

Colon Cancer Screening & Surveillance

Amit Patel, MD PGY-4

GI Fellow

Epidemiology

- CRC incidence and mortality rates vary markedly around the world.
- Globally, CRC is the third most commonly diagnosed cancer in males and the second in females.
- In the United States, both the incidence and mortality have been slowly but steadily decreasing.
- Annually approximately 132,700 new cases of large bowel cancer are diagnosed, of which 93,090 are colon and the remainder rectal cancers.
- Annually, approximately 49,700 Americans die of CRC, accounting for approximately 8 percent of all cancer deaths.

Risk Factors

Non-Modifiable Risk Factors (30%)

- Family history or personal history of CRC
- Family history or personal history of advanced adenomas
- Personal history of IBD
- Personal history of hereditary polyposis syndromes (FAP, HNPCC)

Modifiable Risk Factors:

- Obesity
- Smoking
- Heavy alcohol use
- Inactivity

Polyps

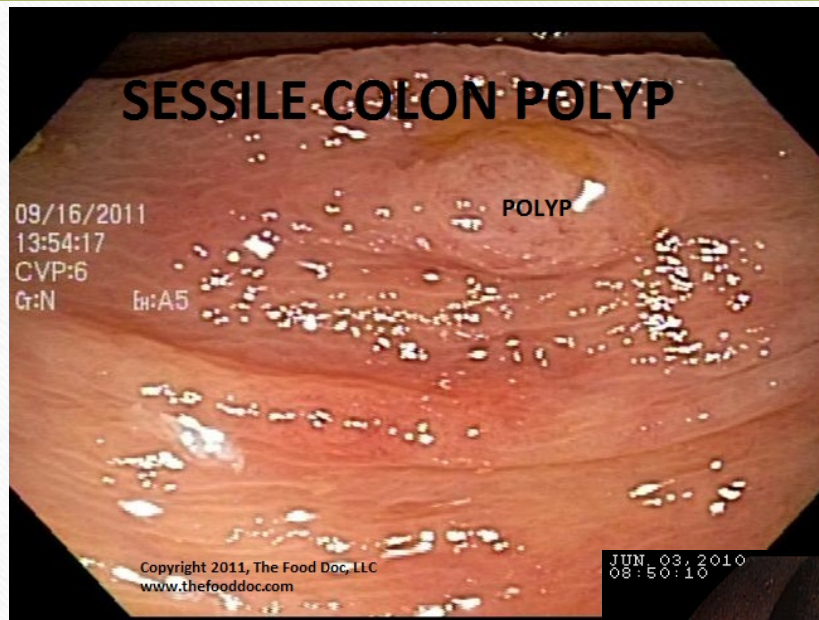
Non-Neoplastic	Neoplastic
Hyperplastic	Adenomatous polyps
Mucosal	Serrated polyps
Pseudopolyps	
Submucosal	
Hamartomatous	

Neoplastic Polyps - Adenomas

- Adenomatous polyps are the most common of the classically neoplastic polyps.
- About two-thirds of all colonic polyps are adenomas.
- Adenomas are by definition dysplastic and thus have malignant potential.
- Most colorectal cancers arise from adenomas, but only a small minority of adenomas progress to cancer (5 percent or less).
- The time for development of adenomas to cancer is about 7 to 10 years. The risk of progression is higher for advanced adenomas.

Adenomas – Endoscopic Classification

- Sessile – Sessile polyps are those in which the base is attached to the colon wall.
- Pedunculated – Pedunculated polyps are polyps in which a mucosal stalk is interposed between the polyp and the wall.
- Flat – Flat polyps are defined as those having a height less than one-half the diameter of the lesion.



Adenomas – Pathologic Classification

- **Tubular –**
 - Tubular adenomas account for more than 80 percent of colonic adenomas.
 - They are characterized by a network of branching adenomatous epithelium
 - To be classified as tubular, the adenoma should have a tubular component of at least 75 percent.
- **Villous –**
 - Villous adenomas account for 5 to 15 percent of adenomas.
 - They are characterized by glands that are long and extend straight down from the surface.
 - To be classified as villous, the adenoma should have a villous component of at least 75 percent.
- **Tubulovillous –**
 - Tubulovillous adenomas having 26 to 75 percent villous component account for 5 to 15 percent of adenomas.

Neoplastic Polyps- Serrated Polyps

- Serrated polyps (“Saw tooth”) are a heterogenous group of polyps with variable malignant potential.
- They include **hyperplastic polyps, traditional serrated adenomas, and sessile serrated polyps** (also known as sessile serrated adenomas).

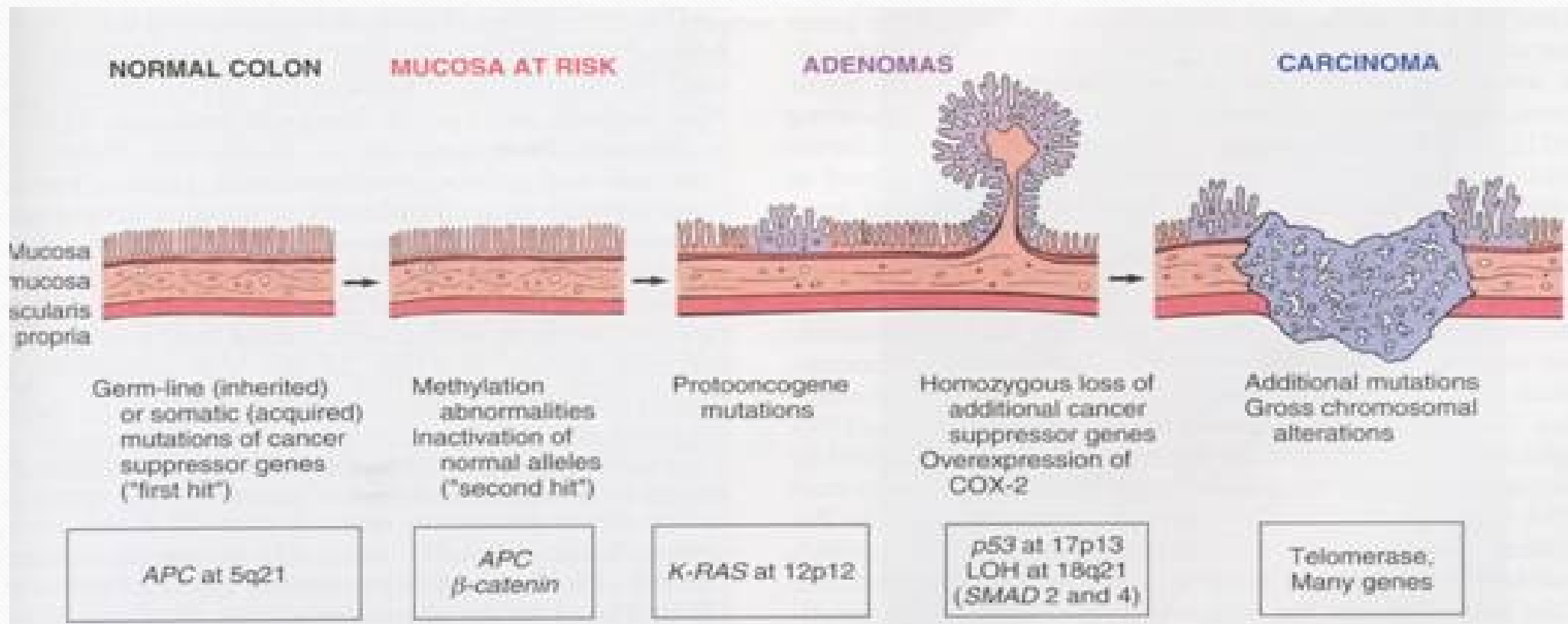
Hyperplastic Polyps

- Histology – Hyperplastic polyps are composed of normal cellular components, do not exhibit dysplasia, and have a characteristic serrated ("saw tooth") pattern when seen sectioned along the crypt axis
- Location – They are typically located in the rectosigmoid and are less than 5 mm in size.
- Risk of cancer – Distal small hyperplastic polyps rarely, if ever, develop into colorectal cancers (CRCs), but large hyperplastic polyps are thought to be a precursor to sessile serrated polyps, which can progress to colorectal cancer.

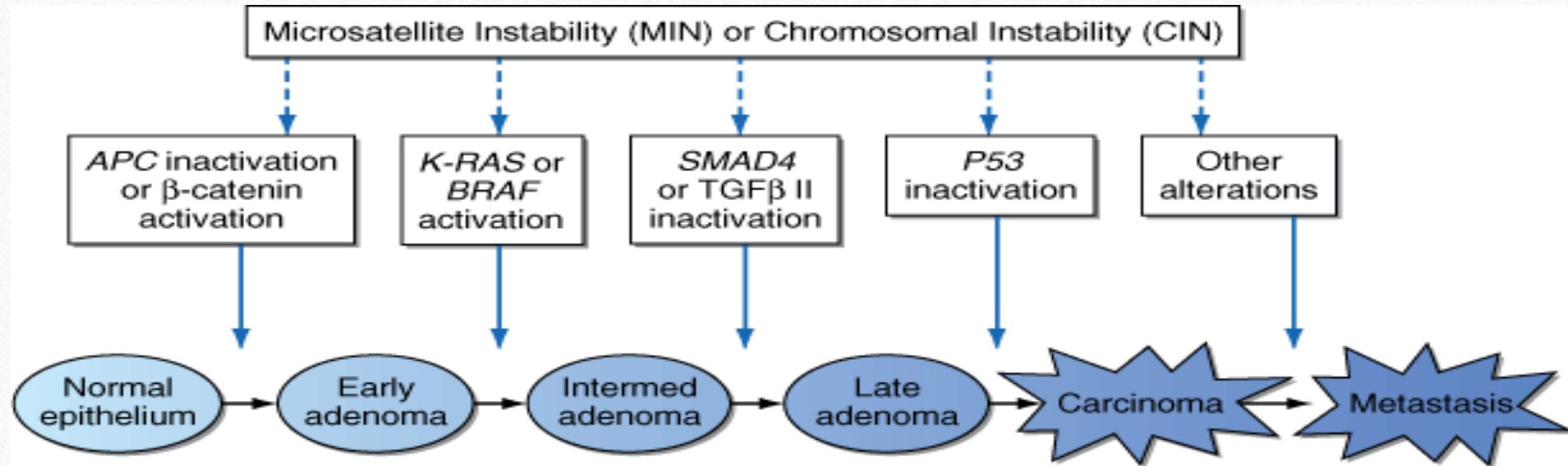
Sessile Serrated vs Traditional Serrated Polyps

- **Sessile serrated adenomas/polyps (SSA/Ps)** are more prevalent in the proximal colon and typically lack classic dysplasia.
 - Foci of classic cytologic dysplasia do occur in SSA/Ps and this should be noted by the pathologist as a sessile serrated adenoma/polyp with cytologic dysplasia, as this lesion is thought to be an important step toward cancer progression.
- **Traditional serrated adenomas (TSAs)** are more prevalent in the rectosigmoid and have diffuse but often mild cytologic dysplasia.
- Classification systems for these polyps are still evolving. Histological interpretation of these serrated polyp types differs among pathologists
- The majority of studies suggest that TSAs and SSPs have significant malignant potential and are associated with subsequent development of metachronous polyps.

Adenoma-Carcinoma Sequence



Adenoma-Carcinoma Sequence



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: <http://www.accessmedicine.com>

Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

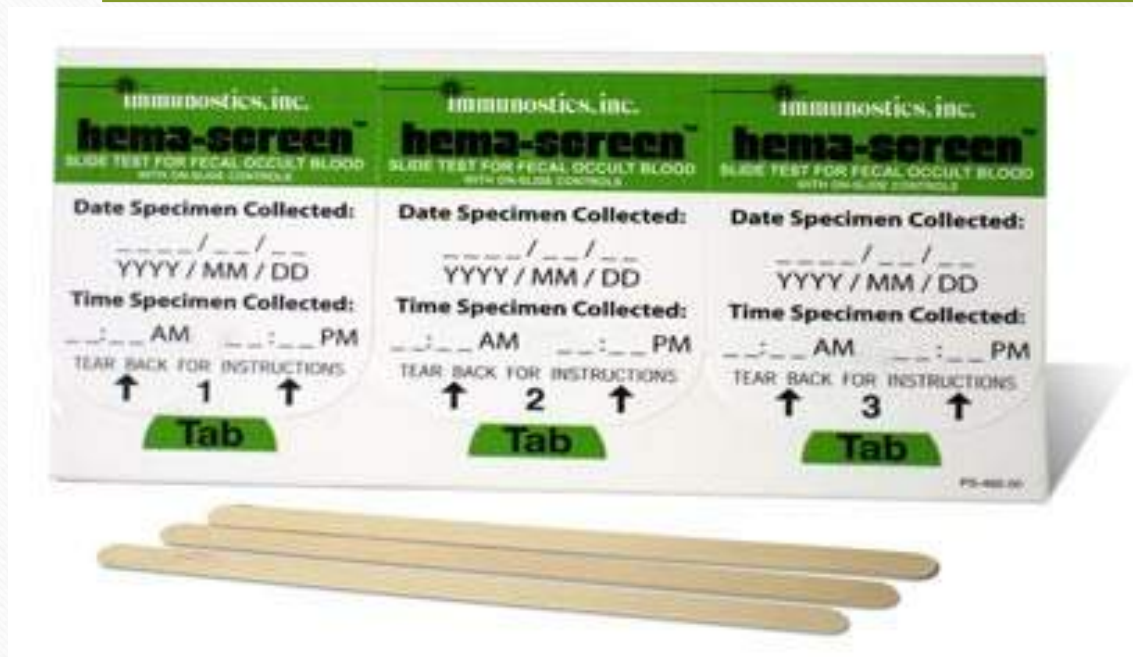
Detection Methods

- **Stool Tests** – Primarily identify CRC, mostly detect blood in the stool which is intermittent and nonspecific
 - The Opportunity for prevention is both limited and incidental and is not the primary goal of CRC screening in these following tests:
 - gFOBT – guaiac based Fecal Occult Blood Test
 - FIT – Fecal Immunochemical Testing
 - sDNA – stool DNA testing
- **Structural Exams** – Partial or Full exams – identify BOTH Adenomas and CRC
 - Flexible Sigmoidoscopy
 - Double Contrast Barium Enema
 - Computed Tomography Colonography
 - Colonoscopy

Stool Tests - gFOBT

- Guaiac-based tests detect blood in the stool through the **peroxidase activity** of heme or hemoglobin.
- The usual gFOBT protocol consists of collecting **2 samples from each of 3 consecutive bowel movements** at home. - Collection of all 3 samples is important because test sensitivity improves with each additional stool sample
- Patients usually will be instructed to avoid :
 - False Positive: aspirin and NSAIDs, red meat, poultry, fish, some raw vegetables and citrus fruits
 - False Negative: Vitamin C.
- The **sensitivity** and **specificity** of a gFOBT has been shown to be **highly variable** and varies based on:
 - the brand or variant of the test; specimen collection technique; number of samples collected per test; whether or not the stool specimen is rehydrated (ie, adding a drop of water to the slide window before processing); and variations in interpretation, screening interval, and other factors.

gFOBT



gFOBT

- **Annual screening** with high-sensitivity gFOBT (such as Hemoccult SENSА) that have been shown in the published, peer-reviewed literature to detect a majority of prevalent CRC in an asymptomatic population is an acceptable option **for colorectal screening in average-risk adults aged 50 years and older**
- Any positive test should be followed up with colonoscopy.
- Screening for CRC with gFOBT in the office following digital rectal exam or as part of a pelvic examination is NOT recommended and should NOT be done.

Fecal Immunochemical Testing (FIT)

- Detects human globin : Heme + globin = hemoglobin
 - More specific than gFOBT, which rely on detection of peroxidase in human blood and also react to the peroxidase that is present in dietary constituents;; no false positive with Vitamin C
 - Globin degradation by the upper GI tract makes positive test more sensitive for lower GI bleeding, which improves sensitivity to CRC screening.
- Annual screening with FIT that have been shown in the published, peer-reviewed literature to detect a majority of prevalent CRC in an asymptomatic population at the time of testing is an acceptable option for colorectal screening in average risk adults aged 50 years and older
- Any positive test should be followed up with colonoscopy.

Stool DNA testing - sDNA

- Rationale:
 - Colon cells are shed continuously into large bowel lumen and passed through feces
 - Polyps and cancer cells contain abnormal DNA → adenoma-carcinoma of colorectal carcinogenesis
 - sDNA tests look for abnormal DNA from cells that are passed in the stool
- Advantages: need only one stool specimen, detects molecular markers associated with colorectal CA (not bleeding)
- Limitations: cost, not all molecular markers are detected

sDNA

- American College of Gastroenterology recommends screening in asymptomatic patients at average risk with **sDNA every 3 years.**
- American Cancer Society, USMSTF and American College of Radiology do not give a recommended interval for sDNA.
- USPSTF does not give any recommendations of sDNA as a tool for CRC screening, endorse gFOBT and FIT.

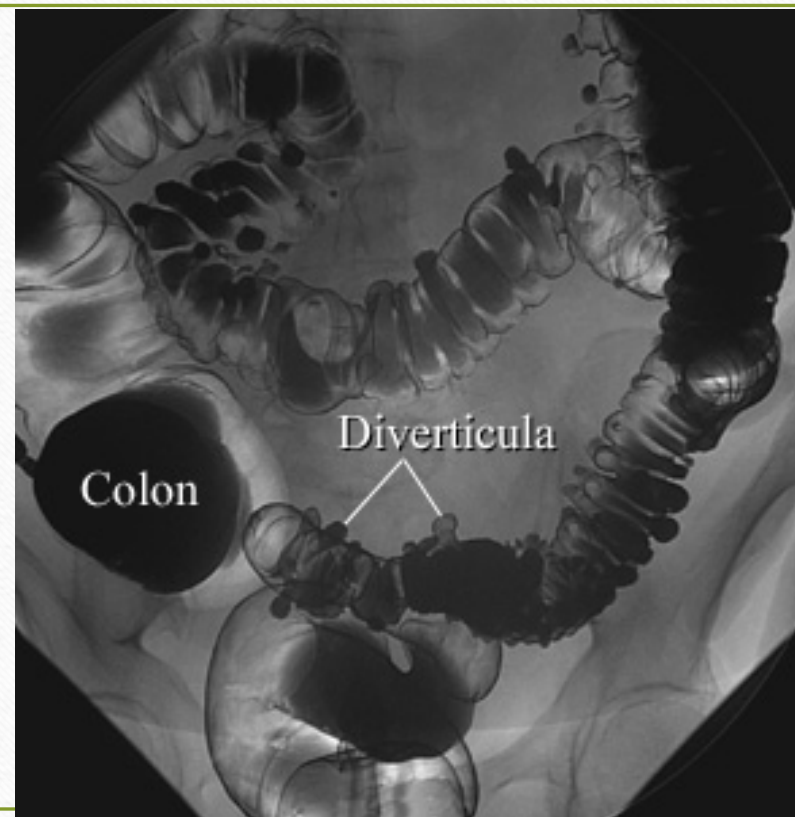
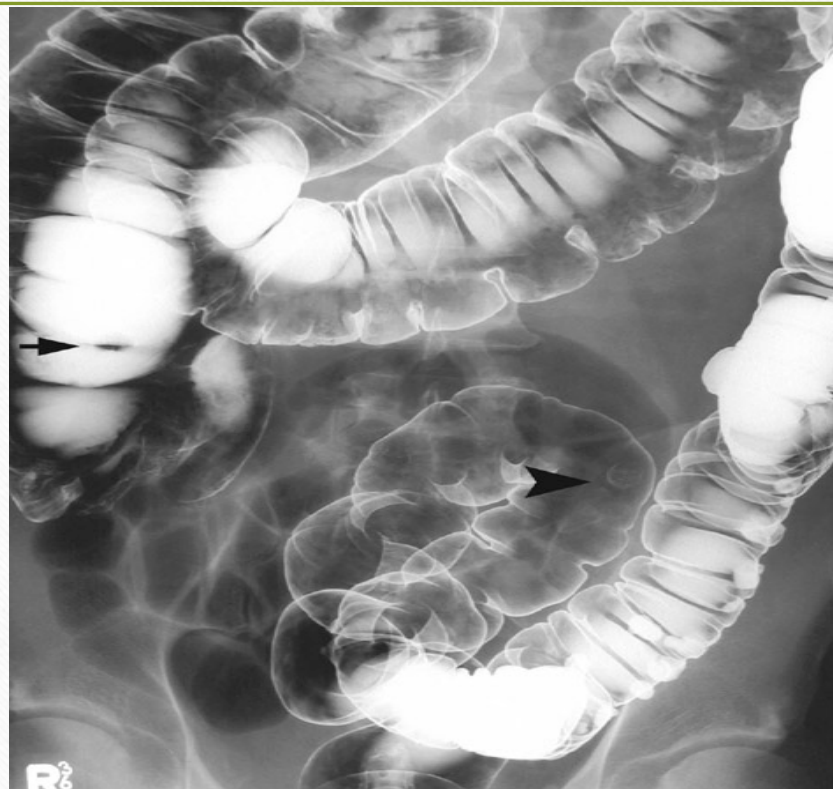
Structural Exams for CRC screening

- Imaging Exams:
 - Double Contrast Barium Enema (DCBE)
 - CT Colonography
- Endoscopic Exams:
 - Flexible Sigmoidoscopy
 - Colonoscopy

DCBE

-
- Referred to as “Air-contrast barium enema”
 - Evaluates the colon in its entirety by coating the mucosal surface with high-density barium and distending the colon with air introduced through a flexible catheter that is inserted into the rectum.
 - Multiple radiographs are acquired while varying the patient position during direct fluoroscopic evaluation.
 - Colonic preparation, usually a 24- hour dietary and laxative regimen, is essential for an optimal examination.
 - Sedation is not utilized, and the duration of the procedure averages about 20 to 40 minutes.

DCBE



DCBE

- **Benefits:**

- Evaluates the entire colon in almost all cases and can detect most cancers and the majority of significant polyps.
- Provides an opportunity for a full structural examination for individuals for whom colonoscopy has either failed or is contraindicated

- **Limitations:**

- Colonic preparation and abdominal discomfort
- There is no opportunity for biopsy or polypectomy,
 - Any polyps >6 mm on DCBE should undergo colonoscopy.
- User dependent (radiologist, technicians)

DCBE

- American Cancer Society, USMSTF and American College of Radiology joint guidelines state that DCBE can be used for CRC in average risk population every 5 years.
- Again, any polyp $> 6\text{mm}$ will need further evaluation with colonoscopy.
- Overall, fallen out of favor as the imaging study of choice for CRC screening due to better resolution methods, ie CT Colonography.

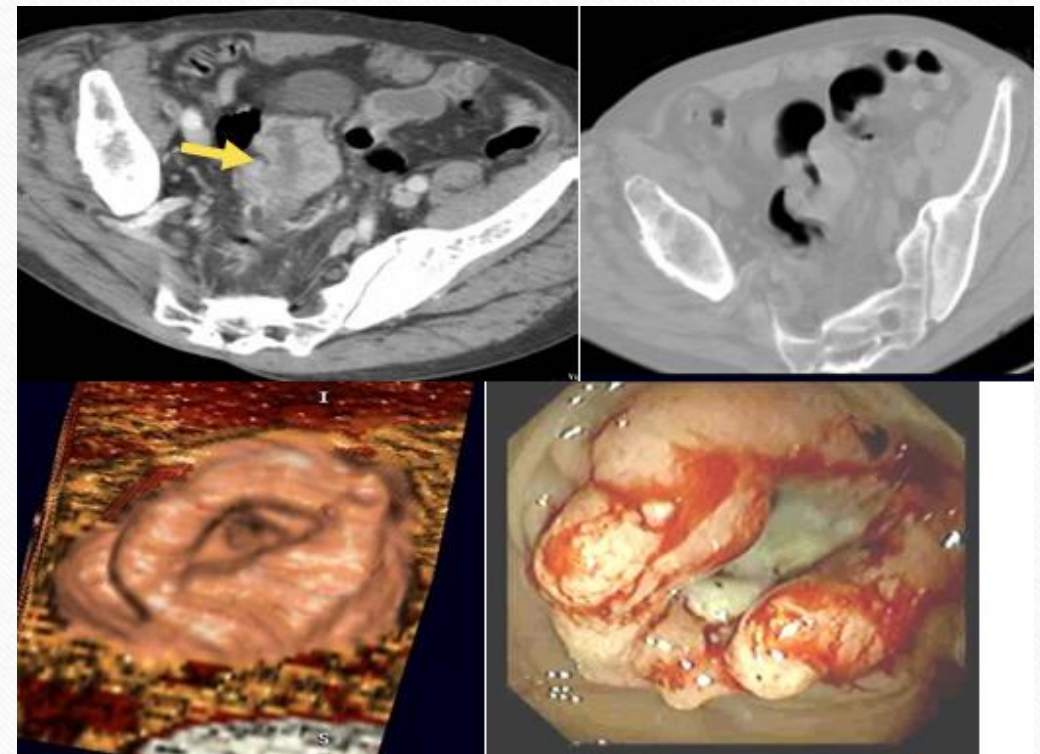
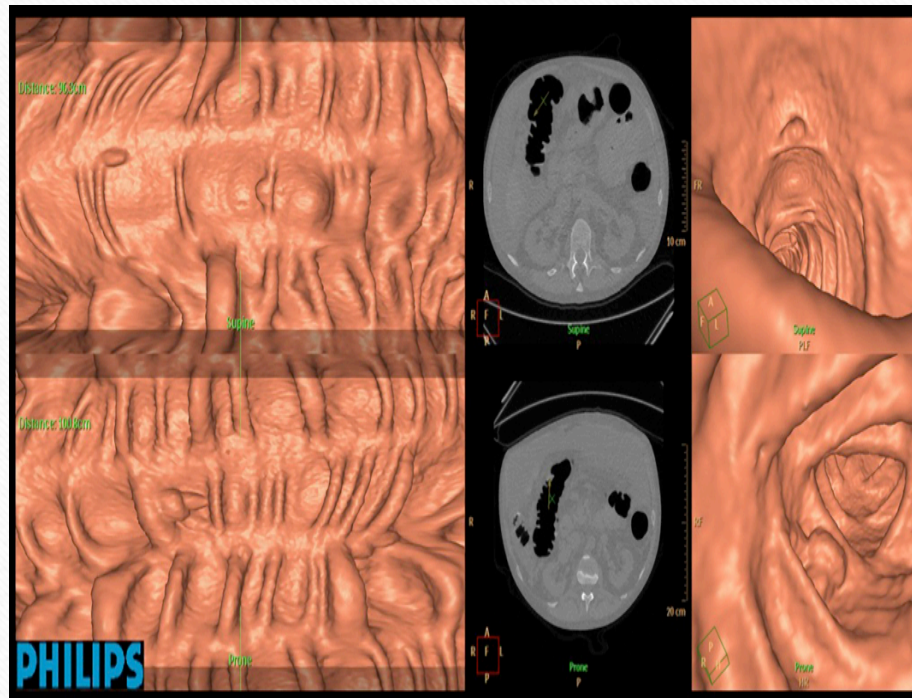
CT Colonography

- Referred to as “virtual colonoscopy.”
- CTC uses CT to acquire images and advanced 2-dimensional (2D)- and 3-dimensional (3D)-image display techniques for interpretation
 - . The integrated use of the 3D and 2D techniques allows for ease of polyp detection, as well as characterization of lesion density and location
- Multidetector CT now permits image acquisition of thin 1 to 2 mm slices of the entire large intestine

CT Colonography

- Patients typically undergo full cathartic preparation along with a clear liquid diet the day before the study
- At CT, a small caliber rectal catheter is inserted into the rectum, followed by automated or manual insufflation of room air or carbon dioxide
- The entire procedure on the CT table takes approximately 10 minutes, with no sedation or recovery time needed.

CT Colonography



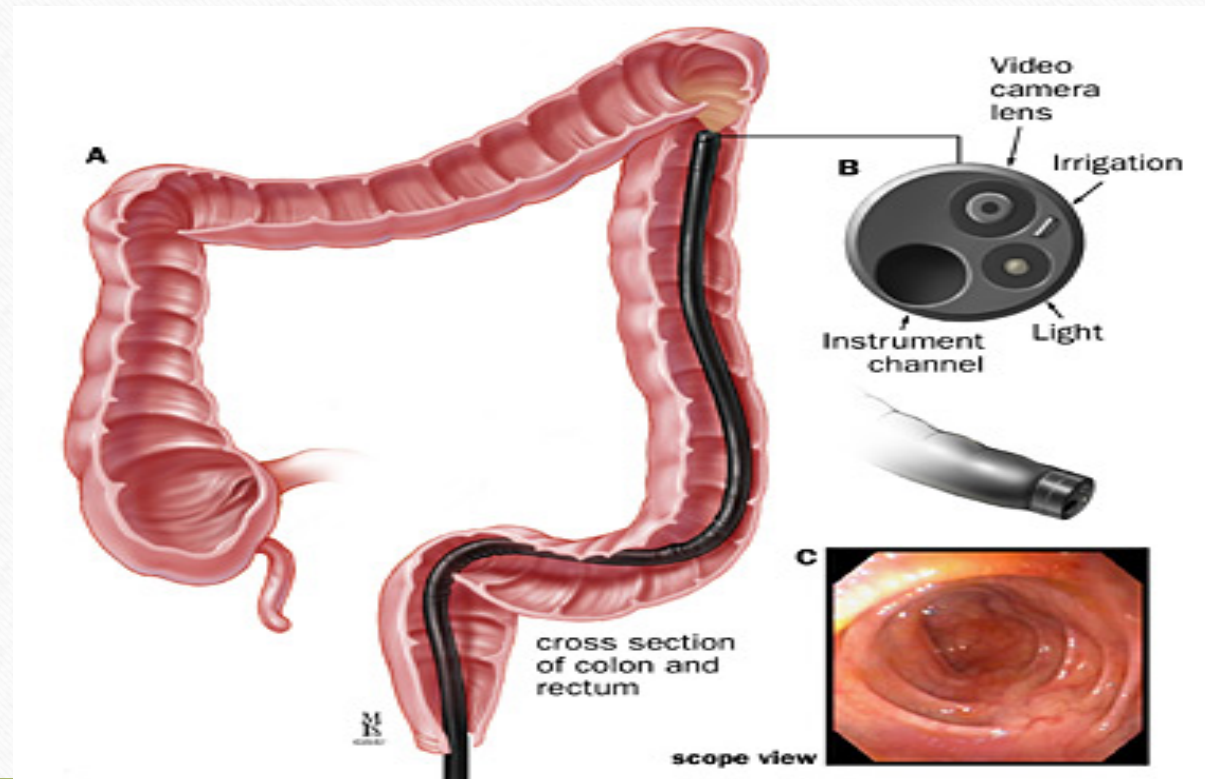
CT Colonography

- Consensus that all patients with one or more polyps >10 mm or 3 or more polyps >6 mm should be referred for colonoscopy.
 - The management of patients with fewer polyps <3 in which the largest polyp is 6 to 9 mm remains controversial.
- American Cancer Society, USMSTF and American College of Radiology joint guidelines state that CT Colonography can be used for CRC in average risk population every 5 years.
- ACG recommends CT Colonography may be used in asymptomatic patients at average risk every 5 years.

Flexible Sigmoidoscopy (FSIG)

- Endoscopic procedure that examines the lower half of the colon lumen using the standard 60cm.
- It is typically performed without sedation and with a more limited bowel preparation than standard colonoscopy.
- Any adenoma found of FSIG, needs referral for colonoscopy
 - If polyp not biopsied, any polyp >5mm needs referral for colonoscopy.

FSIG



FSIG

- USPSTF recommends Flex Sig every 5 years with high sensitivity FOBT every 3 years for CRC screening in asymptomatic patients at average risk.
- ACG recommends Flex Sigmoidoscopy every 5 (10 years in only certain situations)
- American Cancer Society, USMSTF and American College of Radiology joint guidelines state that FSIG can be used for CRC in average risk population every 5 years.

Colonoscopy

- GOLD STANDARD for CRC Screening
- Colonoscopy is one of the most commonly performed medical procedures in the United States, with estimates of up to 14 million procedures per year.
- Colonoscopy allows direct mucosal inspection of the entire colon from the appendiceal orifice to the dentate line and same-session biopsy sampling or definitive treatment by polypectomy in the case of precancerous polyps and some early-stage cancers.
- Colonoscopy every 10 years is an acceptable option for CRC screening in average-risk adults beginning at age 50 years

Table 1. Colorectal Cancer Screening Recommendations in Asymptomatic Adults at Average Risk

<i>Organization</i>	<i>Screening test and interval</i>	<i>Patient age</i>
U.S. Preventive Services Task Force* ⁷	The following options are equally acceptable High-sensitivity FOBT annually Flexible sigmoidoscopy every 5 years with high-sensitivity FOBT every 3 years Colonoscopy every 10 years	Start at 50 years; individualize after 75 years
American College of Gastroenterology† ⁸	Preferred Colonoscopy every 10 years Fecal immunochemical test annually (if colonoscopy is declined) Alternative, prevention Flexible sigmoidoscopy every 5 to 10 years Computed tomography colonography every 5 years Alternative, cancer detection High-sensitivity FOBT annually Stool DNA test every 3 years	Start at 50 years, or 45 years in blacks
American Cancer Society, U.S. Multi-Society Task Force, American College of Radiology‡ ⁹	Tests that detect adenomas and cancer Flexible sigmoidoscopy every 5 years Colonoscopy every 10 years Double-contrast barium enema every 5 years Computed tomography colonography every 5 years Tests that primarily detect cancer High-sensitivity FOBT annually Fecal immunochemical test annually Stool DNA test, interval uncertain	Start at 50 years



Age To Initiate Screening

<i>Risk Factor</i>	<i>Age to Initiate Screening</i>	<i>Interval if Normal</i>
None	50 years (45 in African Americans)	10 years
Single first-degree relative with CRC or an advanced adenoma diagnosed >60 years of age	50 years (45 in African Americans)	10 years
Single first-degree relative with CRC or an advanced adenoma diagnosed <60 years of age	40 years or 10 years younger than the affected relative's age when diagnosed, whichever is earlier	5 years
Two first degree relatives with CRC or an advanced adenoma diagnosed at any age	40 years or 10 years younger than the affected relative's age when diagnosed, whichever is earlier	5 years

Advanced Adenoma: defined as polyp 10mm or larger, villous features or HGD

Recommendations for Surveillance Intervals in Average Risk

Baseline colonoscopy: most advanced finding(s)	Recommended surveillance interval (y)
No polyps	10
Small (<10 mm) hyperplastic polyps in rectum or sigmoid	10
1–2 small (<10 mm) tubular adenomas	5–10
3–10 tubular adenomas	3
>10 adenomas	<3
One or more tubular adenomas ≥ 10 mm	3
One or more villous adenomas	3
Adenoma with HGD	3
Serrated lesions	
Sessile serrated polyp(s) <10 mm with no dysplasia	5
Sessile serrated polyp(s) ≥ 10 mm	3
OR	
Sessile serrated polyp with dysplasia	
OR	
Traditional serrated adenoma	
Serrated polyposis syndrome ^a	1



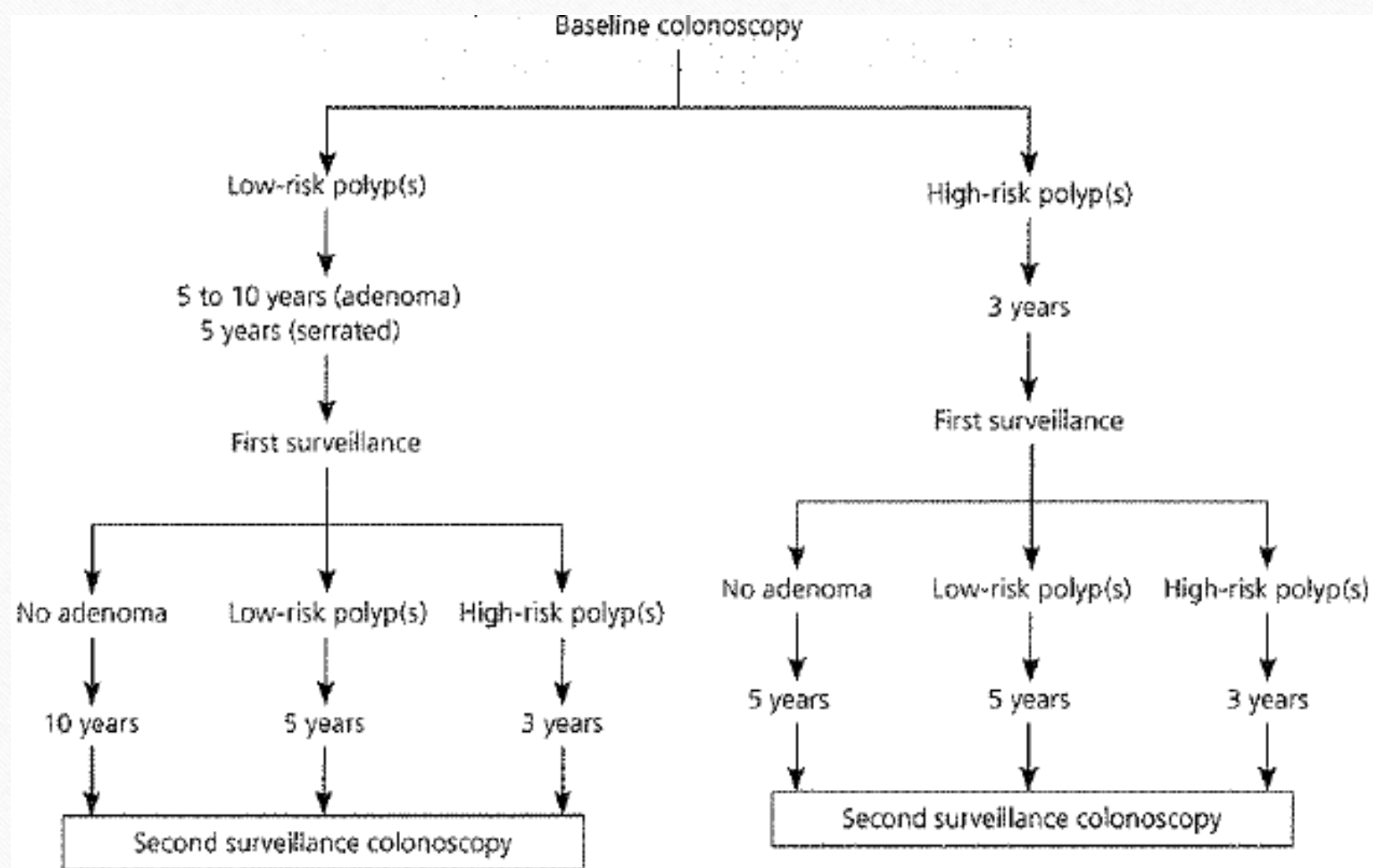


Other Circumstances

<i>Surveillance Recommendations</i>	
More than 10 adenomas	< 3 years
Serrated polyposis syndrome*	1 year
Following piecemeal removal of a large (>15mm) sessile adenoma or serrated polyp	Consider repeat in <1 year if question of residual polyp
Following curative resection of colorectal cancer	1 year after resection, then 3 years and 5 years if normal

^aBased on the World Health Organization definition of serrated polyposis syndrome, with one of the following criteria: (1) at least 5 serrated polyps proximal to sigmoid, with 2 or more ≥ 10 mm; (2) any serrated polyps proximal to sigmoid with family history of serrated polyposis syndrome; and (3) >20 serrated polyps of any size throughout the colon.

Low Risk	High Risk
1 or 2 tubular adenoma (<10mm)	3 to 10 tubular adenomas
Sessile Serrated polyp (<10mm) without dysplasia	Tubular adenoma or serrated adenoma >10mm
	Adenoma with villous features
	Adenoma with HGD
	Sessile serrated polyp with dysplasia
	Traditional serrated adenoma



Quality of Colonoscopy

- The recommended colorectal cancer screening and surveillance intervals assumes high-quality colonoscopy
 - High cecal intubation rates – 95% of screening procedures performed.
 - High adenoma detection rates – 15% of women, 25% of men undergoing screening colonoscopy >50yo
- Poor Bowel Prep – bring back in one year for repeat exam
- Use of fecal occult blood testing is NOT recommended between surveillance exams.

Inflammatory Bowel Disease

- In patients with **ulcerative colitis extending proximal to the splenic flexure or Crohn colitis**, we suggest initiating surveillance colonoscopy **after eight years of disease followed by 1-2 years colonoscopy**.
- In patients with **left-sided UC**, we suggest beginning with **colonoscopy after 12 years of disease**; examinations are then performed every year thereafter.
- Ulcerative colitis limited to the rectum is not at increased risk of CRC and therefore, surveillance is for average risk.
- In patients who have undergone a subtotal colectomy with an ileostomy and have rectum left in place and tied off (ie, a Hartmann's pouch), we suggest surveillance of the remaining rectum every year .
- Multiple biopsies are required to adequately sample the colon - obtain four biopsies every 10 cm from the cecum to the rectum

Familial Adenomatous Polyposis (FAP)

- **Familial adenomatous polyposis (FAP)** is an **autosomal dominant disease** caused by mutations in the adenomatous polyposis coli (**APC**) gene, which is located on chromosome 5q21-q22.
- FAP occurs in approximately 1 out of 10,000 to 1 out of 30,000 live births, and accounts for less than 1 percent of the total colon cancer risk in the United States.
- FAP is characterized by the presence of multiple colorectal adenomas.
 - **Classic FAP** is characterized as the **presence of 100 or more adenomatous colorectal polyps**. Polyposis typically develops in the second or third decade of life and colorectal cancer occurs in essentially 100 percent of untreated individuals by age 45 years.
 - **Attenuated FAP (AFAP)** is characterized by more than **>10 to 20 adenomas but fewer than 100**. Individuals with AFAP have up to an 80 percent risk of developing colorectal cancer at an average age of 56 years.

FAP – Extraintestinal Manifestations

- **Fundic gland polyps** are found in most patients with FAP but rarely progress to cancer.
- **Duodenal adenomas** occur in 45 to 90 percent of patients with FAP.
 - Patients with FAP have a 4 to 12 percent lifetime risk of duodenal cancer.
- At least 50 percent of patients with FAP also have adenomatous change of the periampullary region and 5 to 10 percent develop **periampullary cancer**.
- Individuals with FAP are also at risk for **follicular or papillary thyroid cancer**, childhood hepatoblastoma, and central nervous system (CNS) tumors but these are much less common than colon and duodenal cancer.
- Genetic testing for a germline mutation in the *APC* gene is required to make a diagnosis of familial adenomatous polyposis (FAP).
- Genetic testing for FAP in individuals with >10 to 20 adenomas in their lifetime and for all at-risk relatives of individuals with a known *APC* mutation.

FAP Screening (ACG)

- Patients with classic FAP (>100 adenomas) should be advised to pursue genetic counseling and genetic testing, if they have siblings or children who could potentially benefit from this testing (Grade 2 B)
- Patients with known FAP or who are at risk of FAP based on family history (and genetic testing has not been performed) should undergo annual flexible sigmoidoscopy or colonoscopy (10-12yo), as appropriate, until such time as colectomy is deemed by physician and patient as the best treatment (Grade 2 B)
- Patients with retained rectum after subtotal colectomy should undergo flexible sigmoidoscopy every 6 – 12 months (Grade 2B)

Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

- Lynch syndrome is an autosomal dominant disorder that is caused by a germline mutation in one of several DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) or loss of expression of *MSH2* due to deletion in the *EPCAM* gene.
- Lynch syndrome is the most common inherited colorectal cancer (CRC) susceptibility syndrome and accounts for approximately **3 percent of newly diagnosed cases of CRCs** and 2 percent of endometrial cancers.
- The lifetime risk of CRC in Lynch syndrome is approximately 70 percent.
- Individuals with Lynch syndrome are also at an increased risk for **endometrial cancer**, and several other malignancies including cancers of **the ovary, renal pelvis, ureter, stomach, small bowel, bile duct, skin** (sebaceous neoplasms), and **brain** (gliomas).
- Although the CRCs appear to evolve from adenomas, the adenomas tend to be larger, flatter, are more often proximal, and more commonly have high-grade dysplasia and/or villous histology as compared with sporadic adenomas.
- The adenoma-carcinoma sequence also progresses much more rapidly in Lynch syndrome as compared with sporadic CRC.
- Individuals with Lynch syndrome are at increased risk for both synchronous and metachronous CRCs.

Amsterdam II criteria for Lynch syndrome

There should be at least three relatives with an Lynch syndrome-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis)

One should be a first-degree relative of the other two

At least two successive generations should be affected

At least one should be diagnosed before age 50

Familial adenomatous polyposis should be excluded in the colorectal cancer case(s), if any

Tumors should be verified by pathological examination

Adapted from Vasen HF, Watson P, Mecklin JP, et al. Gastroenterology 1999; 116:1453.

UpToDate®

HNPPC – ACG Recommendations

- Patients who meet the Bethesda criteria should undergo microsatellite instability testing of their tumor or a family member's tumor and/or tumor immunohistochemical staining for mismatch repair proteins (Grade 2 B)
- Patients with positive tests can be offered genetic testing. Those with positive genetic testing, or those at risk when genetic testing is unsuccessful in an affected proband, should undergo colonoscopy every **2 years beginning at age 20 – 25 years, until age 40 years, then annually thereafter** (Grade 2 B)