Optimizing Mortality Reductions through Colorectal Cancer Screening

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Colorectal Cancer Screening Agenda

- Which test is best?
- How to increase screening among Asians?
- How do you prepare for the future?

CRC Screening
U.S. Preventive Services Task Force
2016 Updated Guidelines

- Available Strategies:
  - Fecal occult blood testing annually*
  - Sigmoidoscopy
    - Every 5 years
    - Every 10 years with annual FOBT *
  - Colonoscopy every 10 years
  - FIT-DNA testing every 1 or 3 years
  - CT colonography every 5 years
  - Methylated Septin9 DNA (unknown interval)

*FIT or high-sensitivity gFOBT (Hemoccult Sensa)

CRC Screening
U.S. Preventive Services Task Force

- Start and Stop: Ages 50-75 years
  - 76-85 years: do not screen routinely
  - Older than 85 years: do not screen
- Starting at age 45 years
  - Could reduce cancer and increase life-years
  - Could increase harms of screening (colonoscopy)
- Individuals >75 years of age who have not previously undergone screening may still benefit
  - Depending on comorbid illness, could benefit past age 80 years
FIT Detection of CRC: Meta-Analysis

Fecal Occult Blood Test

- **Benefits**
  - High quality evidence supporting mortality reduction with FOBT (multiple RCTs)
  - FIT easier: single sample, no dietary exclusions
  - Highly cost-effective, may be cost-saving
- **Deficits**
  - Insensitive for cancer precursor (polyps)
  - Annual testing needed

Multitarget Stool (FIT-DNA)

- KRAS mutations
- NDRG4 and BMP3 methylation
- β-actin
- **Immunochromatographic test for human hemoglobin**
- FDA approved
- CMS reimbursed

Multitarget Stool vs. FIT

<table>
<thead>
<tr>
<th>Condition</th>
<th>Colonoscopy</th>
<th>Stool DNA sensitivity</th>
<th>FIT sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal Cancer</td>
<td>65</td>
<td>92.3 (83.0-97.5)</td>
<td>73.8 (61.5-84.0)</td>
</tr>
<tr>
<td>Advanced adenoma / SSP≥ 1cm</td>
<td>757</td>
<td>42.4 (38.9-46.0)</td>
<td>23.8 (20.8-27.0)</td>
</tr>
<tr>
<td>Non-advanced adenomas and negative colon</td>
<td>9167</td>
<td>86.6 (85.9-87.2)</td>
<td>94.9 (94.4-95.3)</td>
</tr>
<tr>
<td>Negative colon</td>
<td>4457</td>
<td>89.8 (88.9-90.7)</td>
<td>96.4 (95.8-96.9)</td>
</tr>
</tbody>
</table>

Multitarget Stool (FIT-DNA)

- **Benefits**
  - Sensitivity higher than FIT (92.3% vs. 73.8%)
  - FDA approved for primary screening of CRC
- **Deficits**
  - Specificity lower than FIT (86.6% vs. 94.9%)
  - Insensitive for cancer precursors (polyps)
  - Unknown screening intervals
  - Cost ($649 retail) – not cost-effective

Virtual Colonoscopy (CT Colonography)

Colonoscopy vs. CT Colonography

- Sessile serrated polyps
  - RCT colonoscopy vs. CT colonography
    - 8,844 participants
  - Diagnosis of high-risk SSP
    - ≥1 cm or any grade of dysplasia
    - OR 5.5 (95% CI 2.6-11.6)
  - CT inferior to colonoscopy for detection of SSP

J Gastroenterol 2013

IJSpeert Am J Gastro 2016
### Adherence to CRC Screening

<table>
<thead>
<tr>
<th>Method</th>
<th>Participation Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>14.8*</td>
</tr>
<tr>
<td>CTC Full prep</td>
<td>25.2*</td>
</tr>
<tr>
<td>CTC Reduced prep</td>
<td>28.1 (NS)</td>
</tr>
<tr>
<td>FIT</td>
<td>50.4*</td>
</tr>
</tbody>
</table>

### Colonoscopy vs. CT Colonography

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base Case (CT $558)</td>
<td>Colon dominates CT</td>
</tr>
<tr>
<td>Cost of CT $100-480</td>
<td>Colon cost-effective</td>
</tr>
<tr>
<td>Cost of CT &lt;$100</td>
<td>CT preferred</td>
</tr>
</tbody>
</table>

*Dominates = more effective and less expensive
Cost-effective = <$50,000 per life year saved
Preferred = ICER for Colon vs. CT >$50,000 per life year saved*
Virtual Colonoscopy

• Benefits
  – Cool name
  – May have greater adherence than colonoscopy

• Deficits
  – Inferior detection of sessile serrated polyps
  – Extracolonic findings in 16%
  – Radiation exposure
  – Not cost-effective compared with FIT or colonoscopy

Blood Based Test

Septin 9

• Gene codes for Guanosine triphosphate (GTP)-binding protein
  – Cytoskeleton formation and filamentous structure

• Oncogene or tumor suppressor gene
  – Methylated Septin 9 is a biomarker for CRC

• FDA approved for CRC screening
  – Individuals who refuse other tests

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>95% CI</th>
<th>Specificity</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer</td>
<td>74.8%</td>
<td>67.0-81.6%</td>
<td>87.4%</td>
<td>83.5-90.6%</td>
</tr>
<tr>
<td>Advanced adenomas</td>
<td>27.4%</td>
<td>18.7-37.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenomas</td>
<td>20.7%</td>
<td>15.1-27.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How To Increase Screening
Adherence to CRC Screening

- Overall adherence 60% (stable since 2010)
  - 55% colonoscopy within 10 years
  - 5% FOBT within the previous year
  - <1% sigmoidoscopy within 5 years
- Large variations between racial/ethnic groups
  - Disparities vs. Differences
  - Access vs. Utilization

Adherence to CRC Screening Methods

- Design
  - Prospective quasi-experimental study
- Interventions:
  - Recommend FOBT
  - Recommend Colonoscopy
  - Choice of FOBT or colonoscopy
- Setting
  - Urban, diverse underserved population

Methods

- Subjects
  - Average risk for development of CRC
    - No family history of CRC
    - No personal history of CRC or adenomas, IBD
  - Not up-to-date with CRC screening
- Outcomes
  - Completion of screening strategy within one year
    - FOBT plus colonoscopy if positive
    - Colonoscopy

Study Design – Clinic Randomization

- General Medicine Clinic:
  - FOBT
  - Choice
  - Colonoscopy

- Family Health Center and Positive Health Program:
  - Colonoscopy
  - Choice
  - FOBT
Methods

- Goal of study: Identify patient factors associated with adherence
- Requirement: reduce systems/access barriers
  - One encounter
  - Language
    - Spanish, Cantonese, Mandarin, English
  - Capacity
    - < 2 week wait for colonoscopy
  - Cost
    - Healthy San Francisco
  - Support
    - Rides to / from hospital if necessary

Results

Subjects: 997 enrolled

Recommendation for Colonoscopy: Lower Adherence
**Recommendation for Colonoscopy:**

Lower Adherence

<table>
<thead>
<tr>
<th>FOBT</th>
<th>Colonoscopy (colonoscopy or FOBT)</th>
<th>Choice (regardless of intent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>67.2%</td>
<td>58.1%</td>
<td>68.8%</td>
</tr>
</tbody>
</table>

\*p = 0.001

Arch Intern Med 2012

**Overall Adherence Varies by Race**

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Adherent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>51.4%</td>
</tr>
<tr>
<td>White</td>
<td>64.9%</td>
</tr>
<tr>
<td>Asian</td>
<td>72.6%</td>
</tr>
<tr>
<td>Latino</td>
<td>69.5%</td>
</tr>
</tbody>
</table>

Arch Intern Med 2012

**Factors Associated with Adherence**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Group</th>
<th>Univariate Analysis</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOBT Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>193/332 (58)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOBT</td>
<td>231/334 (67)</td>
<td>1.50</td>
<td>1.08</td>
<td>2.06</td>
</tr>
<tr>
<td>Choice</td>
<td>221/321 (69)</td>
<td>1.61</td>
<td>1.16</td>
<td>2.24</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>90/177 (51)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>92/149 (62)</td>
<td>1.55</td>
<td>0.99</td>
<td>2.42</td>
</tr>
<tr>
<td>Asian</td>
<td>214/298 (72)</td>
<td>2.46</td>
<td>1.66</td>
<td>3.63</td>
</tr>
<tr>
<td>Latino</td>
<td>234/337 (69)</td>
<td>2.19</td>
<td>1.50</td>
<td>3.20</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>315/556 (57)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spanish</td>
<td>190/240 (73)</td>
<td>2.12</td>
<td>1.53</td>
<td>2.95</td>
</tr>
<tr>
<td>Cantonese or Mandarin</td>
<td>138/175 (78)</td>
<td>2.72</td>
<td>1.82</td>
<td>4.08</td>
</tr>
</tbody>
</table>
Factors Associated with Adherence

<table>
<thead>
<tr>
<th>Variable</th>
<th>no./total no. (%)</th>
<th>Multivariable OR</th>
<th>95% C.I.</th>
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<tbody>
<tr>
<td>Study Group</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>193/332 (58)</td>
<td>1 -</td>
<td></td>
</tr>
<tr>
<td>FOBT</td>
<td>231/344 (67)</td>
<td>1.44</td>
<td>1.03 – 2.02</td>
</tr>
<tr>
<td>Choice</td>
<td>221/321 (69)</td>
<td>1.66</td>
<td>1.18 – 2.35</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>90/177 (51)</td>
<td>1 -</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>92/149 (62)</td>
<td>1.43</td>
<td>0.89 – 2.30</td>
</tr>
<tr>
<td>Asian</td>
<td>214/298 (72)</td>
<td>1.43</td>
<td>0.86 – 2.38</td>
</tr>
<tr>
<td>Latino</td>
<td>234/337 (69)</td>
<td>1.31</td>
<td>0.75 – 2.31</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>315/556 (57)</td>
<td>1 -</td>
<td></td>
</tr>
<tr>
<td>Spanish</td>
<td>190/260 (73)</td>
<td>1.67</td>
<td>0.94 – 2.98</td>
</tr>
<tr>
<td>Cantonese or Mandarin</td>
<td>136/175 (78)</td>
<td>2.13</td>
<td>1.23 – 3.70</td>
</tr>
</tbody>
</table>

Race/Ethnicity and Language

- Latino and Asian subjects adhered more often than white and black subjects
- Effect disappeared when language introduced
  - Increased adherence driven by those who preferred to speak Cantonese, Mandarin or Spanish
  - Within Asian and Latino participants
    - Non-English speakers adhered at higher rate
- What?

Race/Ethnicity and Language

- Language may be a surrogate for:
  - Immigration status: The "healthy immigrant"
  - Health belief system
- Are disparities in screening due to differences in health beliefs?
  - Impact
  - Severity
  - Self-efficacy
  - Family, friends, social network

Adherence to CRC Screening: Study Summary

- The best test is the one that gets done
  - Providing choice of CRC screening test increases adherence to screening
- Variation by race/ethnicity
  - Whites adhere more often to colonoscopy
  - Non-whites adhere more often to FOBT
- Race/ethnicity and language
  - Surrogates for immigrant status, health beliefs, trust in physicians
Optimizing the Effectiveness of Screening

- Colonoscopy Quality
  - Colonoscopy essential for all screening strategies
- How is quality measured?
  - Impact of adenoma detection rate (ADR)
  - Proportion of individuals at average risk for CRC in whom at least one adenoma is removed

Each 1% increase in ADR = 3% reduction in interval CRC

Corley. NEJM 2014
Colonoscopy Quality
You Can’t Remove What You Can’t See
Boston Bowel Preparation Scale

• 3 Segments:
  – Right Cecum / Ascending
  – Transverse Hepatic to Splenic Flexure
  – Left Descending to Rectum

• Score:
  – 0: mucosa not seen due to solid stool
  – 1: mucosa not well seen – staining, residual stool, opaque liquid
  – 2: minor amount of residual staining, small fragments of stool or liquid, but mucosa well seen
  – 3: entire mucosa well seen

Lai et al. GIE 2009; Calderwood et al. GIE 2010

Colonoscopy Quality
Bowel Preparation and ADR

Adenoma Miss Rate

Adenoma >5mm
Advanced Adenoma
Sessile Serrated
Adenoma

0% 2% 4% 6% 8% 10% 12% 14% 16% 18%


Colonoscopy Quality Measures

• Adenoma detection rate: ≥ 25%
  – Each 1% increase in ADR = 3% reduction in interval cancers
• Improvement in ADR reduces interval CRC
• Appropriate screening and surveillance intervals
  – Average-risk, no adenomas = 10 years
  – 1-2 small (<1cm) adenomas = 5-10 years
  – ≥3 small, ≥1cm, HGD = 3 years

New Technology

• Endoscope accessories
• Next gen scopes
• Blood tests
Caps, Cuffs, Rings

- Improve visualization
- Flatten folds
- Center scope
- May increase ADR

Jain. Digestion 2016

Third Eye Panoramic

- Two side-viewing video cameras
- 330 degree image
- Clips onto standard pediatric or adult colonoscope

Self-Propelled Disposable Colonoscope: Aer-O Scope
Self-Propelled Disposable Colonoscope

Confocal Raman Spectroscopy

Blue, normal; red, hyperplastic polyp; green, adenoma; yellow, cancer; cyan, ulcerative colitis. Shaded areas indicate two standard deviations from the mean.

Optimizing Mortality Reductions through Colorectal Cancer Screening

- Which test is best?
  - The one that gets done
  - Racial and ethnic differences in adherence to specific screening strategies

- How can we optimize screening?
  - Increase adenoma detection rate

- How do you prepare for the future?
  - New technology: prepare for disruption