Economic Evaluation of Cancer Screening
- Case of Colorectal Cancer –

Cost-Effectiveness analysis of stool DNA to Screen for Colorectal Cancer

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Frascati, Italy

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SimCRC: Karen Kuntz, Amy Knudsen
Models part of NCI’s CISNET program
Outline

- Background
- Microsimulation modeling
  - MISCAN
  - SimCRC
- Principles of incremental cost-effectiveness analysis
- Results
- Discussion
Background
Colorectal Cancer

- CRC is 2nd cause of cancer death in US
- CRC develops through adenoma-carcinoma pathway:
Colorectal Cancer Screening

- CRC (death) can be prevented by screening

- Several screening options:
  - Fecal Occult Blood Testing (FOBT)
  - Flexible sigmoidoscopy
  - Colonoscopy

- Stool DNA (sDNA) developing technique
EXACT Sciences developed first stool DNA screening test: PreGen-PlusTM

Several improvements in version 1.0 and 1.1

EXACT asked the Centers for Medicare and Medicaid Services (CMS) for national coverage determination on PreGen-PlusTM, version 1.1

Two CISNET modeling groups were asked to:

Determine reimbursement cost at which this stool DNA test could be a cost-effective alternative to current screening options
Microsimulation Modeling of Colorectal Cancer
Comparative modeling approach

- Used two independently developed models for colorectal cancer:
  - MISCAN
  - SimCRC

- Comparative modeling:
  - adds credibility to the modeling results
  - serves as a sensitivity analysis on the underlying structural assumptions of the models
Population Simulation Model

Risk factor trends
Screening behavior
Diffusion of new treatments

CRC Model

CRC incidence & mortality

Calendar Time
Modeling of natural history of CRC

Datasources:
- Adenoma: Autopsy studies, Colonoscopy studies
- Preclinical Cancer: Dwell time
- Clinical Cancer: SEER Incidence
- Death: US Mortality
Modeling of a life-history

Life history without CRC

- Birth
- Development of first adenoma
  - Adenoma
  - Late adenoma
  - Preclinical cancer
  - Clinical cancer
- Death from other causes

Development of second adenoma

- Adenoma
- Late adenoma
- Preclinical cancer
- Clinical cancer
- Death from CRC

Combined life history with CRC

- Birth
- Adenoma
- Late adenoma
- Preclinical cancer
- Clinical cancer
- Death from CRC
Modeling the effect of screening

Life history with CRC, but without screening

- Birth
- Adenoma
- Late adenoma
- Preclinical cancer
- Clinical cancer
- Death from CRC

Development of first adenoma

- Adenoma
- Late adenoma

Development of second adenoma

- Adenoma
- Late adenoma
- Preclinical cancer
- Clinical cancer
- Death from CRC

Life history with CRC, and with screening

- Birth
- Adenoma
- Late adenoma
- Adenoma, carcinoma free
- Screening effect
- Death from other causes

Screening Intervention
Selected model inputs
### Strategies Evaluated for Cohort of 65-year-olds in 2005

<table>
<thead>
<tr>
<th>Strategy*</th>
<th>Screening Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool DNA</td>
<td>3 and 5 years</td>
</tr>
<tr>
<td>FOBT (Hemoccult II, Hemoccult SENSA, FIT)</td>
<td>1 year</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy without biopsy (SIG) OR with biopsy (SIGB)</td>
<td>5 years</td>
</tr>
<tr>
<td>Colonoscopy (COL)</td>
<td>10 years</td>
</tr>
<tr>
<td>SIG/SIGB + FOBT</td>
<td>5 years, 1 year</td>
</tr>
<tr>
<td>No screening</td>
<td>--</td>
</tr>
</tbody>
</table>

*Assuming 100% adherence with all screening, follow-up, and surveillance tests*
<table>
<thead>
<tr>
<th>Parameter</th>
<th>sDNA</th>
<th>HII</th>
<th>HS</th>
<th>FIT</th>
<th>SIG</th>
<th>COL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity adenoma %</td>
<td>4-12</td>
<td>2-5</td>
<td>7.5-12</td>
<td>5-10</td>
<td>75-85</td>
<td>75-85</td>
</tr>
<tr>
<td>Sensitivity late adenoma %</td>
<td>43</td>
<td>10</td>
<td>24</td>
<td>22</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>Sensitivity cancer %</td>
<td>70</td>
<td>40</td>
<td>70</td>
<td>70</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>Specificity %</td>
<td>96</td>
<td>98</td>
<td>92.5</td>
<td>95</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>Unit Cost $</td>
<td>350</td>
<td>4.5</td>
<td>4.5</td>
<td>22</td>
<td>161</td>
<td>497</td>
</tr>
<tr>
<td>Screening Test</td>
<td>CMS Cost</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool DNA</td>
<td>350*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HII or HS</td>
<td>4.54</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIT</td>
<td>22.22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIG without biopsy</td>
<td>160.78</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIG with biopsy</td>
<td>348.19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COL without polypectomy</td>
<td>497.59</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COL with polypectomy or biopsy</td>
<td>648.52</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*No CMS cost available. Estimate based on private insurer reimbursement*
Risks and Costs of Complications, 2007 dollars

<table>
<thead>
<tr>
<th>Complication</th>
<th>Rate per 1000</th>
<th>CMS Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With COL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perforation</td>
<td>0.7</td>
<td>12,446</td>
</tr>
<tr>
<td>Serosal burn</td>
<td>0.3</td>
<td>5,208</td>
</tr>
<tr>
<td>Bleed with transfusion</td>
<td>0.4</td>
<td>5,208</td>
</tr>
<tr>
<td>Bleed without transfusion</td>
<td>1.1</td>
<td>320</td>
</tr>
<tr>
<td><strong>With SIG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perforation</td>
<td>0.02</td>
<td>12,446</td>
</tr>
</tbody>
</table>
Net Payments for CRC Care by Phase, 1998-2003, 2007 dollars*

<table>
<thead>
<tr>
<th>AJCC Stage</th>
<th>Initial Phase</th>
<th>Continuing Phase</th>
<th>Last Year of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Died of CRC</td>
</tr>
<tr>
<td>Direct Medical Costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>25,491</td>
<td>2,028</td>
<td>45,697</td>
</tr>
<tr>
<td>II</td>
<td>35,179</td>
<td>1,891</td>
<td>45,567</td>
</tr>
<tr>
<td>III</td>
<td>42,891</td>
<td>2,702</td>
<td>48,013</td>
</tr>
<tr>
<td>IV</td>
<td>56,009</td>
<td>8,377</td>
<td>64,438</td>
</tr>
</tbody>
</table>

*The initial phase of care is the first 12 months following diagnosis, the last year of life phase is the final 12 months of life, and the continuing phase is all the months between the initial and last year of life phases. Cancer-related costs in the continuing phase of care are an annual estimate.
Cost-effectiveness Analysis
Analyses

- Base-case analyses:
  - Compare strategies in terms of life-years gained vs. no screening
  - Perform cost-effectiveness analysis of stool DNA testing
  - Identify threshold cost per stool DNA test such that stool DNA screening is on efficient frontier

- Sensitivity analyses – how does threshold cost per stool DNA test change with:
  - Adherence
  - Performance characteristics
  - Two microsimulation models used for comparative analysis
Incremental Cost-Effectiveness Analysis & the Efficient Frontier

- Estimate discounted (3%) life-years gained & lifetime costs for all strategies
- Order strategies from least effective to most effective
- Eliminate strategies that are more costly & less effective than another (dominated)
- Eliminate strategies that are more costly & less effective than a combination of other strategies (weakly dominated)
- Remaining strategies lie on efficient frontier, where choice of strategy depends on willingness to pay for a life-year gained
Efficient Frontier

![Graph showing discounted cost vs. discounted life-years gained. The graph illustrates a trend where increased discounted cost is associated with increased discounted life-years gained. The data points and line indicate an upward trend.]
What change in per-test cost would allow this strategy to reach the frontier?
Results

Life-years Gained vs. No Screening
Cost-effectiveness of stool DNA
Threshold Cost per stool DNA test
Life-Years Gained (LYG) vs. No Screening (MISCAN)

- Stool DNA, 3y
- Stool DNA, 5y
- Hemoccult II
- Hemoccult SENSA
- Colonoscopy

LYG per 1,000 65-year-olds

<table>
<thead>
<tr>
<th>Screening Strategy</th>
<th>LYG per 1,000 65-year-olds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool DNA, 3y</td>
<td>70</td>
</tr>
<tr>
<td>Stool DNA, 5y</td>
<td>60</td>
</tr>
<tr>
<td>Hemoccult II</td>
<td>50</td>
</tr>
<tr>
<td>Hemoccult SENSA</td>
<td>80</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>90</td>
</tr>
</tbody>
</table>
Threshold Unit Costs below which stool DNA testing is on the efficient frontier

Base Case: 350

- Stool DNA, 3y
- Stool DNA, 5y

MISCAN

SimCRC

<table>
<thead>
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<th>MISCAN</th>
<th>SimCRC</th>
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<tbody>
<tr>
<td>Stool DNA, 3y</td>
<td>Stool DNA, 5y</td>
</tr>
<tr>
<td>34</td>
<td>51</td>
</tr>
<tr>
<td>40</td>
<td>60</td>
</tr>
</tbody>
</table>
Sensitivity Analyses

Threshold Values by Level of Adherence & Test Performance Characteristics
Threshold Unit Costs below which stool DNA testing is on the Efficient Frontier

(base case cost estimate)
Threshold Unit Costs below which stool DNA testing is on the Efficient Frontier

Percent increase in adherence with stool DNA testing

(base case cost estimate)
Conclusions

- Stool DNA testing provides a benefit in terms of life-years gained compared with no screening
  - If stool DNA test performed every 3-5y, LYG comparable to that of annual Hemoccult II

- Stool DNA is not an efficient screening strategy when cost is $350 per test
  - Threshold analyses indicate stool DNA testing every 3-5 years could be efficient if cost is $34-60 per test (depending upon interval and model)

- Higher cost per scan can be supported if adherence with stool DNA testing is better than that with other tests

- Findings are consistent across two independent microsimulation models
Discussion
Discussion

- Result that stool DNA is currently not cost-effective is not surprising
- Impossible to make stool DNA test cost-effective by improvement of test characteristics alone
- 50% higher adherence with stool DNA testing is unlikely given similarities with other stool tests
Limitations

- Models did not simulate histology of adenomas
- Only simulated traditional adenoma-carcinoma sequence: different pathways may have different mutations
- Screen intervals of current screening options have not been varied
Thank You
We acknowledge:

- Martin Brown, PhD and Robin Yabroff, PhD of NCI for their assistance with obtaining cancer treatment costs using SEER-Medicare data;
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