Stool DNA Testing
A Closer Look at Specificity

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Disclosures

Relationship with Exact Sciences

– *Mayo Clinic*
  • Equity investor
  • Licensed technologies

– *Dr. Ahlquist*
  • Scientific Advisor
  • Inventor of licensed technology
  • Research collaborator
Multi-target Stool DNA Test

- FDA Approved (*Cologuard*, Exact Sciences)
- Endorsed in screening guidelines (ACS, USPSTF, NCCN)
- Included in Quality Measures (HEDIS, STARS)
- Covered by Medicare (CMS) and 3rd party payors
- Exponential growth in adoption
  - 42% of users report no prior CRC screening
Point Sensitivity

Cancer  92-100%
Stage I-II  94-100%
Adenoma
SSP
# Program Sensitivity

**Modeled Estimate (q3yr testing)**

## Cumulative Sensitivity %

**For Lesion Cohort**

<table>
<thead>
<tr>
<th></th>
<th>Large Precancer*</th>
<th>CRC (I-II)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-2 cm</td>
<td>HGD</td>
</tr>
<tr>
<td><strong>Screen 1</strong></td>
<td>42-66</td>
<td>69</td>
</tr>
<tr>
<td><strong>Screen 2</strong></td>
<td>71-91</td>
<td>93</td>
</tr>
<tr>
<td><strong>Screen 3</strong></td>
<td>88-98</td>
<td>(99)</td>
</tr>
</tbody>
</table>

*Assumptions

1. Size doubling time: 6 yrs
2. Independent measurements

Ahlquist. DDS 2015; 60:623
## Point Specificity

From screening studies (using blinded colonoscopy as criterion standard)

<table>
<thead>
<tr>
<th>Study</th>
<th>Specificity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>US study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>90%</td>
<td>Imperiale et al. NEJM 2014</td>
</tr>
<tr>
<td>Ages 50-65</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>Alaska study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>93%</td>
<td>Redwood et al. MCP 2016</td>
</tr>
</tbody>
</table>

Real-world specificity may be higher when endoscopists aware of positive MT-sDNA
Knowledge of **Positive MT-sDNA** Improves Yield & Quality of Colonoscopy

<table>
<thead>
<tr>
<th></th>
<th>Un-blinded</th>
<th>Blinded</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(172)</td>
<td>(72)</td>
<td></td>
</tr>
<tr>
<td>Any polyp</td>
<td>78%</td>
<td>60%</td>
<td>0.0047</td>
</tr>
<tr>
<td>Any adenoma or SSP</td>
<td>70%</td>
<td>53%</td>
<td>0.013</td>
</tr>
<tr>
<td>Advanced CRN</td>
<td>28%</td>
<td>21%</td>
<td>0.27</td>
</tr>
<tr>
<td>Flat R-sided polyp</td>
<td>40%</td>
<td>9%</td>
<td>0.0017</td>
</tr>
<tr>
<td>Med # polyps/patient</td>
<td>2</td>
<td>1</td>
<td>0.0007</td>
</tr>
<tr>
<td>Med withdrawal time</td>
<td>19 min</td>
<td>13 min</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Johnson et al. Gastrointest Endosc 2017; 85:657
Program Specificity

Critical metric: average false positives/year

• **FIT q1yr**
  – With point false pos rate of 3-5%, average false-positives would be $\sim 3\%-5\%/yr$

• **MT-sDNA q3yr**
  – With point false pos rate of 7-10%, average false-positives would be $\sim 2\%-3\%/yr$
  – Compared to conventional CRC screening approaches*
    • Highest benefit/harm ratio
    • Fewest lifetime colonoscopies

*2016 USPSTF Guidelines (JAMA 2016)
Do false-positives warrant further evaluation?
MT-sDNA Screening (from US multicenter study)

F/U on False-positives

- Hilsden et al. DDW 2016 (Calgary)
  - Total studied (772)
    - CRC (7), 100% MT-sDNA pos; Adv ad (49), 53% MT-sDNA pos
    - MT-sDNA pos & Colonoscopy neg or non-adv polyps (118)
      - One metastatic pancreatic cancer after 6 mos F/U

- Geenen et al. DDW 2017 (WI, IN)
  - Colonoscopy neg or non-adv polyps (187); med 4 yr F/U
    - MT-sDNA neg (150) No cancers
    - MT-sDNA pos (37) One parotid tumor
Mayo Clinic “Long-Haul” Study
F/U of false-positive stool DNA

- N=1050 (3 pre-approval studies)
- Median F/U 4 yrs (range 3.5-5.3)
- Only BMP3 + NDRG4 markers eval’d
  - By per protocol & calibrated 90% cutoffs
- HRs for subsequent AD cancers (n=8)
  - Per protocol cutoff  1.3 (0.3–6.7)
  - Calibrated cutoff      4.1 (1.0–17.6)
- Observed incident AD cancers in FP group < expected in gen pop (SEER)

Cotter et al. CEBP 2017;26:614
MT-sDNA Summary

• High program sensitivity and specificity for CRC and advanced polyps
• Program false-positive rate at q3y estimated to be lower than that of FIT at q1yr
• Very low rate of incident AD cancers among false-positives over medium F/U duration

Based on findings to date, clinical workup of MT-sDNA false-positives not warranted.