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**Early Detection of Colorectal Neoplasia by Multi-target Stool DNA: Visions Realized and Voyages Beyond**

Disclosure of Conflict of Interest (List)

<table>
<thead>
<tr>
<th>Exact Sciences (Madison Wisconsin, USA)</th>
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</thead>
</table>

[www.comtecmed.com/cigi | cigi@comtecmed.com]
Early Detection of Colorectal Neoplasia by Multi-target Stool DNA: Visions Realized and Voyages Beyond

John B. Kisiel, MD
Disclosures

Relationship with Exact Sciences

- *Mayo Clinic*
  - Equity investor
  - Licensed technologies
- *Dr. Kisiel*
  - Inventor of intellectual property
  - Research collaborator
  - No financial relationship with Cologuard™
Colorectal Cancer

- Remains a major killer worldwide, #2 in USA

- Shift toward right side
  - Now ~50% R-side in US
  - Olmsted county: ~60% R-side

Figure (CGH 2005;3:150)

- Conventional screening tools
  - Biased toward L-side
  - Invasive, unwieldy prep, costly, insensitive and/or inaccessible

- Imperative to innovate
Detection of CRN\(^1\) by Fecal Blood Screening

**Effect of Tumor Site**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity %</th>
<th>Right</th>
<th>Left</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morikawa (n=21,805)(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIT</td>
<td>16</td>
<td>31</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ahlquist (n=4,482)(^3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoccult</td>
<td>9</td>
<td>21</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Hemoccult Sensa</td>
<td>13</td>
<td>31</td>
<td></td>
<td>0.01</td>
</tr>
</tbody>
</table>

\(^1\)CRC + advanced adenomas
\(^2\)Gastroenterology 2005;125:422 (colonoscopy as gold standard)
\(^3\)Ann Intern Med 2008;149:441 (colonoscopy as gold standard)
Flexible Sigmoidoscopy

- Randomized controlled trial in UK (n=113,195)
  - CRC incidence: 33% ↓
  - CRC mortality: 43% ↓

All distal

- No effect on proximal CRC rates

Atkin et al, Lancet 2010;375:1624
Effectiveness of Screening Colonoscopy?

Large case-control & cohort studies

- **CRC mortality** (Ann Intern Med 2009;150:1)
  - L side ~ 70%
  - R side 0%

- **CRC incidence** (JNCI 2010;102:89)
  - L side ~ 70%
  - R side 0%

- **CRC incidence** (NEJM 2013; 356:1106)
  - L side 76%
  - R side 27%
What are the critical target lesions for CRC screening?

- Curable stage cancer
- Highest risk pre-cancers
  - Large adenoma (i.e. ≥2cm)
  - Large sessile serrated adenoma
  - High grade dysplasia (>80% in polyps >2cm)
Stool DNA Testing

Biological Basis

- Exfoliation
  - Abundant
  - Continuous
  - Cancer > normal
- DNA as marker
  - Signature changes
  - Stable
  - Amplifiable

Ahlquist et al. Hum Pathol 2000 31:51
Multi-target Stool DNA Test

*Addresses all elements for effective detection*

- High sensitivity for CRC & greatest-risk precancer
- Unaffected by tumor site
- Operator independent (automated)
- Noninvasive
- No cathartic preparation
- No diet or medication restriction
- Off-site collection
- Widely accessible

Sensitivity

Compliance

Access
Multitarget Stool DNA Testing for Colorectal-Cancer Screening

Thomas F. Imperiale, M.D., David F. Ransohoff, M.D., Steven H. Itzkowitz, M.D., Theodore R. Levin, M.D., Philip Lavin, Ph.D., Graham P. Lidgard, Ph.D., David A. Ahlquist, M.D., and Barry M. Berger, M.D.

Cologuard™ Multi-target Stool DNA Test
Optimized & Automated

- Simple device for collection & mailing
- Preservative buffer
- Targets multiple markers
  - Methylated BMP3 & NDRG4
  - Mutant KRAS
  - β-actin (human DNA)
  - Hemoglobin (FIT)
- Sensitive multiplex DNA assay (QuARTS)
Pivotal multicenter cross-sectional study: 10,000 patients from 90 sites
Pivotal Screening Study
“DEEP-C”

- Cologuard prior to blinded, high-quality screening colonoscopy

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity*</th>
<th>Superiority over FIT, all categories</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>Stage I-II</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td><strong>Adv Precancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All**</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>HGD</td>
<td>69%</td>
<td></td>
</tr>
</tbody>
</table>

*S at specificity 90% (subset with normal colonoscopy) **Adv adenoma + serrated polyp ≥1cm
CRC Sensitivity by Stage

MT-sDNA  94%
FIT       70%

NO Difference between left and right sided CRC

Stage I
- MT-sDNA: 90%
- FIT: 29%
- N: 29

Stage II
- MT-sDNA: 100%
- FIT: 66%
- N: 21

Stage III
- MT-sDNA: 90%
- FIT: 90%
- N: 10

Stage I-III
- MT-sDNA: 93%
- FIT: 73%
- N: 60

Stage IV
- MT-sDNA: 75%
- FIT: 75%
- N: 4

MT-sDNA — dark blue
FIT — red
Advanced Adenoma Sensitivity by Size

Highest risk to progress

<table>
<thead>
<tr>
<th>Size</th>
<th>MT-sDNA</th>
<th>FIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9 mm</td>
<td>30.3%</td>
<td>15.2%</td>
</tr>
<tr>
<td>10-19 mm</td>
<td>39.0%</td>
<td>20.9%</td>
</tr>
<tr>
<td>20-29 mm</td>
<td>64.6%</td>
<td>43.0%</td>
</tr>
<tr>
<td>&gt;30 mm</td>
<td>68.4%</td>
<td>42.1%</td>
</tr>
</tbody>
</table>
Sessile Serrated Polyp Detection in Screen Setting

Stool DNA vs FIT

Berger et al. DDW 2014
## Cologuard Screening

Hypothetical Program Sensitivity (q3 years)

<table>
<thead>
<tr>
<th></th>
<th>Large Precancer*</th>
<th>CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen 1</td>
<td>42-66</td>
<td>93</td>
</tr>
<tr>
<td>Screen 2</td>
<td>71-91</td>
<td>(99)</td>
</tr>
<tr>
<td>Screen 3</td>
<td>90-98</td>
<td>--</td>
</tr>
</tbody>
</table>

* 1-2cm size cutoff, assume volume doubling time 6 years
Cologuard Stool DNA Test for CRC Screening Approved in United States

- August 11, 2014
- First medical device/test to have parallel approval
  - United States Food and Drug Administration
  - Centers for Medicare/Medicaid Services
- Screening of average-risk, asymptomatic patients
- Age 50-84
- 3-year screening interval
Beyond CRC Screening: New Concepts in Molecular Markers for GI Cancers

• GI tract cancers frequently methylated

• Opportunities for screening/surveillance:
  • Inflammatory bowel disease (IBD)- CRC
  • Barrett’s esophagus
  • Pancreatic cancer

• Site-specific methylation: pan-GI screening
Stool DNA Detects IBD Dysplasia and CRC

Kisiel et al. Aliment Pharm & Ther 2013;37:546
DNA Methylation in Cytology Brushings Detects Barrett’s Esophagus (BE)

Iyer et al. DDW 2014

AUC

NDRG4 = 1.0

BMP3 = 0.99
Methylated *ADCY1* in Pancreatic Juice Detects Pancreatic cancer (PC) and IPMN*

*Intraductal pancreatic mucinous neoplasms

**Chronic pancreatitis

Raimondo et al. DDW 2014
Tissue Methylation Predicts Site of GI Neoplasm

Kisiel et al. DDW 2013
Summary

• Cologuard multi-target stool DNA test:
  • Highly accurate for CRC, high-risk polyps
  • User-friendly, wide access
  • Approved for average-risk CRC screening

• GI tract neoplasms aberrantly methylated
• Feasibility shown to expand molecular testing
• Potential to reduce global cancer impact