki67, P21, CD3, CD8

Immune

CD3, PD-1, CD8, PD-L1

+ Segmentation markers

Cytokeratin (epithelial)
Ribosomal S6 (cytoplasm)
Na⁺/K⁺ATPase (membrane)