Classification & Detection of Colorectal Polyps
A Changing Landscape

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Mayo Clinic, Rochester MN
Disclosures

Relationship with Exact Sciences

• *Mayo Clinic*
  • Equity investor
  • Licensed technologies

• *Dr. Ahlquist*
  • Scientific Advisor
  • Inventor of licensed technology
  • Research collaborator
Polyp Detection by Colonoscopy

Questions

Is there a problem?

What are we looking for?

How can we improve detection?

Which methods benefit most?
The Problem

• Despite screening in US, CRC remains the #2 cancer killer

• Shift to the right (≥ 50% prox)

1980 → 2000 (rate/100,000)
Polypectomies: 86 → 320
CRC incidence: 60 → 46
  Left 32 → 19
  Right 27 → 27

Gupta et al. CGH 2005;3:150

Olmsted County
Colorectal Cancer Screening Modalities in US

No Screening
~50%
Effectiveness of Colonoscopy?
Recent Wake-up Calls

Large case-control studies

• **CRC mortality** (Baxter et al. Ann Intern Med 2009;150:1)
  - L sided ~ 70%
  - R sided 0%

• **CRC incidence** (Brenner et al. JNCI 2010;102:89)
  - L sided ~ 70%
  - R sided 0%
## Screening Outcomes by Specialty

<table>
<thead>
<tr>
<th></th>
<th>Colonoscopy by GI doctors</th>
<th>Colonoscopy by non-GI doctors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rex</strong>&lt;br&gt;Indiana&lt;br&gt;1997</td>
<td>CRC miss rate 3%</td>
<td>CRC miss rate 13%</td>
</tr>
<tr>
<td><strong>Rabeneck</strong>&lt;br&gt;Ontario&lt;br&gt;2010</td>
<td>Reference rate 1.0</td>
<td>HR for interval CRC Surgeons 1.39&lt;br&gt;Others 1.28</td>
</tr>
<tr>
<td><strong>Baxter</strong>&lt;br&gt;Ontario&lt;br&gt;2010</td>
<td>Reference rate 1.0</td>
<td>HR for interval CRC Surgeons 1.23&lt;br&gt;Others 1.87</td>
</tr>
</tbody>
</table>

Adapted from Dr Doug Rex
Long Term CRC Risk Reduction after Colonoscopy & Polypectomy

*Nishihara et al (DDW 2012)*

- Prospective cohort study (Harvard System)
  
  - N ~ 100,000
  - F/U ~ 2.5 million person-yrs

- Relative CRC risk, HR

  - Never screened: 1.0 (ref)
  - Neg colonoscopy: 0.45
    
    - Left: 0.26
    - Right: 0.66

  - After polypectomy: 0.64
Adenoma Detection Rates
 Variation among Gastroenterologists

<table>
<thead>
<tr>
<th>Number doctors</th>
<th>Lowest ADR</th>
<th>Highest ADR</th>
<th>Absolute Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barclay, Illinois 2006</td>
<td>12</td>
<td>9.4%</td>
<td>32.7%</td>
</tr>
<tr>
<td>Chen, Indiana 2007</td>
<td>9</td>
<td>15.5%</td>
<td>41.1%</td>
</tr>
<tr>
<td>Imperiale, Indiana 2009</td>
<td>25</td>
<td>7%</td>
<td>44%</td>
</tr>
<tr>
<td>Shaukat, Minnesota 2009</td>
<td>51</td>
<td>10%</td>
<td>39%</td>
</tr>
</tbody>
</table>

Adapted from Dr Doug Rex
## Serrated Polyp Detection Rates
### Variation among Gastroenterologists

<table>
<thead>
<tr>
<th></th>
<th>Number doctors</th>
<th>Lowest proximal detection rate</th>
<th>Highest proximal detection rate</th>
<th>Absolute Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hetzel Boston</td>
<td>13</td>
<td>1.1%</td>
<td>7.6%</td>
<td>6%</td>
</tr>
<tr>
<td>Kahi Indiana</td>
<td>15</td>
<td>1%</td>
<td>18%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Adapted from Dr Doug Rex
Quality Indicators and Risk of Interval CRC
Kaminski et al. NEJM 2010

- Poland, n=45,026 patients
- Colonoscopists 186
- Stratified results

<table>
<thead>
<tr>
<th>ADR</th>
<th>Interval CRC (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11%</td>
<td>34</td>
</tr>
<tr>
<td>11-19.9%</td>
<td>24</td>
</tr>
<tr>
<td>&gt;20%</td>
<td>~2</td>
</tr>
</tbody>
</table>
Polyp Targets
Size Considerations

• **Most do not progress**
  • 50-70% get polyps
  • 6% get CRC

• **Small (5-9mm) & diminutive (<5mm)**
  • Controversial targets
  • Hard to predict natural hx
  • Relevant because of lengthy (10 yr) colonoscopy screening interval

• **Large (>1cm)—consensus targets**
  • Risk of HGD & CRC increases exponentially with size above 1cm
Premalignant Polyp Types

• **Adenoma**
  • Tubular (T), villous (V), tubulovillous (TV)
  • “Advanced” if ≥1cm, V, or TV

• **Serrated**
  • Hyperplastic
  • Sessile serrated polyp (BRAF + meth)
  • Traditional serrated polyp (KRAS + meth)
  • “Advanced”? (if ≥1cm)
Sessile Serrated Polyps

- Precursors for ~1/3 of CRC
- Now account for ~1/3 of advanced polyps
- R>>L
- Detection requires mindfulness & a trained eye

Images courtesy of Drs Rex & Won Kee Song
Serrated Polyp Pathway to CRC

Normal mucosa

BRAF mutation +/- methylation

MVHP

?additional methylation

SSA/P

BRAF mutation + methylation

Methylation of hMLH1

SSA/P with cytological dysplasia

CIMP+MSI-H carcinoma

Generally slowly progressive or random

Usually rapidly progressive

Mutations or methylation of other genes

Snover, Human Path 2011
Hyperplastic Polyp

Normal Crypt
• Prolif at base
• Cells mature toward lumen

Hyperplastic Polyp
• Expanded basal prolif
• Cells mature toward lumen
• ↓ apoptosis = serrations

Snover, Human Path 2011
Sessile Serrated Polyp

- Proliferative zone moves up side of crypt
- Movement of mature cells all directions

Snover, Human Path 2011
Traditional Serrated Polyp

- Emergence of proliferative zones on side of crypt
- Multiple ectopic crypts form

Snover, Human Path 2011
## Polyp Targets

<table>
<thead>
<tr>
<th>Type*</th>
<th>Site</th>
<th>Detection Barrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pedunculated</td>
<td>AD</td>
<td>L&gt;R</td>
</tr>
<tr>
<td>Sessile</td>
<td>AD,S</td>
<td>Both</td>
</tr>
<tr>
<td>Flat</td>
<td>AD,S</td>
<td>R&gt;L</td>
</tr>
<tr>
<td>Depressed**</td>
<td>AD</td>
<td>R&gt;L</td>
</tr>
</tbody>
</table>

*AD = adenoma, S = serrated polyp

**Rare, disproportionate HGD
The “Mozart Effect”

3x increase in polyp detection

O'Shea, ACG Meeting 2011
Methods Intended to Enhance Surface Exposure

• Insertion to cecum
• Bowel prep & cleansing
• Wide angle endoscopy
• Cap-assisted colonoscopy
• Through-the-scope retroscopes
• Retroflexion

Better views of flexures & prox sides of folds?
Bowel Preparation
Lebwohl et al. GIE 2011

From 12,787 colonoscopies,
24% had **suboptimal prep** (poor/fair)

Among those who had repeat colonoscopy with optimal prep <3yrs*

Adenomas 42%
Adv adenomas 27%

* not seen on index colonoscopy with poor prep
Polyp Detection with Cap-assisted Colonoscopy (CAC): Meta-analysis
Wani et al (DDW 2012)

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Year</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsushita 1998</td>
<td>25.5%</td>
<td>Not estimable</td>
<td>1998</td>
<td></td>
</tr>
<tr>
<td>Kondo 2007</td>
<td>32.5%</td>
<td>1.51 [1.04, 2.19]</td>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>Harada 2009</td>
<td>32.5%</td>
<td>1.05 [0.76, 1.46]</td>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>Tee 2010</td>
<td>19.7%</td>
<td>1.05 [0.69, 1.60]</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>Dai 2010</td>
<td>7.5%</td>
<td>1.08 [0.54, 2.15]</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>Lee 2011</td>
<td>14.8%</td>
<td>1.64 [1.01, 2.68]</td>
<td>2011</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>1.23 [1.02, 1.49]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CAC</th>
<th>Std Colo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All polyps</td>
<td>40%</td>
<td>36%</td>
</tr>
<tr>
<td>Adenomas</td>
<td>32%</td>
<td>34%</td>
</tr>
</tbody>
</table>

Endoscopic image from Dr Doug Rex
Through-the-Scope Retroscopes

Gains in polyp detection rates

- Uncontrolled studies ~10%
- RCT (Leufkens GIE 2011)
  - All adenomas 7%
  - Adv adenomas 2%

Issues

- Distraction from 2 simultaneous images
- Creation of blind spots
- Lens cleaning
- Suctioning impaired
- Procedure time ↑
- Cost & reimbursement

Adapted from Dr Doug Rex
Proximal Colon Retroflexion

From de Groen

From de Groen
Additional Polyp Yield with Retroflexion
Hewett & Rex, GIE 2011

Study
• 1000 consecutive patients
• 2 experienced colonoscopists
• Forward-viewing colonoscopy with removal of all polyps → then retroflex exam

Results
• Successful retroflexion 95%, safe
• Additional adenoma yield
  Any  9.8%
  Advanced  4.4%
Methods Intended to Enhance
Lesion Discrimination

Tools
- Chromoendoscopy
- Narrow band imaging (NBI)
- High definition (HD)

Opportunity/need for optical innovations that better highlight flat/depressed lesions

Individual Performance/Skill
- Mindfulness, recognition clues, education
- Optimal metrics
Chromoendoscopy

• Modest (~10%) increase in detection of small polyps (Randomised studies: Kahi 2010 (US), Pohl 2011 (Germany))

• But, tedious, nonspecific, and ↑ time + cost

• Thoughts
  • Impractical for general CRC screening
  • Helpful to define flat lesions
  • Important role in IBD surveillance
# NBI vs White Light

## Meta-analysis of Randomized Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Pts with adenoma NBI</th>
<th>Pts with adenoma WLE</th>
<th>adenoma/pt NBI</th>
<th>adenoma/pt WLE</th>
<th>O.R. NBI vs WLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rex 2007</td>
<td>65%</td>
<td>67%</td>
<td>1.86</td>
<td>1.82</td>
<td>0.90 (0.61-1.34)</td>
</tr>
<tr>
<td>N=217</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adler 2007</td>
<td>23%</td>
<td>17%</td>
<td>0.33</td>
<td>0.26</td>
<td>1.27 (0.88-1.84)</td>
</tr>
<tr>
<td>N=198</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inoue 2008</td>
<td>42%</td>
<td>34%</td>
<td>0.84</td>
<td>0.55</td>
<td>1.55 (1.14-2.11)</td>
</tr>
<tr>
<td>N=122</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>44%</td>
<td>41%</td>
<td>1.06</td>
<td>0.96</td>
<td>1.23 (0.93-1.61)</td>
</tr>
</tbody>
</table>

Van den Broek et al. GIE 2009;69:124 (Adapted from Dr. Mike Wallace)
### HD vs Standard Colonoscopy Meta-analysis

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Polyps/total</th>
<th>Incremental yield (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IY</td>
<td>Lower limit</td>
<td>Upper limit</td>
</tr>
<tr>
<td>East</td>
<td>0.019</td>
<td>−0.119</td>
<td>0.158</td>
</tr>
<tr>
<td>Pellise</td>
<td>0.048</td>
<td>−0.029</td>
<td>0.126</td>
</tr>
<tr>
<td>Burke</td>
<td>0.031</td>
<td>−0.035</td>
<td>0.096</td>
</tr>
<tr>
<td>Buchner</td>
<td>0.029</td>
<td>−0.010</td>
<td>0.068</td>
</tr>
<tr>
<td>Tribonias</td>
<td>0.109</td>
<td>0.012</td>
<td>0.207</td>
</tr>
<tr>
<td>Pooled</td>
<td>0.038</td>
<td>0.010</td>
<td>0.067</td>
</tr>
</tbody>
</table>

**Increase adenoma detection by HD**
- **Any** 3.5%
- **Advanced** (no increase)

Subramanian et al Endoscopy 2011;43:499 (Adapted from Dr. Mike Wallace)
Metachronous & Interval CRC

Program Failures

• Metachronous CRC incidence (%)

<table>
<thead>
<tr>
<th>Years post-resection</th>
<th>3</th>
<th>5</th>
<th>6</th>
<th>10</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonvier 2008</td>
<td>--</td>
<td>1.8</td>
<td>--</td>
<td>3.4</td>
<td>7.2</td>
</tr>
<tr>
<td>Mulder 2012</td>
<td>1.1</td>
<td>--</td>
<td>2</td>
<td>3.1</td>
<td>--</td>
</tr>
</tbody>
</table>

• Interval CRC
  • 30-50% of CRC in screen/surveillance programs not detected soon enough or at all
  • R>L

• Potential causes and solutions
  Non-compliance
  Missed lesions
  New lesions
Effect of Didactic Sessions on ADR

Coe et al. Am J Gastro 2011 (Adapted from Dr Wallace)
Quality Metrics

• **Ultimate metric:** Interval CRC

• **Surrogate measures**
  - Precursor targets
    - Adenoma detection rate (ADR)
    - Polyps per patient rate
  - Technical elements
    - Cecal intubation rate, withdrawal time, etc

 aggregate quality score
  - **Real-time computer systems**
Real-time Quality Analysis and Feedback

- Clear frame
- Retroflexion
- Circumferential inspection
- Withdrawal time
- Stool/fluid (score & map)

From Dr Piet de Groen, Mayo Clinic
EndoMetric Report
Prototype for Colonoscopy

Overall Quality Score

Preparation Score 8 (Min-Max)
Cleaning Score 8 (Min-Max)
Spiral Score 7 (0-∞)

Insertion Time (min):
Total 8  Clear 6
Withdrawal Time (min):
Total 10  Clear 7

Retroflexion:

Image EoI

Start  EoI  End
0  20  60
20  20  40
40  20  60

0.8  1.0
Stool DNA Testing

• Biologically rational
• Noninvasive
• No cathartic prep
• No diet or med restriction
• Can be mailed
• Not affected by site*
• High sensitivity for both CRC (85-98%) & precancer *
• Primary screen + interval test

*Mucus at Cancer Surface

<table>
<thead>
<tr>
<th>Adenoma Size (cm)</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>31</td>
</tr>
<tr>
<td>&gt;1</td>
<td>64</td>
</tr>
<tr>
<td>&gt;2</td>
<td>79</td>
</tr>
<tr>
<td>&gt;3</td>
<td>91</td>
</tr>
</tbody>
</table>

*Ahlquist et al. Gastroenterology 2012, Lidgard et al, DDW 2012
# Interventions for Polyp Detection

## Potential to Increase Yield?

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Potential Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capture the unscreened</td>
<td>40-50%</td>
</tr>
<tr>
<td>Reduce operator variation</td>
<td>15-20%</td>
</tr>
<tr>
<td>Optimize longitudinal program</td>
<td>10%</td>
</tr>
<tr>
<td>Retroflex routinely</td>
<td>5-10%</td>
</tr>
<tr>
<td>Perfect preparation</td>
<td>5-10%</td>
</tr>
<tr>
<td>Use ancillary tools</td>
<td>0-10%</td>
</tr>
<tr>
<td>e.g. NBI, CAC, TTS retroscope</td>
<td></td>
</tr>
</tbody>
</table>
Summary

• Colonoscopy is operator-dependent, and quality varies widely
• Polyp miss rates highest on right
• Impact: population screen capture > quality/skill > ancillary tools

Clear opportunities to improve polyp detection