More vs. Less Intensive Surveillance after Polypectomy

RESULTS FROM MICROSIMULATION MODELING


WEO meeting, June 1st 2018
Background

Few trials to directly inform adenoma surveillance

▪ National Polyp Study (Winawer SJ et al. NEJM 1993)
  › All types of baseline adenomas
  › Advanced adenomas after 1+3 vs. 3y

▪ No randomized trials with
  › Low-risk adenomas, High-risk adenoma, Serrated polyps
  › CRC outcomes after various intervals

▪ European Polyp Surveillance trials (Jover R et al. Endoscopy 2016)

Alternative evidence, modeling

▪ Greuter MJ et al. Annals Internal Med 2017
  › US surveillance guidelines not cost-effective
  › Single clinical source study, no external validation
Aim

To predict cost and effectiveness of more vs. less intensive surveillance

- At 3 vs. 5y intervals for HRA patients
- At 5 vs. 10y intervals for LRA patients

US Multi-Society Task Force definitions

- HRA: ≥3 small tubular or ≥1 large tubular, tubulovillous, or advanced
- LRA: 1-2 small tubular
Methods

Microsimulation Screening Analysis (MISCAN)
- 2016 US Preventive Service Task Force screening guidelines
- 2018 American Cancer Society screening guidelines

Model features
- Patient heterogeneity
- Polyp multiplicity, size, location
- Not histology

Model validity
- Natural history calibrated to high-quality data (autopsy; registry; trials)
- Screening outcomes contrasted to main CRC trials
- Not previously used and validated for subset adenoma patients
  › *Special attention for external validity*
Main analysis

**Screening**

- **LRA**
  - LI surveillance at 10y
  - Subsequent at 5-10y* through 80y

- **HI surveillance at 5y**
  - Subsequent at 3-10y through 80y

- **Shared reference scenarios**
  - No screen/surveillance (Natural Hx)
  - Screening continued through 75y

- **HRA**
  - LI surveillance at 5y
  - Subsequent at 5-10y* through 80y

  - HI surveillance at 3y
  - Subsequent at 3-10y through 80y

**CRC incidence after 10-50y; Cost/QALY gained** lifetime

*potential return to screening*
Model validity

COMPARISON TO VARIOUS SOURCES OF EVIDENCE
Validation analysis

Three outcomes, four settings

▪ Short-term adenoma recurrence

▪ Intermediate-term post-polypectomy incidence

▪ Long-term post-polypectomy mortality
Predicted vs. observed short-term adenoma recurrence

![Graphs showing predicted vs. observed short-term adenoma recurrence for LRA and HRA patients.](image-url)
Predicted vs. observed long-term CRC mortality (cont’d)

Observed in Løberg 2014

Risk of Death from CRC (%)

Years of follow-up

P<0.001 with the use of Gray’s test

High-risk adenoma

Low-risk adenoma

Simulated

Risk of Death from CRC (%)

Years of follow-up

Stanford University
Risk of Death from Colorectal Cancer* (%)

- High-risk adenoma (Simulated)
- Low-risk adenoma (Simulated)

*Løberg 2014 data

Zauber 2012 data

Realistic projected risk increase?

* cumulative incidence of CRC deaths lower due to other-cause mortality
Main results

EFFECTIVENESS AND COST-EFFECTIVENESS ANALYSIS
Predicted CRC incidence in 50y-old LRA patients

*Screening comprised colonoscopy at age 60 and 70y*
Predicted CRC incidence in LRA vs. HRA patients

**LRA patients aged 50 y**
- No screen/surveillance
- COL screening
- LI surveillance
- HI surveillance

**HRA patients aged 50 y**
- No screen/surveillance
- COL screening
- LI surveillance
- HI surveillance

*Screening comprised colonoscopy at age 60 and 70y*
Predicted CRC incidence in LRA and HRA patients

▪ Most of the benefit is achieved through screening
▪ Incremental benefit for surveillance
  › Modest, but clinically relevant
  › Mostly achieved after 15-20y follow-up

Q: Is the surveillance gain cost-effective?
Cost-effectiveness of surveillance

Age 50, LRA

Total QALY (per 1000 adults)

<table>
<thead>
<tr>
<th>Total cost ($ thousand per 1000 adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19,250</td>
</tr>
<tr>
<td>19,300</td>
</tr>
<tr>
<td>19,350</td>
</tr>
<tr>
<td>19,400</td>
</tr>
<tr>
<td>19,450</td>
</tr>
<tr>
<td>19,500</td>
</tr>
<tr>
<td>19,550</td>
</tr>
<tr>
<td>19,600</td>
</tr>
<tr>
<td>19,650</td>
</tr>
</tbody>
</table>

LI-S $4k/ QALY
HI-S $18k/ QALY
SCR <$0/ QALY

Age 50, HRA

Total QALY (per 1000 adults)

<table>
<thead>
<tr>
<th>Total cost ($ thousand per 1000 adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5400</td>
</tr>
<tr>
<td>5600</td>
</tr>
<tr>
<td>5800</td>
</tr>
<tr>
<td>6000</td>
</tr>
<tr>
<td>6200</td>
</tr>
<tr>
<td>6400</td>
</tr>
<tr>
<td>6600</td>
</tr>
<tr>
<td>6800</td>
</tr>
</tbody>
</table>

LI-S $5k/ QALY
HI-S $8k/ QALY
SCR <$0/ QALY

O No further screening/surveillance scenario
◇ Continued colonoscopy screening
△ Low-intensity surveillance
▲ High-intensity surveillance
Uncertainty analysis

ALTERNATIVE MODEL CONFIGURATIONS
Uncertainty analysis

Parameter uncertainty (e.g. test sensitivity, cost, utility)
- Does not explain discrepancies
- Does not change outcomes

Structural uncertainty
- Different assumptions on adenoma behavior over time
  › MISCAN base-case (adenoma risk ~ patient age at adenoma onset)
  › MISCAN alternative (adenoma risk ~ adenoma age)*
  › SimCRC alternative (adenoma risk ~ patient age)

* Time-independent risk was not compatible with cancer registry data
Predicted lifetime CRC incidence across models

50y-old LRA patient

- **Absolute risks decrease in alternative models**
- **Relative benefit of screening and surveillance increases**
- **Incremental benefit of HI vs LI surveillance varies: 4-10/1,000**

**Lifetime CRC incidence (per 1000 adults)**

- **MISCAN_Base-Case** (risk~patient age): 109, 65, 59, 49
- **MISCAN_Alternative** (risk~polyp age): 68, 18, 14, 8
- **SimCRC**: 68, 23, 17, 13

Legend:
- No screen/surveillance
- COL screening
- LI surveillance
- HI surveillance

Stanford University
# Predicted cost-effectiveness across models ($/QALY)

<table>
<thead>
<tr>
<th>Index age &amp; strategy</th>
<th><strong>LRA patients</strong></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th><strong>HRA patients</strong></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MISCAN</td>
<td>MISCAN</td>
<td>SimCRC</td>
<td>MISCAN</td>
<td>MISCAN</td>
<td>SimCRC</td>
<td>MISCAN</td>
<td>MISCAN</td>
<td>SimCRC</td>
<td>MISCAN</td>
</tr>
<tr>
<td></td>
<td>Base-case</td>
<td>Alternative</td>
<td></td>
<td>Base-case</td>
<td>Alternative</td>
<td></td>
<td>Base-case</td>
<td>Alternative</td>
<td></td>
<td>Base-case</td>
</tr>
<tr>
<td>Age 50y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screen only</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LI surveillance</td>
<td>4,000</td>
<td>52,800</td>
<td>51,700</td>
<td>4,500</td>
<td>15,300</td>
<td>26,400</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI surveillance</td>
<td>18,400</td>
<td>71,200</td>
<td>74,100</td>
<td>8,400</td>
<td>82,200</td>
<td>75,700</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 60y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screen only</td>
<td>-</td>
<td>-</td>
<td>1,500</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LI surveillance</td>
<td>10,500</td>
<td>75,000</td>
<td>Dom.</td>
<td>300</td>
<td>14,800</td>
<td>18,200</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI surveillance</td>
<td>17,400</td>
<td>75,300</td>
<td>64,100</td>
<td>7,700</td>
<td>95,300</td>
<td>83,900</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 70y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screen only</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LI surveillance</td>
<td>27,400</td>
<td>78,700</td>
<td>Dom.</td>
<td>4,300</td>
<td>18,800</td>
<td>20,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI surveillance</td>
<td>29,500</td>
<td>81,400</td>
<td>74,700</td>
<td>19,500</td>
<td>165,700</td>
<td>154,900</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions & Discussion

POSSIBLE LESSONS FROM MODELING
Conclusions

- Screening provides majority of clinical benefit (COL every 10y)
- LI surveillance provides modest incremental benefit at acceptable cost with a willingness-to-pay threshold of $100,000/QALY gained
- HI surveillance generally provides add. benefit at acceptable cost
  - Except for 70y-old HRA patients, in alternative models
- Benefit is mainly accrued in the long-term

Caveat

- Uncertainty in long-term post-polypectomy risk
- Cost-effectiveness conclusions based on US data
Discussion

- Should policy be based on intermediate-term outcomes?
- Should RCTs aim for longer term follow-up?
- Should observational data be more important for decision making?
Meeting agenda

- 10:15 General assumptions for surveillance guidelines: endpoints, cutoffs and comparators - R. Jover

- 10:45 Performance targets for lesion detection in surveillance – U. Ladabaum

- 11:15 More vs. less intensive surveillance after polypectomy: Results from microsimulation modeling - R. Meester
Law of diminishing marginal returns

![Graph showing the relationship between total risk reduction (%) and number of colonoscopies. The graph illustrates how the risk reduction increases with the number of colonoscopies, but at a decreasing rate.](image-url)

Stanford University
Main analysis

Study population
- Screen-detected patients; COL and FIT
- Ages 50, 60, and 70y
- HRA and LRA

Strategies
- No intervention
- Colonoscopy screening at age 50, 60 and 70y
- Low-Intensity (LI) colonoscopy surveillance through age 80y:
  - Initial exam at 5y for HRA and 10y for LRA
  - Subsequent exam/screening at 10y if negative
- High-Intensity (HI) colonoscopy surveillance through age 80y:
  - Initial exam at 3y for HRA and 5y for LRA
  - Subsequent exam at 10y if negative

Main outcomes
- Lifetime CRC incidence
- Cost/QALY gained
Predicted post-polypectomy mortality across models

Risk of Death from Colorectal Cancer (%)

Years of Follow-up

High 15y risk not reproduced

Possible overestimation of lifetime risk
Predicted lifetime CRC incidence across models

50y-old HRA patient

- Absolute risks decrease in alternative models
- Relative benefit of screening and surveillance increases
- Incremental benefit of HI vs LI surveillance: 4-14/1,000

<table>
<thead>
<tr>
<th>Model</th>
<th>No screen/surveillance</th>
<th>COL screening</th>
<th>LI surveillance</th>
<th>HI surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MISCAN_Base-Case</td>
<td>172</td>
<td>105</td>
<td>89</td>
<td>75</td>
</tr>
<tr>
<td>(risk~patient age)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MISCAN_Alternative</td>
<td>114</td>
<td>31</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>(risk~polyp age)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SimCRC</td>
<td>98</td>
<td>33</td>
<td>23</td>
<td>19</td>
</tr>
</tbody>
</table>

Stanford University
Predicted vs. observed intermediate-term CRC incidence

No surveillance

Single surveillance

Multiple surveillances

- Observed in Atkin 2017 *
(with 95% CI) - Simulated

* Atkin W, et al included a subset of intermediate-risk HRA patients.
Predicted vs. observed long-term CRC mortality

Cumulative CRC mortality (%) vs. Years of follow up

- Observed in the National Polyp Study (with 95% CI)
- Simulated