## Colorectal Cancer Screening Guidelines

Douglas K Rex  
Indiana University Hospital  
Indianapolis, IN

### Colorectal Cancer – Molecular Basis

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Frequency</th>
<th>Genes</th>
<th>MSI</th>
<th>Precursor</th>
<th>Speed</th>
</tr>
</thead>
</table>
| CIN     | 65-70%    | APC  
K-ras  
p53 | No    | Adenoma    | Slow     |
| Lynch   | 3%        | MLH1  
MLH2  
MLH6  
PMS2 | Yes   | Adenoma    | Fast     |
| CIMP    | 30-35%    | BRAF           | Sometimes | Serrated | Can be fast |
Expanded Terminology of Serrated Lesions (WHO)

- Hyperplastic polyp (HP)
  - Goblet cell HP
  - Microvesicular HP
  - Mucin Poor HP
- Sessile serrated adenoma/polyp (SSA/P)
  - With cytological dysplasia
  - Without cytological dysplasia
- Traditional serrated adenoma (TSA)

Pathologic differentiation of SSA/P from HP

<table>
<thead>
<tr>
<th>Goblet cell HP</th>
<th>SSA/P</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
</tbody>
</table>
## Pathologic differentiation of SSA/P from HP

<table>
<thead>
<tr>
<th>MVHP</th>
<th>SSA/P</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
</tbody>
</table>

## SSA/P without and with cytological dysplasia

<table>
<thead>
<tr>
<th>SSA/P without dysplasia</th>
<th>SSA/P with dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
</tbody>
</table>
Agreement for pathologic interpretation of SSA/P vs HP

  - SSA commonly read as HP
  - TSA commonly read as TVA
- Khalid et al World J Gastroenterol 2009
  - 30-80% of proximal HPs in 2001 read as SSP by experts; kappas 0.14-0.38

Histology of colon polyps – reliable or not?

Yes
- Serrated vs conventional adenoma
- Cancer or no cancer

Not very
- Tubular vs tubulovillous
- HGD vs LGD
- Tumor differentiation
- SSA/P vs HP
The serrated pathway

Hyperplastic polyp
  ? ↓ ?
Sessile serrated adenoma/polyp
  ↓ probably slow
SSA/P with cytologic dysplasia
  ↓ sometimes fast
CIMP colon cancer

2416 SSA/Ps

mean age

- SSA/P  61y
- SSA/P with LGD  66y
- SSA/P with HGD  72y
- SSA/P with cancer  76y

- Lash J Clin Pathol 2010;63:681-6
Conclusions

- SSA/P is the main precursor of CIMP-high CRC
- Variability in detection >> conventional adenomas
- No reliable way to distinguish HP from SSA/P endoscopically right now
- Agreement for pathologists distinguishing HP from SSA/P is moderate
- Larger serrated lesions in the proximal colon are SSA/P
- SSA/P with cytological dysplasia is dangerous

Features of major categories of serrated lesions

<table>
<thead>
<tr>
<th>WHO classification</th>
<th>Prevalence</th>
<th>Shape</th>
<th>Size</th>
<th>Distribution</th>
<th>Malignant potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic polyp</td>
<td>Very common</td>
<td>Sessile/flat</td>
<td>small</td>
<td>Mostly distal</td>
<td>Very low</td>
</tr>
<tr>
<td>Sessile serrated adenoma/Polyp</td>
<td>Common</td>
<td>Sessile/flat</td>
<td>Big</td>
<td>80% proximal</td>
<td>Significant</td>
</tr>
<tr>
<td>Traditional serrated adenoma</td>
<td>Rare</td>
<td>Sessile/ pedunculated</td>
<td>Big</td>
<td>Mostly distal</td>
<td>Significant</td>
</tr>
</tbody>
</table>
Spectrum of pre-cancerous lesions in the colorectum

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Paris shape</th>
<th>Distribution</th>
<th>Prevalence</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional adenomatous polyps</td>
<td>1p</td>
<td>Left</td>
<td>Low</td>
<td>Mostly LGD</td>
</tr>
<tr>
<td></td>
<td>1s</td>
<td>Throughout</td>
<td>Common</td>
<td>Mostly LGD</td>
</tr>
<tr>
<td>Flat adenomas (lesions)</td>
<td>2a</td>
<td>Greater to right</td>
<td>Common</td>
<td>Mostly LGD</td>
</tr>
<tr>
<td>Depressed adenomas (lesions)</td>
<td>2c</td>
<td>Greater to right</td>
<td>rare</td>
<td>↑↑ HGD and invasive cancer</td>
</tr>
<tr>
<td></td>
<td>2a + 2c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2c + 2a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sessile serrated adenoma (polyp)</td>
<td>1s or 2a</td>
<td>Right colon</td>
<td>Common</td>
<td>Distinction from HP may not be reliable</td>
</tr>
<tr>
<td>TSA</td>
<td>1s or 1p</td>
<td>Left colon</td>
<td>rare</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

CRC Screening Guidelines

**MSTF-ACS-ACR**
- Annual FIT or HOS
- Flex sig q 5-10 y
- CTC q 5y
- Fecal DNA (interval not stated)
- DCBE q 5 y
- Colonoscopy q 10 y

**ACG and ASGE**
- Colonoscopy q 10y preferred
# Cancer Prevention vs Cancer Detection

## Cancer Prevention
- Colonoscopy
- Flexible sigmoidoscopy
- CTC
- Double contrast barium enema
  - Not ready: capsule

## Cancer Detection
- Fecal blood tests
  - FIT
  - Hemoccult Sensa
- Fecal DNA tests
  - Vimentin hypermethylation
  - Not ready: hypermethylation and proteomic assays

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## ACG: if colonoscopy declined
- Annual FIT
- Fecal DNA q 3 y
- Flex sig q 5-10 y
- CTC q 5 y
Colorectal Cancer Screening Guideline

- USPSTF
  - Continues to endorse screening as A recommendation
  - Annual FOBT, FS q 5y, DCBE q 5y, CS q 10y all options – “none preferred”
  - Declined to recommend CTC or fecal DNA
  - Recommended no screening or stop screening in the elderly

RCT of FIT vs g-FOBT

- 20,623 screenees
- RCT of FIT (OC-Sensor) vs g-FOBT (HII)
- Adherence 59.6% vs 46.9% (HII)
- Positivity 5.5% vs 2.4% (HII)
  - Van Rossum; GASTRO 2008;135:82
Variable Performance of FITs
Hundt Ann Intern Med
2009;150:162-9

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Sens AA</th>
<th>Spec</th>
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<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>30</td>
<td>10</td>
</tr>
</tbody>
</table>

**gFOBT vs FIT**

- FIT: better performance
- FIT: 10-12% gains in adherence
- FIT: Doubling of number of patients detected with advanced neoplasia
- FIT: may maintain positive predictive value after a negative colonoscopy
- Commercially available FITs may variable performance
Fecal DNA Tests

1.0
- APC, k-ras, p 53, DIA, BAT-26
  • Imperiale NEJM 2004;351:2704-14

1.1
- 1.0 plus gel-based DNA capture and stabilization of DIA
  • Whitney J Mol Diag 2004;6:386-95

2.0
- DIA plus Vimentin hypermethylation
  • Itzkowitz CGH; 2007;5:111-7

Under investigation
- Hypermethylation of BMP3, NGR4, vimentin, TPFI2; also mutant k-ras and fecal Hgb
  • Ahlquist GASTRO; 2012
### Fecal DNA testing vs Septin 9
Ahlquist CGH 2012;10:272

<table>
<thead>
<tr>
<th></th>
<th>Fecal DNA test</th>
<th>Septin 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity for cancer</td>
<td>91%</td>
<td>50%</td>
</tr>
<tr>
<td>Stage I-III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity for cancer</td>
<td>75%</td>
<td>88%</td>
</tr>
<tr>
<td>Stage IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity for large</td>
<td>82%</td>
<td>14%</td>
</tr>
<tr>
<td>adenomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>93%</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Are screening tests able to detect proximal serrated lesions?

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity for serrated lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT</td>
<td>?</td>
</tr>
<tr>
<td>Fecal DNA</td>
<td>?</td>
</tr>
<tr>
<td>CT colonography</td>
<td>?</td>
</tr>
<tr>
<td>Flex sig</td>
<td>?</td>
</tr>
<tr>
<td>Capsule colonoscopy</td>
<td>?</td>
</tr>
<tr>
<td>Serum assays</td>
<td>?</td>
</tr>
</tbody>
</table>
Cancer Prevention (Adenoma Detection) Tests

- Colonoscopy q 10 y
- Flex sig q 5-10 y
- CTC q 5 y
- DCBE q 5 y

CTC Screening: ACRIN Trial

<table>
<thead>
<tr>
<th></th>
<th>&gt;5mm</th>
<th>&gt;6mm</th>
<th>&gt;7mm</th>
<th>&gt;8mm</th>
<th>&gt;9mm</th>
<th>&gt;1cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENS</td>
<td>65%</td>
<td>78%</td>
<td>84%</td>
<td>87%</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>SPEC</td>
<td>89%</td>
<td>88%</td>
<td>87%</td>
<td>87%</td>
<td>86%</td>
<td>86%</td>
</tr>
<tr>
<td>PPV</td>
<td>45%</td>
<td>40%</td>
<td>35%</td>
<td>31%</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>NPV</td>
<td>95%</td>
<td>98%</td>
<td>99%</td>
<td>99%</td>
<td>99%</td>
<td>99%</td>
</tr>
</tbody>
</table>

Per polyp sensitivities

<table>
<thead>
<tr>
<th>Size</th>
<th>≥ 5</th>
<th>≥ 6</th>
<th>≥ 7</th>
<th>≥ 8</th>
<th>≥ 9</th>
<th>≥ 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sens</td>
<td>0.59</td>
<td>0.70</td>
<td>0.75</td>
<td>0.80</td>
<td>0.82</td>
<td>0.84</td>
</tr>
<tr>
<td>Number polyps</td>
<td>374</td>
<td>270</td>
<td>220</td>
<td>187</td>
<td>143</td>
<td>128</td>
</tr>
</tbody>
</table>

Interpreting the ACRIN Result

- Selected radiologists
- Not as good as Pickhardt
- CTC clearly better than DCBE
  - 90% vs 50% sensitivity
  - Dramatically better acceptance
- CTC will result in long colonoscopies and repeat CTCs for false positive results (low PPV)
- CTC will generate a lot of colonoscopies (low specificity)
### First RCT of Colonoscopy vs CTC
Netherlands (abstract 353; DDW 2011)

<table>
<thead>
<tr>
<th>Colonoscopy: 5,924 invited</th>
<th>CTC: 2,920 invited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence: 21%</td>
<td>Adherence: 32%</td>
</tr>
<tr>
<td>Advanced adenomas per 100 participants:</td>
<td>Advanced adenomas per 100 participants:</td>
</tr>
<tr>
<td>– 8.4</td>
<td>– 5.2</td>
</tr>
<tr>
<td>Advanced adenomas per 100 invitees:</td>
<td>Advanced adenomas per 100 invitees:</td>
</tr>
<tr>
<td>– 1.7</td>
<td>– 1.7</td>
</tr>
</tbody>
</table>

### Expected vs actual burden - prep

#### Colonoscopy

- Embarrasss
- Painful
- Burden

#### CTC

- Burden
- Embarrasss
Expected vs Actual burden - procedure

Colonoscopy

CT colonography

- Burden
- Painful
- Embarrass

0 50 100

Will CTC Increase Adherence?

- Adherence is a complex phenomenon
- No evidence currently that CTC will increase adherence or by how much
- Australian study: Adherence
  - Colonoscopy 16.3
  - CTC 18.1
  - Colonoscopy or CTC 17.5
    • Scott Am J Gastroenterol 2004
Diagnosis-Only Tests (CTC, capsule, Aer-O-Scope)

- Increased Adherence
- Increased polypectomy
- Decrease in CRC

- Displacement of patients from colonoscopy
- Decreased polypectomy
- Increase in CRC

CT Colonography Issues

- Adherence?
- Extracolonic findings
- Radiation risk
- Reporting and management of small polyps
- Positioning CTC in practice
  - Primary screening for all?
  - Use only for patients who refuse colonoscopy?
  - Triaged screening based on risk, informed consent?
- Who will do it?
  - GI directed colorectal cancer screening
Screening colonoscopy is vulnerable to disruption

- Bowel preparation
- Highest risk of perforation
- Adherence incomplete (perceived as inconvenient, invasive, and risky)
- Less protection than previously thought

Variable detection of adenomas among GI docs during colonoscopy

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of doctors</th>
<th>Lowest ADR</th>
<th>Highest ADR</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barclay Illinois 2006</td>
<td>12</td>
<td>9.4%</td>
<td>32.7%</td>
<td>3.5</td>
</tr>
<tr>
<td>Chen Indiana 2007</td>
<td>9</td>
<td>15.5%</td>
<td>41.1%</td>
<td>2.7</td>
</tr>
<tr>
<td>Imperiale Indiana 2009</td>
<td>25</td>
<td>7%</td>
<td>44%</td>
<td>6.3</td>
</tr>
<tr>
<td>Shaukat Minnesota 2009</td>
<td>51</td>
<td>10%</td>
<td>39%</td>
<td>3.9</td>
</tr>
</tbody>
</table>
## Variable detection of proximal serrated lesions (GI docs) during colonoscopy

<table>
<thead>
<tr>
<th></th>
<th>Number of doctors</th>
<th>Lowest proximal colon serrated lesion detection rate</th>
<th>Highest proximal colon serrated lesion detection rate</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hetzel Boston</td>
<td>13</td>
<td>1.1%</td>
<td>7.6%</td>
<td>6.9</td>
</tr>
<tr>
<td>Kahi Indiana</td>
<td>15</td>
<td>1%</td>
<td>18%</td>
<td>18</td>
</tr>
</tbody>
</table>

### Residual risk after colonoscopy: right vs left colon

- **Brenner 2011**
- **Singh, G 2007**
- **Singh, H 2010**
- **Baxter, 2009**

![Bar chart showing residual risk after colonoscopy](chart.png)

Legend:
- Red: Left-sided
- Yellow: Right-sided
Associations with interval cancer

- Proximal location
- CIMP positive
- MSI
- Low ADR, low polypectomy rate
- Low cecal intubation rate
- Performance by non-GI
- Indication of positive FOBT vs screening

Operator dependence – cancer prevention
Kaminski et al NEJM2010;362:1795-803

<table>
<thead>
<tr>
<th>Adenoma detection rate (ADR)</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 11%</td>
<td>10.94</td>
</tr>
<tr>
<td>11.0-14.9%</td>
<td>10.75</td>
</tr>
<tr>
<td>15.0-19.9%</td>
<td>12.50</td>
</tr>
</tbody>
</table>
Issues in Colonoscopy

- Huge operator dependency
  - 10 fold variation in ADR
  - 3 fold variation in large adenoma detection
  - Worse problems in PCPs
- Poor documentation
  - Cecal landmarks and photography
- Ineffective preparation
  - Split dosing

Potential corrections to poor protection by colonoscopy

- Split-dose preparation
- Correction or exclusion of low ADR endoscopists
- Revamping training?
  - Spectrum of pre-cancerous lesions, recognition
  - Withdrawal technique
- Technical solutions?
Colonoscopy is recommended for average-risk screening at which of the following intervals?

- a. 20 years
- b. 10 years
- c. 5 years
- d. 3 years
- e. 1 year

Colonoscopy intervals

- Recent evidence from Germany indicates negative screening colonoscopy associated with protection for 20 years
- Screening colonoscopy often performed in the US screening population at 5 year intervals
Post-Polypectomy Surveillance

(assumes good prep, exam to cecum)

**Category**  
- One or two TA < 1cm  
  - Follow up normal:  
- 3-10 adenomas, any villous component, HGD  
  - Follow up normal:  
- > 10 adenomas  
- Large sessile adenoma removed piecemeal

**Interval**  
- 5-10 y  
- 5-10 y  
- 3 y  
- 5y (indefinitely)  
- <3 y  
- 2-6 mo

Winawer, *Gastroenterology* 2006

New surveillance recs coming

<table>
<thead>
<tr>
<th>baseline</th>
<th>First follow-up</th>
<th>Recommended interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRA</td>
<td>HRA</td>
<td>3y</td>
</tr>
<tr>
<td>LRA</td>
<td>No adenoma</td>
<td>10y</td>
</tr>
<tr>
<td>HRA</td>
<td>HRA</td>
<td>3y</td>
</tr>
<tr>
<td>LRA</td>
<td>No adenoma</td>
<td>5y</td>
</tr>
<tr>
<td>LRA</td>
<td>No adenoma</td>
<td>5y</td>
</tr>
</tbody>
</table>
New surveillance recs – serrated lesions

<table>
<thead>
<tr>
<th>Finding</th>
<th>Recommended interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sessile serrated adenoma (sessile serrated polyp) with cytological dysplasia or ≥ 1 cm</td>
<td>3 y</td>
</tr>
<tr>
<td>SSA (SSP) &lt; 1 cm</td>
<td>5y</td>
</tr>
<tr>
<td>Only hyperplastic polyps</td>
<td>10 y</td>
</tr>
</tbody>
</table>

Post Colon Cancer Resection Surveillance

- Clear colon of synchronous disease
- First follow up colonoscopy 1 year
- If first follow up negative next exam in 3-5 years
- If patient under 50 years consider closer intervals
- CEA every 2-3 mos first 2 years
- Consider annual liver CTs and CXRs (Renehan, *BMJ* 324:813)
Post Rectal Cancer Resection Surveillance

- Best approach may depend on how the cancer was treated
- Lower local recurrence rates associated with Total Mesorectal Excision and with neoadjuvant radiation/chemotherapy
  - Kapiteijn, NEJM 2001;345:638
- If risk of local recurrence high, consider flex sig or rectal EUS every 3 to 6 mos for first 2 years
- Other surveillance same as for colon cancer
  - Rex Gastroenterology 2006

Summary

- Principle strategies:
  - Colonoscopy dominates: quality is key
  - FIT should be replacing gFOBT
- Otherwise:
  - Flex sig a good test but unlikely to make return in U.S.
  - CTC status in U.S. unlikely to be affected by the Netherlands RCT
  - Fecal DNA has made further improvements: results of large screening trial pending
  - First serum test has lower performance than other screening tests
  - More information needed on sensitivity for proximal colon serrated lesions
Surveillance Summary

- Low risk adenoma cohort expanding
- New recs coming for serrated lesions
- Colon cancer – stage II and III
  - CEA q 2-3 months for 2 y
  - Consider annual CT of liver, CXR
  - Colonoscopy for metachronous lesions at 1 y, then 3 y, then 5
- Rectal cancer
  - Same as colon + consider EUS every 3-6 months

Summary, Conclusions

- FIT is the preferred non-imaging test
- Colonoscopy q 10 y still dominates: quality of performance will determine its future
- CTC will emerge as a screening test; its impact and role will depend on how persistent questions are answered and the extent to which colonoscopy performance improves