

Small and Large Intestinal pathology, part 3

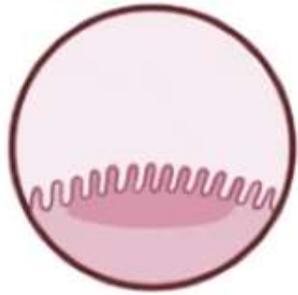
Dr, Sura Al Rawabdeh, MD
April 13 2022

COLONIC POLYPS AND NEOPLASTIC DISEASE

- ▶ **Colon is most common site for polyps:**
 - **Flat**
 - ***Sessile polyp: no stalk***
 - ***Pedunculated polyp: stalk.***

POLYPS CLASSIFIED by APPEARANCE

FLAT



- * DON'T PROTRUDE into the LUMEN
- * FLAT AGAINST the MUCOSA

PEDUNCULATED



- * PROTRUDE into the LUMEN
- * ATTACHED to the WALL by a STALK

SESSILE



- * PROTRUDE into the LUMEN
- * BASE ATTACHED to the MUCOSA

COLONIC POLYPS

- ▶ □ Non neoplastic polyps:
 - ▶ 1. Inflammatory,
 - ▶ 2. Hamartomatous
 - ▶ 3. Hyperplastic.
- ▶ □ Neoplastic polyps: adenoma.

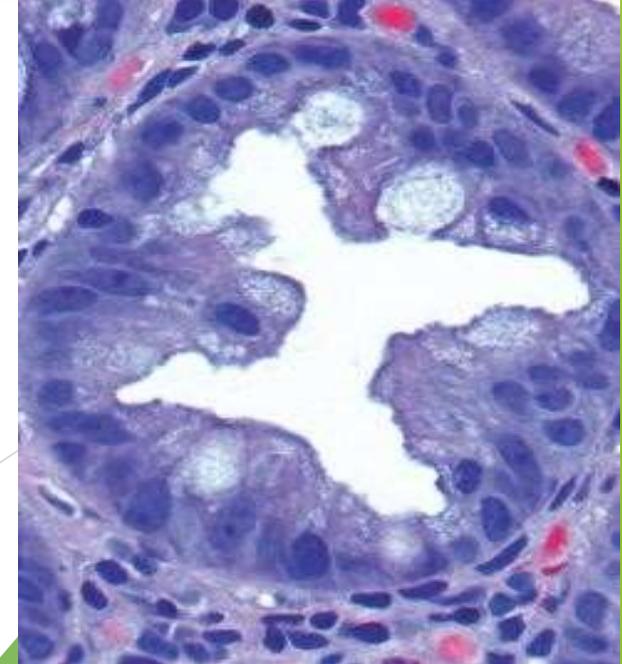
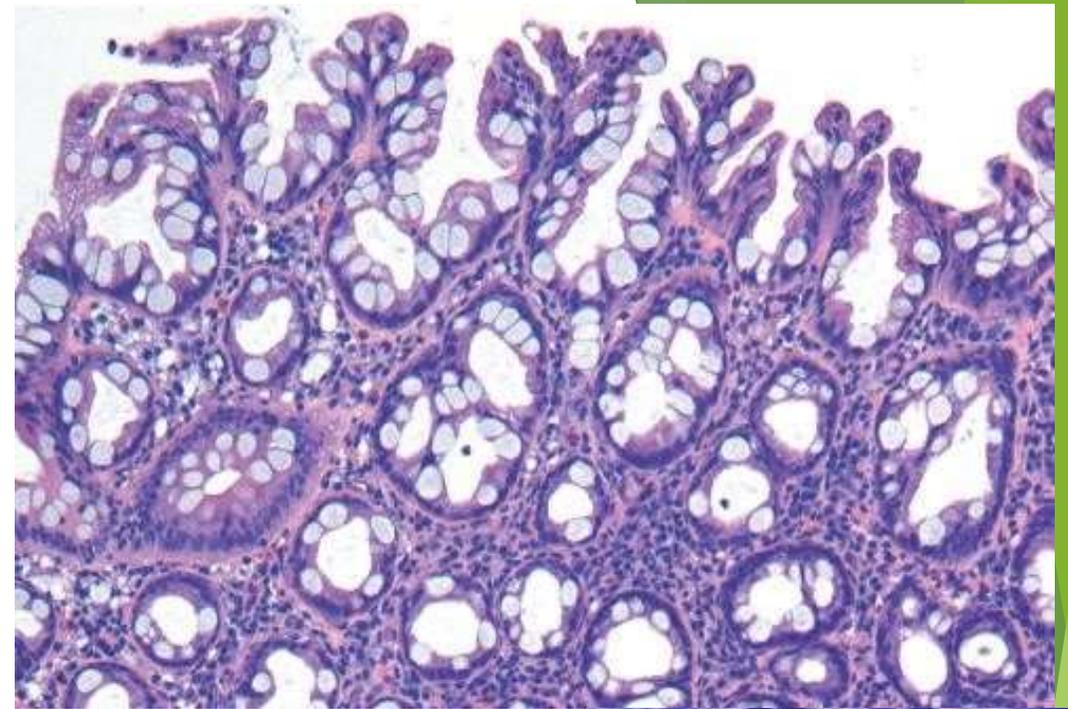
Hyperplastic Polyps

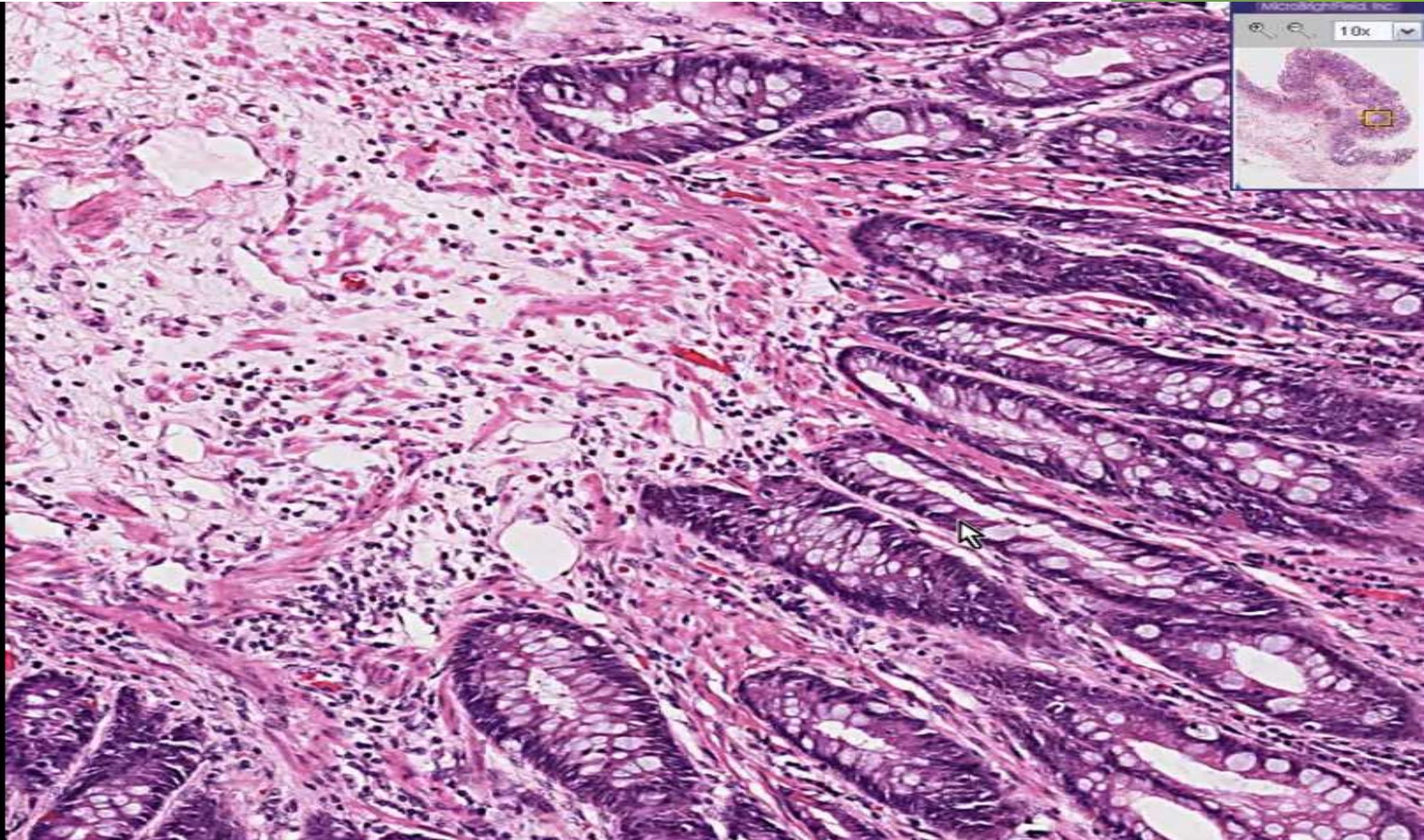
- ▶ **Common**
- **5th-6th decade.**
- **Decreased epithelial turnover and delayed shedding of surface epithelium >>> pileup of goblet cells & epithelial overcrowding**
- **No malignant potential**

Hyperplastic polyp

- ▶ Left colon
 - Rectosigmoid.
 - Small < 5 mm
 - Multiple

- Crowding of goblet & absorptive cells.
- Serrated surface: hallmark of these lesions



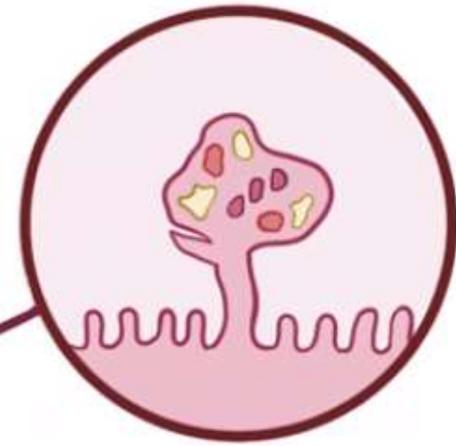
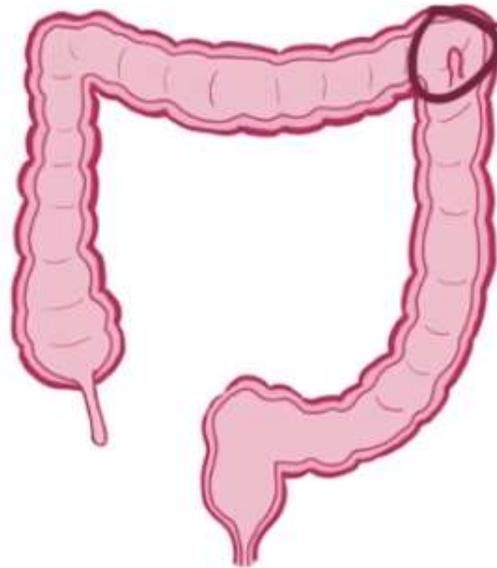


Inflammatory Polyps

- ▶ *Solitary rectal ulcer syndrome.*
- Recurrent abrasion and ulceration of the overlying rectal mucosa.
- Chronic cycles of injury and healing give a polypoid mass of inflamed and reactive mucosal tissue.

INFLAMMATORY POLYPS

- ↳ FOLLOW BOUTS of
 - * ULCERATIVE COLITIS
 - * CROHN'S DISEASE
- ↳ NOT MALIGNANT



HAMARTOMATOUS POLYPS

- ↳ MIX of TISSUES
- ↳ DISTORTED ARCHITECTURE
- ↳ ASSOCIATED WITH:
 - * JUVENILE POLYPOSIS
 - * PEUTZ-JEGHER'S SYNDROME

Hamartomatous Polyps

- ▶ **Sporadic or syndromatic.**
- **Disorganized, tumor-like growth composed of mature cell types normally present at that site.**

- ▶ **Juvenile Polyps**
- **Peutz-Jeghers Syndrome**

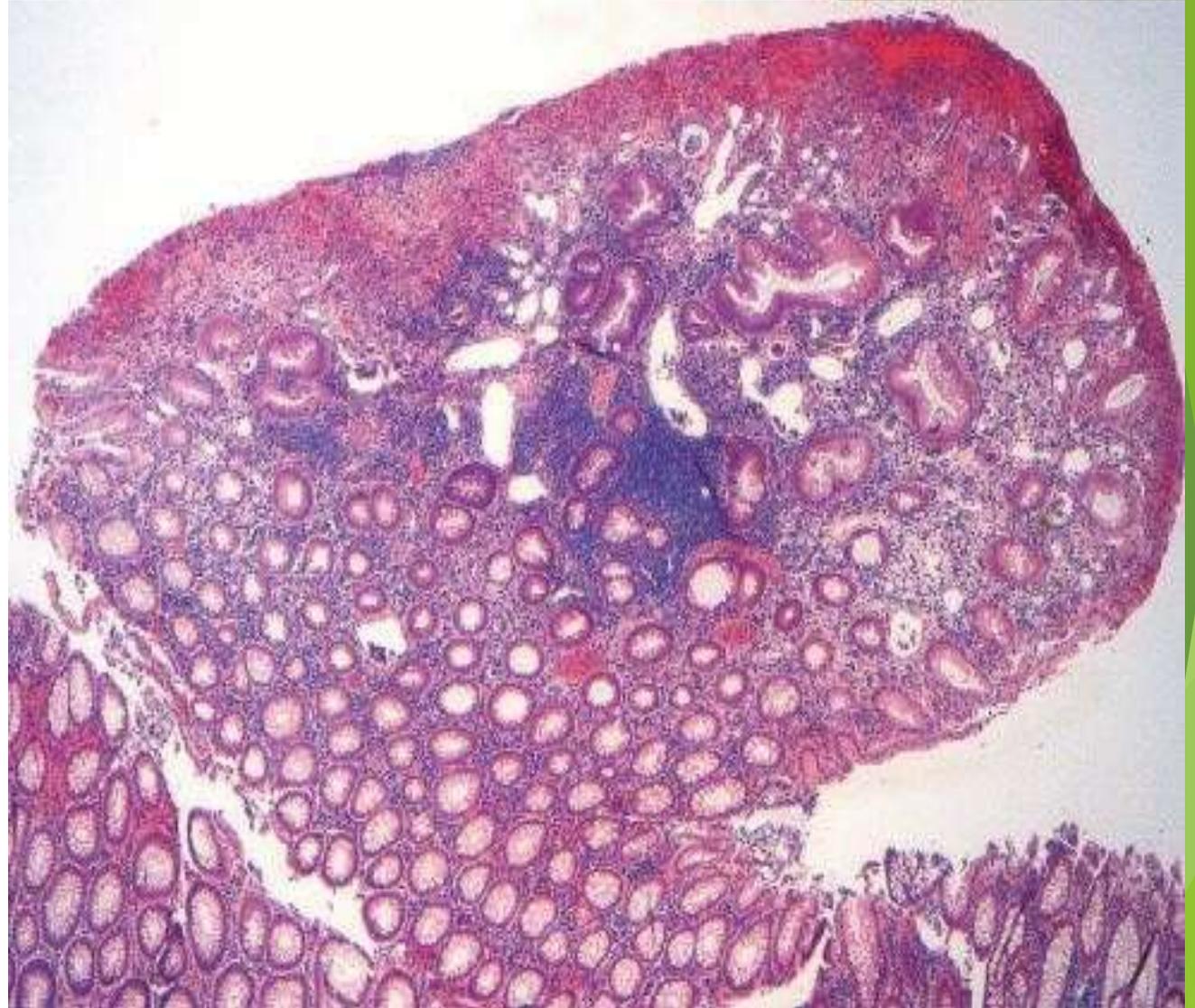
Juvenile Polyps

- ▶ **Most common hamartomatous polyp**
- **Sporadic are solitary.**
- **Children younger than 5 years of age**
- **Rectum.**

- **Syndromic are multiple.**
- **3 to as many as 100. Mean age 5 years**
- **Autosomal dominant syndrome of juvenile polyposis**
- **Transforming growth factor- β (TGF- β) mutation.**
- **Increased risk for colonic adenocarcinoma.**

Juvenile Polyps

- ▶ **Pedunculated**
- **Reddish lesions**
- **Cystic spaces on cut sections**
- **Dilated glands filled with mucin and inflammatory debris.**
- **Granulation tissue on surface.**

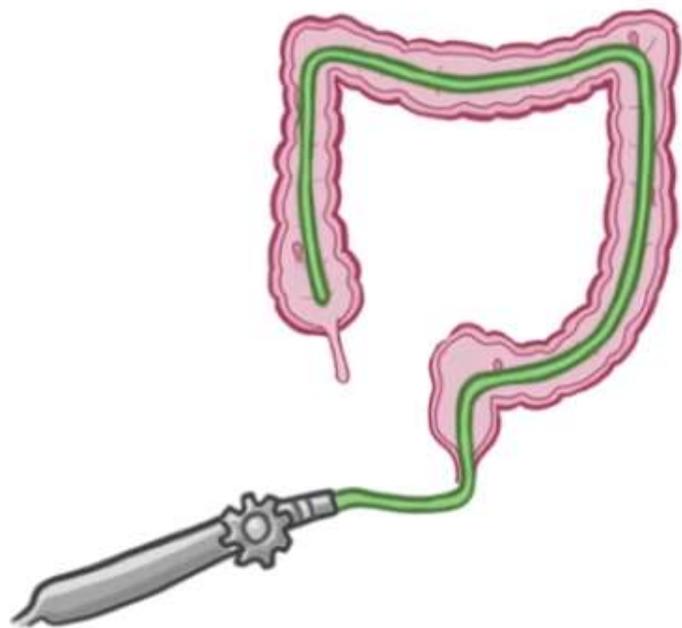


JUVENILE POLYPOSIS SYNDROME

↳ AUTOSOMAL DOMINANT CONDITION
↳ MUTATION of SMAD4

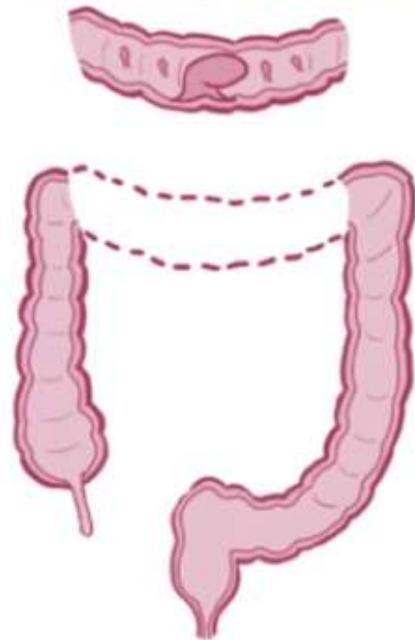


* HAMARTOMAS



* REGULAR ENDOSCOPIC MONITORING

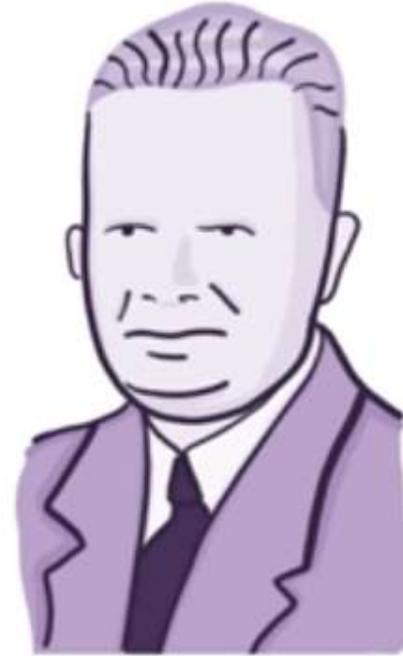
* PROPHYLACTIC SURGERY



PEUTZ-JEGHERS SYNDROME



DR. HAROLD
JEGHERS



DR. JAN
PEUTZ

Peutz-Jeghers Syndrome

▶ AD

- Mean age: 10-15 years.
- Multiple gastrointestinal hamartomatous polyps
- Most common in the small intestine.
- Mucocutaneous hyperpigmentation
- Increased risk for several malignancies: colon, pancreas, breast, lung, ovaries, uterus, and testes,

- *LKB1/STK11* gene mutation.

PEUTZ-JEGHERS SYNDROME

MUTATION OF THE STK11 GENE

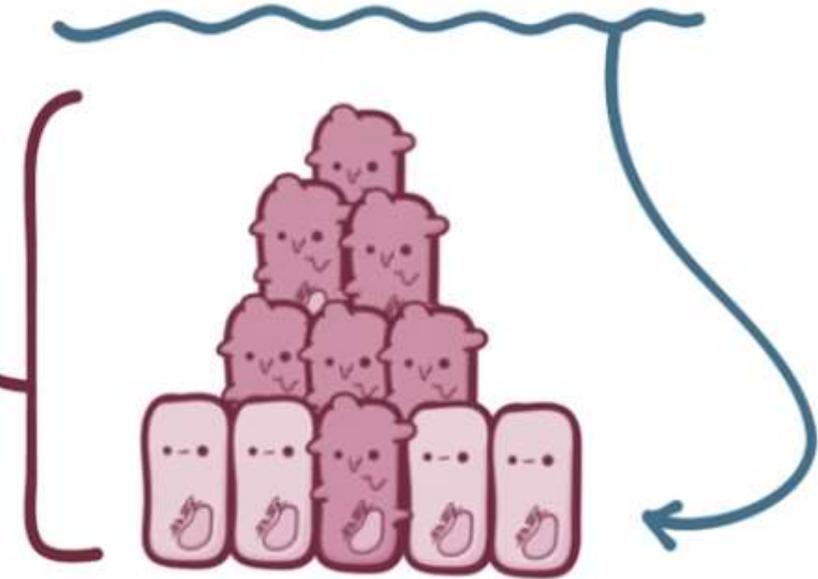
POLYP

- * **BENIGN** OUTGROWTHS
- * **MOSTLY** IN THE **SMALL** INTESTINE
- * ACCUMULATE **MORE** MUTATIONS



CANCER

- * **ONE** POLYP
~ LOW CANCER RISK
- * **MANY** POLYPS
~ SIGNIFICANT CANCER RISK



GI CELLS
ACCUMULATE MUTATIONS
&
DIVIDE **FASTER** THAN USUAL

PEUTZ-JEGHERS SYNDROME

CAUSED BY A MUTATION OF THE **STK11 GENE**



CHARACTERIZED BY MULTIPLE HAMARTOMAS THE GI TRACT



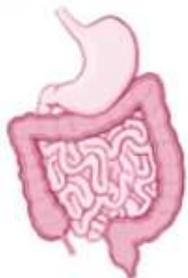
ALONG WITH

MELANOTIC MACULES IN THE **SKIN & MUCOSA**

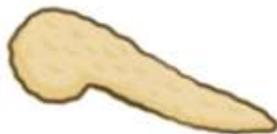


INCREASED RISK CANCERS OF

GI TRACT



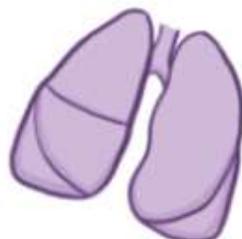
PANCREAS



BREAST



LUNGS



OVARIES AND UTERUS

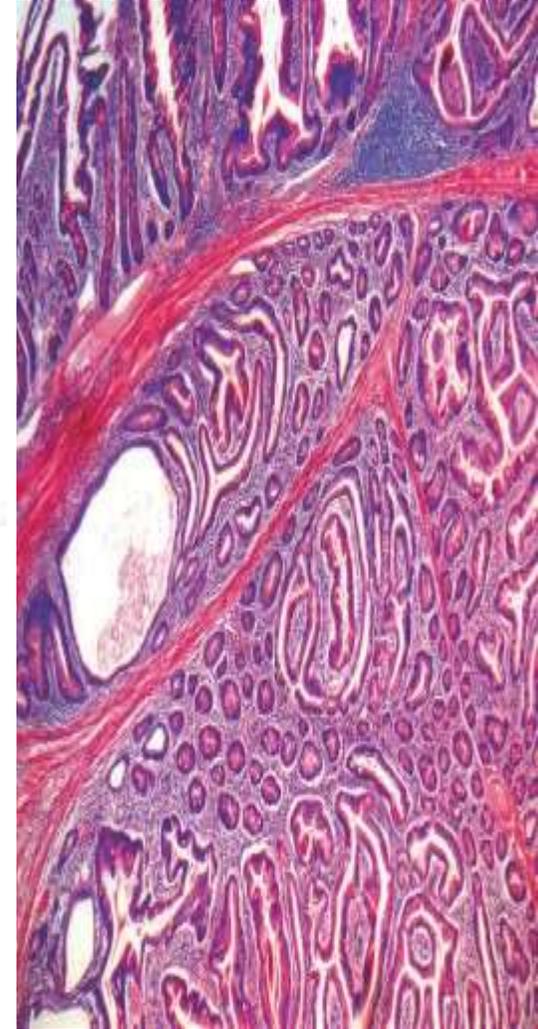


TESTICLES



Peutz-Jeghers polyp

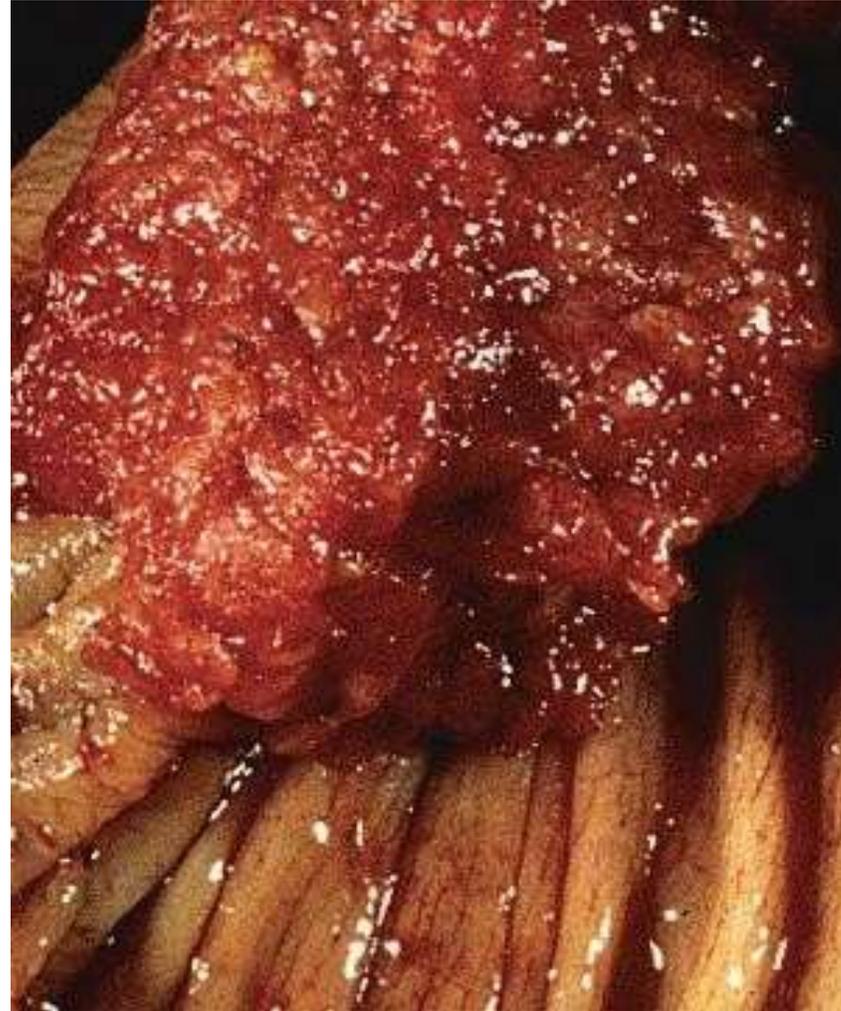
- ▶ Large.
- Arborizing network of connective tissue, smooth muscle, lamina propria
- Glands lined by normal-appearing intestinal epithelium
 - Christmas tree pattern.



Adenomas

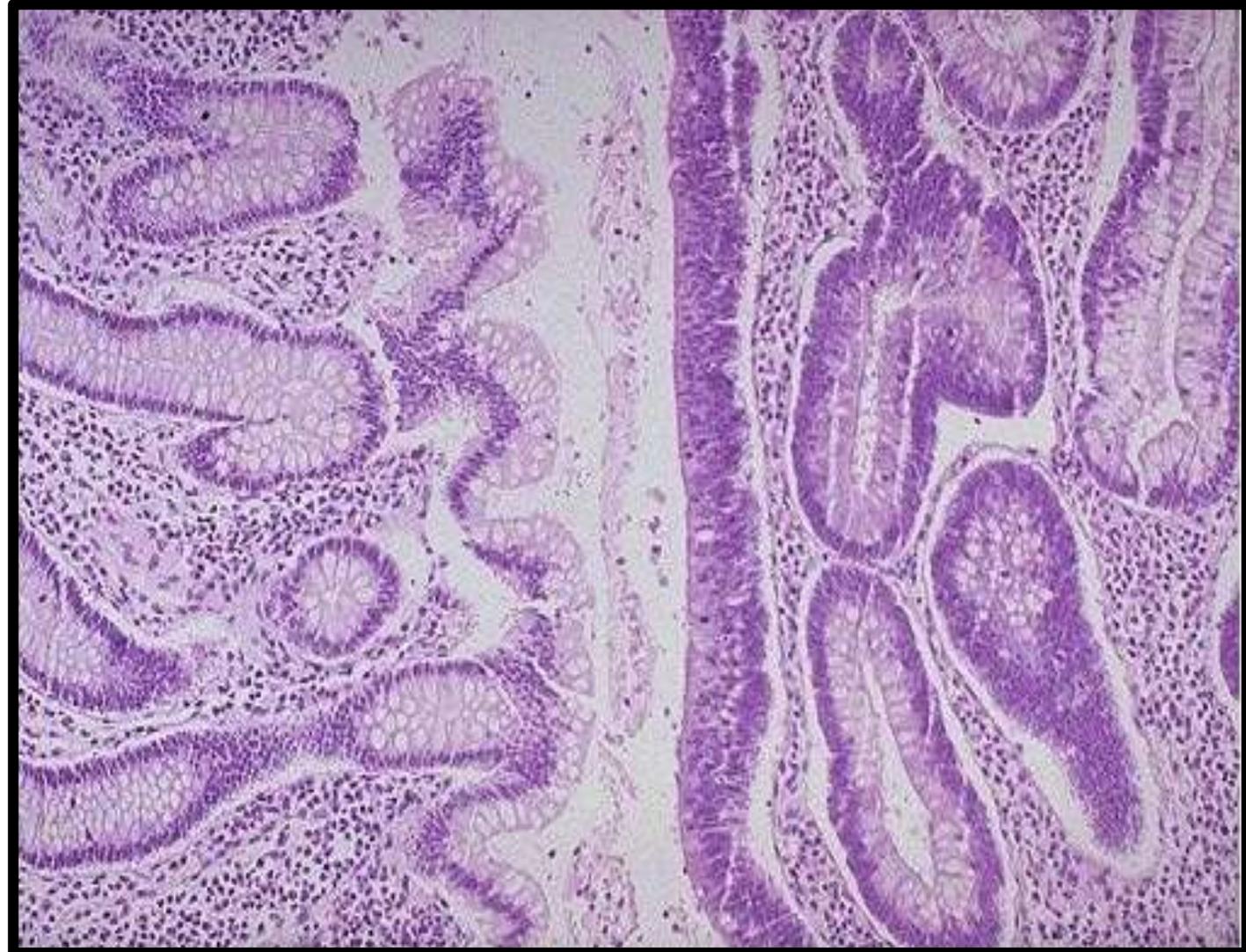
- ▶ **Most common and clinically important**
- *Increase with age.*
- *Definition: presence of epithelial dysplasia (low or high).*
- **Precursor for majority of colorectal adenocarcinomas**
- ***Most adenomas DO NOT progress to carcinoma.***
- *USA: screening colonoscopy starts at 50 yrs.*
- *Earlier screening with family history.*
- **Western diets and lifestyles increase risk.**

Pedunculated or sessile



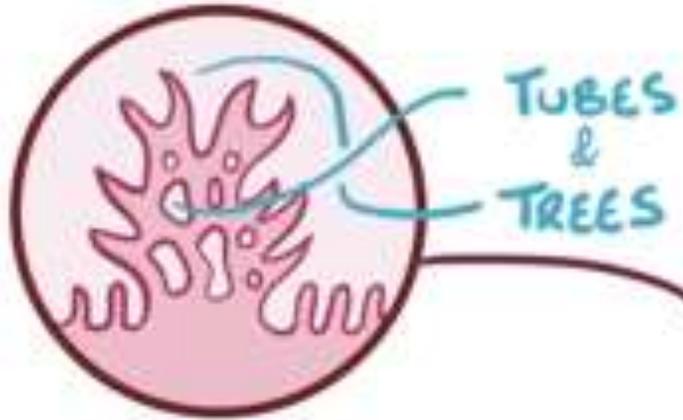
Colon adenoma

- ▶ **Hallmark: epithelial dysplasia**
- **Dysplasia: nuclear hyperchromasia, elongation, stratification, high N/C ratio.**
- **Size : most important correlate with risk for malignancy**
- **High-grade dysplasia is the second factor**

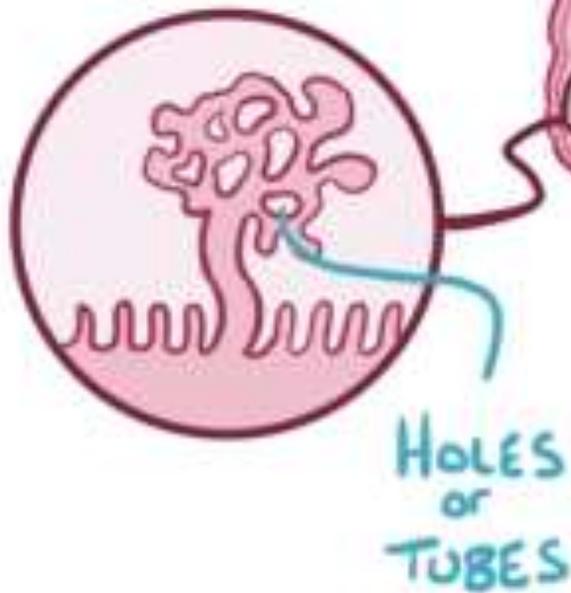


ADENOMATOUS POLYPS can be CLASSIFIED HISTOLOGICALLY

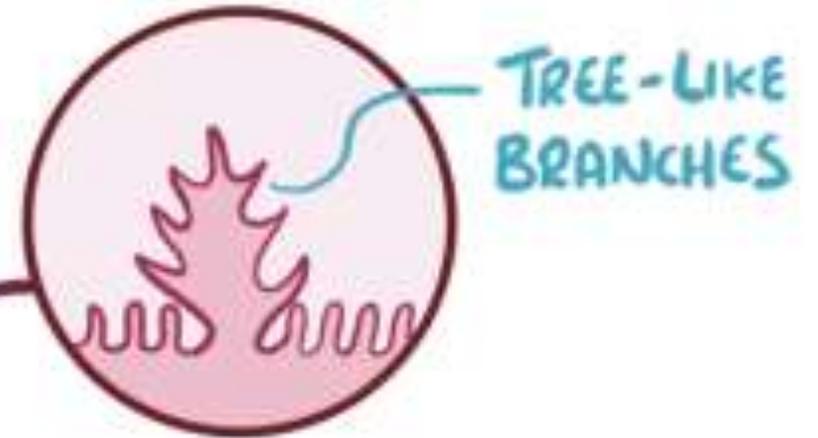
TUBULOVILLOUS



TUBULAR

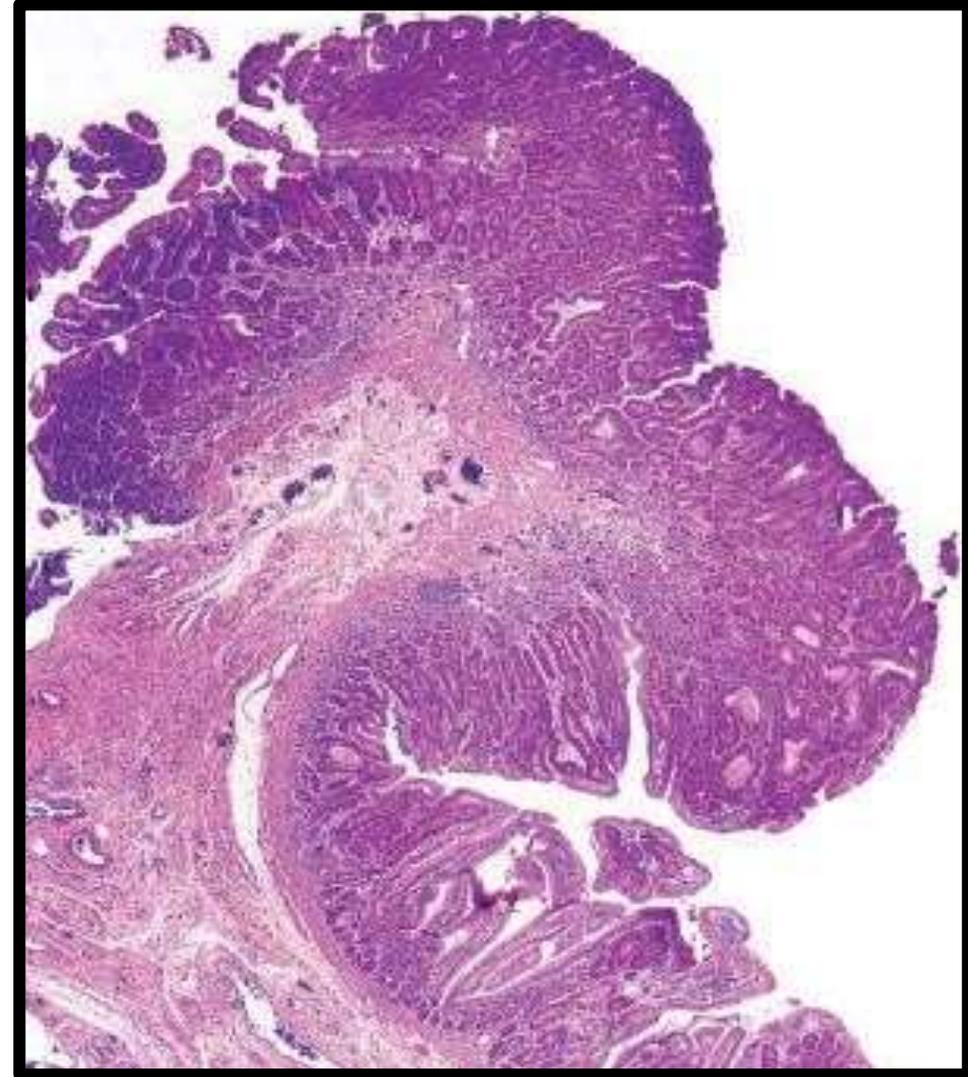
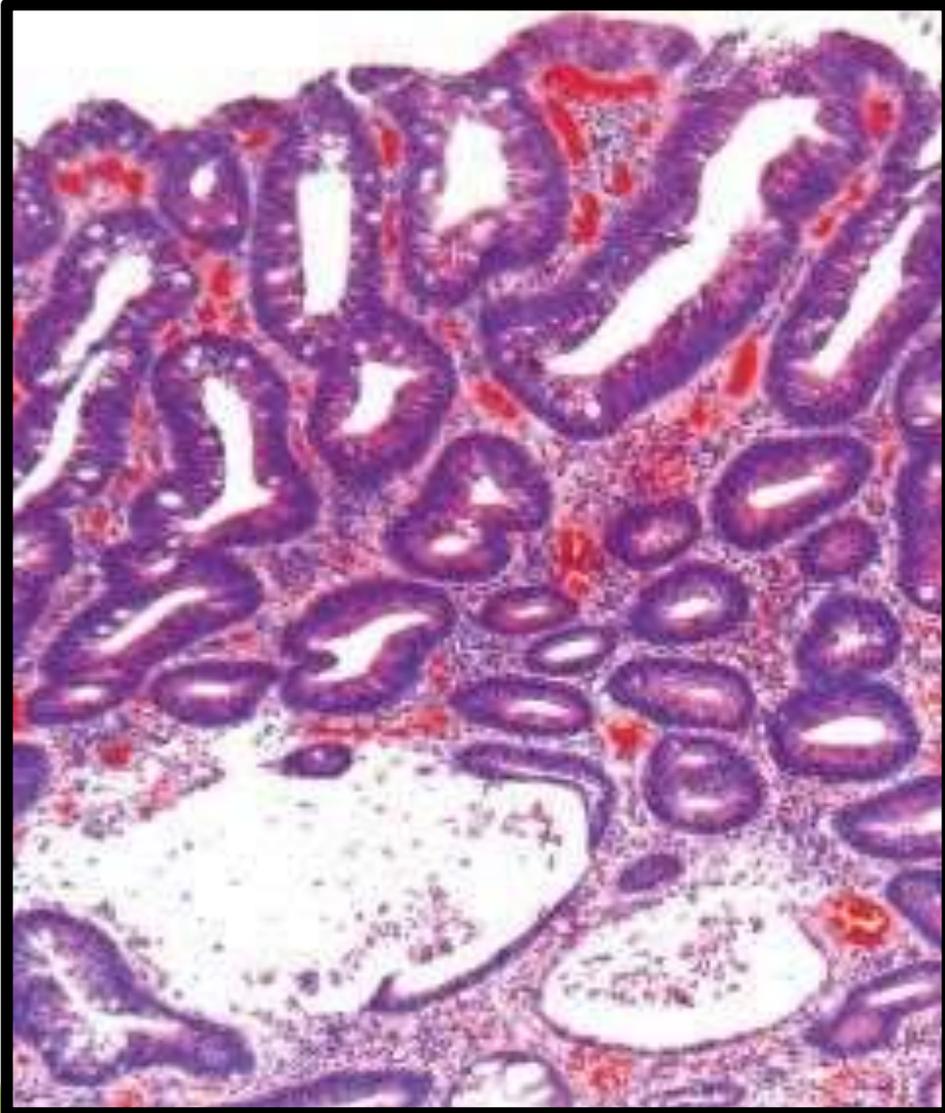


VILLOUS



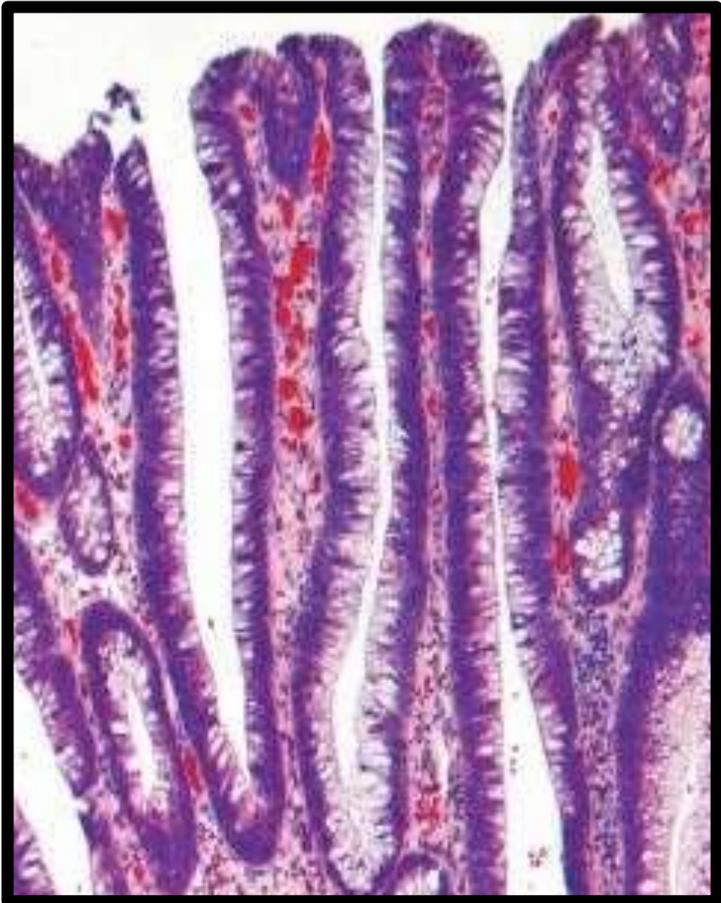
VILLOUS MORE often MALIGNANT

Tubular adenoma



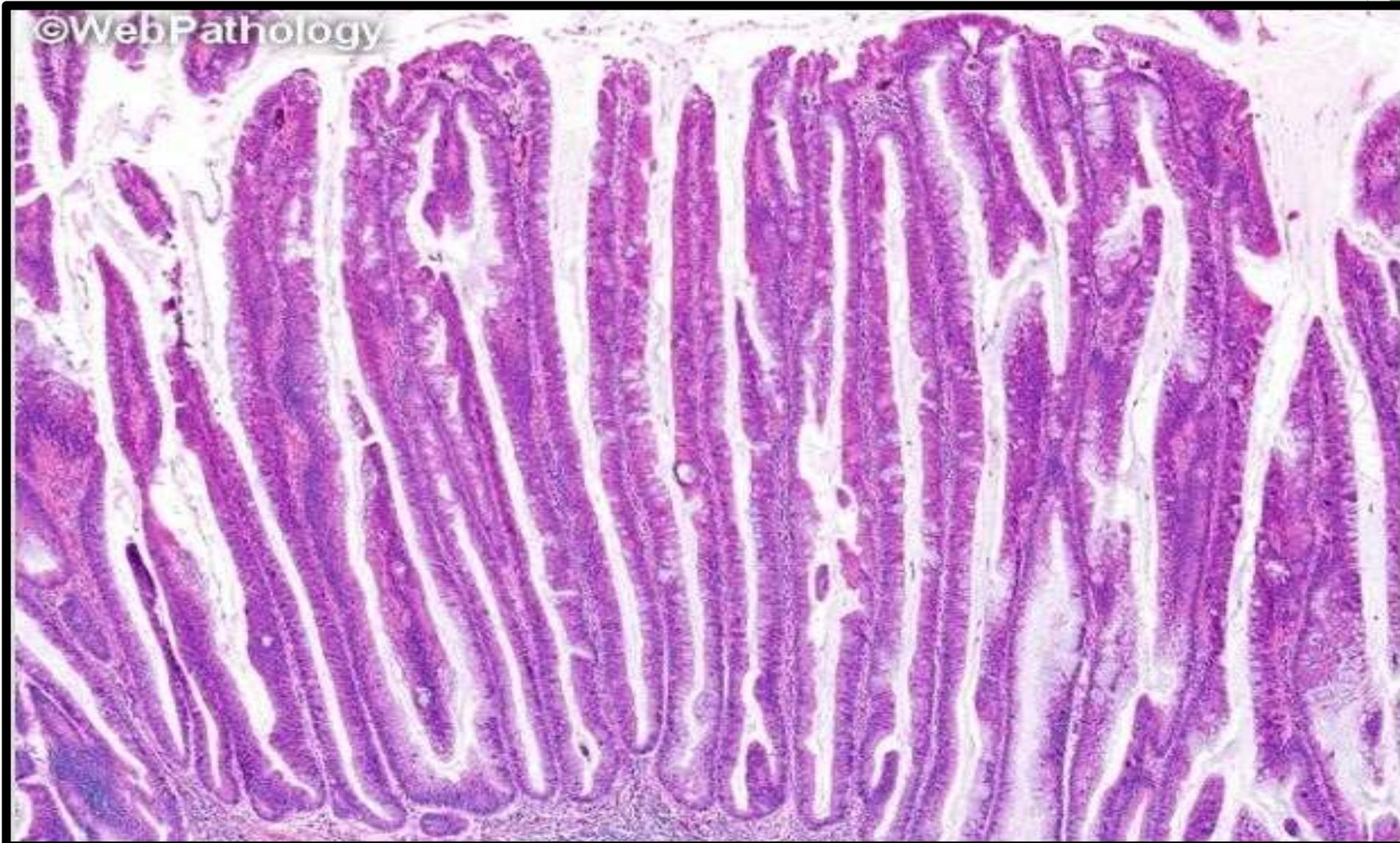


Villous adenoma.



- ▶ Long slender villi.
 - More frequent invasive foci
-
- ▶ Architecture:
 - ▶ Tubular.
 - ▶ Tubulovillous.
 - Villous.

Villous adenoma



Familial Syndromes

▶ Syndromes associated with colonic polyps and increased rates of colon cancer

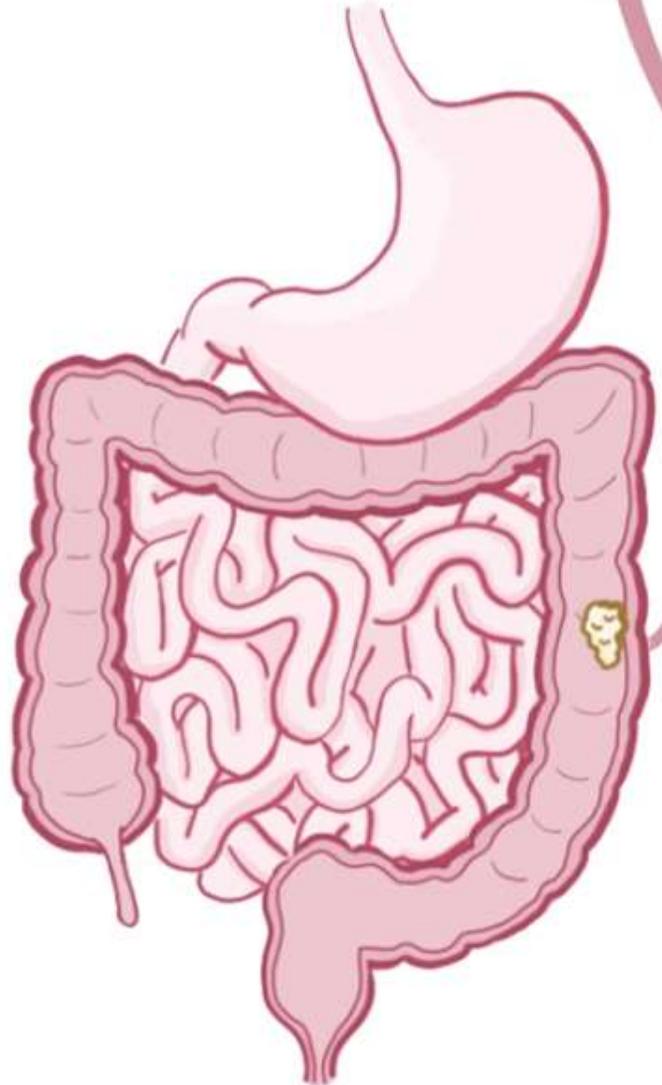
□ Genetic basis.

▶ **Familial Adenomatous Polypos (FAP)**

▶ **Hereditary Nonpolyposis Colorectal Cancer (HNPCC)**

Familial adenomatous polyposis (FAP)

- ▶ Autosomal dominant.
- Numerous colorectal adenomas: teenage years.
- Mutation in APC gene.
- At least 100 polyps are necessary for a diagnosis of classic FAP.
- Morphologically similar to sporadic adenomas
- 100% of patients develop colorectal carcinoma, IF UNTREATED, often before age of 30.
- Standard therapy: prophylactic colectomy before 20 Year of age.
- Risk for *extraintestinal manifestations*,

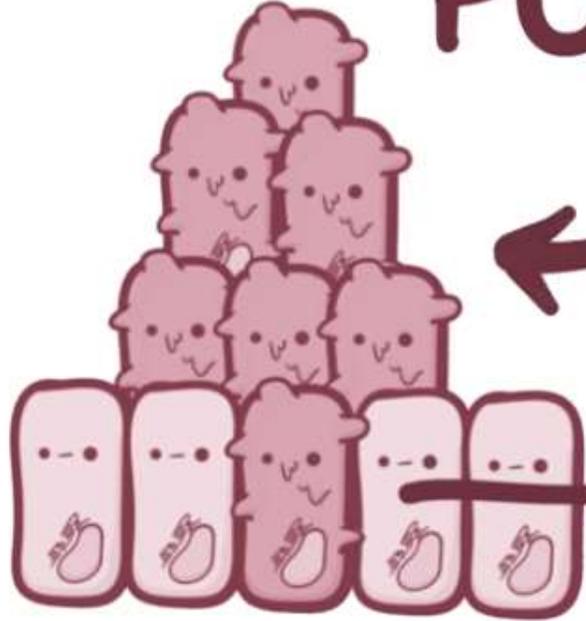


MOST DUE TO SPORADIC MUTATIONS

SOME DUE TO KNOWN MUTATIONS

E.G. ADENOMATOUS POLYPOSIS COLI GENE (APC)

POLYP

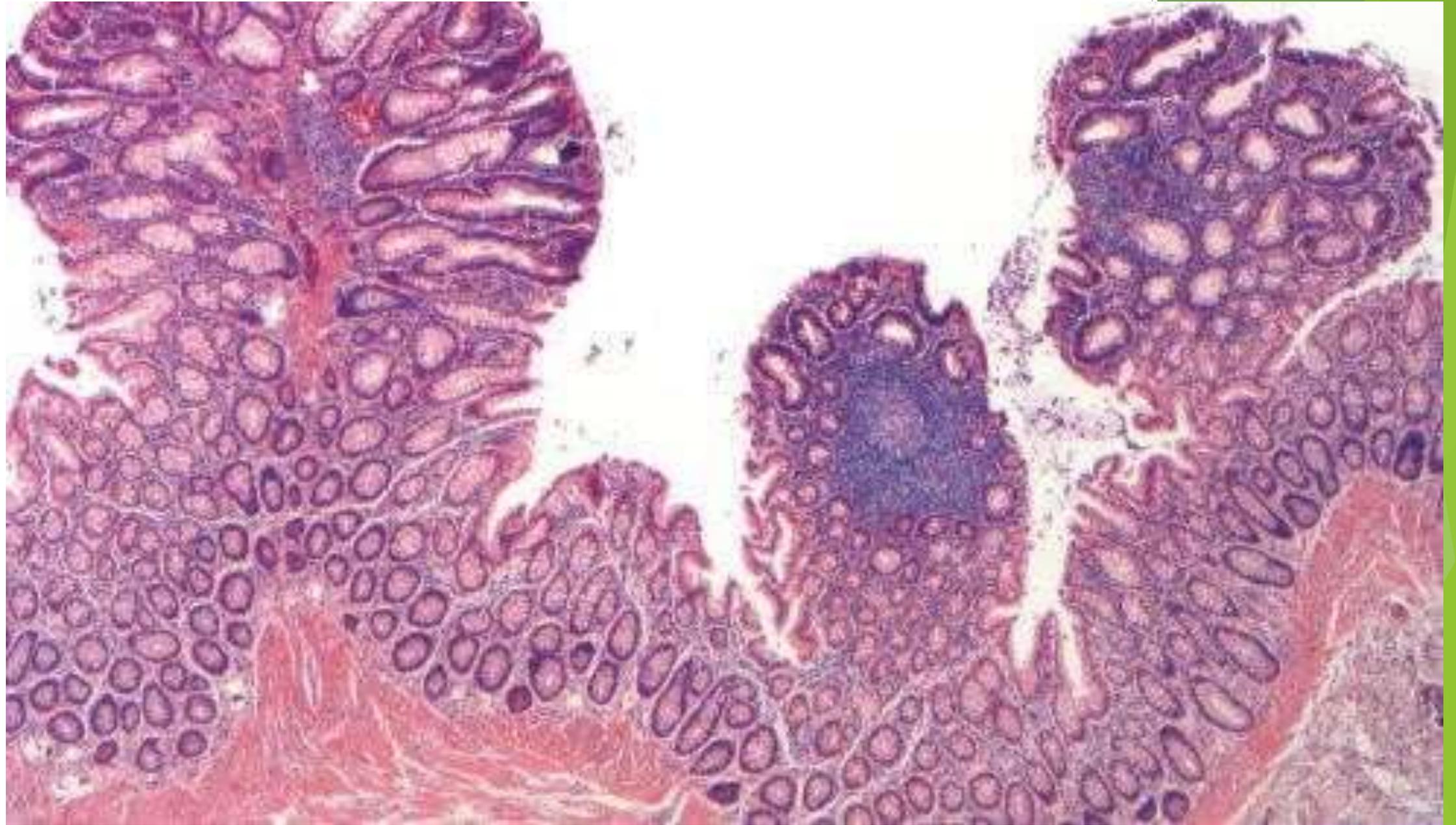


**IF APC IS
MUTATED
IT CAN ALLOW
UNCONTROLLED
DIVISION**



- ▶ **Variants of FAP: Gardner syndrome and Turcot syndrome.**
- ▶ **Gardner syndrome:** intestinal polyps + osteomas (mandible, skull, and long bones); epidermal cysts; desmoid and thyroid tumors; and dental abnormalities.
- **Turcot syndrome:** intestinal adenomas and CNS tumors (medulloblastomas >> glioblastomas)



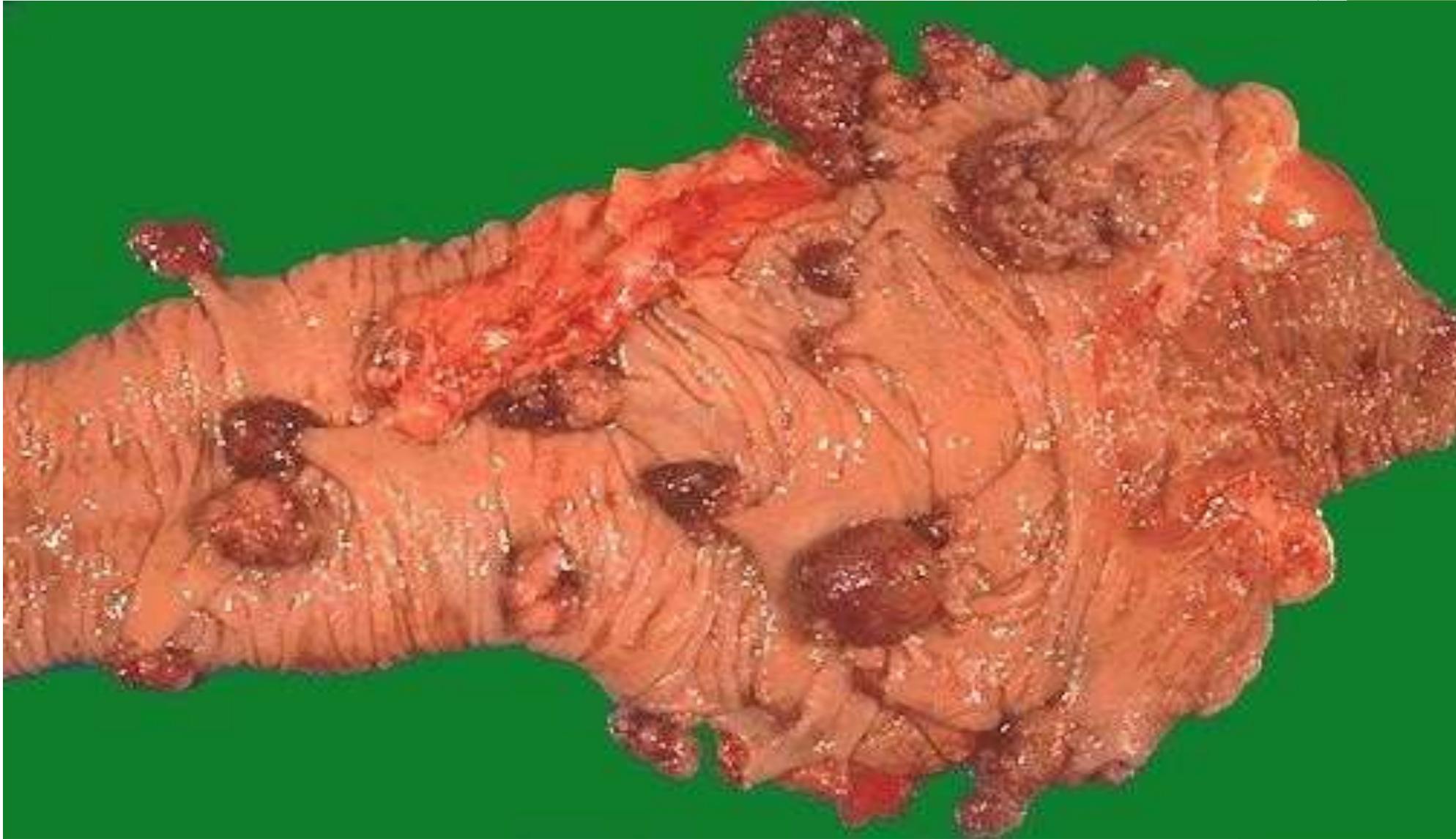


Hereditary Nonpolyposis Colorectal Cancer (HNPCC, *Lynch syndrome*)

- ▶ Clustering of tumors: **Colorectum, endometrium, stomach, ovary, ureters, brain, small bowel, hepatobiliary tract, and skin**
- Colon cancer at younger age than sporadic cancers
- Right colon with excessive mucin production .
- Adenomas are present, BUT POLYPOSIS IS NOT.

- Inherited germ line mutations in DNA mismatch repair genes.
- Accumulation of mutations in *microsatellite DNA (short repeating sequences)*
- Resulting in *microsatellite instability*
- Majority of cases involve either *MSH2* or *MLH1*.

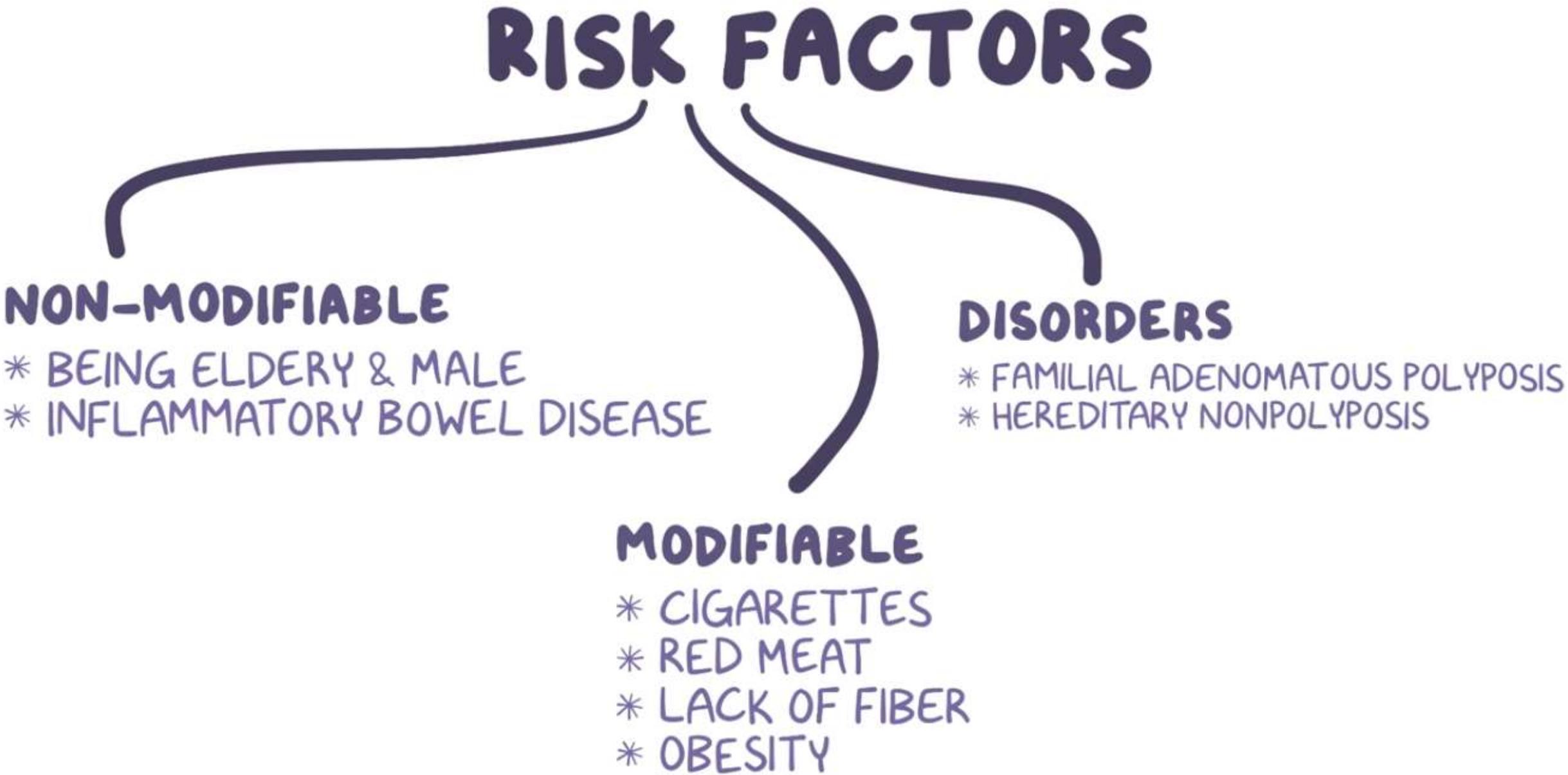
Cecal polyps in HNPCC.



Colonic Adenocarcinoma

- ▶ **Most common malignancy of the gastrointestinal tract**
- Small intestine is uncommonly involved by neoplasia.
- **Peak: 60 to 70 years**
- **20% under 50 years.**
- **Low intake of vegetable fibers and high intake of carbohydrates and fat.**
- **Aspirin or other NSAIDs have a protective effect.**
- **Cyclooxygenase-2 (COX-2) promotes epithelial proliferation.**

RISK FACTORS



NON-MODIFIABLE

- * BEING ELDERLY & MALE
- * INFLAMMATORY BOWEL DISEASE

DISORDERS

- * FAMILIAL ADENOMATOUS POLYPOSIS
- * HEREDITARY NONPOLYPOSIS

MODIFIABLE

- * CIGARETTES
- * RED MEAT
- * LACK OF FIBER
- * OBESITY

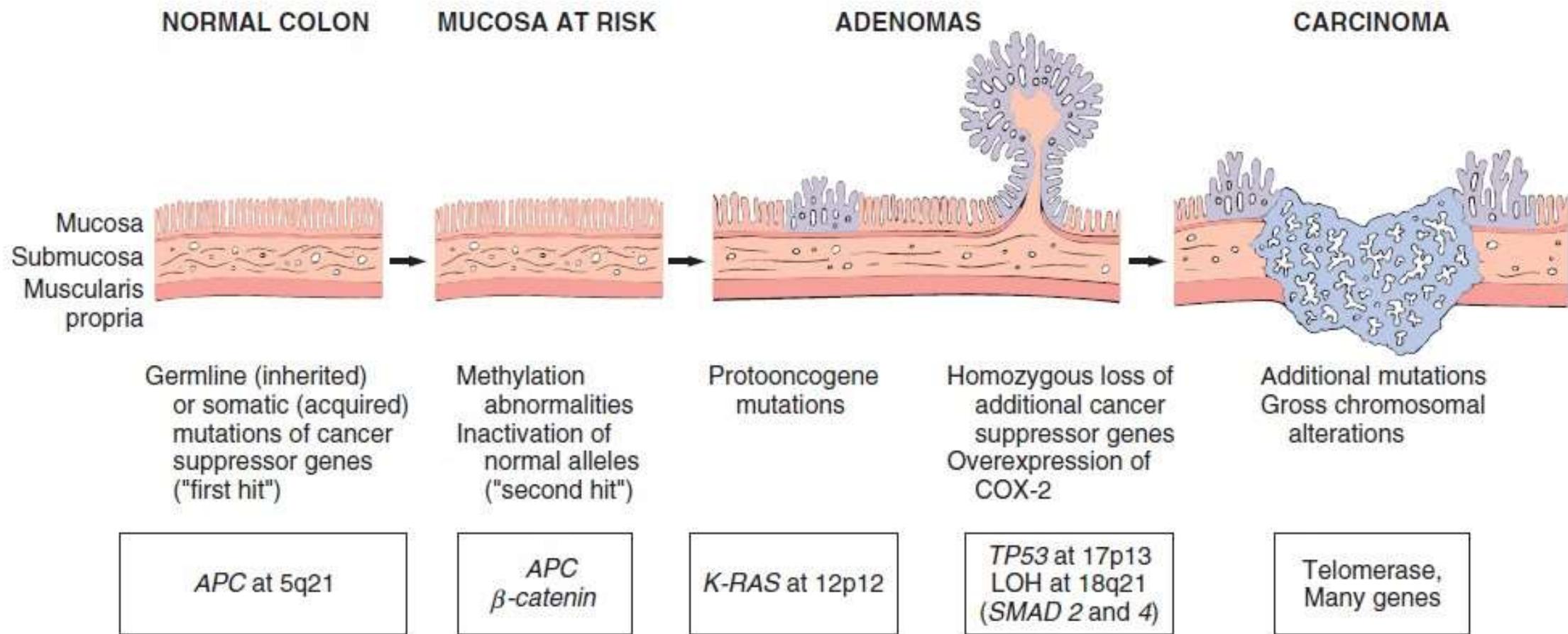
Pathogenesis

- ▶ Sporadic >>>> familial.
- Two pathways:
- **APC/ β -catenin pathway >> increased WNT signaling.**
- **Microsatellite instability pathway >> defects in DNA mismatch repair.**
- Stepwise accumulation of multiple mutations.

The APC / β -catenin pathway: chromosomal instability

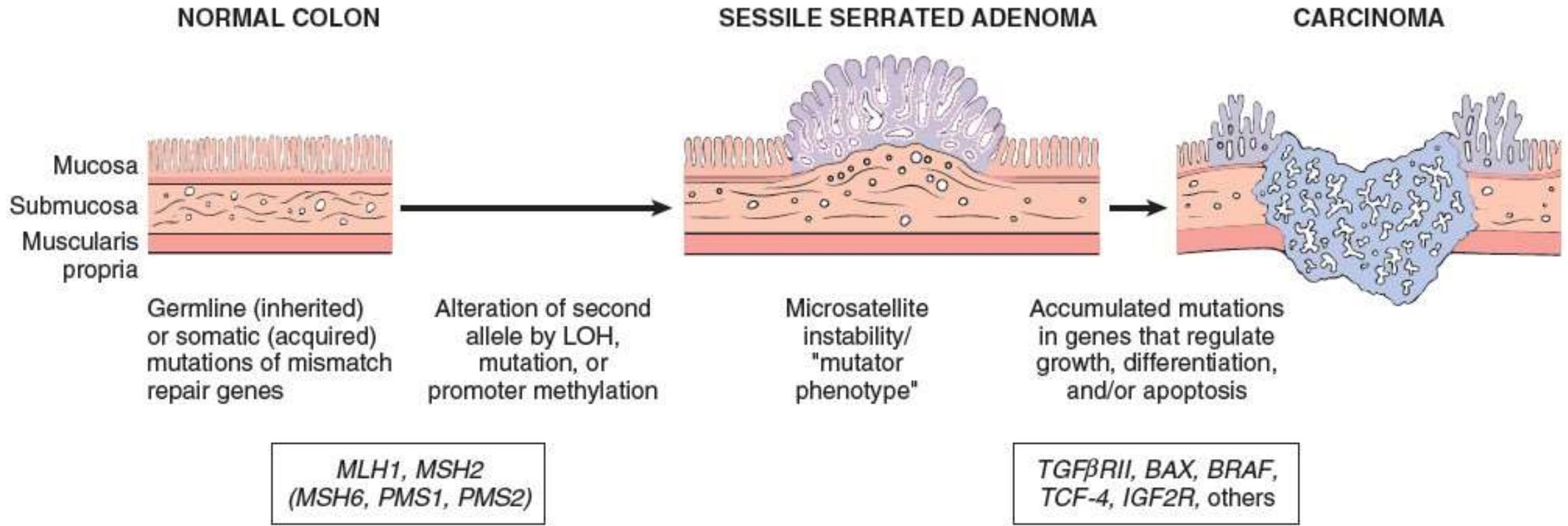
- ▶ **Classic *adenoma carcinoma sequence*.**
- **80% of sporadic colon tumors**
- **Mutation of the *APC* tumor suppressor gene: EARLY EVENT**
- ***APC is a key negative regulator of β -catenin, a component of the WNT signaling pathway.***
- ***Both copies of APC should be inactivated for adenoma to develop (1st and 2nd hits).***

- ▶ *Loss of APC >>> accumulation of B-catenin >> enters nucleus >> MYC and cyclin-D1 transcription >> promote proliferation.*
- *Additional mutations >> activation of KRAS (LATE EVENT) >> inhibits apoptosis.*
- *SMAD2 and SMAD4 mutations (tumor suppressor genes.)*
- **TP53 is mutated in 70% -80% of colon cancers (LATE EVENT IN INVASIVE)**
- **TP53 inactivation mutation**
- **Expression of telomerase also increases as the tumor advances.**



The microsatellite instability pathway

- ▶ DNA mismatch repair deficiency
 - Loss of mismatch repair genes
 - Mutations accumulate in microsatellite repeats
 - *Microsatellite instability*
- Silent if microsatellites located in noncoding regions
- Uncontrolled cell growth if located in coding or promoter regions of genes involved in cell growth and apoptosis (TGF-B and BAX genes)

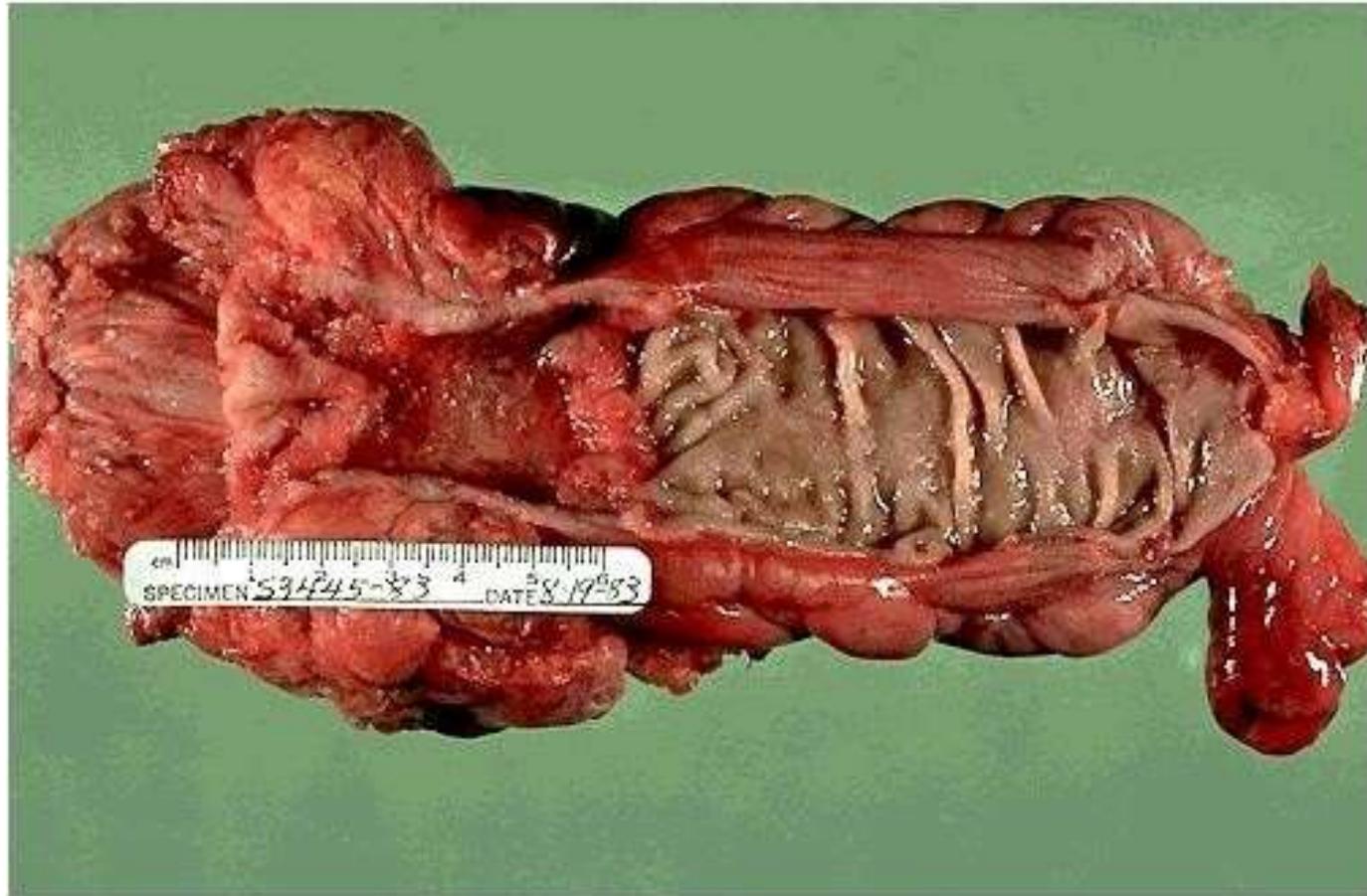


Etiology	Molecular Defect	Target Gene(s)	Transmission	Predominant Site(s)	Histology
Familial adenomatous polyposis (70% of FAP)	APC/WNT pathway	<i>APC</i>	Autosomal dominant	None	Tubular, villous; typical adenocarcinoma
Hereditary nonpolyposis colorectal cancer	DNA mismatch repair	<i>MSH2, MLH1</i>	Autosomal dominant	Right side	Sessile serrated adenoma; mucinous adenocarcinoma
Sporadic colon cancer (80%)	APC/WNT pathway	<i>APC</i>	None	Left side	Tubular, villous; typical adenocarcinoma
Sporadic colon cancer (10%–15%)	DNA mismatch repair	<i>MSH2, MLH1</i>	None	Right side	Sessile serrated adenoma; mucinous adenocarcinoma

MORPHOLOGY

- ▶ Proximal colon tumors: polypoid, exophytic masses
- Proximal colon: rarely cause obstruction.
- Distal colon: annular lesions “napkin ring” constrictions & narrowing
- Tall columnar cells of dysplastic epithelium forming GLANDS with strong desmoplastic response.
- Necrotic debris are typical.
- Some tumors give abundant mucin.
- Some form signet ring cells.

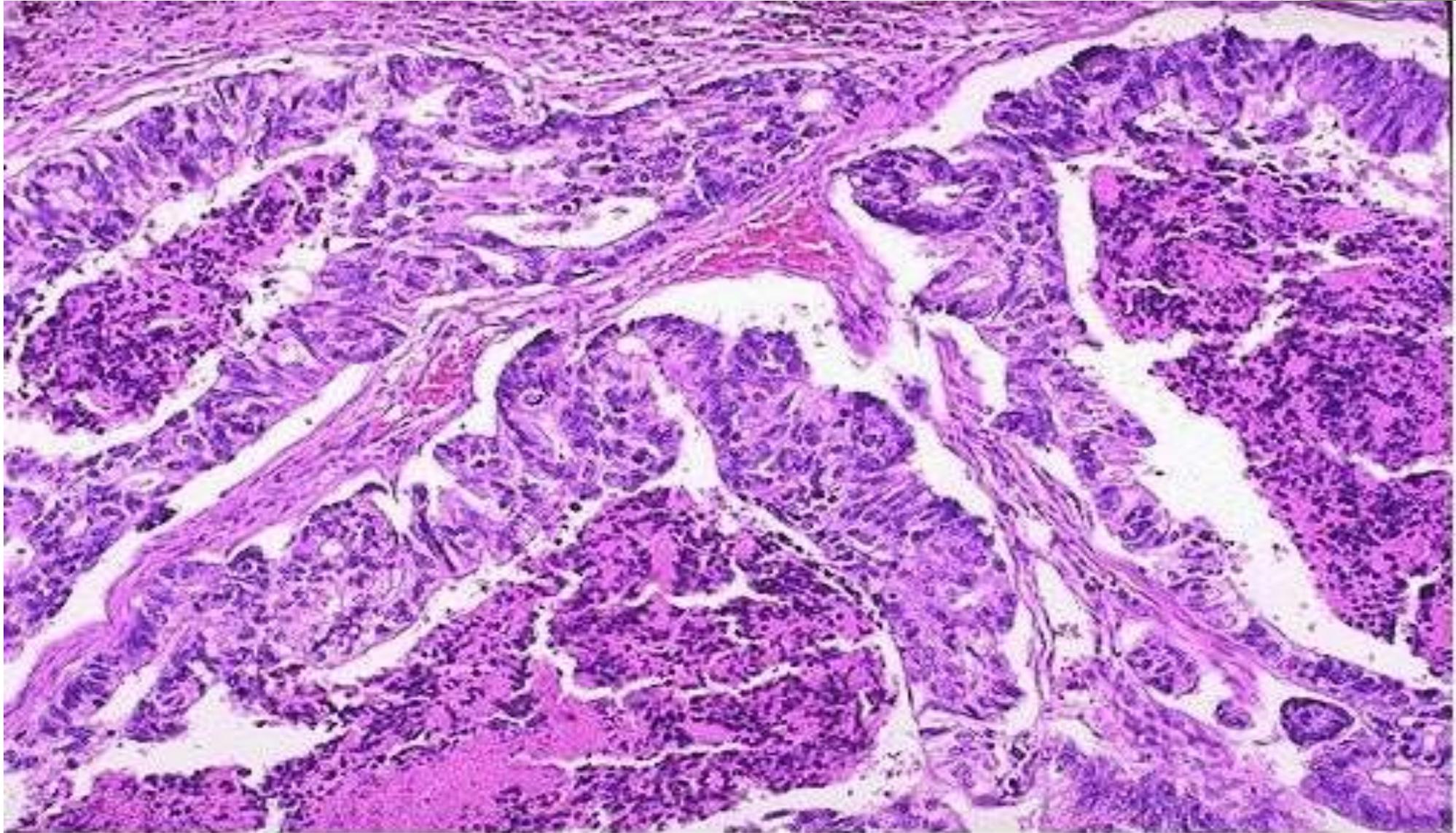
Rectosigmoid adenocarcinoma, napkin ring

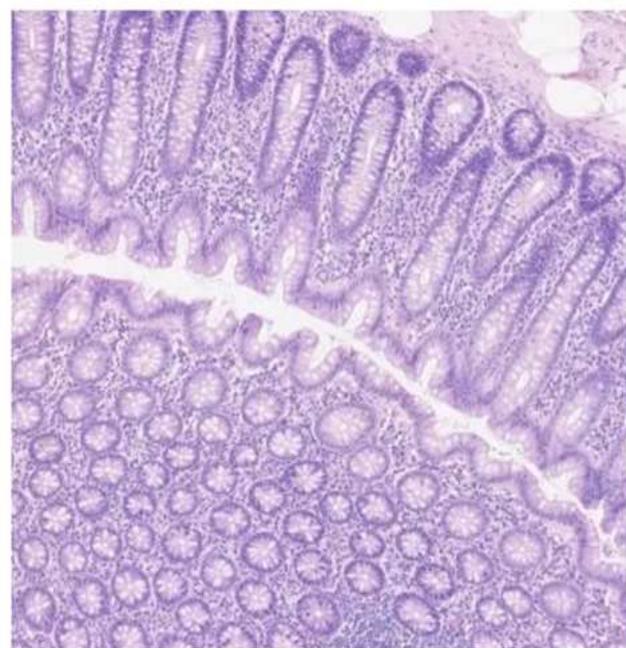


Exophytic adenocarcinoma

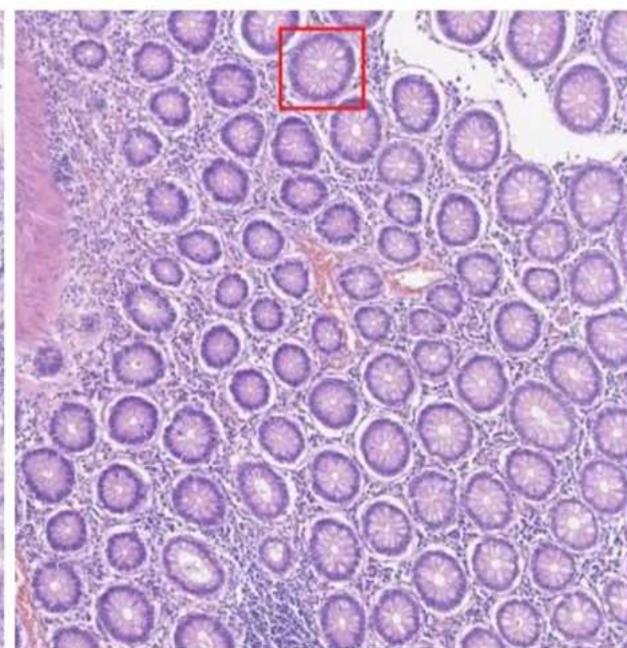


Adenocarcinoma with necrosis

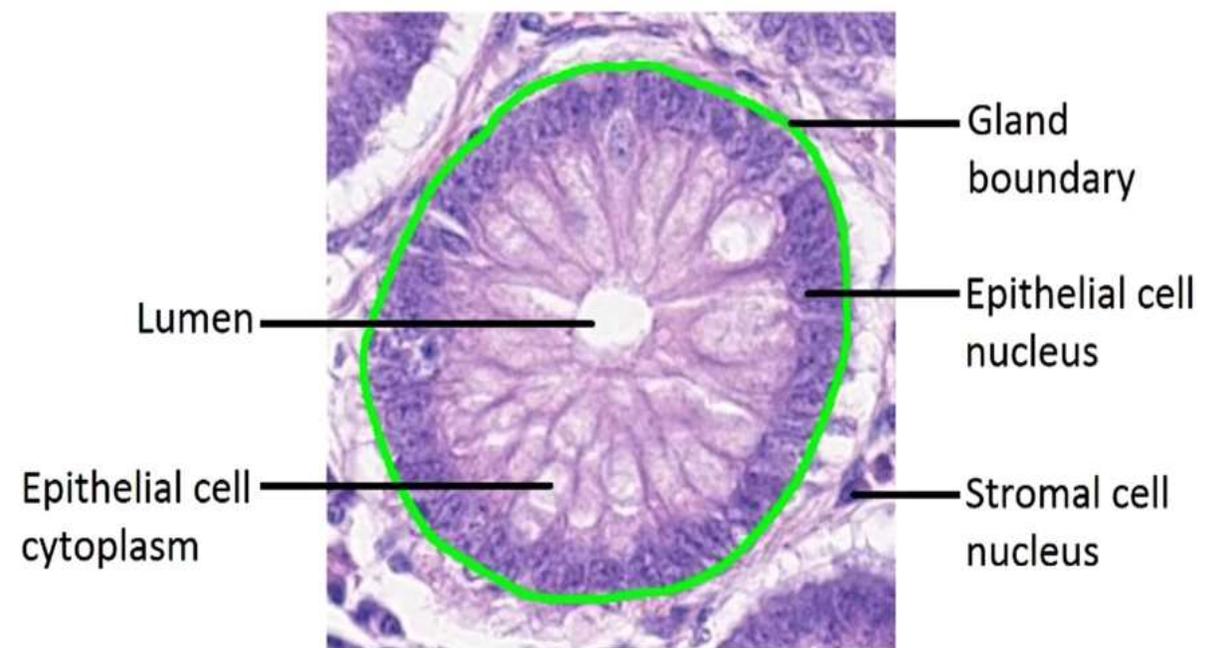




(a)



(b)



Lumen

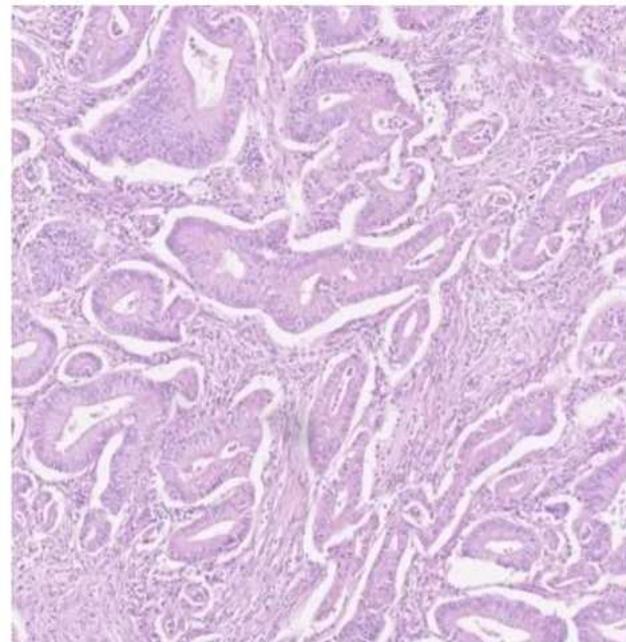
Epithelial cell
cytoplasm

Gland
boundary

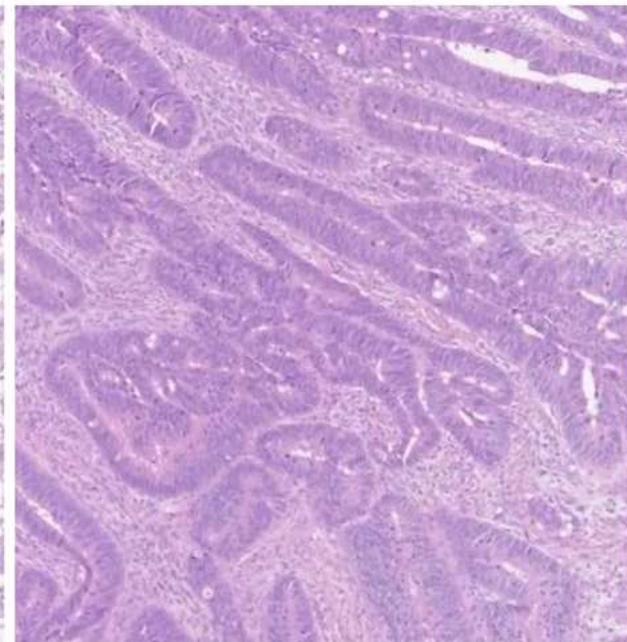
Epithelial cell
nucleus

Stromal cell
nucleus

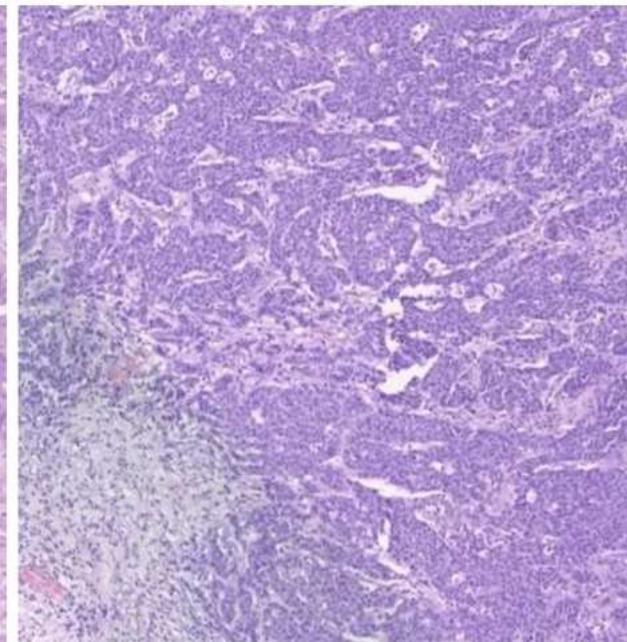
(c)



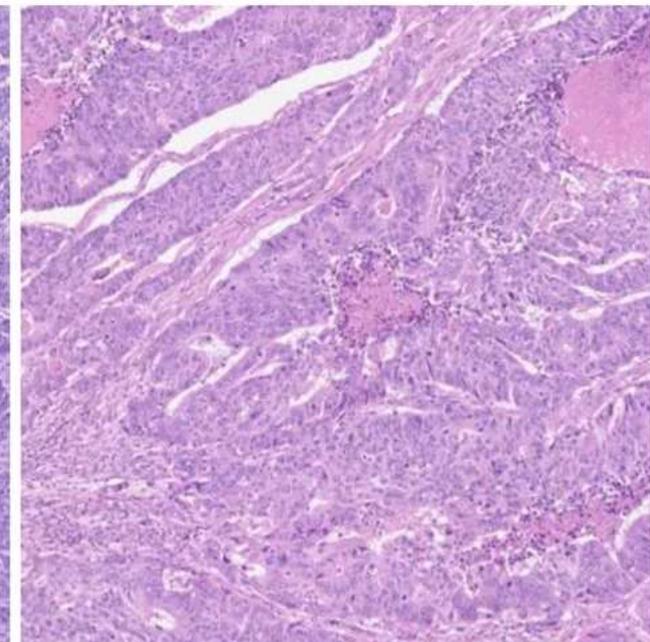
(d)



(e)



(f)



(g)

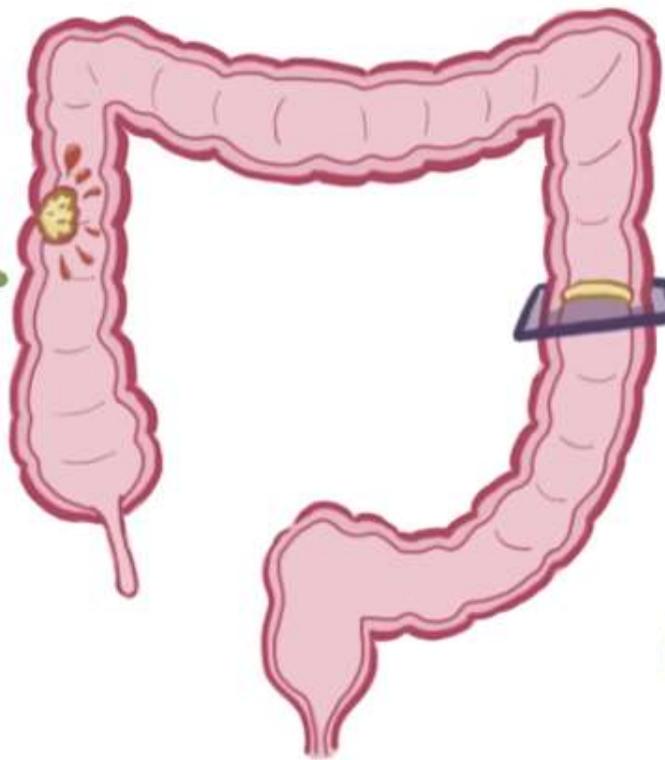
Clinical Features

- ▶ Endoscopic screening >> cancer prevention
- Early cancer is asymptomatic !!!!!!!
- Cecal and right side cancers: *Fatigue and weakness (iron deficiency anemia)*
- **Iron-deficiency anemia in an older male or postmenopausal female is gastrointestinal cancer until proven otherwise.**
- *Left sided carcinomas: occult bleeding, changes in bowel habits, cramping left lower-quadrant discomfort.*

SYMPTOMS

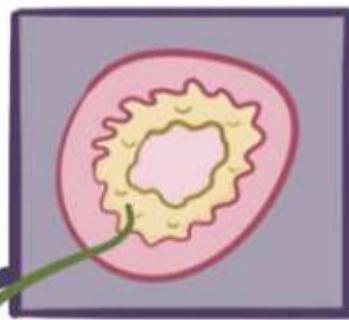
ASCENDING

- * GROW BEYOND MUCOSA
 - ↳ PAIN & WEIGHT LOSS
- * NO BOWEL OBSTRUCTION
 - ↳ GROWS LARGE
 - ↳ LATE DIAGNOSIS
- * CAN ULCERATE & BLEED
 - ↳ ANEMIA



DESCENDING

- * INFILTRATING MASSES
 - ↳ RING-SHAPED



- * LUMEN NARROWING (NAPKIN-RING CONSTRICTION)
 - ↳ PAIN
 - ↳ HEMATOCHEZIA

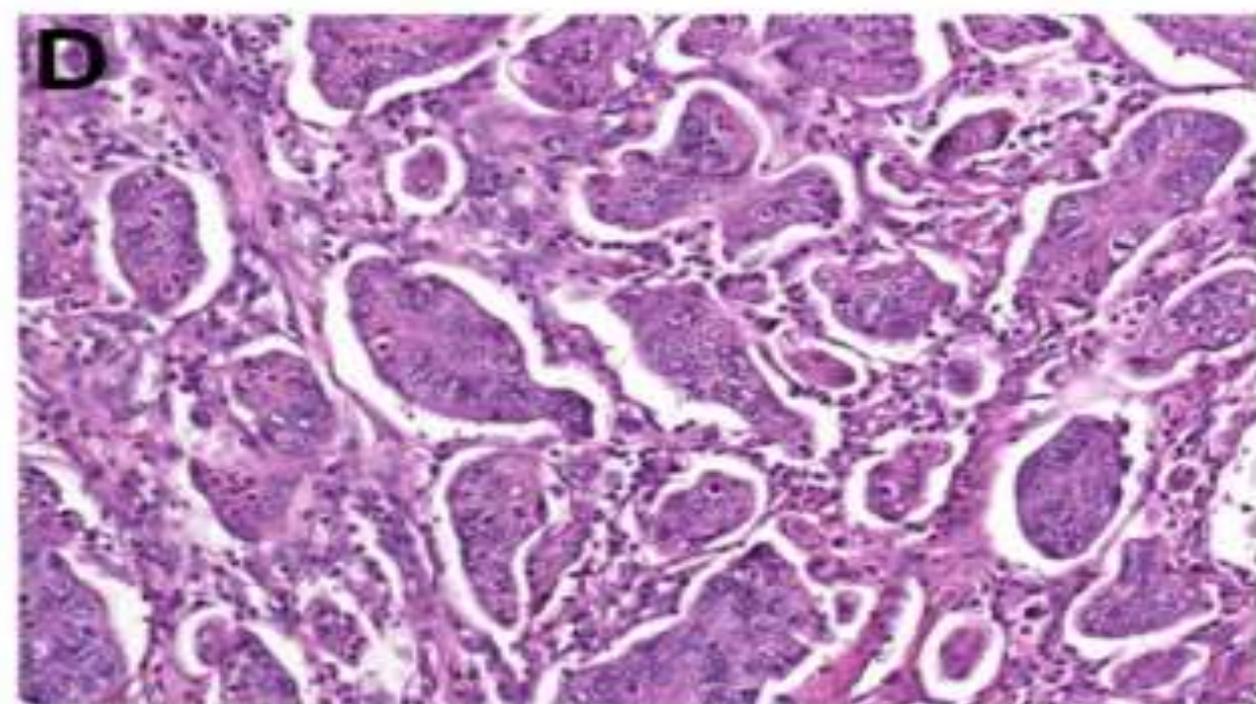
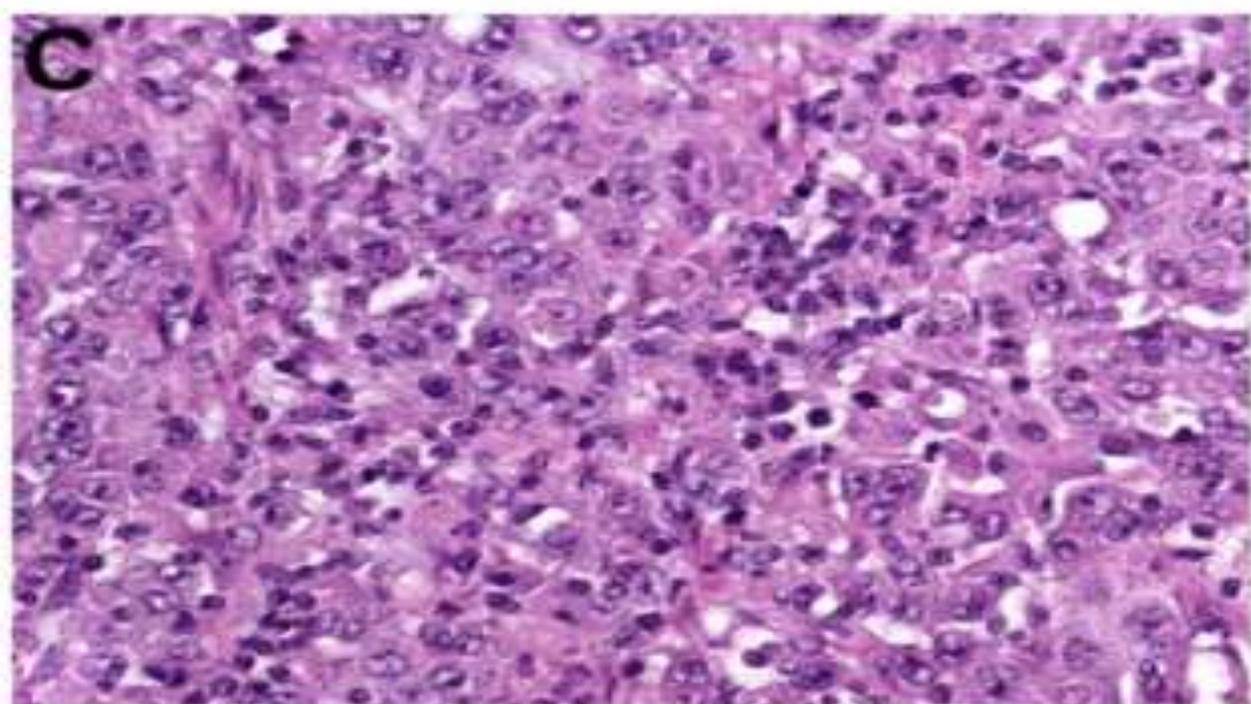
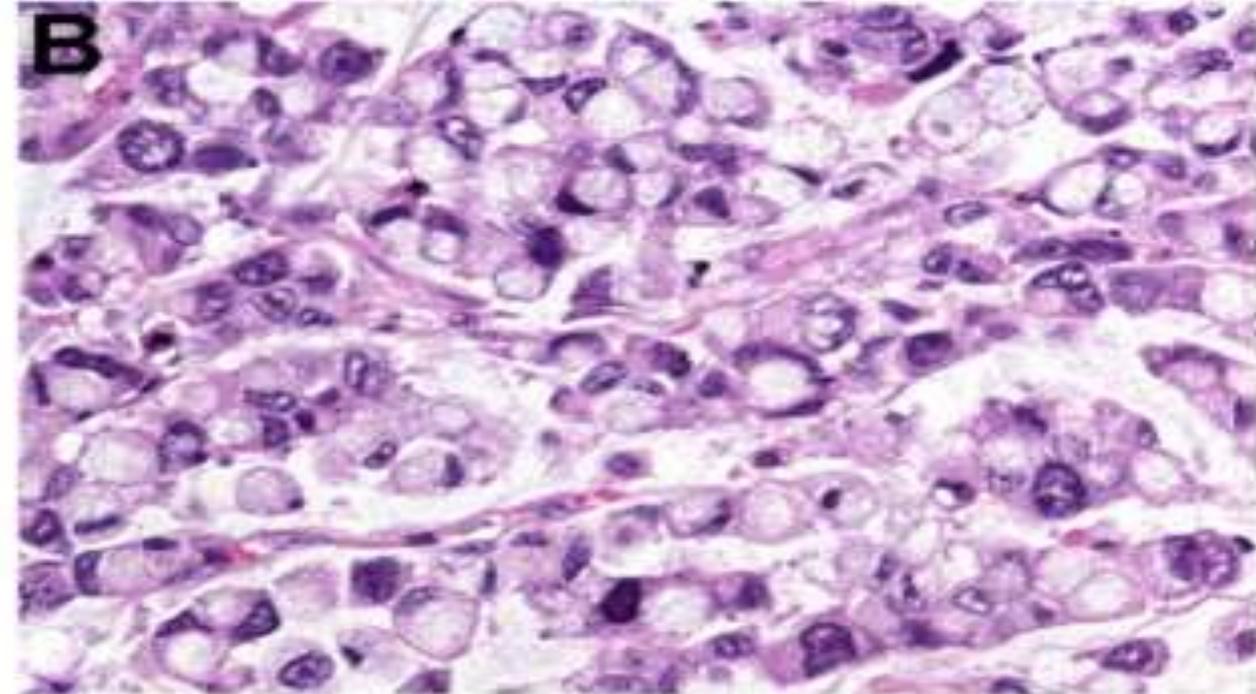
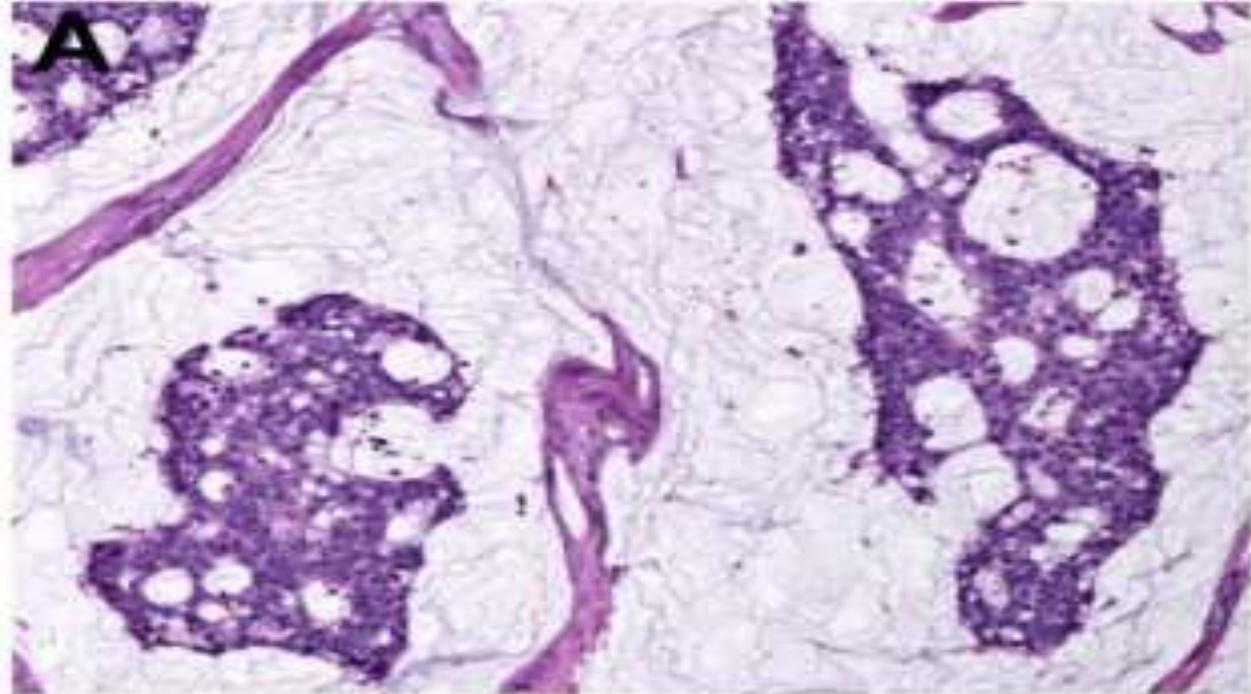
▶ **Poor differentiation and mucinous histology >> poor prognosis**

□ ***Most important two prognostic factors are***

□ ***Depth of invasion***

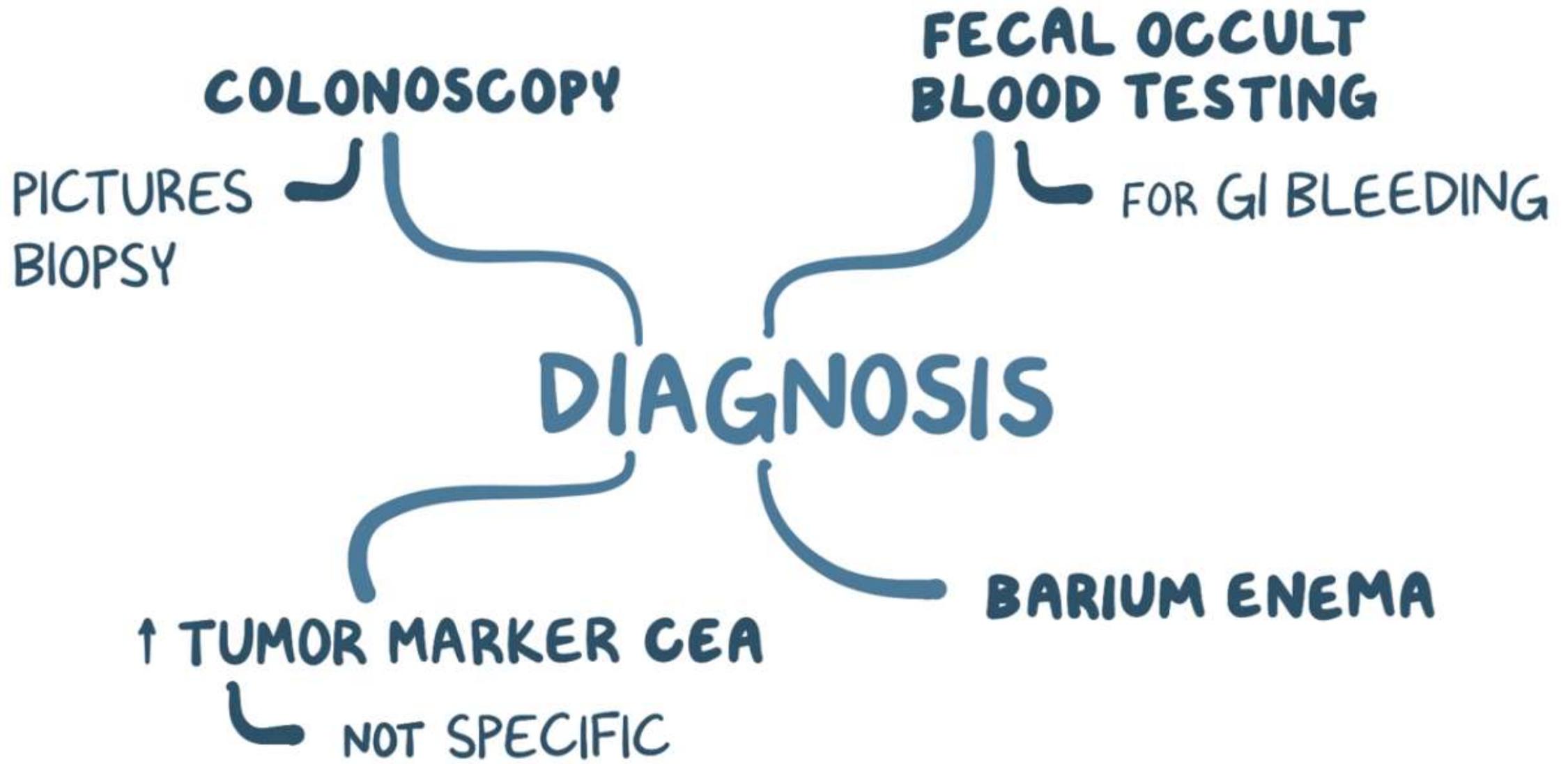
□ ***Lymph node metastasis.***

▶ ***Distant metastases (lung and liver) can be resected.***



Liver metastasis.





Appendix

- ▶ Normal true diverticulum of the cecum

- ▶ **ACUTE APPENDICITIS**

- **TUMORS OF THE APPENDIX**

ACUTE APPENDICITIS

- ▶ **Most common in adolescents and young adults.**
- **May occur in any age.**
- **Difficult to confirm preoperatively**

- ▶ **DDx:**
- **Mesenteric lymphadenitis,**
- **Acute salpingitis,**
- **Ectopic pregnancy,**
- **Mittelschmerz (pain associated with ovulation),**
- **Meckel diverticulitis.**

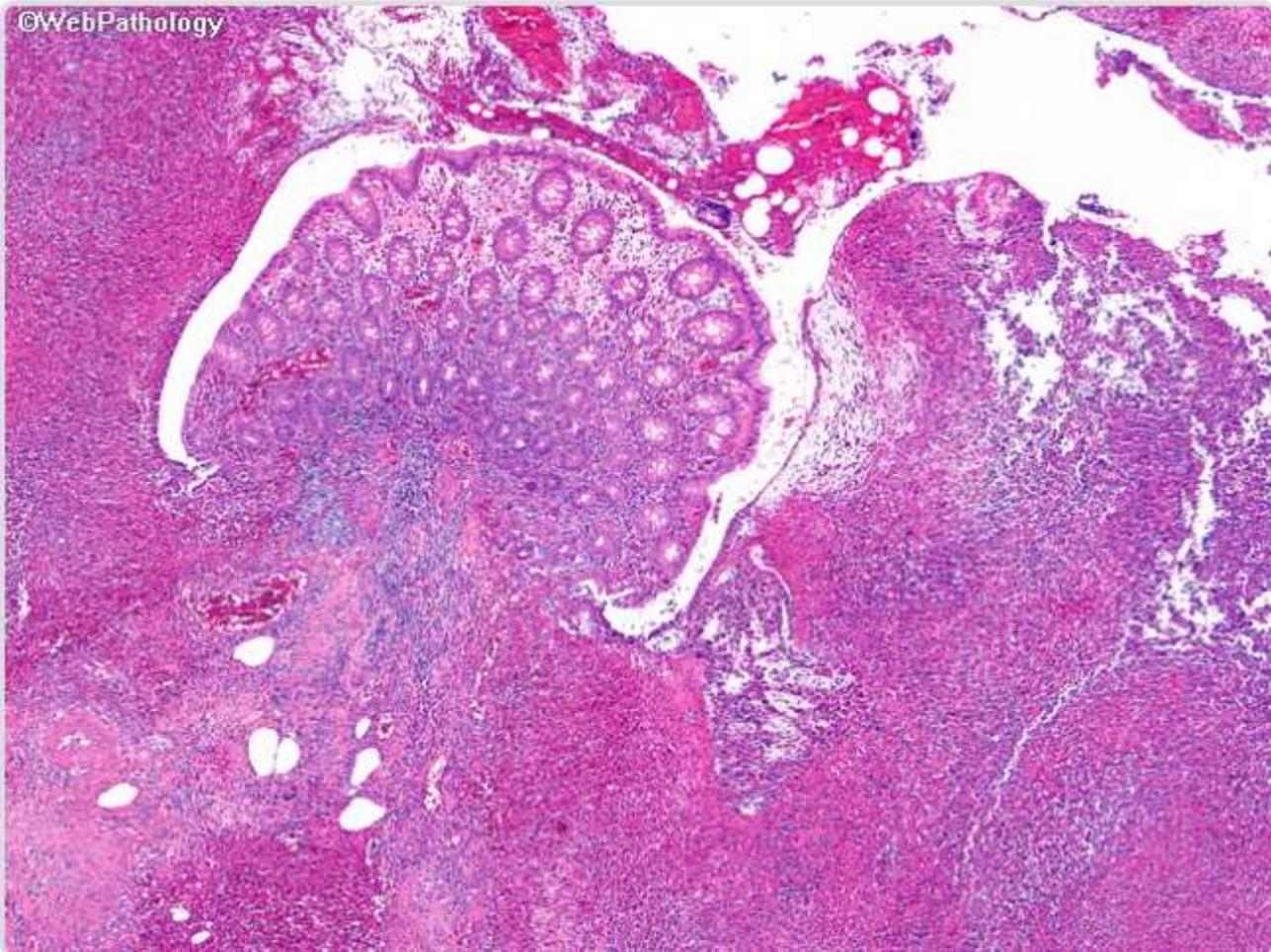
- ▶ Luminal obstruction in 50-80% of cases >> increased luminal pressure >> impaired venous drainage >> ischemic injury & stasis associated bacterial proliferation >>> inflammatory response rich in neutrophils & edema.
- ▶ *Obstruction by fecalith (A **fecalith** is a stone made of feces), less commonly : gallstone, tumor, worms....*
- ▶ Diagnosis requires neutrophilic infiltration of the muscularis propria
- ▶ **Acute suppurative appendicitis >> more severe >> focal abscess formation.**
- ▶ **Acute gangrenous appendicitis >> necrosis and ulceration.**



HÔPITAL
SAINTE-JUSTINE



1 cm



Clinical Features

- ▶ Early acute appendicitis: periumbilical pain
- ▶ Later: pain localizes to the right lower quadrant,
- ▶ Nausea, vomiting, low-grade fever, mildly leukocytosis.
- ▶ A classic physical finding is *McBurney's sign* (McBurney's point).
- ▶ Signs and symptoms are often absent, creating difficulty in clinical diagnosis.

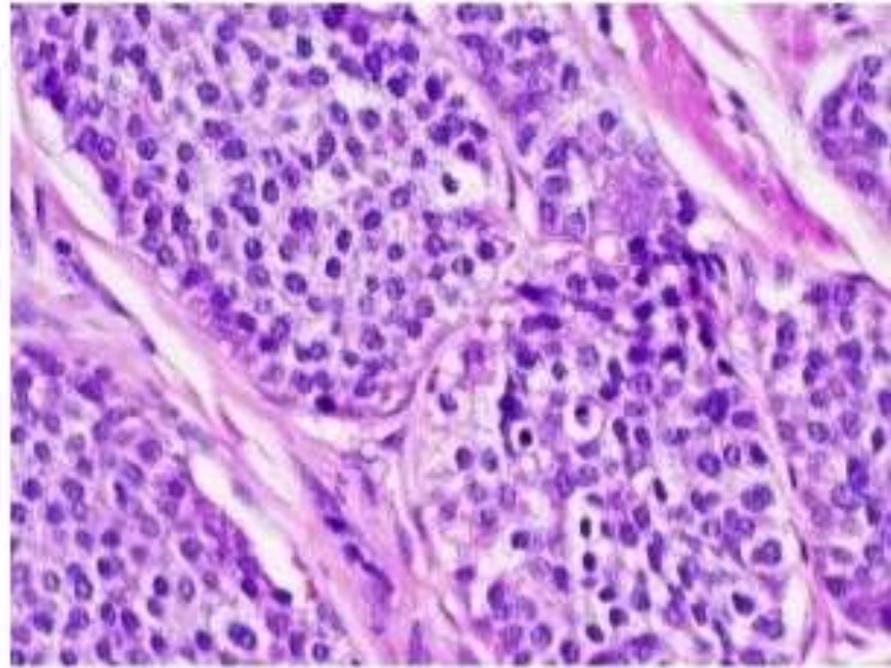
TUMORS OF THE APPENDIX

- ▶ **The most common tumor: *carcinoid* (neuroendocrine tumor)**
- ▶ Incidentally found during surgery or on examination of a resected appendix
- ▶ Distal tip of the appendix
- ▶ Nodal metastases & distant spread are rare.

Carcinoid tumor



Gross



Microscopic