How Do We Get New CRC Screening Tests From Bench to Bedside?

The Dilemma of Intended Use, Sufficient Sample Size, and Regulatory Oversight

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How Good Should a Test Be?

RESOURCES

Sensitivity
Specificity

Individual Versus Population Benefit

Cost
Early health economic modelling

Typical health economic studies

I

II

III

Coverage and adoption

Market Access

First clinical use

First in-human testing

Product life cycle

Early-stage Value Assessment

Mainstream Value Assessment

Decision uncertainty

Ijzerman & Steuten, Applied Health Econ Health Policy 2011
Biggest Challenges?

• Lack of sensitivity for early CRCs and Advanced Adenomas

  Depends on point of view (how good is “good enough” ?)

• **Availability of (intended use) samples and funding beyond Phase II/III studies**


• Clinical vs Laboratory assays

• Cost of Phase IV Trial

  Don’t have for FIT/Colonoscopy

  Comparison to accepted test adequate?

• Meaning of false positives?
## Study Design Requirements for Biomarker Development

<table>
<thead>
<tr>
<th>Phase</th>
<th>Process</th>
<th>Sample selection</th>
<th>Sample size</th>
<th>Time frame</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I - Preclinical discovery</td>
<td>Hypothesis –driven Identification of candidates</td>
<td>Model systems</td>
<td>10s</td>
<td>6-12 mos</td>
<td>Prioritized list of candidates</td>
</tr>
<tr>
<td>Phase II - Preclinical verification</td>
<td>Development of assays and candidate testing</td>
<td>Proof of concept; case and control subjects</td>
<td>10-50</td>
<td>6-12 mos</td>
<td>Assessment of analytical platform; Detection of disease in serum</td>
</tr>
<tr>
<td>Phase III - Preclinical validation</td>
<td>Generation of protein signature for study objective</td>
<td>Retrospective selection with known disease outcomes</td>
<td>100-500</td>
<td>6-12 mos</td>
<td>Performance of biomarker Define criteria for clinical evaluation</td>
</tr>
<tr>
<td>Phase IV - Clinical evaluation</td>
<td>Clinical assay development Determine accuracy</td>
<td><strong>Prospective collection from intended population</strong></td>
<td>500-1000</td>
<td>&gt;24 mos</td>
<td>Sensitivity and specificity</td>
</tr>
<tr>
<td>Phase V - Disease Control</td>
<td><strong>Define population impact</strong></td>
<td>Randomly from target population</td>
<td>Many 1000s</td>
<td>Many years</td>
<td>Effect on disease management</td>
</tr>
</tbody>
</table>
Figure 3

NCI’s Early Detection Research Network

- Candidate Biomarkers Identified (BDLs, CVCs, BRLs)
- Development (BDLs, CVCs, BRLs)
- Pre-validation (BDLs, CVCs, BRLs, DMCC)
- Validation (BDLs, CVCs, BRLs, DMCC)
- Cost Effective?

- Discovery Biomarkers from both EDRN and Non-EDRN researchers
- Determine sensitivity and specificity. Case control
- If sensitivity and specificity meet defined performance standards, verify using new blinded specimens. Cross sectional
- Perform longitudinal biomarker validation trial.
- Utilization of biomarker in clinical care setting

Re-evaluate biomarker for utility as an early detection or risk marker
Re-evaluate biomarker use in clinical setting
EDRN GLNE 10 Study
Prospective Collection in Average-Risk CRC Screening Population

Stool Collection
Blood Collection
Urine Collection
Data Elements

FIT
Preparation procedure
Colonoscopy

4,881 screening subjects with complete data set

Colorectal cancer 10 (0.20%)
8 early stage (one stage 0, five stage I, two stage 2), one stage III, one stage IV

Screen-relevant neoplasia (cancer + advanced adenomas) 501 (10.3%)
How Do We Reach Adequate CRC Event Rates in CRC Screening Trials?

• Enrich by age of screening population
  
  Common in several previous and ongoing trials

• Primary practice networks versus tertiary referral centers

• Supplement prospective screening events with cross sectional collections in patients with in situ untreated screen-detected cancers

  Example: supplement EDRN GLNE 10 (prospective trial) with EDRN 007

What Will The FDA Allow?

True “screening” (first time/subsequent within guideline-defined interval) versus surveillance?
This Little Piggy Went to Market

Guidelines USPSTF
Regulatory FDA
Payors CMS

The Yellow Brick Road to Market
Follow the Yellow Brick Road

- **Regulatory Path:** The candidate product as described will be required to follow a Class III device regulatory pathway, requiring a Pre-Market Approval (PMA) submission, demonstration of safety and efficacy, and premarket approval prior to market entry. In fact, FDA specifically states in its guidance documents that tumor marker in vitro diagnostic assays intended for cancer screening use will be classified as Class III based on risk benefit analysis.

- **Reimbursement Strategy:** Colorectal cancer screening is broadly considered a health benefit that is cost effective, and with the advent of expensive new treatments, may be cost saving. CRC screening guidelines have been issued by the US Preventive Services Task Force, and by a number of professional societies (ACS, AGA, ACG, Multi-Society Task Force, NCCN, etc.). Based on these recommendations and their supporting evidence, CMS and most private payers provide coverage for CRC screening, though co-pay requirements vary. In addition, beginning in 2004, the NCQA included CRC screening as a HEDIS measure to help drive participation and most recently, under the Affordable Care Act (ACA), colorectal cancer screening tests meeting standards (a US Preventive Services Task Force rating of A or B) are covered without co-pay.

How is this determined for a screening test?
The Long and Winding Road
In the United States, the development and marketing of commercial tests are regulated by the U.S. Food and Drug Administration (FDA). They are considered "medical devices" and, specifically, "in vitro diagnostic devices (IVD)." As such, they must be evaluated and approved by the FDA. Likewise, many countries around the world have agencies comparable to the FDA that are responsible for approving the use of clinical laboratory tests. Examples of commercial tests and tests systems that are often sold as kits to various laboratories include tests that detect and/or measure glucose, cholesterol, therapeutic drugs, tumor markers, and infectious diseases.
FDA Class 3 Tests

• This is the most stringent category. This class includes tests that have a new use or for which there is not enough information about their safety and effectiveness to protect the public with just general or even special controls and/or tests that are of substantial importance in preventing impairment of human health.

• These tests generally require submission of a pre-market approval (PMA) application with valid findings from human clinical trials that demonstrate that the device is clinically effective for its intended use. In addition to reviewing and approving the clinical data from the company-sponsored trials, FDA also confirms that the device will be manufactured in conformance to good manufacturing practices.
Clinical Application

• Define the target population and clinical setting intended for use of the biomarker or screening test.

• Define subject inclusion and/or exclusion criteria and process for enrollment.

• Define the setting for specimen collection.

• Ensure adequate generality in the population studied.

Outcome

• Define the outcome of interest (early detection versus mortality reduction).

• Specify procedures for ascertaining and measuring the outcome.

What comparator is acceptable?
Rewriting Life

White-people-only DNA tests show how unequal science has become

Companies are selling disease-risk tests that only work in people of European ancestry. They hope to fix that soon.

by Antonio Regalado  October 18, 2018

Genetics research 'biased towards studying white Europeans'

Ethnic minorities set to miss out on medical benefits of research, scientist warns

Hannah Devlin Science correspondent

Mon 8 Oct 2018 01.00 EDT

Genetics has learned a ton — mostly about white people. That’s a problem.

The overwhelming whiteness of genetics research is holding back medicine.
Centers for Medicare and Medicaid Services (CMS) Reimbursement Criteria for Average-Risk CRC Screening (Blood-Based Biomarkers)

- FDA market authorization with an indication for colorectal cancer screening; and

- Proven test performance characteristics for a blood based screening test with both sensitivity greater than or equal to 74% and specificity greater than or equal to 90% in the detection of colorectal cancer compared to the recognized standard (accepted as colonoscopy at this time), based on pivotal studies included in the FDA labeling; and

- Inclusion as a recommended routine colorectal cancer screening test in at least one professional society guideline or consensus statement or United States Preventive Services Taskforce (USPSTF) recommendation.
Commercial Blood Tests on the Horizon

Cell-free circulating tumor-derived DNA (ctDNA) /Methylated DNA markers
  • Epi proColon -Methylated septin 9 FDA approved (limited indication) but not guideline recommended- Epigenomics
  
  • ColveraDS ™ Methylated BCAT1 and IKZF1 Clinical Genomics (FDA submitted)
  
  • ECLIPSE (Evaluation of the ctDNA LUNAR Test in Average Patients Screening Episode) Guardant Health

Combined ctDNA and protein markers
  • Cancer SEEK ➔ THRIVE ➔ EXACT ( BLUE-C 2 complementing stool panel)
  
  • PREEMPT CRC (PREvention Employing a Multiomics Plasma-Based Test for Colorectal Cancer Freenome Inc

Glycoproteins
  • Galectin-3 ligand assay panel (EDRN-derived )

Nucleosome Markers
  • Nu.Q™ technology VolitionRx
… if the current trends continue, the number of cancer cases diagnosed annually by 2050 is likely to double as a result of population aging. So if we as a society hope to head off the coming storm, we better get more serious about cancer prevention soon.

“If people are constantly falling off a cliff, you could place ambulances under the cliff or build a fence on top of the cliff. We are placing too many ambulances under the cliff” — Denis Burkitt
SAVE THE DATE!

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In cooperation with
103rd Congress of the Japan Gastroenterological Endoscopy Society

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