Now that we can walk are we ready to run?

From single-cancer screening to multi-cancer early detection

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Fred Hutchinson Cancer Research Center
And
CEDAR at the Knight Cancer Institute
Disclosures

• Dr Etzioni has consulted for Grail in the past
• Dr Etzioni holds shares in Seno Medical
Ovarian cancer - a poster child for early detection
Flashback: A biomarker for ovarian cancer

• CA-125 is a protein that is encoded by the MUC16 gene
• Discovered as marker for ovarian cancer in the early 1980s
• Initially detected using a murine monoclonal antibody OC125

Reactivity of a Monoclonal Antibody with Human Ovarian Carcinoma

ABSTRACT A murine monoclonal antibody (OC125) has been developed that reacts with each of six epithelial ovarian carcinoma cell lines and with cryopreserved tumor tissue from 12 of 20 ovarian cancer patients. By contrast, the antibody does not bind to a variety of nonmalignant tissues, including adult and fetal ovary. OC125 reacts with only 1 of 14 cell lines derived from nonovarian neoplasms and has failed to react with cryostat sections from 12 nonovarian carcinomas.

Journal of Clinical Investigation 1981
Toward an Optimal Algorithm for Ovarian Cancer Screening with Longitudinal Tumor Markers

Steven J. Skates, Ph.D.,* Feng-Ji Xu, M.D.,† Yin-Hua Yu, M.D.,† Kerstin Sjövall, M.D., Ph.D.,‡ Nina Einhorn, M.D., Ph.D.,‡ YuChiao Chang, Ph.D.,* Robert C. Bast, Jr., M.D.,† and Robert C. Knapp, M.D.*
Risk Algorithm Using Serial Biomarker Measurements Doubles the Number of Screen-Detected Cancers Compared With a Single-Threshold Rule in the United Kingdom Collaborative Trial of Ovarian Cancer Screening


• UKCTOCS trial started in 2001: N = 202,000
• 2 screen arms  **MMS** used ROCA to triage to ultrasound  
  **USS** used ultrasound only

MMS sensitivity was 85.8%
MMS specificity was 99.8%
3.8 unnecessary surgeries per cancer detected
Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

15% mortality reduction on MMS arm (p=0.1)
Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

Usha Menon, Aleksandra Gentry-Maharaj, Matthew Burnell, Naveena Singh, Andy Ryan, Chloe Karpinskyj, Giulia Carlino, Julie Taylor,
Susan K Massingham, Maria R Cabral, Simon Leeson, Tim Mould, Mark Bristow,
Steven J Skates, Ian J Jacobs, Martin Donovan,
Peter Smith, David Elmore, Mark H vine, Michael Sung, Andrew J Heath, Matthew T Coulam, John D Jewett

MORTALITY

- No screening group
- MMS group
- USS group

Cumulative incidence of invasive epithelial ovarian and endometrial cancer per 100,000 women

MMS vs no screening HR 1.01 (95% CI 0.90–1.13); p=0.92
USS vs no screening HR 1.01 (95% CI 0.90–1.13); p=0.89
Early detection at a crossroads

Disappointment: Screening for Ovarian Cancer Does Not Cut Deaths

A large-scale randomised trial of annual screening for ovarian cancer, led by UCL researchers, did not succeed in reducing deaths from the disease, despite one of the screening methods tested detecting cancers earlier.

Multi-Cancer Molecular Screening Assays Primed for Clinical Implementation in 2021

Jan 11, 2021 | Molika Ashford
freenome
Spot the pattern,
treat the cancer.
Tests differ in their algorithms and outputs

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cancers</td>
<td>Up to <strong>50 cancers</strong> Sensitivity assessed for 12</td>
<td><strong>7 cancers</strong></td>
<td>Latest prospective study identified cancer in <strong>10 organs</strong></td>
</tr>
<tr>
<td>Features</td>
<td>cfDNA methylation patterns</td>
<td>cfDNA fragment size distributions cfDNA mutations</td>
<td>cfDNA mutations Protein biomarkers</td>
</tr>
<tr>
<td>Output</td>
<td><strong>Cancer indicator</strong> <strong>Tissue of origin</strong></td>
<td><strong>Cancer indicator</strong> <strong>Tissue of origin</strong></td>
<td><strong>Cancer indicator</strong> (Whole-body PET-CT for tissue of origin)</td>
</tr>
</tbody>
</table>
What we know about the new tests

1. They can find cancer when we know it is there

(With high specificity)

Detection and localization of surgically resectable cancers with a multi-analyte blood test

Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA

M. C. Liu¹, G. R. Oxnard², E. A. Klein³, C. Swanton⁴,⁵, M. V. Seiden⁶ & on behalf of the CCGA Consortium⁷

Annals of Oncology, 2020

**B. Sensitivity**

**Pre-specified cancer types**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Training set</th>
<th>Validation set</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (143</td>
<td>62)</td>
<td></td>
</tr>
<tr>
<td>II (142</td>
<td>62)</td>
<td></td>
</tr>
<tr>
<td>III (241</td>
<td>102)</td>
<td></td>
</tr>
<tr>
<td>IV (302</td>
<td>130)</td>
<td></td>
</tr>
</tbody>
</table>

**Sensitivity by stage**

**C. Tissue of origin (TOO) accuracy**

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>Training set</th>
<th>Validation set</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (49</td>
<td>22)</td>
<td></td>
</tr>
<tr>
<td>II (107</td>
<td>41)</td>
<td></td>
</tr>
<tr>
<td>III (202</td>
<td>82)</td>
<td></td>
</tr>
<tr>
<td>IV (271</td>
<td>120)</td>
<td></td>
</tr>
</tbody>
</table>

**Fraction correctly localized by stage**
What we know about the new tests
2. They are highly specific

- A highly specific test has a **low false-positive rate**
- This is important in cancer screening because the majority of persons tested do not have cancer

High specificity means low:

- False positives
- True positives

Unnecessary biopsies
Cancers detected
But policy is driven by outcomes

**PERFORMANCE**
- Sensitivity
- Specificity

**OUTCOMES**
- Lives saved
- Metastases prevented
- Overdiagnosis/overtreatment
- Unnecessary biopsies
- Costs
From performance to outcomes: three drivers

**PERFORMANCE**

1. **Sensitivity** to detect latent disease
2. **Opportunity** to detect early latent disease
3. **Curability** of early* disease

**OUTCOMES**
From performance to outcomes
1. Sensitivity to detect latent disease

- Published sensitivities relate to time of (non-screen) diagnosis not before
- Required: ability to readily and accurately confirm presence of disease
From performance to outcomes
2. Opportunity to detect early latent disease

- Published studies tell us nothing about the duration of early-stage disease
- Varies across cancers; not easy to identify without data from screened cohorts
From performance to outcomes

3. Curability of early* disease

Early stage survival  Advanced stage survival

Early* : a diagnosis that has been shifted to an early stage by screening
From performance to outcomes: three drivers

1. **Sensitivity** to detect latent disease
2. **Opportunity** to detect early latent disease
3. **Curability** of early* disease
What did we learn from the ovarian trial?

<table>
<thead>
<tr>
<th>Sensitivity of MMS to detect latent disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated sensitivity close to 85% based on CA125 and ultrasound imaging of the ovaries. But early Type II (aggressive) tumors begin in the <strong>Fallopian tubes</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Curability of early* disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Despite <strong>10%</strong> reduction in stage III+IV incidence, <strong>no difference</strong> in disease-specific mortality</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opportunity to detect early latent disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>In MMS arm incidence of stage IV reduced by almost <strong>25%</strong></td>
</tr>
<tr>
<td>But incidence of stage II+IV reduced by only <strong>10%</strong></td>
</tr>
</tbody>
</table>
How can we learn about whether performance of multi-cancer tests will translate to outcomes?

**Screening trials**
- Least do-able, most informative but rarely the final word

**Prospective screening studies**
- More do-able, less informative, no control group

**Modeling analyses**
- Subject to information gaps and make many assumptions
- Can give ballpark predictions

Sensitivity? Opportunity? Curability?
A prospective study

- 10,000 women given DETECT-A test
- Two positive tests followed by PET-CT

**26 cancers detected by the test**
- 24 additional cancers by standard screening
- 46 cancers diagnosed by neither approach
- 127 positives recommended imaging

Sensitivity? Opportunity? Curability?

Lennon et al., Science 369, 49 (2020)
A modeling study

Expected harms and benefits of multi-cancer early detection tests

This calculator provides a transparent computational framework for translating the diagnostic performance of a multi-cancer test to clinically relevant outcomes. Outcomes of single-occasion testing performed at age 50, 60, or 70 for 100,000 persons with specified sex and race category are generated given test characteristics specified by the user and estimates of disease prevalence and disease-specific mortality in the United States. A user can specify test characteristics for detecting specific cancers, the associated mortality reduction for cancers detected by the test, and which cancers to include in the test's target set.

See the Details tab for more information and the Calculator tab to see the calculator in action.

Test characteristics

<table>
<thead>
<tr>
<th>Site</th>
<th>Sensitivity</th>
<th>Localization</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung and Bronchus</td>
<td>0.67</td>
<td>0.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>0.67</td>
<td>0.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Ovary</td>
<td>0.67</td>
<td>0.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.67</td>
<td>0.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Urinary Bladder</td>
<td>0.67</td>
<td>0.9</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Expected outcomes per 100,000 persons

- Exposed to unnecessary confirmation: 1038
- Cancers detected: 403
- Cancer deaths prevented: 24

http://mced-calculator.fredhutch.org

Wrap-up

• Multi-cancer early detection is a **critically important technology advance**
  • Complexities of early detection are as present as ever
• Expect **few exposed to unnecessary biopsy** per versus cancer detected
  • More complex confirmation process: **how should this be done?**
• Tests will likely detect some cancers that we do not currently screen for
  • Unclear from current data **whether their fate will be altered**
• Heed timing and message of the **ovarian cancer screening** story
  • Learn also from the **prostate cancer story**
PSA and prostate cancer screening
Take action

• Multi-cancer early detection is a critically important advance
• Expect few exposed to unnecessary biopsy per versus cancer detected
  • More complex confirmation process: how should this be done?
• Tests will likely detect some cancers that we do not currently screen for
  • Unclear at this point whether their fate will be altered
• Heed timing and message of the ovarian cancer screening story
  • Learn also from the prostate cancer story

_Strongly urge the development of a data resource to track utilization and outcomes of these tests while we await further results regarding harm, benefit and cost._
Thank you!

- Boshen Jiao
- Roman Gulati
- Noel Weiss
- Scott Ramsey
- Tina Clarke-Dur
- Earl Hubbell
- Christos Patriotis

Rosalie and Harold Rea Brown chair at Fred Hutch
CEDAR at the Knight Cancer Institute
NCI’s Cancer Intervention and Surveillance Modeling Network

See http://mced-calculator.fredhutch.org for our new multi-cancer test calculator that permits configuration of a multi-cancer test and projection of select outcomes