Predictive modeling based on the National Colonoscopy Study

Simulated effectiveness of colonoscopy vs. sensitive FOBT screening

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PRECIS(1) framework *

- Patient selection
- Protocol for intervention
- Provider expertise
- Follow-up intensity
- Protocol for intervention
- Provider expertise
- Patient adherence
- Provider adherence
- Per intention or protocol
- Outcome relevance to patients
- Primary Analysis
- Participant Compliance
- Eligibility Criteria
- Flexibility of the Comparison Intervention
- Practitioner Expertise (Experimental)
- Flexibility of the Experimental Intervention

## Predictive modeling based on NCS

<table>
<thead>
<tr>
<th>Knowns</th>
<th>Unknowns</th>
</tr>
</thead>
<tbody>
<tr>
<td>COL receipt</td>
<td>Long-term COL utilization</td>
</tr>
<tr>
<td>FOBT completion ≤7 rounds</td>
<td>Long-term FOBT adherence</td>
</tr>
<tr>
<td>FOBT positivity</td>
<td>Serial correlation</td>
</tr>
<tr>
<td>FOBT+ follow-up</td>
<td></td>
</tr>
<tr>
<td>Adenoma findings</td>
<td></td>
</tr>
<tr>
<td>CRC diagnoses</td>
<td>Long-term CRC incidence &amp; mortality</td>
</tr>
</tbody>
</table>
Aim

Estimate the long-term effectiveness of COL vs sensitive FOBT

- Model: Microsimulation Screening Analysis (MISCAN)
- Input: NCS data on test adherence and positivity -> extrapolated
- Validation: Predicted intermediate outcomes
- Outcome: 15y CRC incidence & mortality
  - Without screening
  - With screening as observed ("intention to screen")
  - With screening as offered ("per protocol")
RESULTS

Predicted long-term effects for NCS
Simulated vs. observed FOBT adherence*

* Adherence in the COL arm was 86%, COL was repeated after 10y
Predicted vs. observed adenoma findings

**COL arm**

- Observed
- Predicted

**FOBT arm** *

- Observed
- Predicted

*Not adjusted for censoring or loss to follow-up*
Predicted risk difference for FOBT and colonoscopy

<table>
<thead>
<tr>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years of follow-up</td>
<td>Years of follow-up</td>
</tr>
<tr>
<td>sFOBT</td>
<td>sFOBT with colonoscopy crossover</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
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<tr>
<td>4</td>
<td>4</td>
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<td>5</td>
<td>5</td>
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<td>14</td>
<td>14</td>
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<tr>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

Δ=6.9 (33%)  
Δ=1.3 (31%)

What is the impact on screening effectiveness?
Predicted relative mortality reduction

### Colonoscopy

- **100% adherence**
- **Actual adherence**
- **sFOBT with 100% adherence**

#### Years of follow-up:
- 0
- 5
- 10
- 15

#### Cumulative mortality reduction:
- 0%
- 20%
- 40%
- 60%
- 80%
- 100%

**14% relative loss in effectiveness**

### FOBT

- **100% adherence**
- **Actual adherence**
- **COL with 100% adherence**

#### Years of follow-up:
- 0
- 5
- 10
- 15

#### Cumulative mortality reduction:
- 0%
- 20%
- 40%
- 60%
- 80%
- 100%

**31-36% relative loss in effectiveness**
Sensitivity analysis: exploring the “PRECIS” continuum

- Assuming stable COL adherence
  
  +16% vs. colonoscopy attenders

Cumulative mortality reduction:
- FOBT arm
- COL arm

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FOBT arm</th>
<th>COL arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attenders 1st FOBT</td>
<td></td>
<td>+6%**</td>
</tr>
<tr>
<td>Per protocol</td>
<td></td>
<td>+6%</td>
</tr>
<tr>
<td>Quality COL</td>
<td></td>
<td>+14%</td>
</tr>
<tr>
<td>Performance FIT</td>
<td></td>
<td>+13%</td>
</tr>
<tr>
<td>Age inclusion ≥50y</td>
<td></td>
<td>16%</td>
</tr>
<tr>
<td>Lifetime horizon</td>
<td></td>
<td>27%*</td>
</tr>
<tr>
<td>Base case</td>
<td>18% absolute difference</td>
<td></td>
</tr>
</tbody>
</table>

* assuming stable COL adherence ** +16% vs. colonoscopy attenders
Conclusion

*In patients willing to undergo screening colonoscopy or FOBT*

- Modeling suggests COL is more effective than fecal-based screening
  - Due mostly to suboptimal FOBT adherence over time
- Need to emphasize importance and effect of high FOBT adherence
Discussion

Limitations

- Randomization after informed consent
- Differential financial incentives and follow-up
- Small observed numbers for years 5-7
- Imperfect model validation
  - Overestimated colonoscopy performance?
  - Overestimated risk?
Thank you
Observed adherence from NCS (recap)

<table>
<thead>
<tr>
<th>Colonoscopy (n=1761)</th>
<th>gFOBT (n=1762) Per-protocol</th>
<th>gFOBT (n=1762) Intention-to-Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence in each study arm *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/4 →</td>
<td>33%</td>
<td>27%</td>
</tr>
<tr>
<td>3/4 →</td>
<td>4/4 →</td>
<td>Pos →</td>
</tr>
<tr>
<td>2/4 →</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>3/4 →</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>1/4 →</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Pos →</td>
<td>7%</td>
<td></td>
</tr>
</tbody>
</table>

Colonoscopy (n=1761) 86%

gFOBT (n=1762) Per-protocol 33%
gFOBT (n=1762) Intention-to-Screen 33%
Observed vs. Simulated FOBT positivity

Return to screening (modeling artifact)