Colon Cancer Screening and Surveillance

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Outline
• Colon cancer screening
  • Why do we do it?
  • Guidelines
    • When to start
    • Options on modality
• Colon cancer surveillance
  • Guidelines
  • Serrated polyps

Definitions
• Screening
  • To identify polyps/cancer in a patient without a personal history of cancer or precancerous lesions
  • No signs/symptoms of suspected colorectal disease
• Surveillance
  • To identify polyps/cancer in an individual with previously identified polyps/cancer
  • No signs/symptoms of suspected colorectal disease

Why is colon cancer important?
• 3rd most common cancer in women and men
  • 8% of all new cancer diagnoses
• Overall lifetime risk is ~ 5-6%


American Cancer Society, 2014 estimates
Colon Cancer Screening

- Multiple modalities have been shown to reduce colon cancer mortality
  - Colonoscopy
  - Flexible sigmoidoscopy
  - Fecal occult blood testing (FOBT)
    - Shaukat et al. Long-Term Mortality after Screening for Colorectal Cancer. NEJM 9/2013
  - Fecal immunochemical testing (FIT)
    - Chiu et al. Effectiveness of Fecal Immunochemical Testing in Reducing Colorectal Cancer Mortality From the One Million Taiwan Screening Program. Cancer 2015.

* Remember - Whatever screening your patient will accept is better than none…

Colon cancer screening guidelines

- I generally use ACG 2008 guidelines due to simplicity

- Average risk screening should start at age 50
  - African Americans should begin at age 45

- Recommend cancer prevention tests first
  - Both prevent and detect colon cancer

- Colonoscopy is preferred, if normal repeat in 10 years

Colon cancer screening guidelines

- Alternative cancer prevention tests
  - Flexible sigmoidoscopy
    - If normal, repeat in 5-10 years (USMSTF – every 5 years)
    - If polyp found, requires colonoscopy for completion
      - Detects 60-70% of neoplasia found at colonoscopy

ACG 2008
Colon cancer screening guidelines

- CT colonography
  - If normal, repeat in 5 years
    - Performs fairly well for polyps > 1 cm (90% detection)
    - Does not detect polyps 5 mm or smaller
    - Still requires bowel prep (despite “virtual colonoscopy” tagline)
  - If polyp found, requires colonoscopy for completion

ACG 2008

Why start African Americans early?

- Average annual age-specific colorectal cancer incidence rates by race in California (per 100,000 persons)

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Asian (13.6–23.2)</th>
<th>Black (16.5–29.9)</th>
<th>Latino (7.68–12.8)</th>
<th>White (14.2–17.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>35.2 (27.4–42.9)</td>
<td>56.6 (44.5–68.4)</td>
<td>36.6 (21.7–31.4)</td>
<td>33.2 (30.3–36)</td>
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<tr>
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Colon cancer screening guidelines with family history

- First degree relatives (FDR) with colon cancer or advanced adenoma at age < 60 years or 2 FDR with this
  - Start screening at age 40 or 10 years younger than age of youngest affected relative
  - Colonoscopy every 5 years
- FDR ≥ 60 years with CRC or adv. Adenoma
  - Treat as average risk
- ACG 2008 – no comment on 2nd degree relatives

ACG 2008

Colon cancer screening guidelines with family history

- I use USMSTF 2008 guidelines when a patient has 2nd degree relatives with CRC

- If colon cancer or adenomas in 2 or more second degree relatives
  - Start screening at age 40
  - Screening intervals are same as average risk

*FDR with small adenomas – Increased risk USMSTF Average risk ACG

Colon cancer screening guidelines with family history

- Why do we care about second degree relatives (SDR)?
- Population-based studies have shown SDR of patients with colon cancer have:
  - Increased risk of colon cancer: 1.32 (CI 1.19 – 1.47)
  - Increased risk of adenomas: 1.19 (CI 1.08 – 1.31)


Importance of EFFECTIVE CRC screening

<table>
<thead>
<tr>
<th>Adenoma detection rate</th>
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<th># of interval cancers</th>
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<td>ADR: 7-19%</td>
<td>0.85</td>
<td>8</td>
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<td>4.8</td>
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<td>Quintile 5 - High performers</td>
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Each 1.0% increase in the adenoma detection rate was associated with a 3.0% decrease in the risk of cancer

Importance of Effective CRC Screening

Adenoma detection rate | Hazard Ratio | # of interval cancers
---|---|---
Quintile 1 - Low performers | Reference | 9.8

Each 1.0% increase in the adenoma detection rate was associated with a 3.0% decrease in the risk of cancer.

| Quintile 3 - High performers | 0.85 | 8 |
ADR: 24-28%

| Quintile 5 - High performers | 0.52 | 4.8 |
ADR: 33-52%


Non-Endoscopic options

- FIT preferred to FOBT
  - Better performance
  - Less reliance on dietary restrictions
  - Less samples to collect (FOBT is usually 2-3 samples)
  - Remember – FOBT in the office with rectal exam is **NOT ACCEPTABLE**


Non-Endoscopic options

- Fecal DNA testing – Testing for CRC DNA from a stool sample
  Benefit: No prep, no procedure (good for average risk patients unwilling/unable to undergo colonoscopy)

Downsides:
1. Only works for cancer, inadequate for polyps
2. 3 year interval has no basis in literature at this point
3. If positive but no colon lesions, is this a marker from above in GI tract or a false positive?
4. People do not like to collect stool samples


Fecal DNA testing

- Performed well for cancer detection
  - 92.3% (60/65) CRC detected
  - Significantly better than FIT (92.3% vs 73.8%, P = 0.002)
- True colon cancer screening - no polyp detection/removal!
  - 42% (321/758) of advanced adenomas detected

*Wait for guidelines to endorse prior to using given questions regarding safe intervals

Colon cancer surveillance recommendations

- No polyps (average risk): 10 years
- No polyps (increased risk due to FH): 5 years
- 1-2 small adenomas (< 1 cm): 5 - 10 years
  - Most recommend 5 years
- ≥1 large adenoma (≥1 cm): 3 years
- Any high grade dysplasia: 3 years
- Any villous histology: 3 years
- 3-10 adenomas: 3 years
- ≥10 adenomas: <3 years (most do 1 year, refer to Genetics)

Colon cancer surveillance

- Recommendations after the 1st Surv. Colonoscopy

**Index procedure:** LRA, then on first surveillance:
  - If no adenomas, can return to 10 years.
  - If LRA/HRA, continue with standard surveillance recs

**Index procedure:** HRA, then on first surveillance:
  - If no adenomas, repeat in 5 years.
  - If LRA/HRA, continue with standard surveillance recs

**Serrated colon polyps**

- Includes:
  - Sessile serrated adenomas (SSA)
  - Sessile serrated polyps
    - Use interchangeably with SSA
  - Proximal hyperplastic polyps
    - Difficult for pathologists to differentiate from an SSA/P
  - Traditional serrated adenomas.
- SSA/P likely the source of most interval cancers
- Rectal and sigmoid hyperplastic polyps are not thought to confer an increased risk

- They can be very hard to see!
Serrated polyp surveillance intervals

- Sessile serrated adenomas/polyps (SSA/P)
  - Also applies for traditional serrated adenomas (TSA)
  - SSA / P: < 1 cm, 1 or 2 polyps: 5 years
  - SSA / P: ≥ 1 cm, 1 polyp: 3 years
  - SSA / P: ≥ 1 cm, ≥ 2 polyps: 1 – 3 years
    - Consider serrated polyposis syndrome
  - SSA / P: < 1 cm, ≥ 3 polyps: 3 years
  - SSA / P: Any with dysplasia: 1 – 3 years

Rex et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. AJG 2012.

Hyperplastic polyps

- Rectosigmoid: < 1 cm, any number polyps: 10 years
- Proximal: small (≤ 5 mm), ≤ 3 polyps: 10 years
- Proximal: Any size, ≥ 4 polyps: 5 years
- Proximal: > 5 mm, ≥ 1 polyps: 5 years

Rex et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. AJG 2012.

Rectal hyperplastic polyps

Rectal hyperplastic polyps

Colon cancer surveillance guidelines

| No polyps, or hyperplastic polyps in rectum/sigmoid | Repeat in 10 years |
| Neoplasia found |

<table>
<thead>
<tr>
<th>Serrated polyps/lesion</th>
<th>High risk adenomas</th>
<th>Low risk adenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serrated polyposis</td>
<td>&gt;10 Adenomas</td>
<td>Repeat in less than 3 years</td>
</tr>
<tr>
<td>Repeat in 1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10mm or With dysplasia or traditional serrated adenoma</td>
<td>3-10 Adenomas</td>
<td>Repeat in 3 years</td>
</tr>
<tr>
<td>Repeat in 3 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10mm in Proximal colon and without dysplasia</td>
<td>Adenoma(s) with high grade dysplasia</td>
<td>Repeat in 3 years</td>
</tr>
<tr>
<td>Repeat in 5 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1-2 Tubular adenomas
≤ 10 mm
Repeat in 5 – 10 years


These recommended intervals assume a complete exam to cecum, adequate bowel prep, and complete removal of polyps at the baseline exam.
Why might clinical recommendations differ?

- Piecemeal resection - If polyp was not removed in one piece, follow-up in 3-6 months recommended
- Large polyp requiring mucosal resection - Similar
- Bowel prep – if prep is not up to par, then shorter intervals likely to be recommended
- Not aware of personal or family history – might give average risk recommendations when should be high risk

*If not sure, ask the endoscopist for clarification*

When to stop?

- Screening – USPSTF recommends stopping at 75, with consideration of continuing through 85 based on comorbidities
- Surveillance – Should be individualized, based on assessment of risks, benefits and comorbidities
  - 75-85 is likely reasonable
  - If colon cancer found, would patient accept/be offered surgery and/or chemotherapy?


Key Points

- Colon cancer screening is important and effective
  - Start at age 50, consider starting at age 45 in African Americans
- Colonoscopy is preferred as it both prevents and detects colon cancer in a single session
- Any screening modality is better than none
- Surveillance recommendations are more complicated than screening – but equally or more important!

Thank you

- For any questions or referrals, please contact me at:
  - Peter.Stanich@osumc.edu
  - http://go.osu.edu/INHP
  - (614) 293 – 6255
What is the best bowel prep for a colonoscopy?

Capsule endoscopy

Recognizing the Red Flags: Does my patient have Hereditary Colorectal Cancer?

1. Major Hereditary Causes of Colorectal Cancer
2. Red Flags for Polyposis
3. Red Flags for Lynch syndrome
4. Tumor Screening Red Flags for Lynch syndrome
5. Tools to Use in Clinic
6. Genetic Information Nondiscrimination Act

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Associate Director, Division of Human Genetics
Associate Director, Biospecimen Research
Professor, Internal Medicine
The Ohio State University Comprehensive Cancer Ctr
The Ohio State University Wexner Medical Center
Hereditary Susceptibility to CRC

Adapted from Burt RW et al. Prevention and Early Detection of CRC, 1996

Sporadic (65%–85%)
Familial (10%–30%)
Rare CRC (≤0.1%)
Familial adenomatous polyposis (FAP) (1%)
Hereditary nonpolyposis colorectal cancer (HNPCC) (3%)

Flowchart for Hereditary Colon Cancer Differential Diagnosis

Presence of >10 polyps

Type of polyps
Lynch syndrome
Familial Colorectal Cancer syndrome type X
MYH-Associated Polyposis

Hamartomatous
Adenomatous

Juvenile Polyposis
Peutz-Jeghers syndrome
Hyperplastic Polyposis syndrome
Cowden syndrome/BRB

Familial Adenomatous Polyposis
Attenuated FAP
MYH-Associated Polyposis

Lynch Syndrome Genes

MLH1
PMS2
MSH2
MSH6

Sporadic

Normal gene
Somatic mutation

Inherited

Germline mutation
Somatic mutation

• Later age at onset (60s or 70s)
• Little or no family history of cancer
• Single or unilateral tumors

Early age at onset (<50)
•Multiple primary tumors
•Multiple generations with cancer
•Clustering of certain cancers (i.e. breast/ovarian)
Autosomal Dominant Inheritance

<table>
<thead>
<tr>
<th>Carrier Parent</th>
<th>Non-carrier Parent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aa</td>
<td>aa</td>
</tr>
<tr>
<td>Aa</td>
<td>Aa</td>
</tr>
<tr>
<td>Aa</td>
<td>aa</td>
</tr>
<tr>
<td>Carrier</td>
<td>Carrier</td>
</tr>
<tr>
<td>Non-carrier</td>
<td>Non-carrier</td>
</tr>
<tr>
<td>1/2</td>
<td>1/2</td>
</tr>
</tbody>
</table>

Lynch Syndrome Cancer Risks (to 70)

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>MLH1 &amp; MSH2</th>
<th>MSH6</th>
<th>PMS2</th>
<th>General Public</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer</td>
<td>40-80%</td>
<td>10-22%</td>
<td>15-20%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>25-60%</td>
<td>16-26%</td>
<td>15%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Stomach</td>
<td>1-13%</td>
<td>&lt;3%</td>
<td>6%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>4-24%</td>
<td>1-11%</td>
<td>6%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

Lynch Syndrome Surveillance Options

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>Every 1-2 y beginning at age 20-25 (MLH1 &amp; MSH2), or 25-30 (MSH6 &amp; PMS2); or 2-5 y prior to the earliest colon cancer</td>
</tr>
<tr>
<td>Endometrial sampling</td>
<td>No clear evidence to support but could consider every 1 y beginning at age 30-35</td>
</tr>
<tr>
<td>Transvaginal U/S &amp; CA-125</td>
<td>No clear evidence to support but clinicians could consider at their discretion every 1 y beginning at age 30-35</td>
</tr>
<tr>
<td>EGD with extended duodenoscopy</td>
<td>Every 2-3 y beginning at 30-35</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Every 1 y beginning at age 25-30</td>
</tr>
<tr>
<td>History &amp; Exam w/ review of systems</td>
<td>Every 1 y beginning at age 25</td>
</tr>
</tbody>
</table>

Lynch Syndrome Prophylactic Surgery Options

- Options include subtotal colectomy, hysterectomy, and oophorectomy
- Subtotal colectomy does not eliminate cancer risk
- Hysterectomy eliminates risk of endometrial and ovarian cancer
- Expert panels made no recommendation for or against surgery due to unproven efficacy


## Tumor Tests to Screen for Lynch Syndrome

- Microsatellite Instability (MSI) testing
  - Performed on DNA extracted from tumor and normal tissue – requires laboratory
  - Test is positive in 15% of CRC cases
  - Test is positive in 77-89% of LS cases
- Immunohistochemistry staining
  - Performed on thin slide of tumor – can be done in pathology department
  - 1-2 proteins are absent in 20% of CRC cases
  - 1-2 proteins are absent in 83% of LS cases

## Red Flags for Polyposis

- >10 adenomas (at one time)
  - Familial Adenomatous Polyposis (FAP) and Attenuated FAP due to APC mutations
  - MUTYH-Associated Polyposis (MAP) due to biallelic MUTYH mutations (*Note this is the only recessive hereditary colon cancer syndrome)
  - Polymerase Proofreading Associated Polyposis (PPAP) due to mutations in POLE or POLD1
- >5 juvenile polyps
  - Juvenile Polyposis due to SMAD4 or BMPR1A mutations
- >2 Peutz Jegher polyps
  - Peutz Jegher syndrome due to STK11 mutations

## Red Flags for Lynch Syndrome

- Bethesda Guidelines
  - CRC dx <50
  - Synchronous or metachronous CRC, or other Lynch syndrome-associated tumors regardless of age
  - CRC with MSI-H histology dx <60
  - CRC with >1 FDR with an HNPCC-associated tumor, with one cancer dx <50
  - CRC with >2 FDRs or SDRs with an HNPCC-associated tumor, regardless of age
  - 82% Sensitivity
  - 77% Specificity

## Family History is Key to Diagnosing Lynch Syndrome – or is it?

- CRC dx 45
- CRC dx 61
- CRC dx 75
- Ovarian Ca, dx 64
- CRC dx 48
- Endometrial 45
- CRC dx 52
- Ca, dx 59
- CRC dx 42
Warning: Family Histories can be Deceiving

- Family size is getting smaller
- Wider use of colonoscopy likely to prevent many colon cancers
- MSH6 & PMS2 have lower cancer risks

Tumor Red Flags for Lynch Syndrome

Microsatellite Instability (MSI) testing
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Immunohistochemistry staining
- Performed on thin slide of tumor – can be done in pathology department
- 1-2 proteins are absent in 20% of CRC cases
- 1-2 proteins are absent in 83% of LS cases
- Recommended to be performed routinely on CRC biopsy or surgical resection specimens
- EGAPP, US Multi-Society Task Force on CRC, NCCN
- Can be requested on TVAs on a case-by-case basis


Tumor Red Flags for Lynch Syndrome:
Microsatellite Instability Testing (MSI)
- Microsatellites are repetitive sequences in the DNA (eg. BAT-26)
- 5 microsatellites are usually assessed during testing
- If 2 or more are unstable, tumor is considered MSI-high > likely LS
- If 1 is unstable, tumor is considered MSI-low (can be treated like MSI-negative)
- If 0 are unstable, tumor is considered MSI-negative or MSS (microsatellite stable) > unlikely LS

Tumor Red Flags for Lynch Syndrome:
Immunohistochemistry
- Identify MMR proteins
- Normally present
- If protein is absent, gene is not being expressed (mutation or methylation)
- Helps direct gene testing by predicting likely involved gene
- If abnormal IHC (absent), MSI+
Tumor Red Flags for Lynch Syndrome: Immunohistochemistry

- Identify MMR proteins
- Normally present
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**Normal – All 4 Stains Present**

- 80% of the time you will get this result
- CRC is probably not MSI+
- Prognosis worse than if MSI+
- Refer to Genetics ONLY if
  - you suspect polyposis
  - patient dx <45
  - patient has had multiple CRC primaries, or
  - patient has a FDR with CRC at any age

**Abnormal – MLH1 & PMS2 Absent**

- 15% of the time
- CRC is MSI+
- Better prognosis
- 80% acquired methylation of MLH1
- 20% will be LS
- BRAF test or MLH1 promoter methylation test is done to help sort this out.
Tumor Red Flags for Lynch Syndrome: Abnormal – MLH1 & PMS2 Absent

- 15% of the time
- CRC is MSI+
- Better prognosis
- Patients with the BRAF V600E mutation or MLH1 promoter hypermethylation in their tumor do NOT need to be referred to Genetics as they are very unlikely to have Lynch syndrome.
- 20% will be LS
- BRAF test or MLH1 promoter methylation test is done to help sort this out.

Tools to Use in Clinic: Colorectal Cancer Risk Assessment Tool

1. Do you have a first-degree relative (mother, father, brother, sister, or child) with any of the following conditions diagnosed before age 50?
   - Colorectal cancer
   - Cancer of the ovary, esophagus, stomach, small intestine, urinary tract
   - Melanoma, urinary bladder, bile duct, pancreas, or brain

2. Have you had any of the following conditions diagnosed before age 50?
   - Colorectal cancer
   - Uterine cancer
   - Primary peritoneal cancer

3. Do you have three or more relatives with a history of colon or rectal cancer? (This includes parents, brothers, sisters, children, grandparents, aunts, uncles, and cousins.)

Sensitivity 77%
If all 3 questions were answered Yes, correctly identified 95% of LS families

Yes to any question
No to all questions

Refer for additional assessment or genetic evaluation


PREMM1,2,6 - http://premm.dfci.harvard.edu/

- Probability of MLH1, MSH2, or MSH6 mutation
- Proband
  - # of CRCs & youngest age at dx
  - Y/N adenomas & youngest age at dx
  - Y/N EC & youngest age at dx
- FDRs & SDRs
  - # with CRC & youngest age at dx
  - # with EC & youngest age at dx
  - Y/N any with another HNPCC cancer
- Refer patients with >5% chance of having LS
  - 90% Sensitivity
  - 67% Specificity

Summary: Who should be referred to consider genetic testing

- Clinical testing criteria
  - Patients who meet Bethesda criteria
  - Patients with Endometrial cancer dx <50
  - Individuals with MMR mutation likelihood >5%
  - Individuals with abnormal tumor screening
  - Individuals with known dx of LS (or any hereditary cancer syndrome) in family
  - Individuals with >10 adenomatous polyps
  - Individuals with >5 juvenile polyps or >2 PJS polyps

- Routine tumor testing criteria
  - All CRC patients; OR
  - CRC patients dx <70 & CRC patients dx >70 who meet Revised Bethesda guidelines

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Genetic Information Nondiscrimination Act (GINA)

- Prevents health insurers from denying coverage, adjusting premiums, or otherwise discriminating on the basis of genetic information.
  - Group and self-insured policies
  - Insurers may not request that an individual undergo a genetic test.
  - Employers cannot use genetic information to make hiring, firing, compensation, or promotion decisions.
  - Sharply limits a health insurer's or employer's right to request, require, or purchase someone's genetic information.