Colorectal Cancer Screening: Choosing the right test at the right time

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Objectives:

- Review colorectal cancer epidemiology, statistics
- Discuss current screening and surveillance guidelines
- Review screening technologies and implementation
- Discuss incidence trends
- Wrap-up and questions

Pre-test questions

- 35 y/o patient presents to your office to discuss screening colonoscopy. He has no GI symptoms or alarm symptoms. Upon review of his family history, you discover his father had colon cancer diagnosed at age 70 and his brother had a large villous adenoma at age 50. When would you recommend he have a screening colonoscopy?
- A.) Age 40
- B.) Age 50
- C.) Age 60
- D.) Age 45

Pre-test Questions

- Which of the following screening tests would be considered in the category of detection vs prevention?
- A. Colonoscopy
- B. CT colonography
- C. FIT-fecal DNA
- D. Flexible sigmoidoscopy

Pre-test Questions

- The most common inheritable cause of colorectal cancer is?
  - A. Familial adenomatous polyposis
  - B. Lynch syndrome (HNPCC)
  - C. Cowden syndrome
  - D. Peutz-Jeghers syndrome

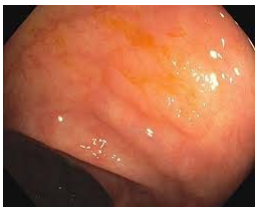
Colorectal Cancer

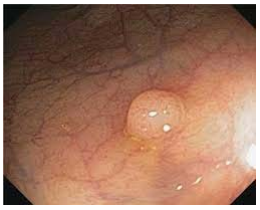
- 3rd most common cancer in U.S. and 2nd leading cause of cancer deaths
- Colon
  - 93,090 new cases of colon cancer
- Rectal
  - 49,700 new cases of rectal cancer
- Lifetime risk of colorectal cancer--men
  - 1 in 19 (5.2%)
- Lifetime risk in women
  - 1 in 20 (5%)
- Average pt loses 13 yrs of life

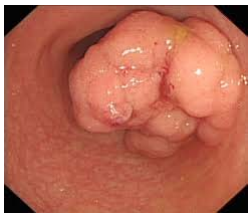
- UpToDate. Accessed April 16, 2018. https://www.uptodate.com/contents/colorectal-cancer-epidemiology-risk-factors-and-protective-factors

Colorectal polyps

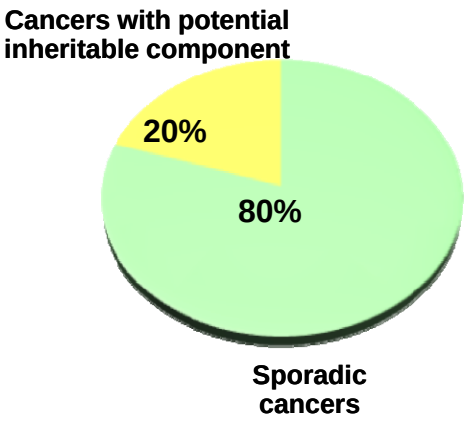
- Conventional adenomas (precursors to 70% of CRCs)
  - High grade dysplasia
  - Low grade dysplasia
  - Villous architecture
    - Tubulovillous
    - Tubular
    - Villous
- Serrated lesions
  - Hyperplastic (not precancerous)
  - Sessile serrated polyp
    - With/without dysplasia
  - Traditional serrated adenoma
- "Advanced adenoma"
  - Lesion >1cm or HGD or villous elements







Colorectal Cancers



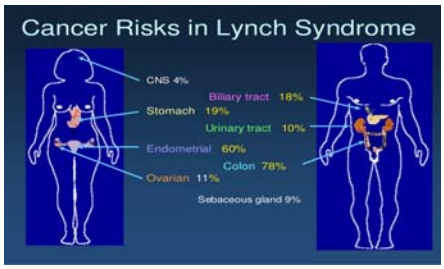
Polyposis syndromes

- **Lynch syndrome (HNPCC)**
  - 3-5% of colorectal cancers
  - Most common cause of inheritable CRC
  - Autosomal dominant
  - Germline mutation in DNA mismatch repair gene (MLH1,MSH2,MSH6,PMS2)
  - Amsterdam/Bethesda criteria for testing at risk
  - Prediction models available to calculate risk of germline mutation
    - PREMM5
  - Testing typically starts on tumor due to cost
    - Confirmed by germline testing
  - Extracolonic malignancies common
  - 10-47 % lifetime risk (depending on genotype)
  - Colonoscopy at age 20-25 if confirmed dx

Table 2: Amsterdam II Criteria and Bethesda Guidelines

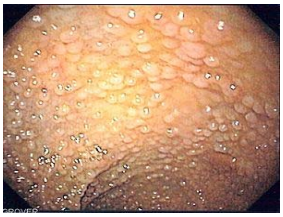
Amsterdam II Criteria[11]
1. There should be at least 3 relatives with an HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis)
2. One relative is a first degree relative of the other two
3. At least 2 successive generations are affected
4. At least one individual is diagnosed before age 50
5. FAP is excluded in the individuals with colorectal cancer
6. Tumors should be verified by pathologic examination
Revised Bethesda Guidelines for Testing Colorectal Tumors for Microsatellite Instability[12]
1. Colorectal cancer diagnosed in a patient who is less than 50 years of age
2. Colorectal cancer with the MSI-H histology diagnosed in a patient who is less than 60 years of age
3. Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50
4. Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

FAP = familial adenomatous polyposis; HNPCC = hereditary nonpolyposis colorectal cancer.



Polyposis syndromes

- **Familial adenomatous polyposis**
  - <1% of colorectal cancers
  - APC gene mutation
  - Autosomal dominant
  - >100 adenomatous polyps
  - Nearly 100% cancer of CRC
  - Attenuated FAP (10-99 polyps)
- **MUTYH-associated polyposis (MAP)**
  - Autosomal recessive
  - Typically 20-99 adenomatous polyps
    - Consider genetic testing if >20 adenomas
  - Germline mutations in excision repair gene mutY homolog
  - May lead to somatic mutation of APC gene
  - Potentially responsible for familial CRC without dominantly inherited syndrome
  - 43% risk CRC by age 60
- Others
  - Peutz-Jeghers syndrome, Juvenile polyposis syndrome, Serrated polyposis syndrome, Li-Fraumeni syndrome, Cowden syndrome



Lynch syndrome (HNPCC)

- most common cause of inherited colorectal cancer
  - AD inherited CRC secondary to mismatch-repair defect
- Amsterdam criteria
  - Three or more relatives with histologically verified Lynch syndrome-associated cancers (CRC, cancer of the endometrium or small bowel, transitional cell carcinoma of the ureter or renal pelvis), one of whom is a first-degree relative of the other two
  - Lynch syndrome-associated cancers involving at least two generations
  - One or more cancers were diagnosed before the age of 50 years
  - "3-2-1 rule" (3 affected members, 2 generations, 1 under age 50)

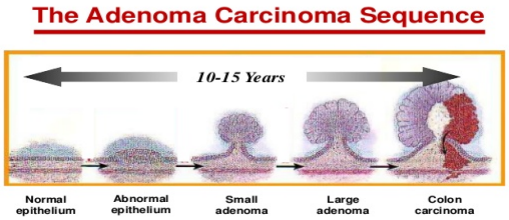
Risk Factors for CRC Development

- Increasing Age
- Prior personal history of colorectal adenoma or colorectal carcinoma
- Family hx advanced adenomas or CRC
- Personal history of inflammatory bowel disease
- Obesity
- Hx of abdominal radiation
- Potential environmental factors
  - High fat and low fiber consumption
  - Low dietary selenium
  - Environmental carcinogens and mutagens (from colonic bacteria and charbroiled meats)
  - Heavy alcohol consumption
    - Moderate consumption may have protective effect

Bresalier RS. Chapter 115. Sleisenger & Fordtran's Gastrointestinal and Liver Disease. 7th ed.

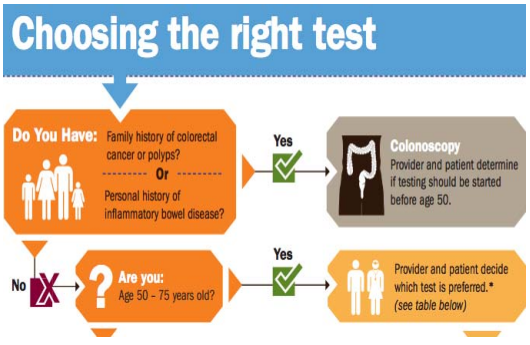
Screening Rationale

- CRC is a common malignancy with a long asymptomatic phase
- Can be prevented by detection and removal of precursor adenomas
- Emerges from a progression of several mutations in genes controlling cell growth and DNA repair
- Has a high survival rate if detected in its early stages
  - Survival rates for both colon and rectal cancers found early (stage I) have a 5 year survival rate of 75%



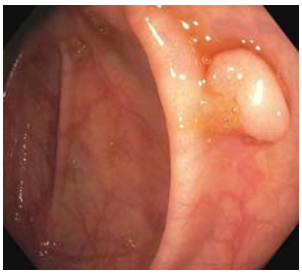
Screening Options

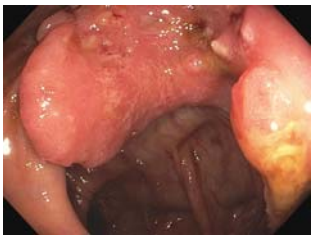
- Rectal exam (rectal cancer)
- Flexible sigmoidoscopy
- Colonoscopy
- Virtual colonoscopy (CT)
- Fecal occult blood testing (FOBT)
  - Hemoccult SENSA recommended
- Fecal immunochemical testing (FIT)
  - No modification of diet or medications
- FIT-Fecal DNA testing
- Double contrast barium enema
- Capsule colonoscopy



Cancer prevention vs detection

- American College of Gastroenterology recommends offering cancer prevention screening first. Other options can be utilized if patient declines or is poor candidate
- Prevention
  - Preferred: colonoscopy
  - Alternative: flexible sigmoidoscopy, CT colonography
- Detection
  - Preferred: annual FIT stool testing
  - Alternative: annual hemoccult, fecal DNA every 3 yrs

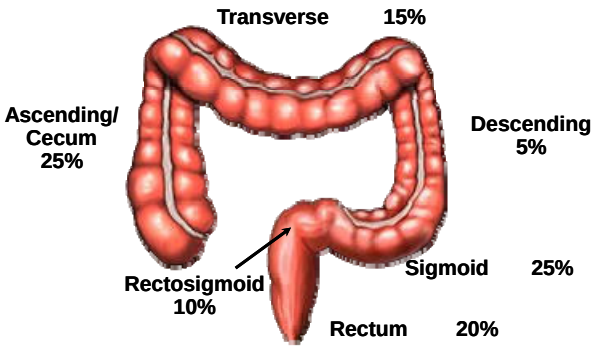




Colonoscopy: The Gold Standard

Advantages	Limitations
Ability to visualize entire colon, hence the highest detection rate for colonic polyps and cancer	Highest complication rate of all screening modalities (0.3%-0.56%)
Can perform polypectomy without need for another procedure	Manpower and cost are major obstacles
	Potential for missed lesions remains (6% of advanced adenomas)

Distribution of Colorectal Cancers



Only about half of all colon cancers are within reach of the flexible sigmoidoscope

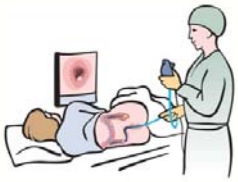
Adapted from Bresalier RS. Chapter 115. In *Sleisenger & Fordtran's Gastrointestinal and Liver Disease*. 7th ed.

Endoscopist and report considerations

- Endoscopist
  - Adenoma detection and cecal intubation rates
  - Split dosing bowel preparations
- Report
  - Photograph of cecum and/or terminal ileum
  - Bowel preparation quality
- These factors may be important in deciding on who to send your patients to and how to recommend surveillance

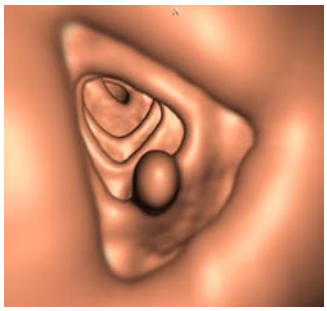
New direction of quality indicators

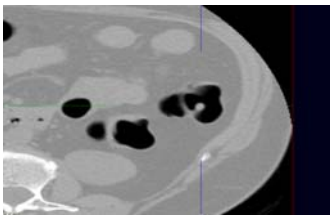
- Previously: "Was it done?"
- Now: "Was it done well?"
- Quality of screening program
- Quality of the colonoscopy itself



CT (virtual) Colonography

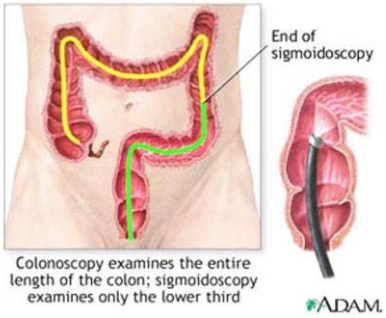
- Largely replaced barium enema
- Test of choice for colorectal imaging
- Lower risk of perforation than colonoscopy
- Still need bowel preparation
- Poor sensitivity for polyps <1cm, flat, and sessile serrated polyps
- Radiation exposure
- Niche of people willing to do bowel prep and concerned about colonoscopy risks
- Polyps >6mm generally require colonoscopy
- Folllow-up 5 yrs if normal





Flexible sigmoidoscopy

- Shown to reduce incidence/mortality of distal colon cancers
- Potentially lower cost and risk than colonoscopy
- Potential for less or no sedation
- Lower benefit in protection from right-sided colon cancers
- Can be combined with FIT
- Recommended repeat examination in 5-10 yrs if normal
- Usage in screening programs dramatically declined in U.S.

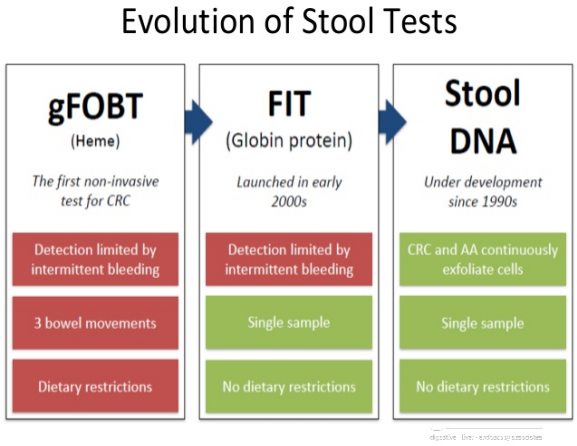


Fecal immunochemical test and gFOBT

- FIT more specific for human blood (globin)
- Guaiac-based tests (gFOBT)react to blood and dietary peroxidase
- FIT twice as effective in detecting advanced neoplasia than gFOBT
- Any positive test should be followed by colonoscopy
- Not designed to be used with digital rectal exam
- Should be used annually for screening

Fecal DNA Testing

- Large adenomas and carcinoma cells contain altered DNA which is continuously shed in stool
- DNA is stable in stool and can be isolated
- Multiple gene mutations are checked for sensitivity
- 92% sensitivity for CRC
- Only 40% effective for SSPs
- Commercial test is combined with FIT (Cologuard)
- Repeat every 3 yrs
- Positive test requires colonoscopy
- Not indicated for high-risk screening or surveillance
- Cost-$500-600 for commercial insurance. Medicare usually covered



Capsule colonoscopy

- FDA approved for incomplete colonoscopy and patients not candidate for colonoscopy or sedation
- Not approved for average-risk screening
- Requires more extensive bowel preparation
- Good sensitivity for polyps >6mm (88%). Poor for SSPs
- 9% failed exams-inadequate prep or rapid transit
- Poor reimbursement at this time
- Similar indications as CT colonography

Septin9 assay

- First FDA-approved serum test for CRC screening
- Sensitivity 48% for CRC detection and no detection of precancerous polyps
- May increase adherence due to convenience
- Positive test requires colonoscopy
- Testing intervals not known
- Currently not recommended by MSTF for screening

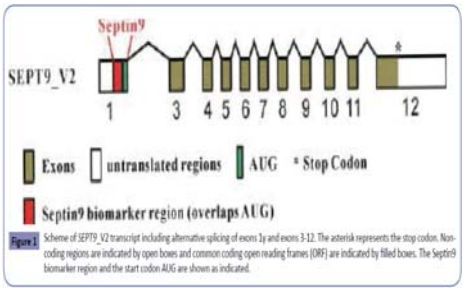


Figure 1 Scheme of SEPT9_V2 transcript including alternative splicing of exons 1y and exons 3-12. The asterisk represents the stop codon. Non-coding regions are indicated by open boxes and common coding open reading frames (ORF) are indicated by filled boxes. The Septin9 biomarker region and the start codon AUG are shown as indicated.

Guidelines

- American Cancer Society
- U.S. Preventive Services Task Force
- U.S. Multi-Society Task Force on Colorectal Cancer (AGA, ACG, ASGE)
- National Comprehensive Cancer Network

Why so many guidelines?

- Subtle differences in screening approach
  - Multiple options
  - Sequential testing
  - Risk stratified approach
- Most are very similar regarding age at initiation
- Age cut-offs for screening varies among societies
- All are acceptable but practitioners must choose one they are most comfortable with
- For this discussion, we will focus on the guidelines by the U.S. Multi-Society Task Force on Colorectal Cancer
  - Joint collaboration of American College of Gastroenterology, American Gastroenterological Society and American Society for Gastrointestinal Endoscopy

United States Preventive Services Task Force (USPSTF)

- Options for screening
  - Annual fecal occult blood testing (FOBT) with a sensitive test
  - Flexible sigmoidoscopy every five years, with sensitive FOBT every three years
  - Colonoscopy every 10 years
  - Consider discontinuation at age 75 or <10 yrs life expectancy
  - Patients over 85 should not be screened

Multi-Society Task Force on Colorectal Cancer

- Three tiers based on performance, costs, and practical considerations
  - Tier 1
    - Colonoscopy every 10 yrs.
    - FIT annually
  - Tier 2
    - CT colonography every 5 yrs.
    - FIT-fecal DNA every 3 yrs.
    - Flexible sigmoidoscopy every 5-10 yrs.
  - Tier 3
    - Capsule colonoscopy every 5 yrs.
  - Not recommended
    - Septin9

Screening-average risk

- No personal history of colorectal polyps, family history of advanced adenomas or CRC, personal history of IBD, or hereditary colon cancer syndrome
- Begin screening at 50
  - African Americans at 45
- Discontinue at age 75 with previous negative screening (colonoscopy preferred) or have <10 yrs. life expectancy
- Consider screening up to age 85 with no previous screening and no significant comorbidities

Screening-high risk

- CRC or an advanced adenoma in two first degree relatives diagnosed at any age OR CRC or advanced adenoma in a single first-degree relative at age <60
  - colonoscopy every 5 years beginning at age 40 years or 10 years younger than age at diagnosis of the youngest affected relative
- CRC or advanced adenoma in a single first-degree relative diagnosed at age>60
  - Begin screening at age 40, tests and intervals per average-risk recs
- Family colon cancer syndrome X
  - Pts in families that meet criteria for HNPCC but have microsatellite-stable CRCs
  - Begin screening at 40, tests and intervals per average-risk recs
- Lynch Syndrome (HNPCC), hereditary polyposis syndromes, IBD
  - Discussed separately

Surveillance after polypectomy (US Multi-Society Task Force on Colorectal Cancer)

- Average risk patients
- No polyps
  - repeat colonoscopy in 10 yrs
- 1- 2 small tubular adenomas (<10mm)
  - Repeat colonoscopy in 5-10 yrs
- 3-10 tubular adenomas
  - repeat colonoscopy in 3 yrs
- Adenomas >10mm
  - repeat colonoscopy in 3 yrs
- Villous adenoma
  - repeat colonoscopy in 3 yrs
- Tubular adenoma with high-grade dysplasia
  - repeat colonoscopy in 3 yrs

Surveillance after CRC resection(US Multi-Society Task Force on Colorectal Cancer)

- TNM stages I-III CRC, and selected patients with resected stage IV cancer
- Cumulative incidence of metachronous cancers of the colon and rectum is estimated to be about 0.3%-0.35% per year.
- Thus, **postoperative** colonoscopic surveillance is indicated long term, or until the benefit is outweighed by decreased life expectancy due to age and/or competing comorbidity.
- Patients should receive their first surveillance colonoscopy 1 year after surgery (colon cancer)
  - interval to the next colonoscopy should be 3 years and then 5 years after that exam. Continue at every 5 yrs thereafter.

Surveillance after resected rectal cancer

- important distinction is made between colon and rectal cancer because of the latter's higher propensity for local recurrence
- sigmoidoscopy or rectal EUS is recommended every 3 to 6 months for the first 2 or 3 years after surgery, in addition to colonoscopic surveillance for metachronous neoplasms

CRC in younger patients

- American Cancer Society study analyzed death rates from 1970-2014
- Adults age 20-54 increased 1% each year from 2004-2014
  - Previously decreased 2% each year from mid 70s-90s
  - Unclear cause, young people often delay exams even with symptoms
- 1.4% increase in Caucasians
  - Unknown cause
- Slow decrease in death rate of African Americans over 45yrs
- Death rates also increased for age 50-54
  - Screening often delayed due to lack of symptoms
  - Fear of results
  - 46% screening rate age 50-54, 67% for 55 and older

"Study Finds Sharp Rise in Colon Cancer and Rectal Cancer Rates Among Young Adults." American Cancer Society. Accessed April 16, 2018. https://www.cancer.org/latest-news/study-finds-sharp-rise-in-colon-cancer-and-rectal-cancer-rates-among-young-adults.html.

Future of CRC screening?

- Suspect advancements in serum and fecal DNA testing. These tests will not likely replace colonoscopy for CRC prevention
- Improved genomic testing may reveal pts at increased risk. Most cases of CRC are “sporadic” and therefore mutations may be hard to detect
- The age of CRC screening initiation may need to be lowered if there is a continued trend in pts diagnosed before age 50
- Obesity and smoking significantly increase adenoma and CRC rates. Guidelines may need to reflect these as high-risk indicators

Treatment advances

- Overall survival has increased from 11-12 months to about 3yrs over last 10-15 yrs
- Biomarkers and genetic mutations now important in treatment planning
  - EGFR, VEGF, RAS, BRAF, PD-1, etc
- Treatment more individualized and on continuum
  - Maintenance chemo interspersed with more aggressive protocols, reutilizing initial chemotherapeutics with new agents based on genomic analysis
- Surgical advances now allow some stage IV pts to have curative resection (oligometastatic liver/lung lesions)
- Monoclonal abs and immunotherapy now present new array of side-effects
  - Immune-mediated phenomenon-pneumonitis, hepatitis, colitis

Post-test questions

- 35 y/o patient presents to your office to discuss screening colonoscopy. He has no GI symptoms or alarm symptoms. Upon review of his family history, you discover his father had colon cancer diagnosed at age 70 and his brother had a large villous adenoma at age 50. When would you recommend he have a screening colonoscopy?
- A.) **Age 40**
- B.) Age 50
- C.) Age 60
- D.) Age 45

Post-test questions

- Which of the following screening tests would be considered in the category of detection vs prevention?
- A. Colonoscopy
- B. CT colonography
- C. **FIT-fecal DNA**
- D. Flexible sigmoidoscopy

Post-test questions

- The most common inheritable cause of colorectal cancer is?
  - A. Familial adenomatous polyposis
  - B. **Lynch syndrome (HNPCC)**
  - C. Cowden syndrome
  - D. Peutz-Jeghers syndrome

Summary

- Key points
  - Incorporate a screening program and be consistent. Recommend printing the guidelines!
  - Colonoscopy is preferred for detection but not right for every patient, know other methods
  - Consider tier approach to screening tests
  - Remember to take accurate family history to detect need for earlier screening
  - Any patient with >10 adenomatous polyps on colonoscopy should be considered for genetic testing
  - 1/7 of all new colorectal pts are under 50-evaluate patients with symptoms!
  - Don't forget to follow surveillance guidelines for polyps and cancers, unfortunately many pts don't see gastroenterologist in follow-up

Questions?

American Cancer Society

For more information on the different ways you can be tested, call 1.800.227.2345 or visit www.cancer.org/NYNJ.

Questions?

References

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