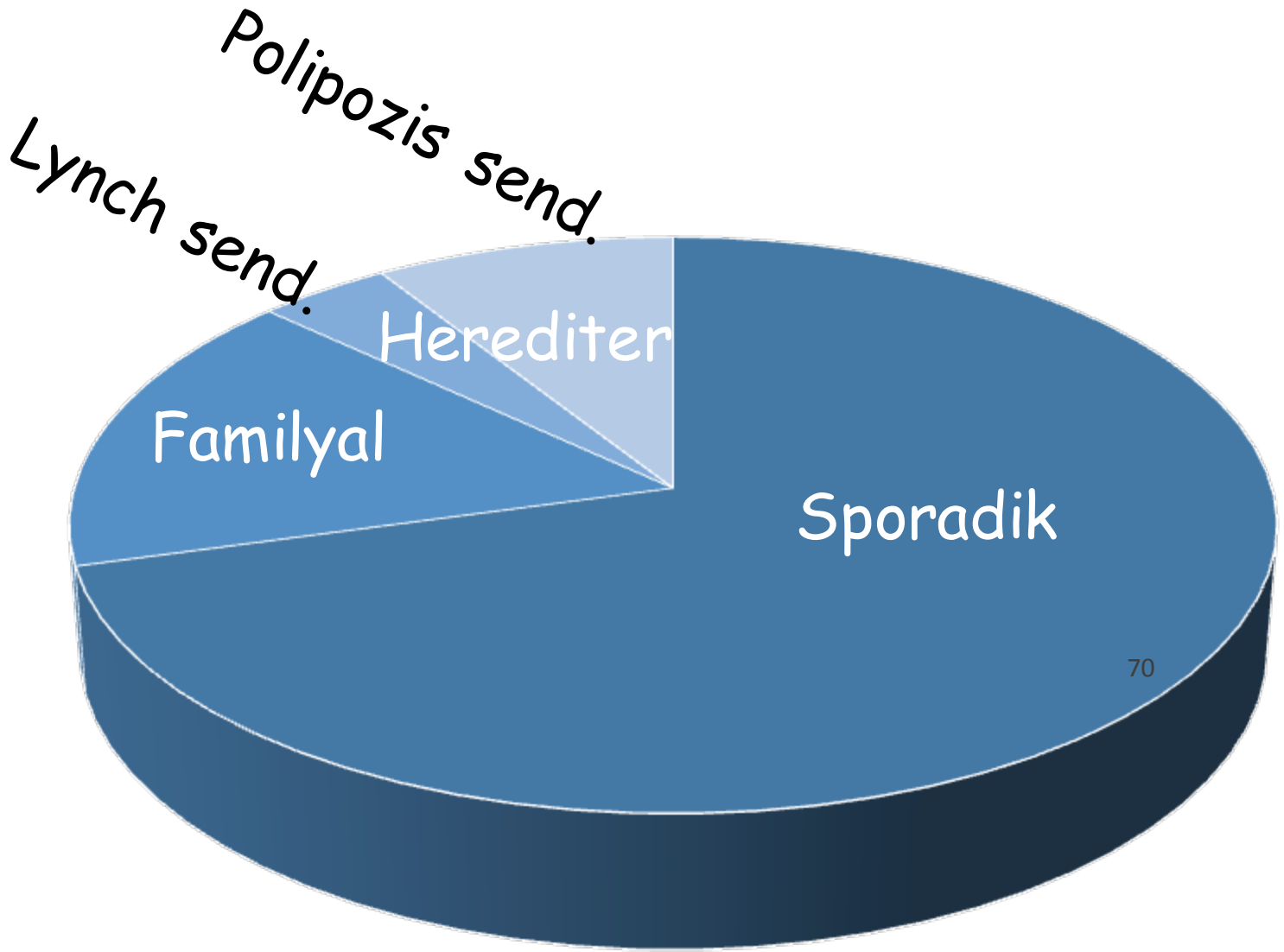
Herediter Kanser ve Polipozis sendromları: Alt GİS

Arzu Ensari
AÜTF Patoloji ABD


Polipozis send.
Lynch send.
Herediter
Familyal
Sporadik


Blue Cruise
Aegean Cruise
Mandalya Bay
AEGEAN SEA
BODRUM
Çökertme Bay
Kargılı Bükü
Oraklar
Cleopadra's Island
SÖĞÜT
Tuzla
İngiliz Limanı
MARMARİS
KOS
Gökova Bay
Kütrü
Seven Islands
Salimiye
DATÇA
Turunç
Cnidos
Palamut
Aktur
Çiftlik
Simi
Bozukkale
N
W
E
S
Mediterranean Sea

- Ender (<%1 yeni tanı GI kanser)
- Otozomal dominant (MAP-otozomal resesif)
- Yüksek GI ve ekstra-GI kanser riski
- Polip tipinde çeşitlilik
- Fenotipik «overlap»
- Klasifikasyon
  - polip tipi, prezentasyon yaşı, GI dağılımı, polip sayısı, ekstraintestinal bulgulara göre yapılır
- Ekstra-GI semptomlar
  - Konjenital retinal hipertrofi, osteoma, perioral pigmentasyon, multipl epidermoid kist, multipl subkutanöz lipoma, sebase gland tm, medulloblastoma & hepatoblastoma

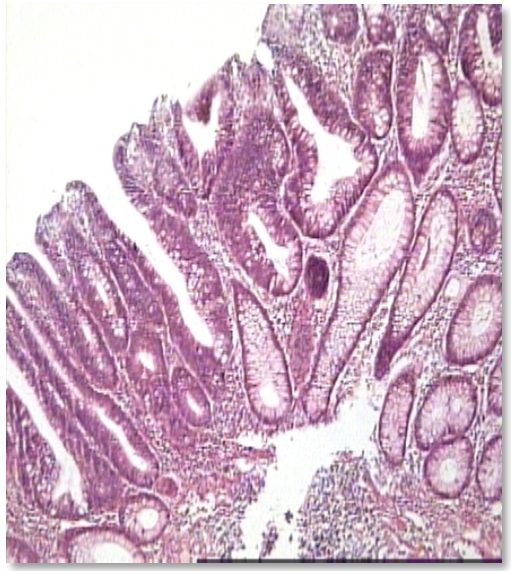
Polip tipleri:

- Adenomatöz polip
- Hamartomatöz polip
  - Peutz-Jeghers polibi
  - Juvenil polip
- Hiperplastik polip
- Serrated polip
  - Sessil «serrated» adenoma/polip/lezyon
  - Traditional serrated adenoma
- Inflamatuar polip
- Ganglionöromatöz/ lipomatöz polip

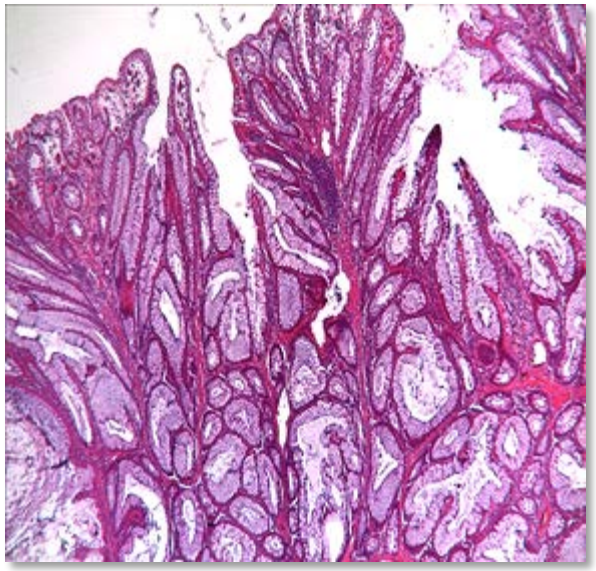
Polipozis Sendromları

Herediter Polipozis Sendromları

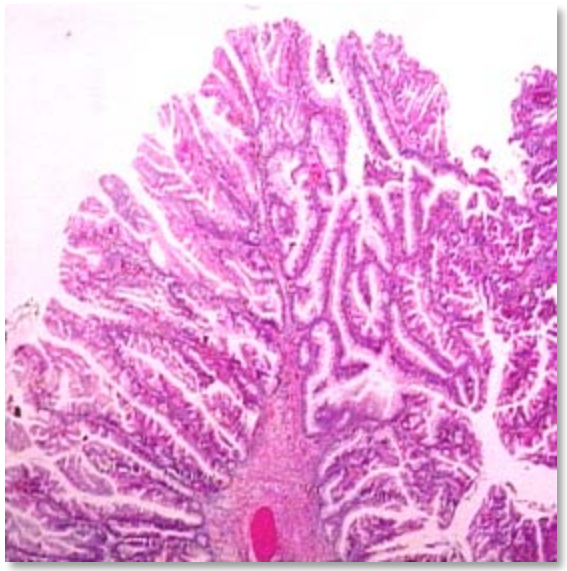
Adenomatöz Polipozis Sendromları



Hamartomatöz Polipozis Sendromları



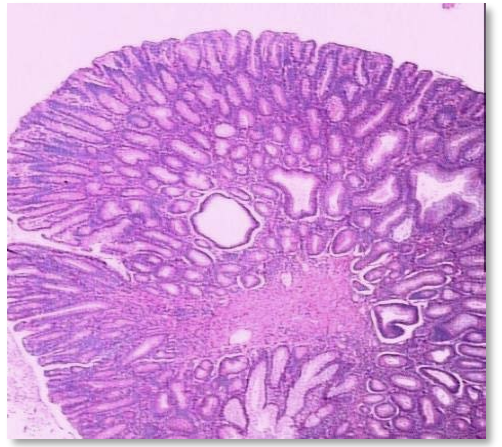
Non-herediter Polipozis Sendromları



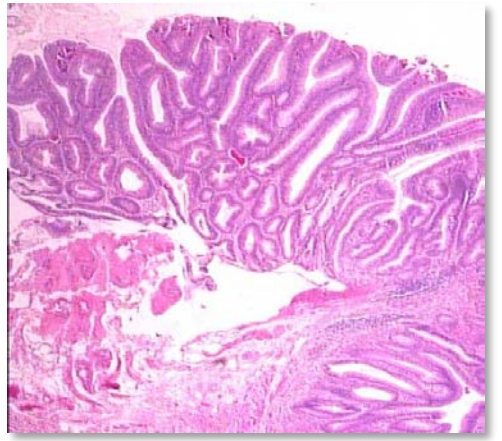
Adenomatöz Polipozis Sendromları

- FAP
  - Gardner
  - Turcot
  - Attenue FAP (AFAP)
- MAP (MUTYH Polipozis)
- Lynch
- Muir-Torre

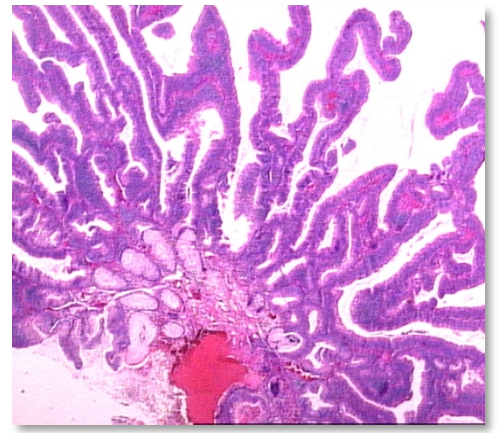
Tubuler adenoma



Tubulovillöz adenoma



Villöz adenoma



FAP ve FAP-assosiye polipozis sendromları

- 1:5000-1:10000
- >100 adenomatöz polip

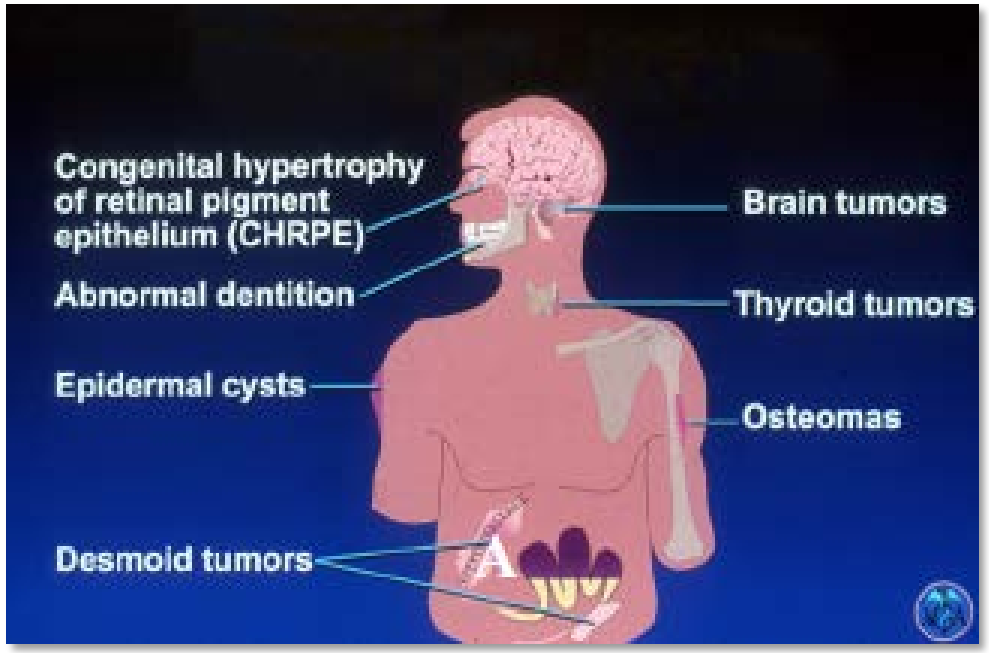
(AFAP dışında!)

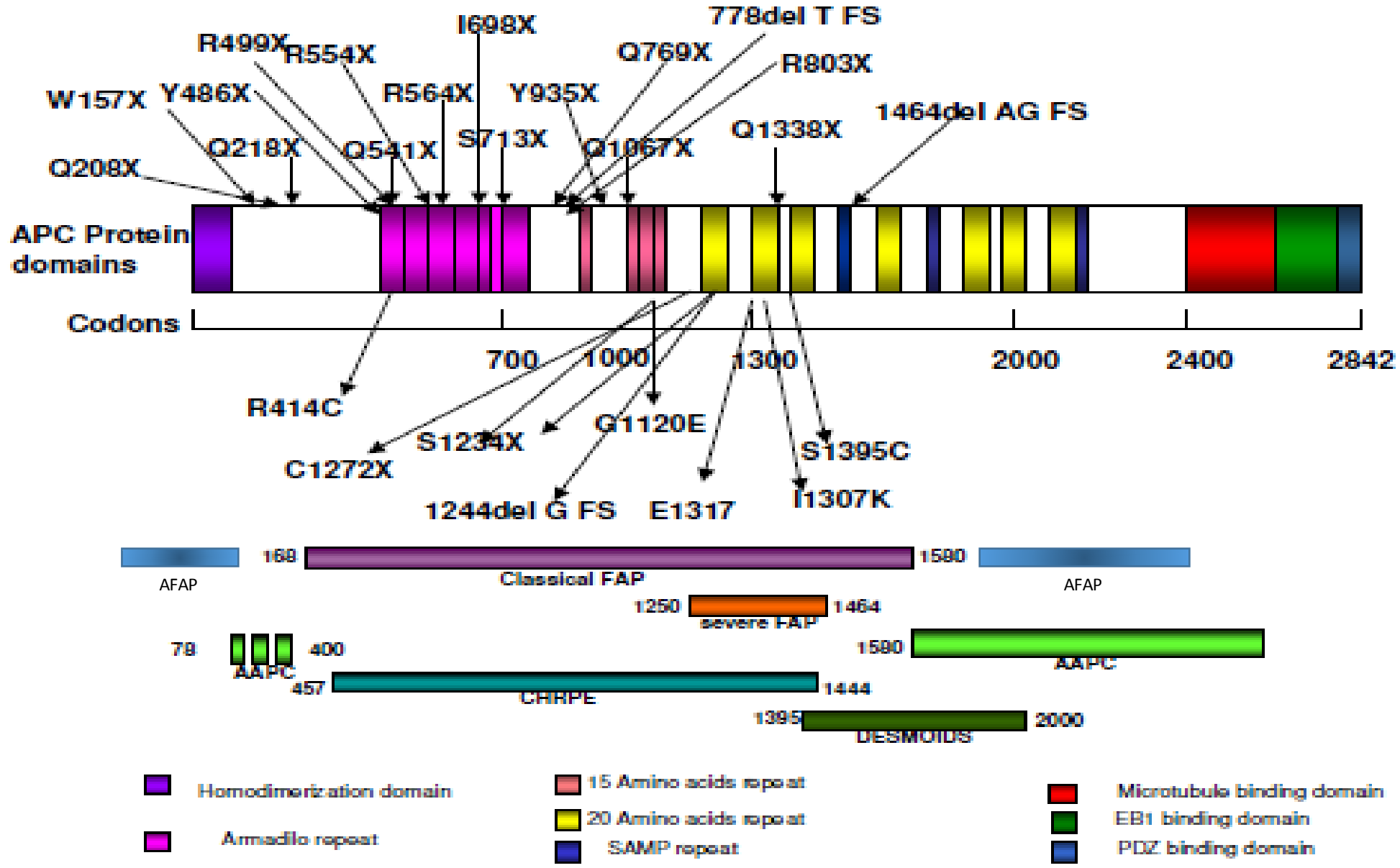
- Kolorektum > mide & ince barsak

(AFAP'da polipler proksimal kolonda ve üst GİS tutulumu daha sık)

- Germline APC mutasyonları
- Tumör supresör gen - 5q21
- Mutasyon bölgesi - fenotip

- Gardner ve Turcot sendromları ekstra GI semptomlara göre ayrılırlar

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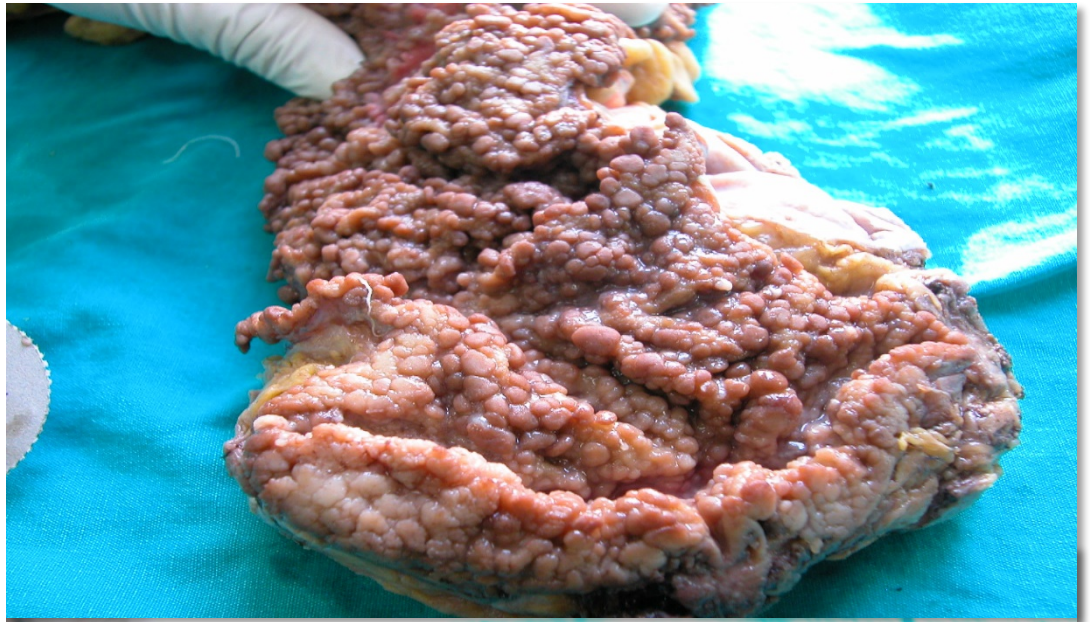
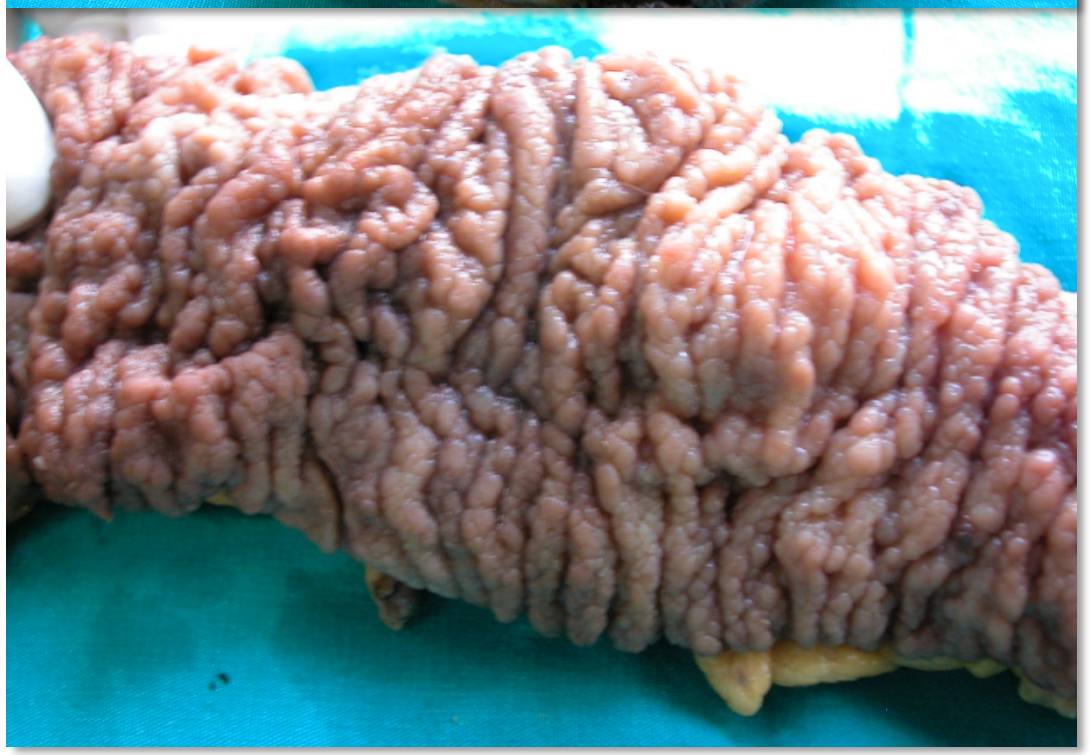
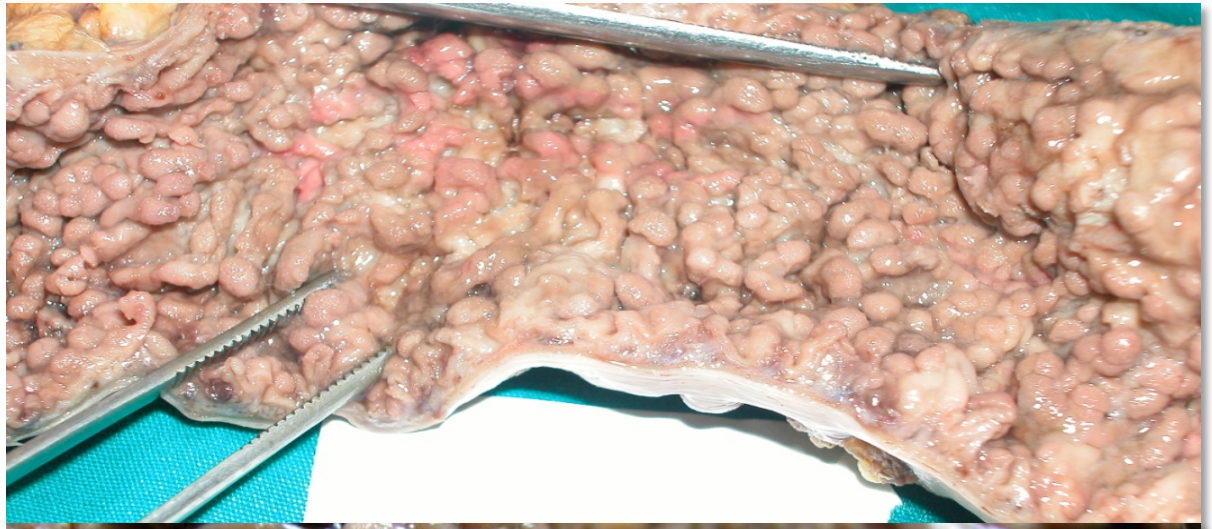
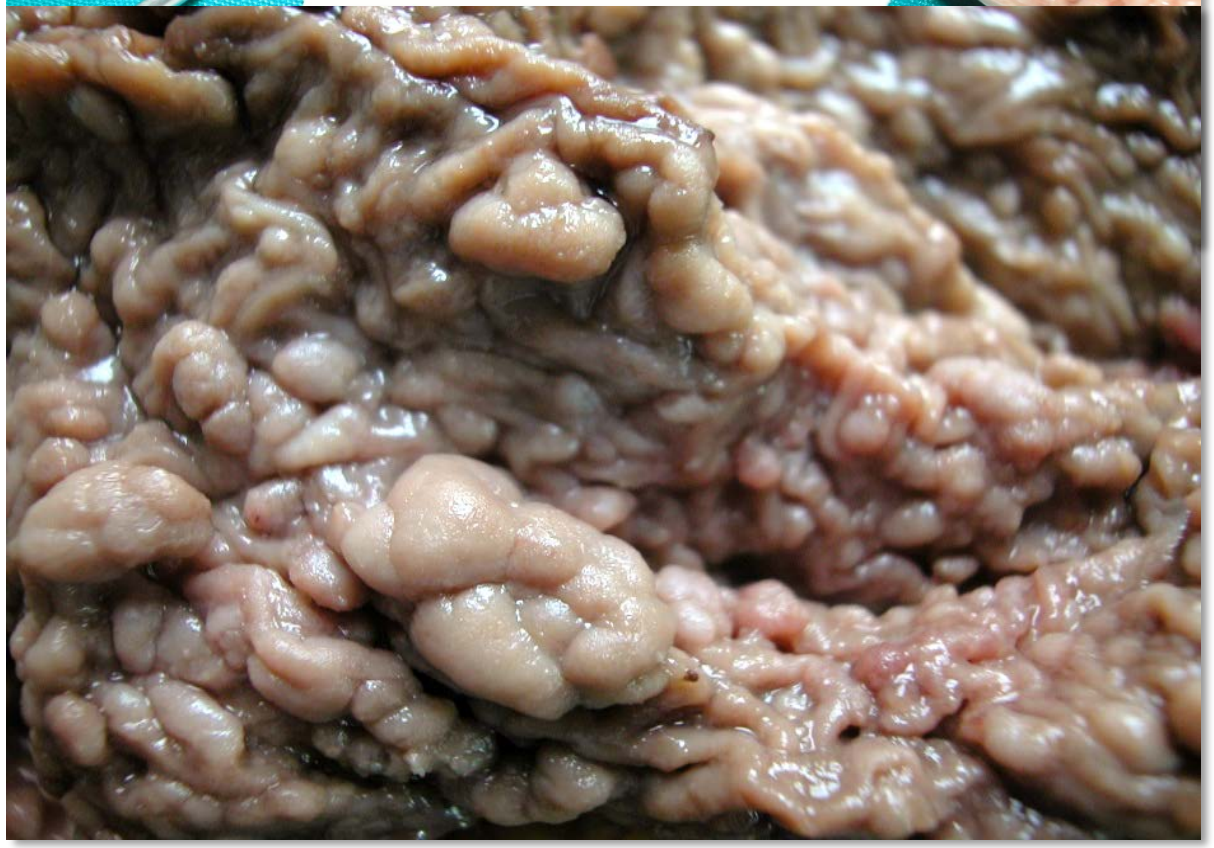
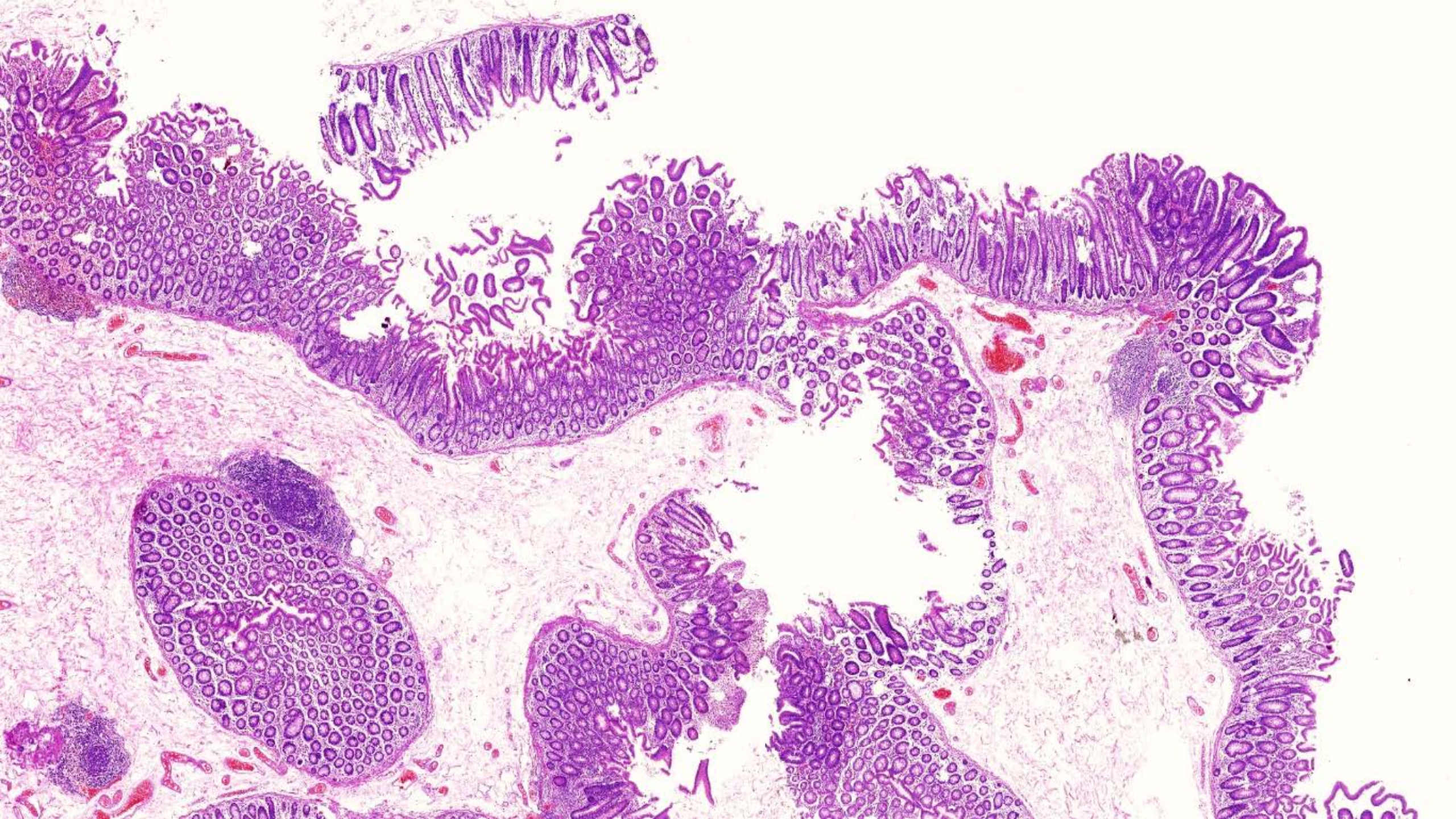
R499X
R554X
Q769X
R803X
W157X
Y486X
R564X
Y935X
1464del AG FS
Q1338X
S713X
Q218X
Q541X
Q1067X
Q208X
APC Protein domains
Codons
700
1000
1300
2000
2400
2842
R414C
S1234X
G1120E
S1395C
C1272X
1244del G FS
E1317
I1307K
169
AFAP
Classical FAP
1590
AFAP
1250
severe FAP
1464
78
400
AAPC
1590
AAPC
457
CRRPE
1444
1395
DESMOIDS
2000
Homodimerization domain
Armadillo repeat
15 Amino acids repeat
20 Amino acids repeat
SAMP repeat
Microtubule binding domain
EB1 binding domain
PDZ binding domain

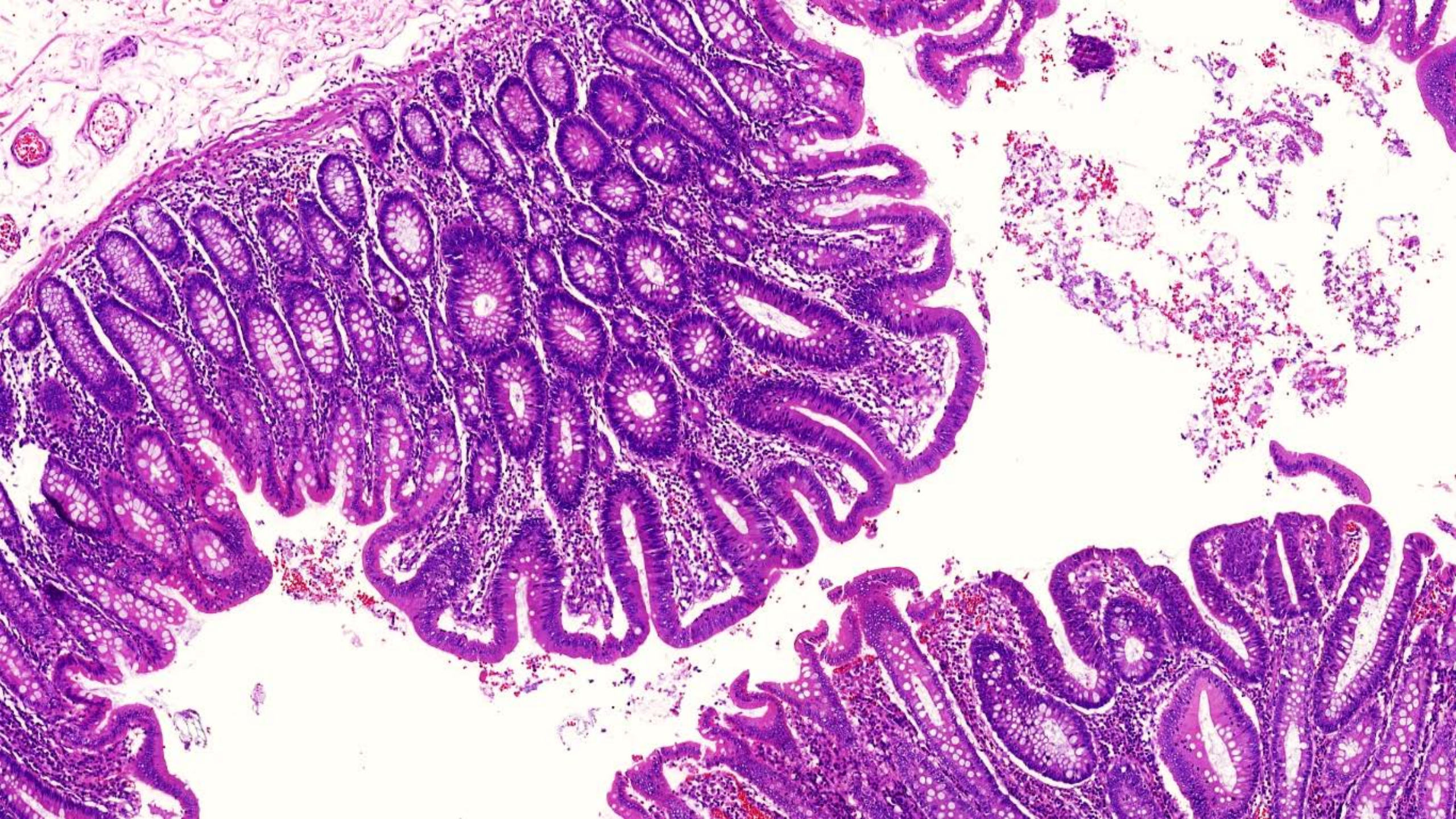












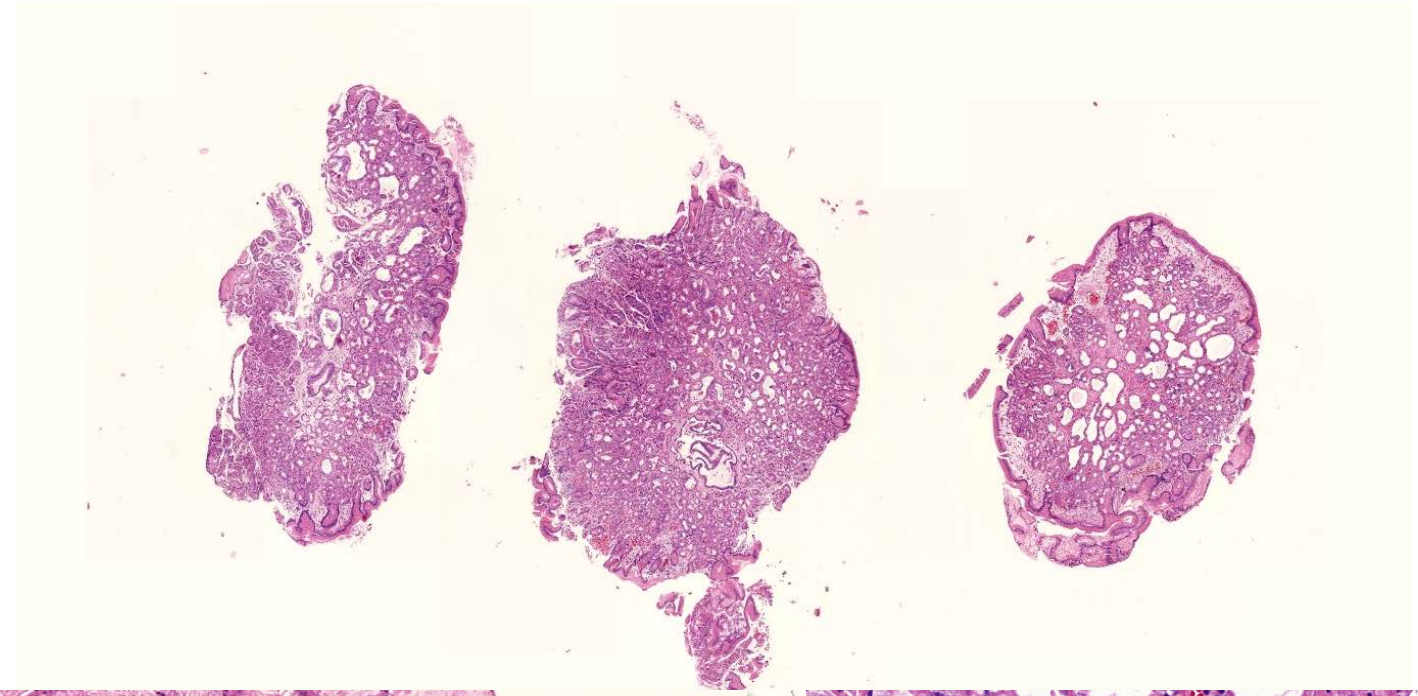
FAP - Üst GİS polipleri

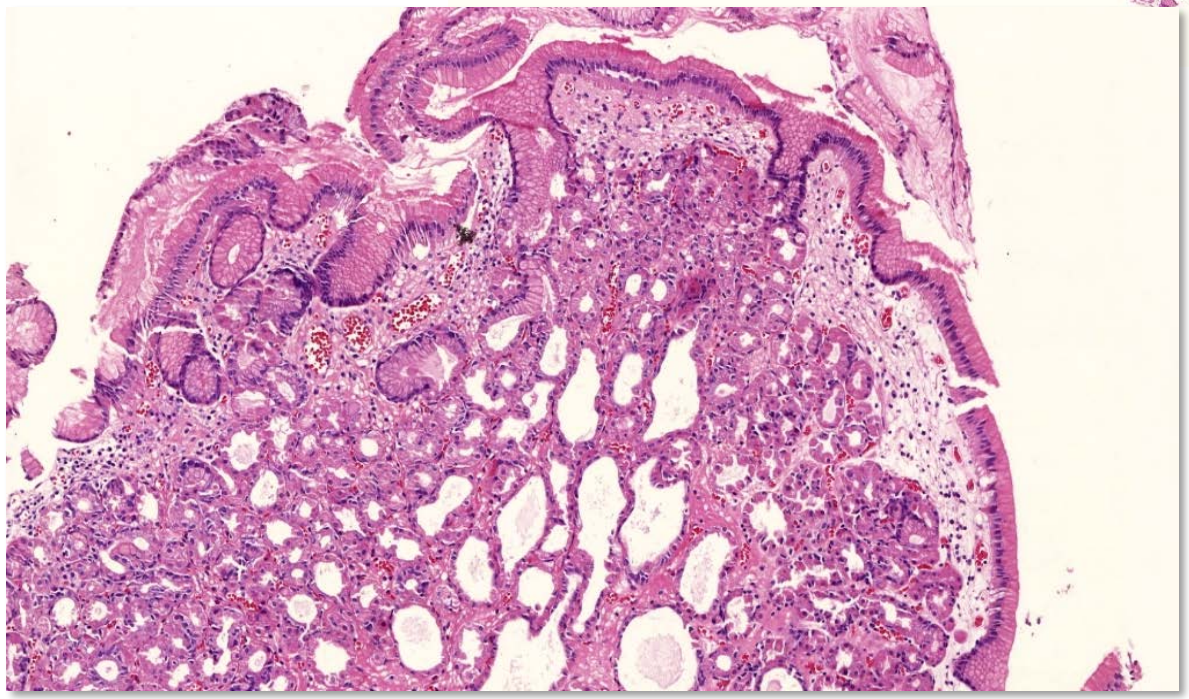
- fundik gland polibi/ polipozisi (%25-50 LGD)
- foveolar tip gastrik adenoma
- pilorik gland adenomu
- duodenal adenoma

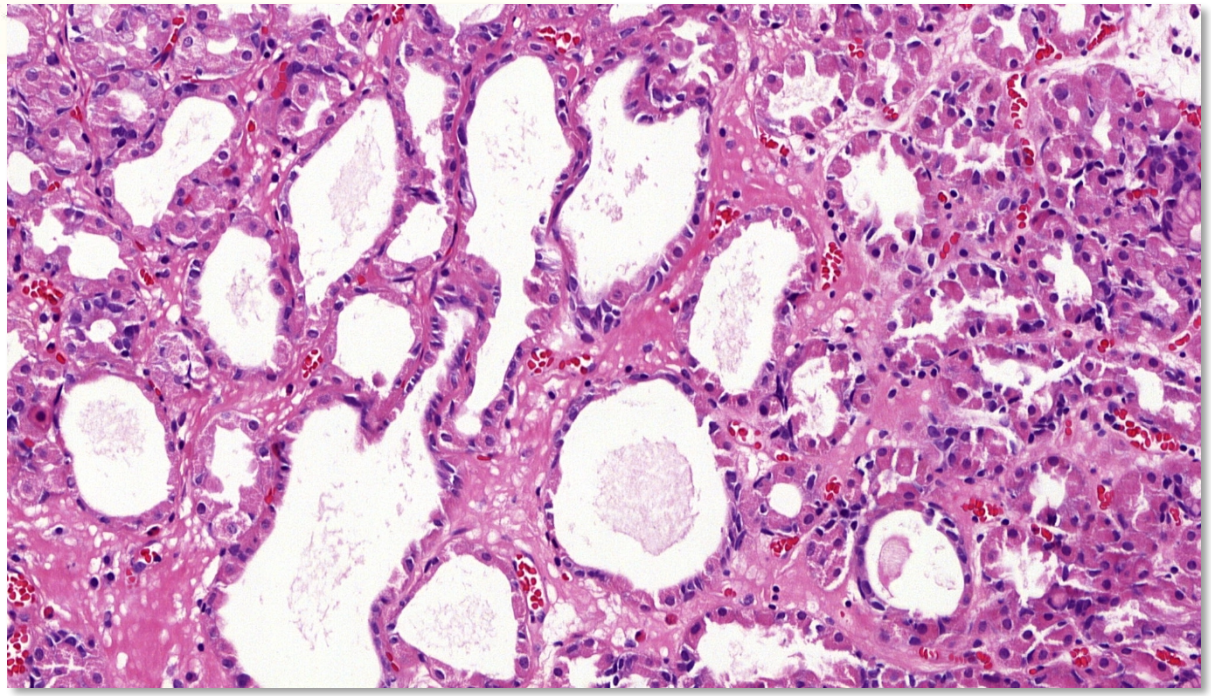
Gastric Neoplasms in Patients With FAP

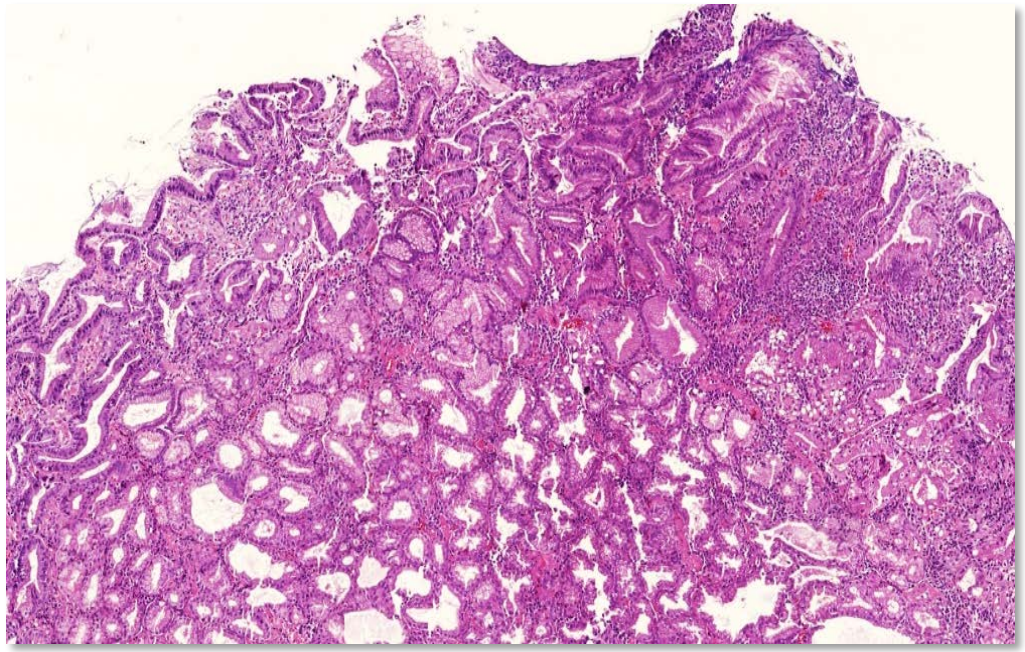
Gastric Neoplasm	No. Polyps (n=261)	No. Patients (n=66) (N [%])	Mean Age at Diagnosis (y)	% Female	% Male
FGP	203	43 (65)	40	78	22
FGP, negative for dysplasia	134	38 (58)	43	76	24
FGP, low-grade dysplasia	67	24 (36)	35	82	18
FGP, high-grade dysplasia	2	2 (3)	32	100	0
Gastric foveolar–type gastric adenoma	43	15 (23)	34	81	19
PGA	7	4 (6)	47	81	19
Gastric hyperplastic polyp	6	4 (6)	52	100	0
Intestinal-type gastric adenoma	1	1 (2)	25	100	0
Carcinoma	1	1 (2)	39	0	100

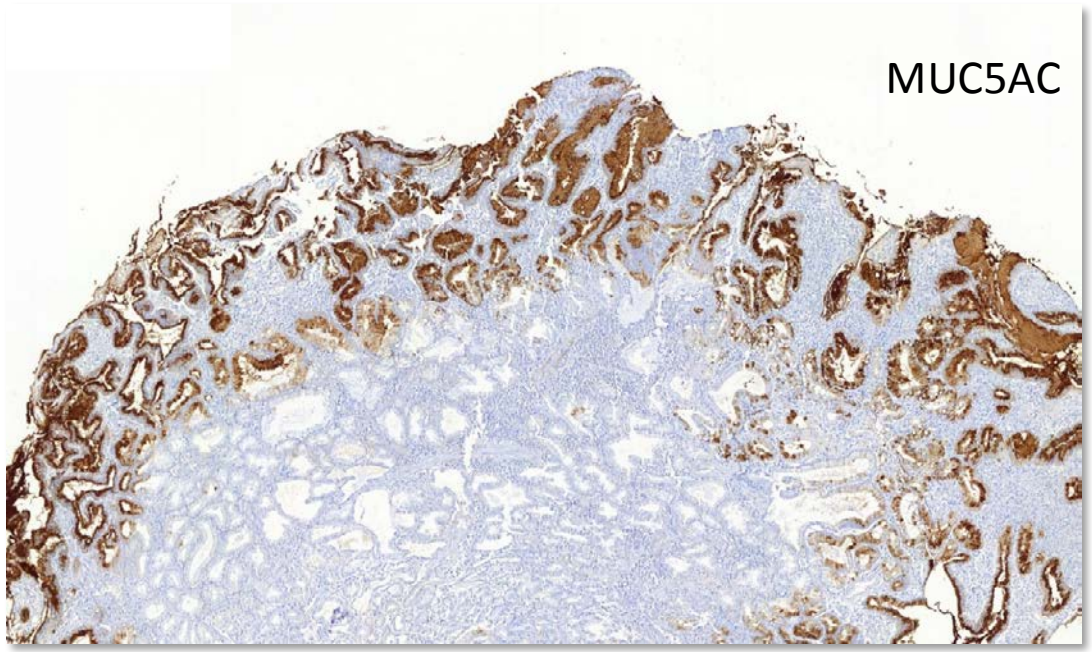
Am J Surg Pathol. 2014 March ; 38(3): 389–393.

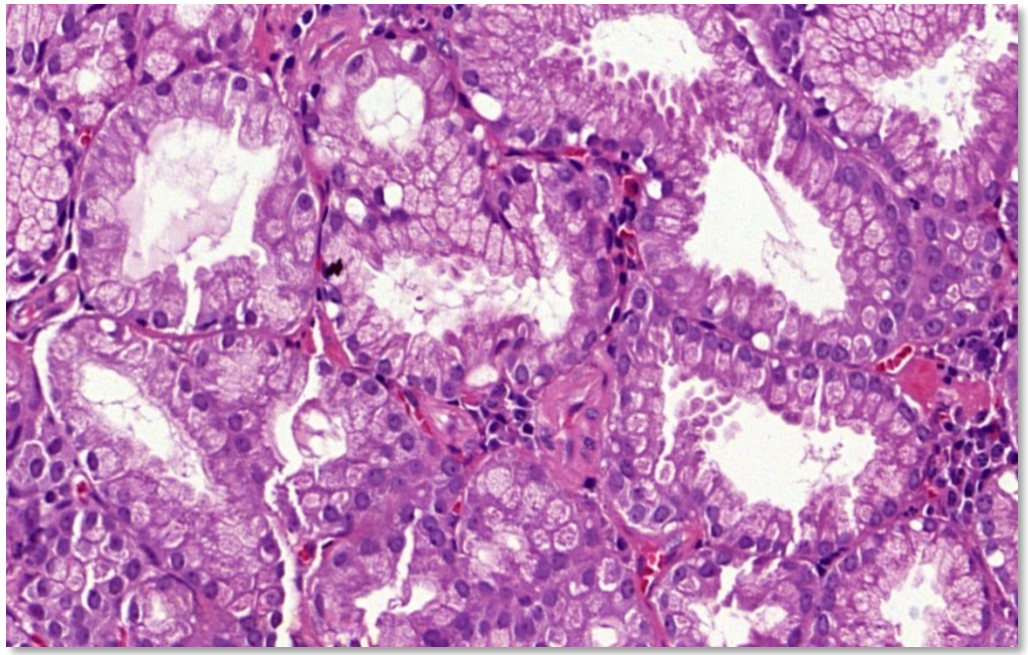


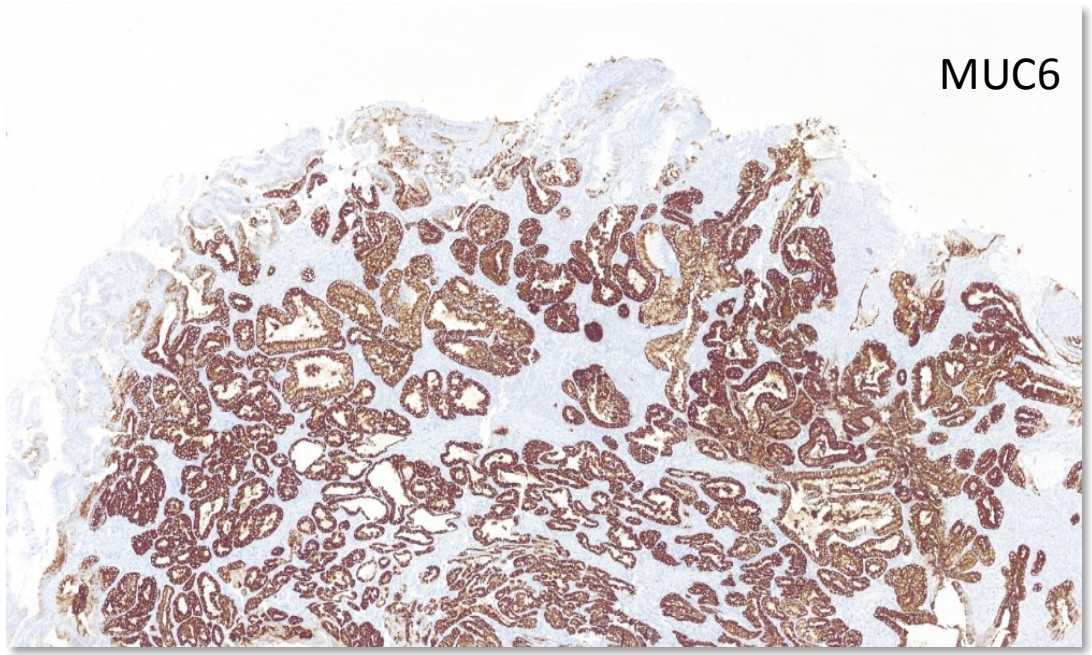


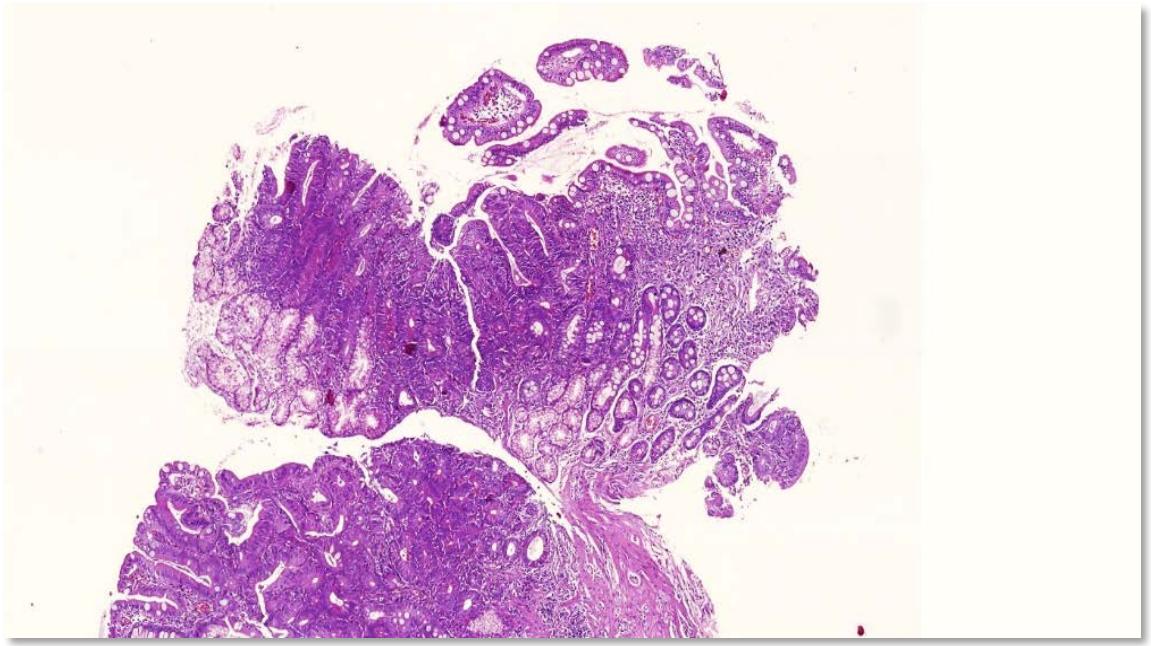


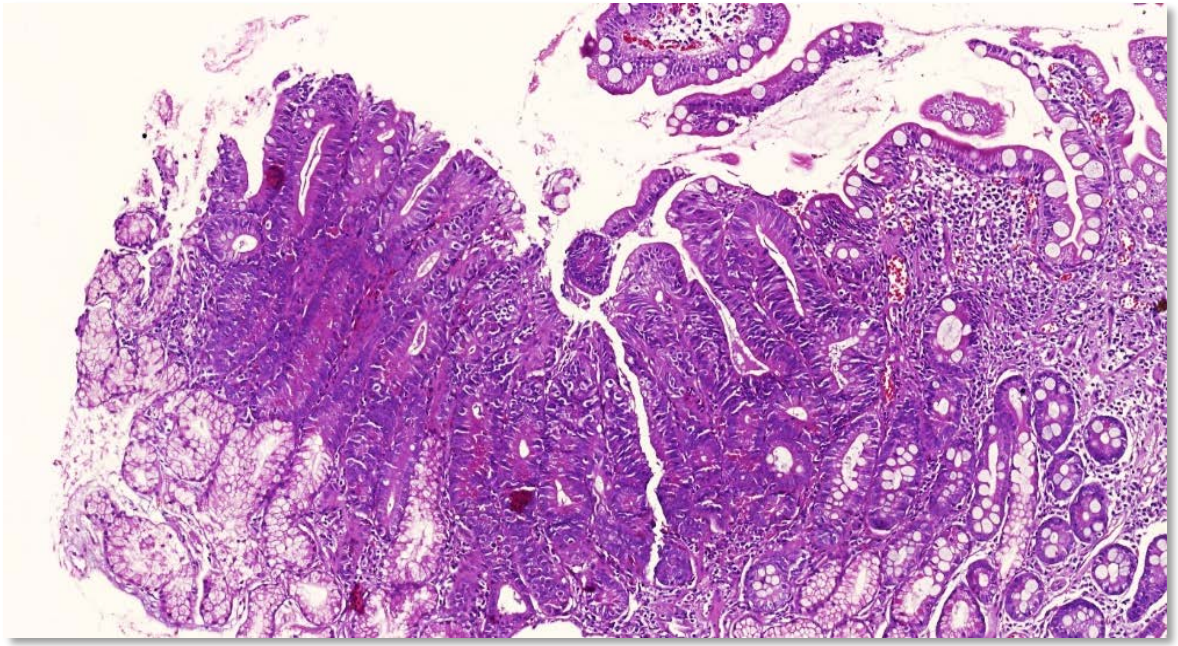


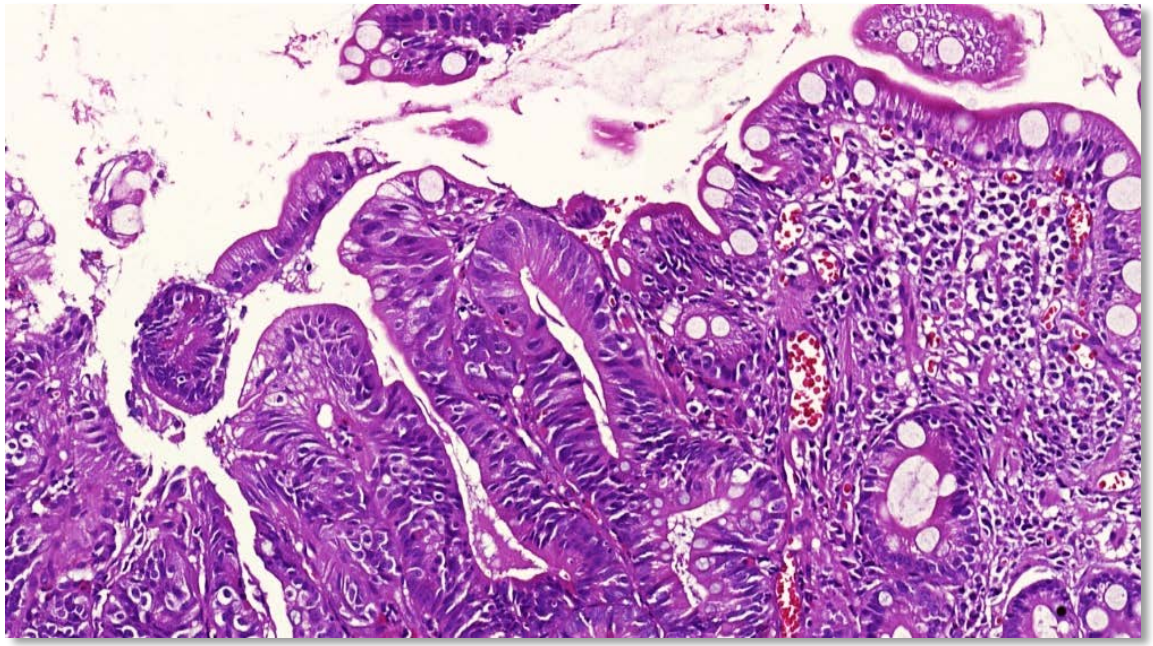

MUC5AC

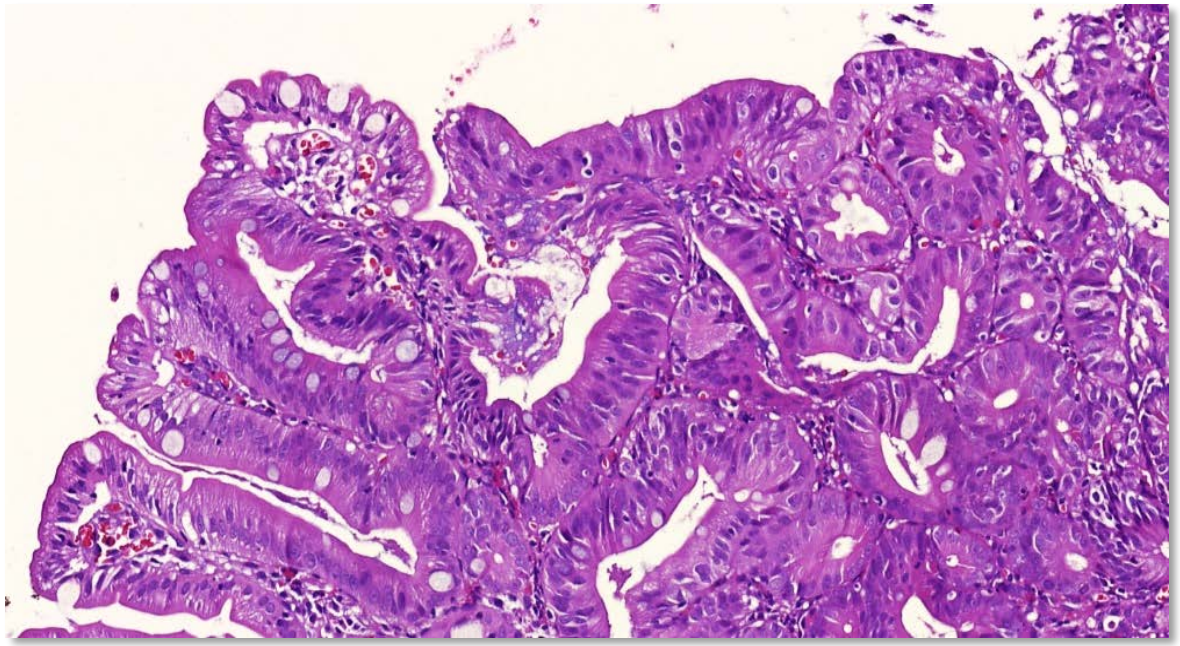



MUC6







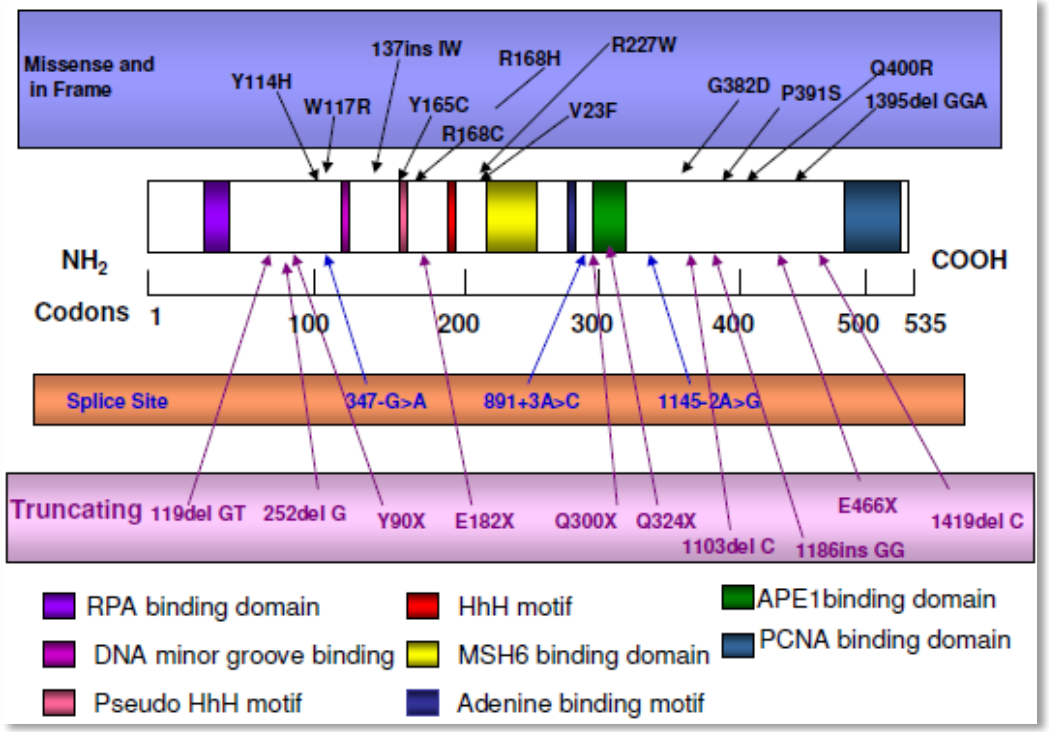


MAP (MUTYH-Assosiye Polipozis)

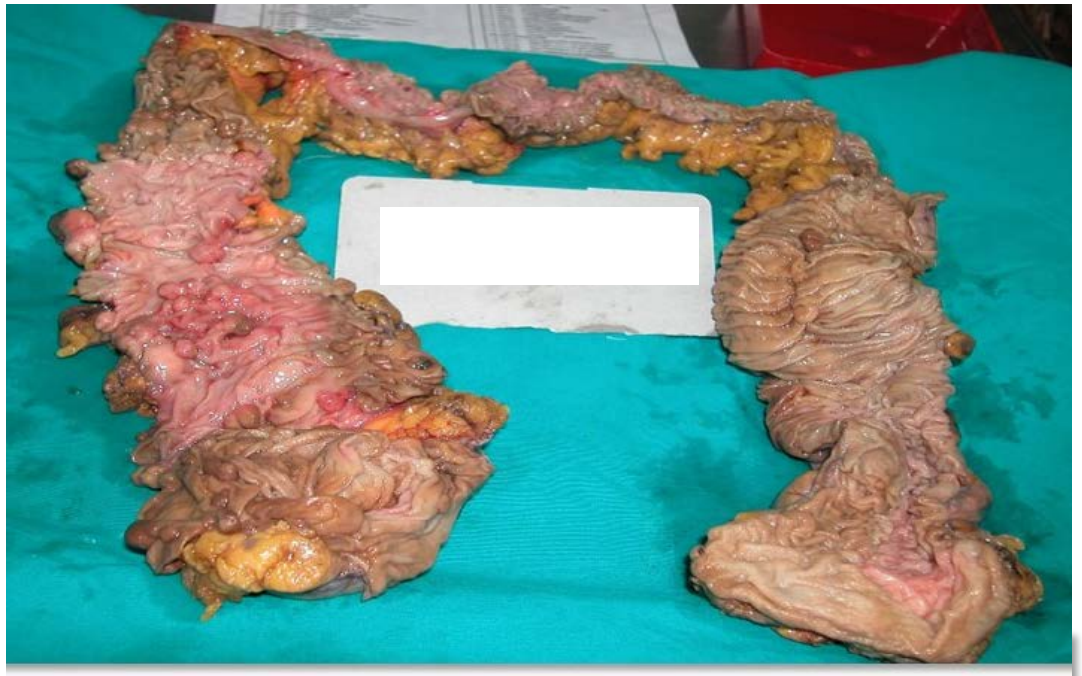
- Otozomal resesif
- >10 (<100) adenoma – AFAP'a benzer
- Üst GIS'te çok sayıda polip

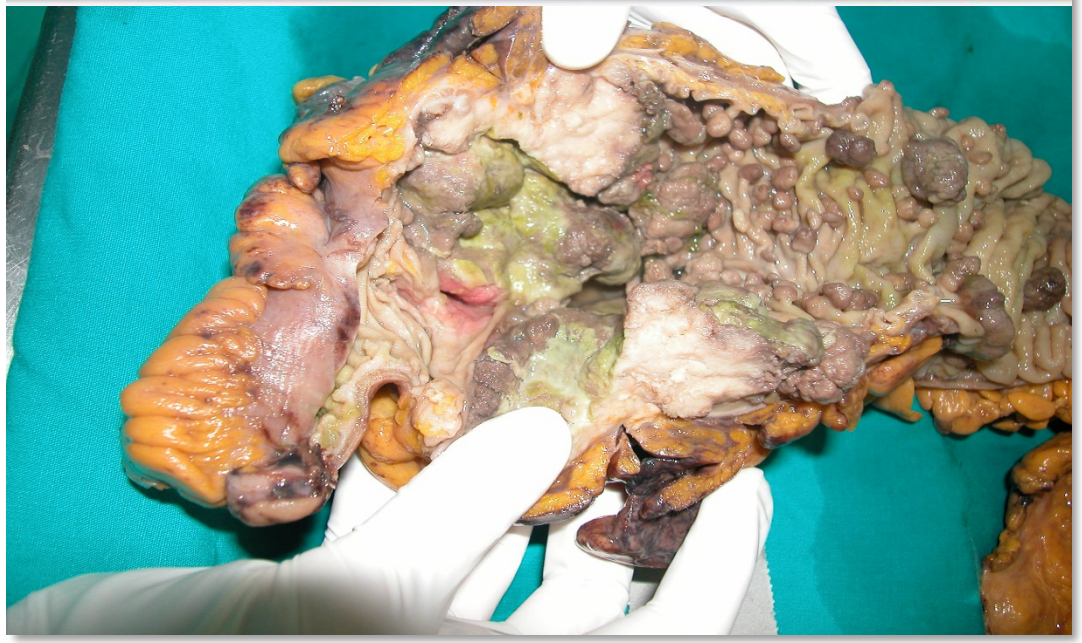
(FGPozis ve duodenal adenoma)

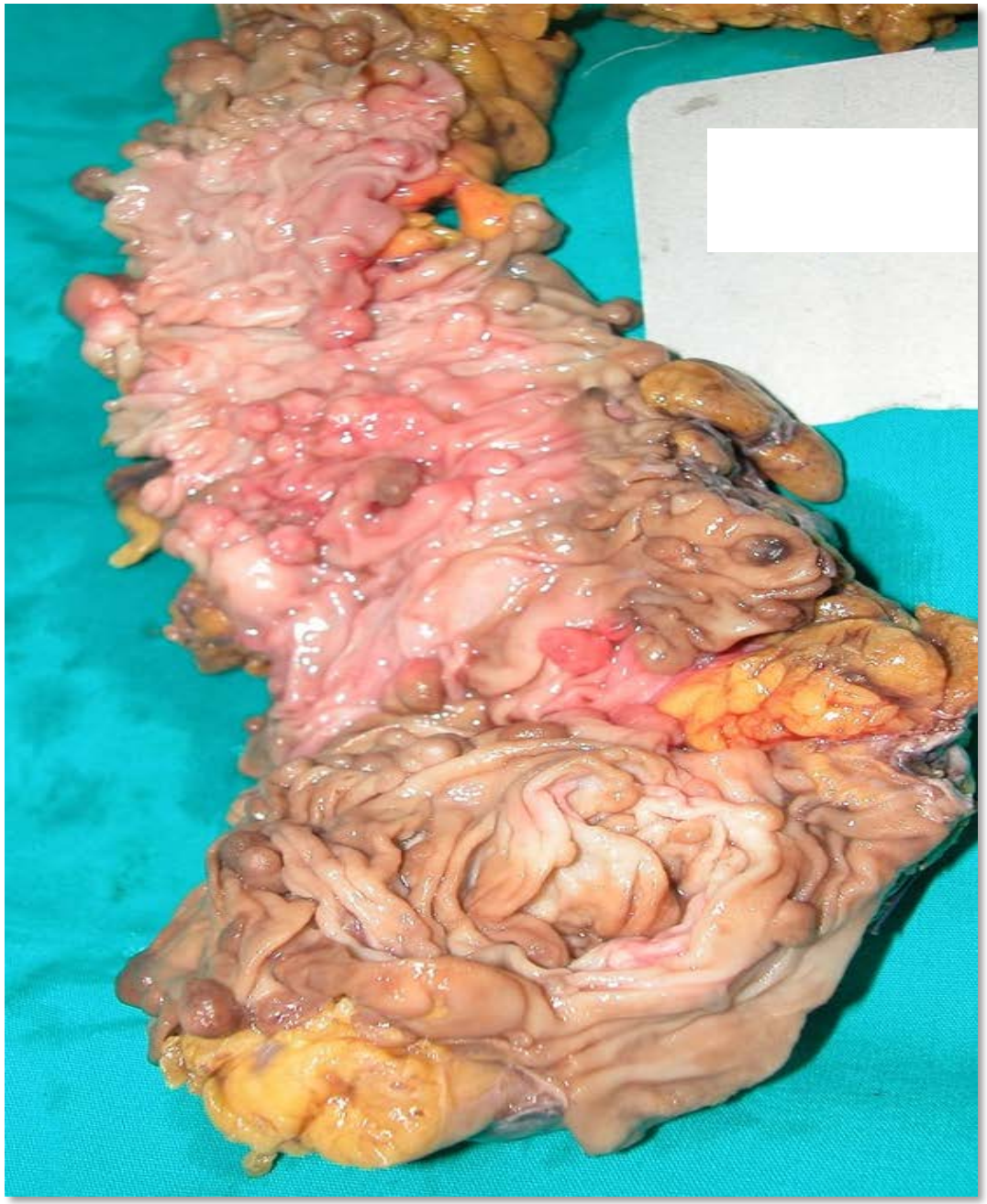
- Adenoma + hiperplastik p + SSA/P



- MUTYH kodladığı glikozilaz 8-oxoG'nin guanine dönüşmesini sağlar ve oksidatif DNA hasarını onarır
- Biallelik germline inaktive edici mutasyonlar (1p32-34) sonucu 8-oxoG guanine dönüşmez ve sitozin yerine adeninle birleşerek büyümeyi kontrol eden genlerde (APC & KRAS) G:C > T:A transversiyon sıklığında ve T-A artışına neden olur







Lynch Sendromu (HNPCC)

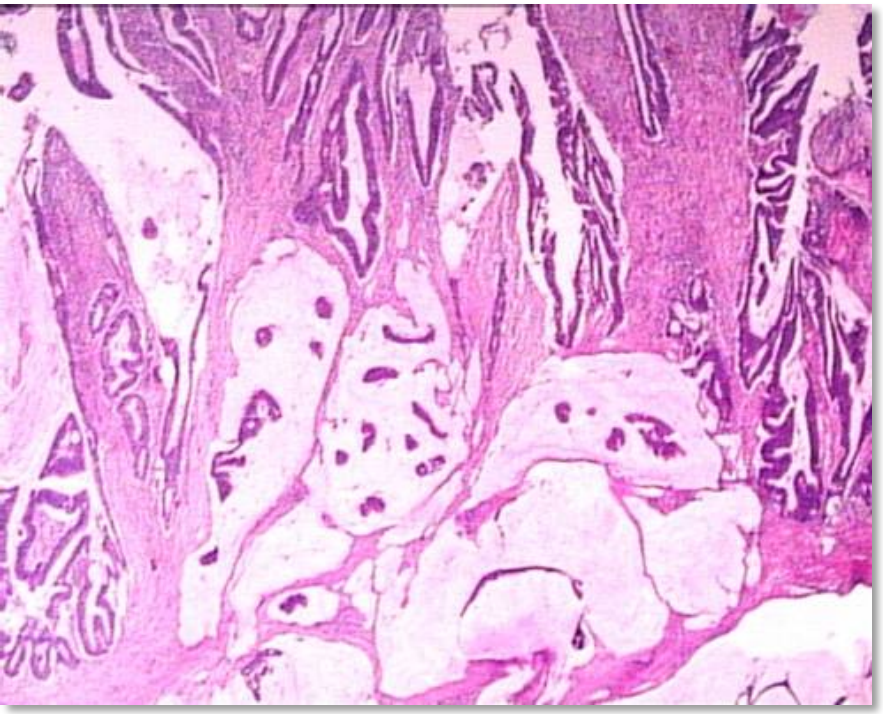
- Birkaç adenoma, erken yaşta, villöz ve displastik
- DNA MMR genlerinde germline mutasyonlar (MLH1, MSH2, MSH6, PMS2)
- MSI-H KRK
- % 30-40 ailede MMR mutasyonu yok = Familyal KRK tip X
- Sebase gland tümörleri+ Lynch sendromu = Muir-Torre sendromu

- Ekstraintestinal: Endometrial, ovarian, mesane, beyin ve deri tümörleri

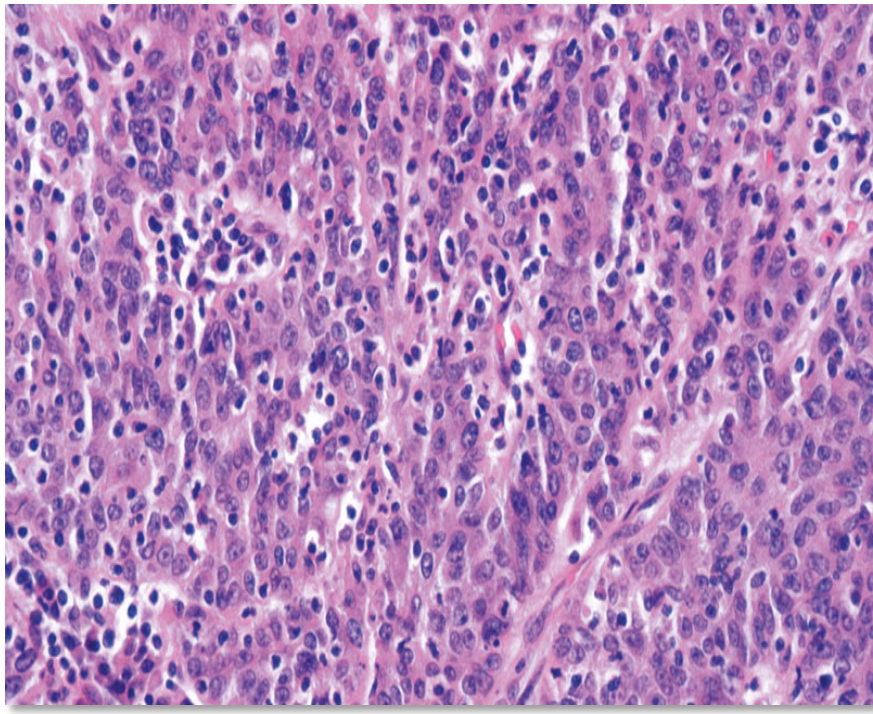
Müsinöz

Lynch sendromu = proksimal tümörler

Medüller

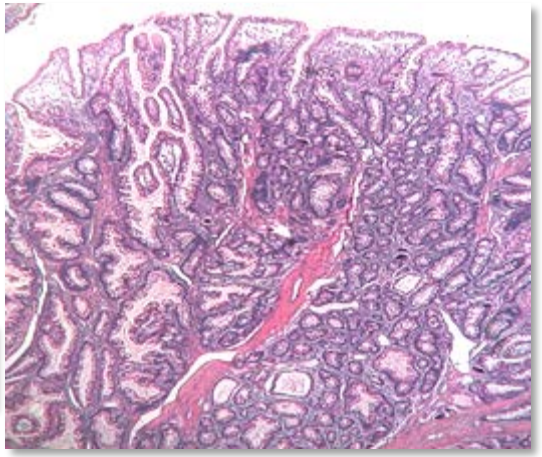


- İyi sınırlı
- TIL/Crohn benzeri stromal reaksiyon

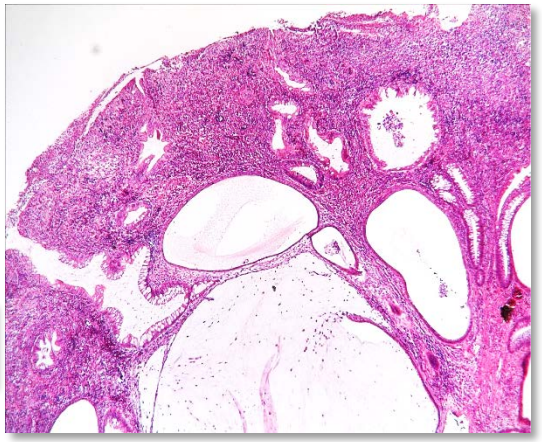


Hamartomatöz Polipozis Sendromları

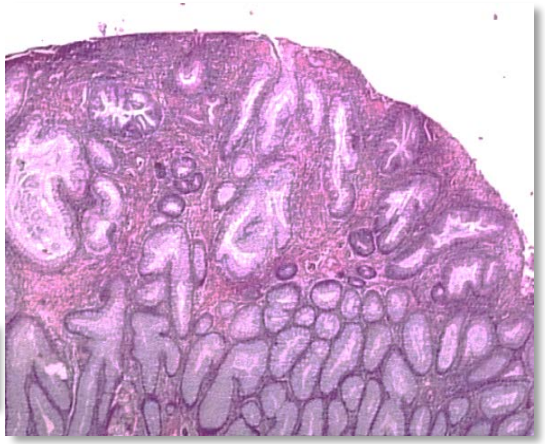
- Peutz-Jeghers Sendromu
- Juvenil polipozis
- PTEN Hamartoma sendromu
  - Cowden Sendromu
  - Bannayan-Riley-Ruvalcaba Sendromu
- Herediter hemorajik telenjiektazi
- Herediter Mikst Polipozis
- Diğer
  - Birt-Hogg-Dube sendromu (BHD)
  - Nörofibromatozis Tip 1
  - MEN Tip 2



Peutz Jeghers polibi



Juvenile polip



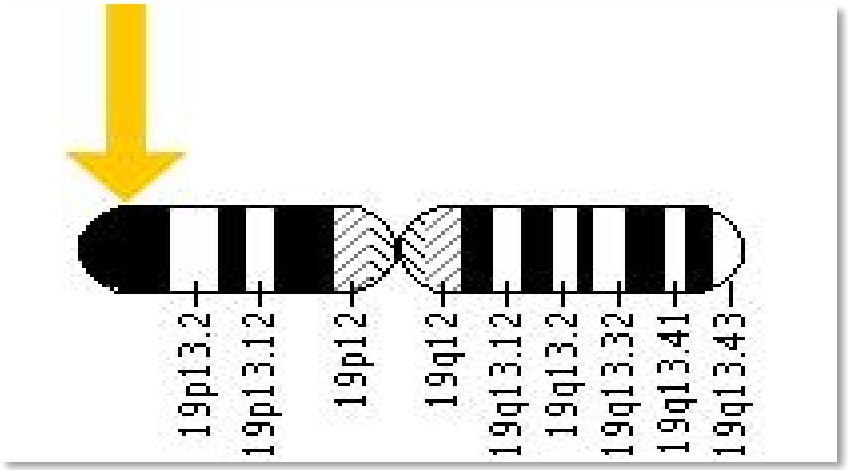
Hiperplastik polip

Peutz Jeghers Sendromu

- Hamartomatöz polipler & mukokutanöz pigmentasyon
- Pigmente lezyonlar pubertede solar

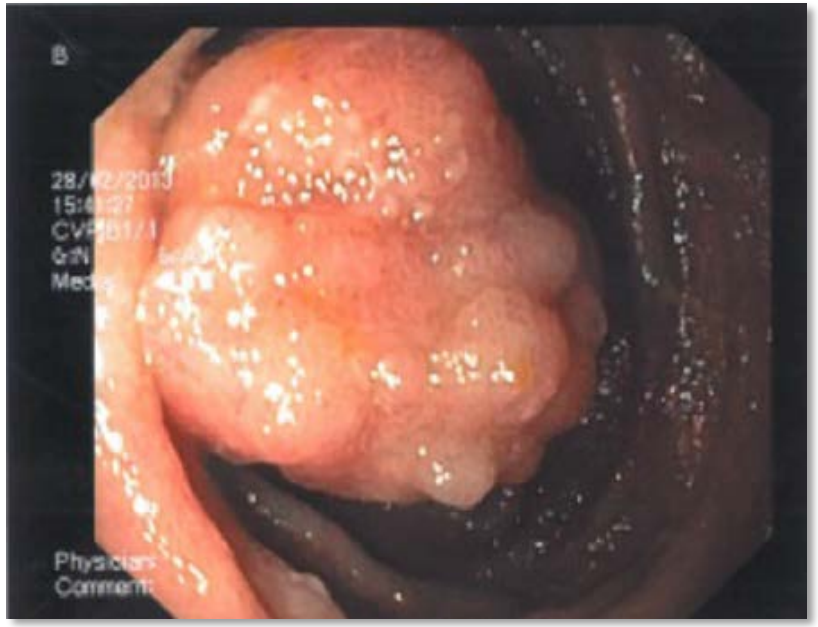
- İnce barsak > kolon > mide > rektum
- Kanser riski %20-40 (mide, ince barsak, kolon)
- Polipler nazofarinks, mesane ve safra kesesinde de görülür

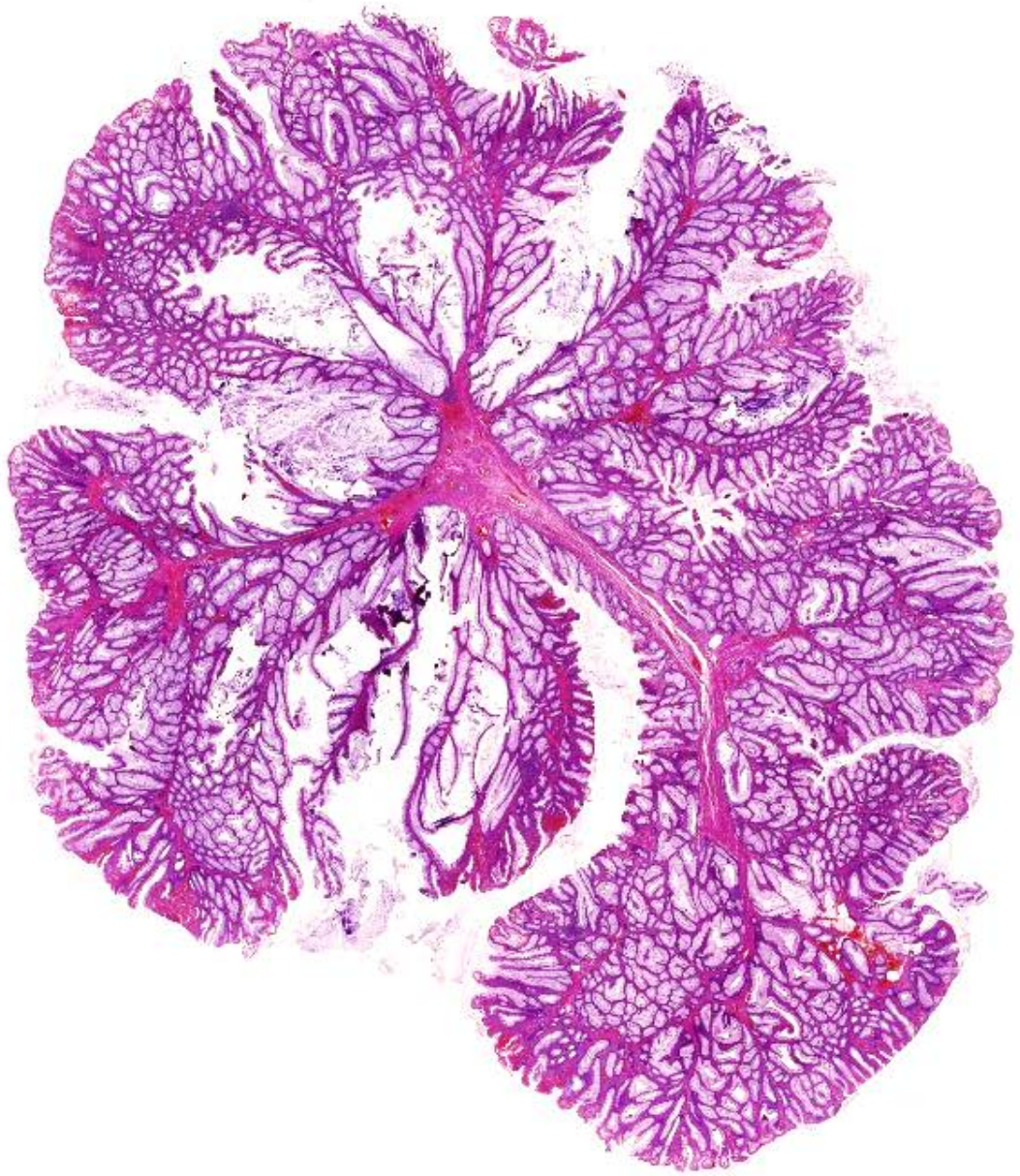
- MTOR arayolunda tümör süpresör gen – STK11/LKB1 (serine threoinine protein kinase 11)
- Kromozom 19p13.3
- LKB1-MAPK sinyal yolu MTOR arayolunu negatif olarak regüle eder – PJS da sürekli aktive olur

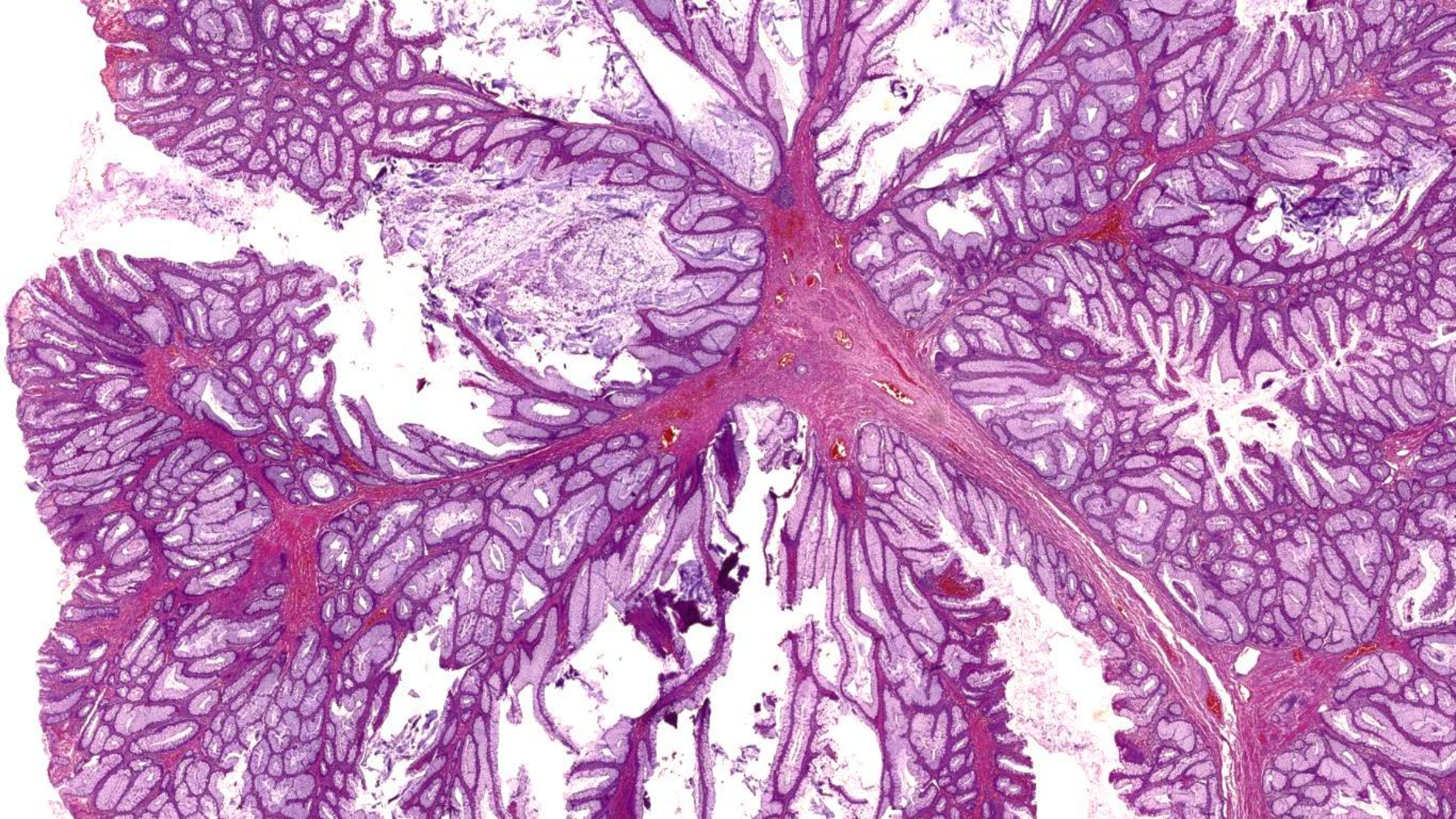


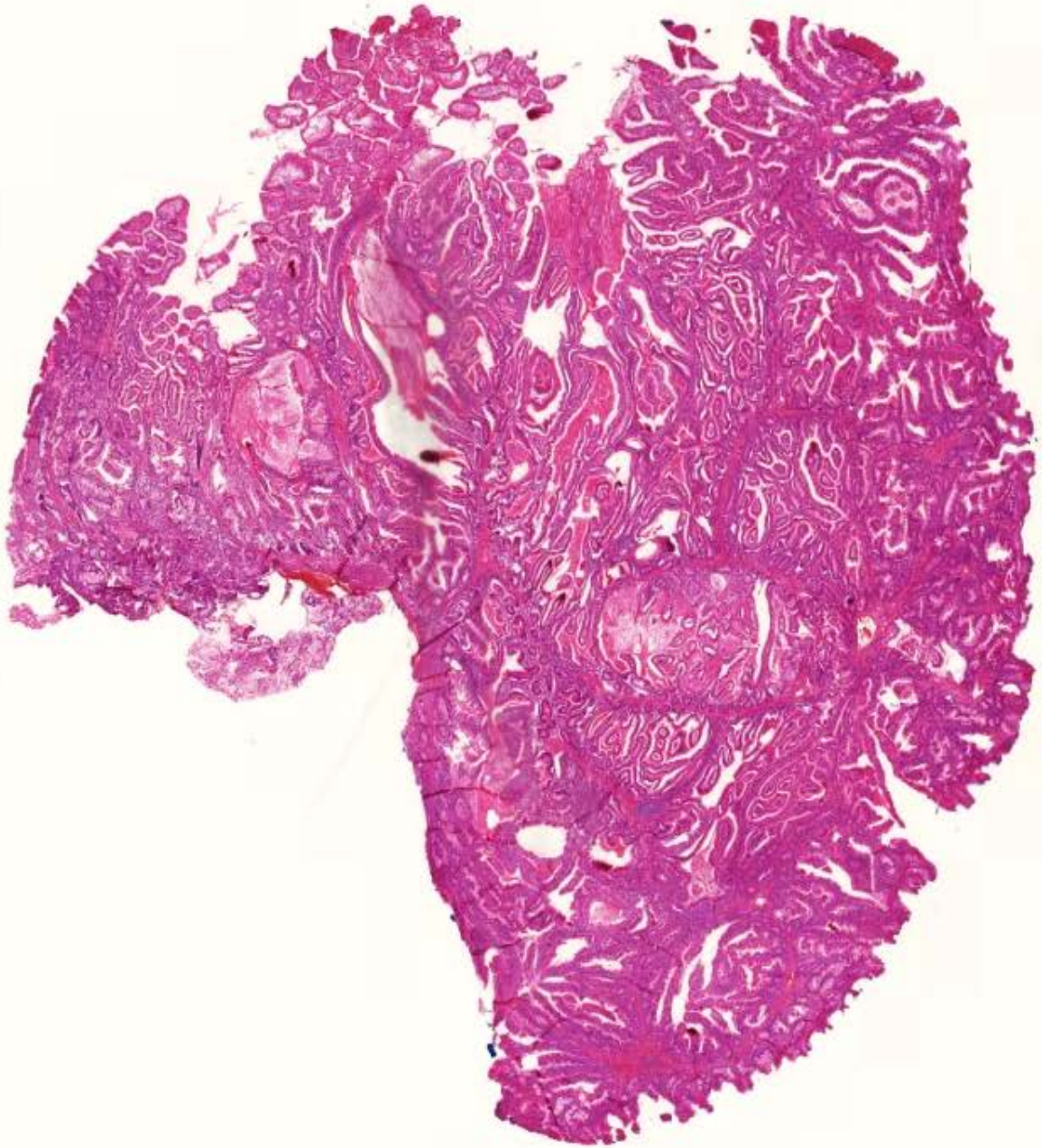
PJ polibi

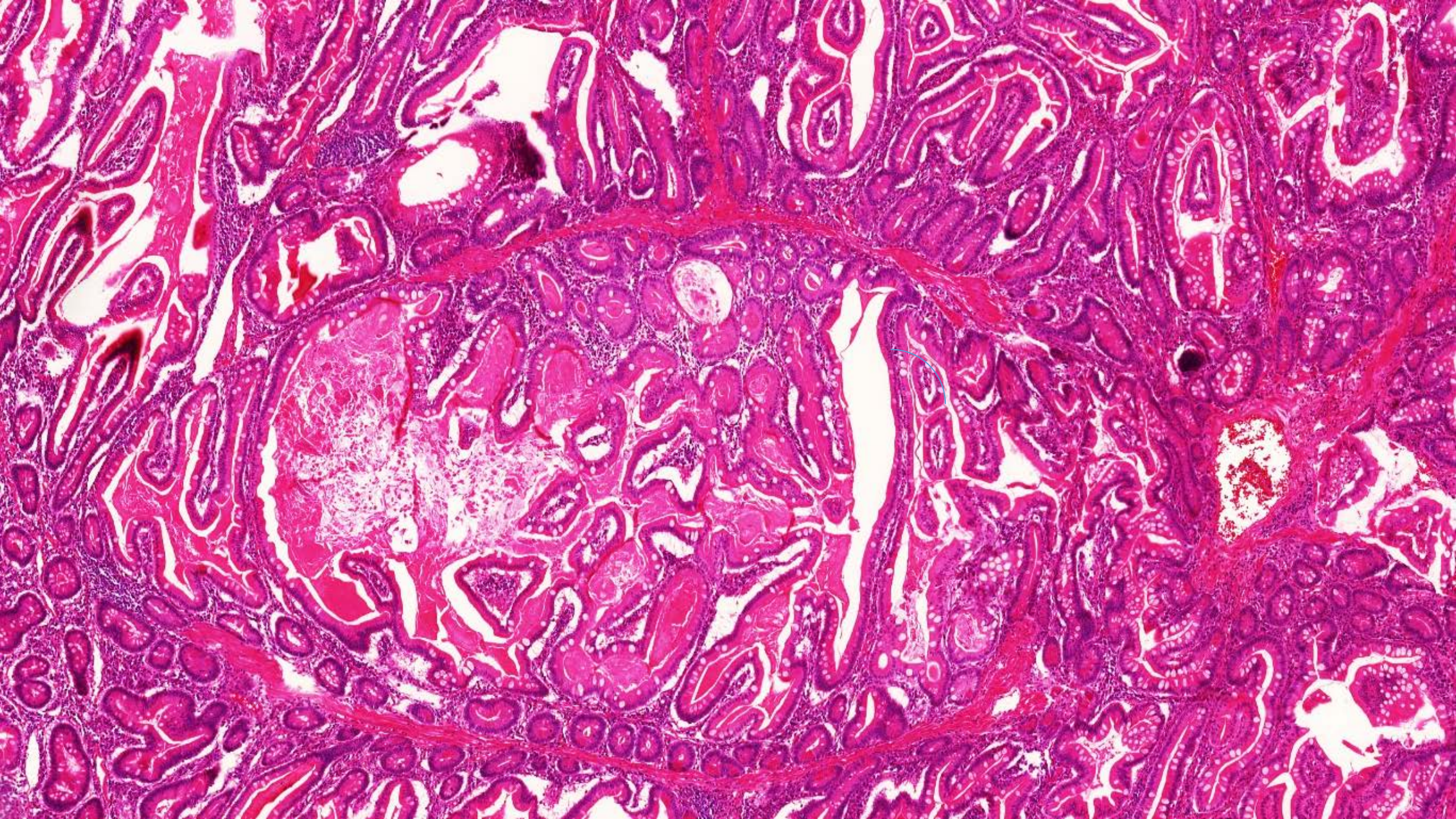
- 5-50mm çaplı, lobüle yüzeyli
- Stromada dallanan düz kas demetleri
- İnvajinasyon - kompleks arkitektür
- Gland lümeninde kondanse müsin
- Displazi görülebilir



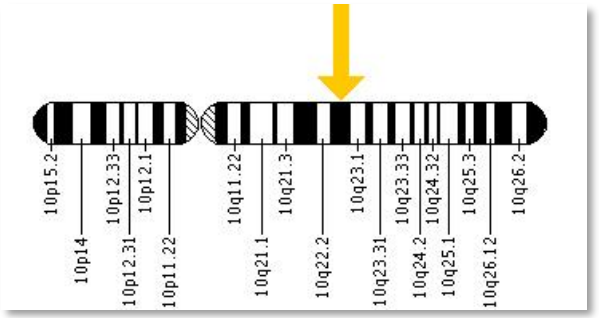


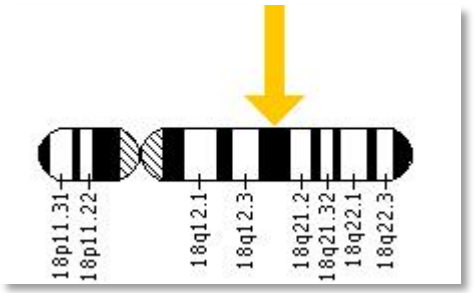






Juvenil Polipozis Sendromu

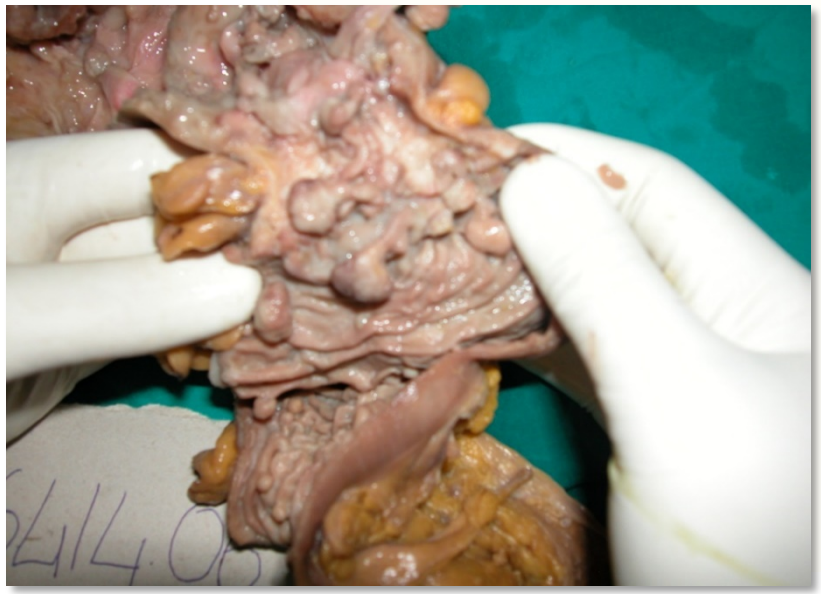


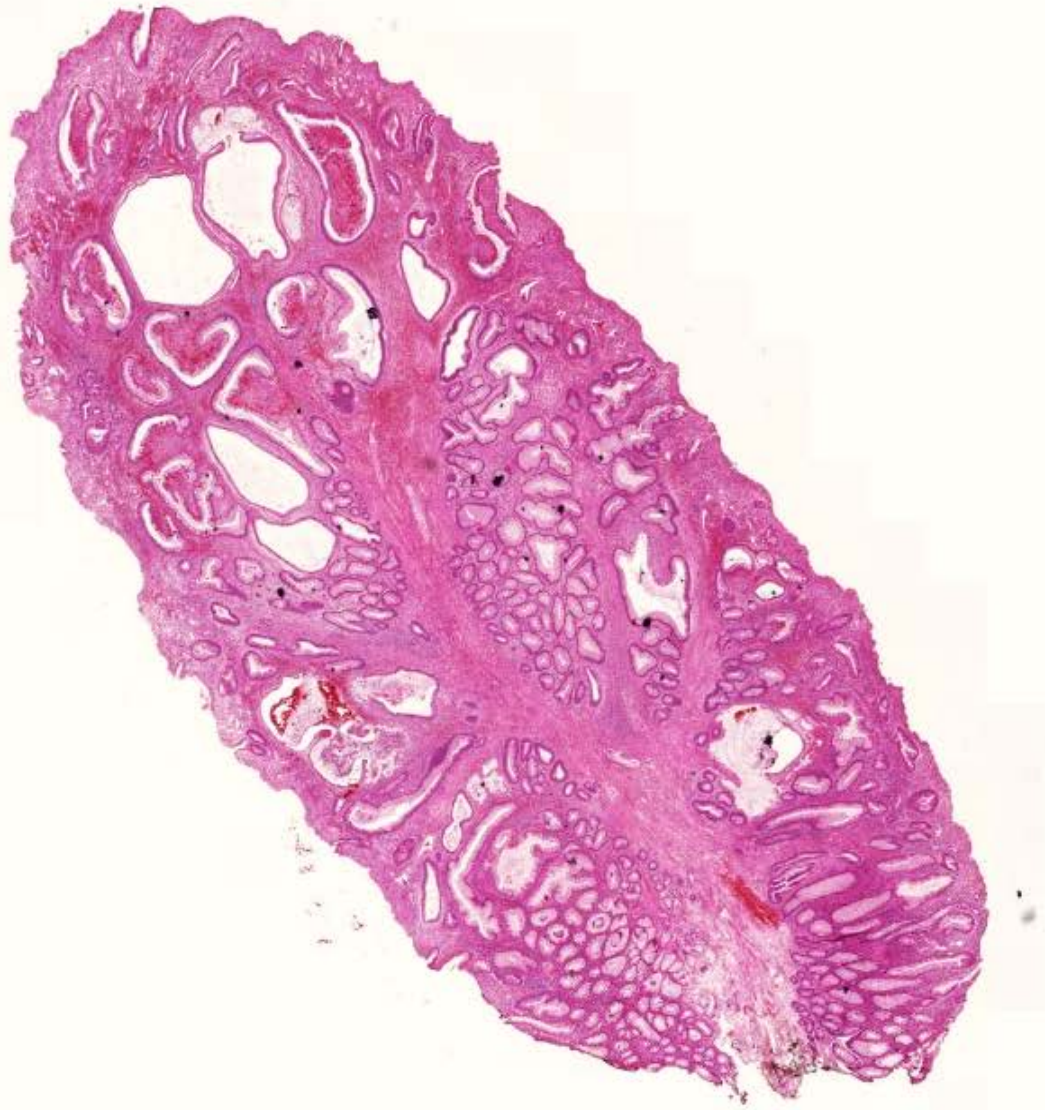


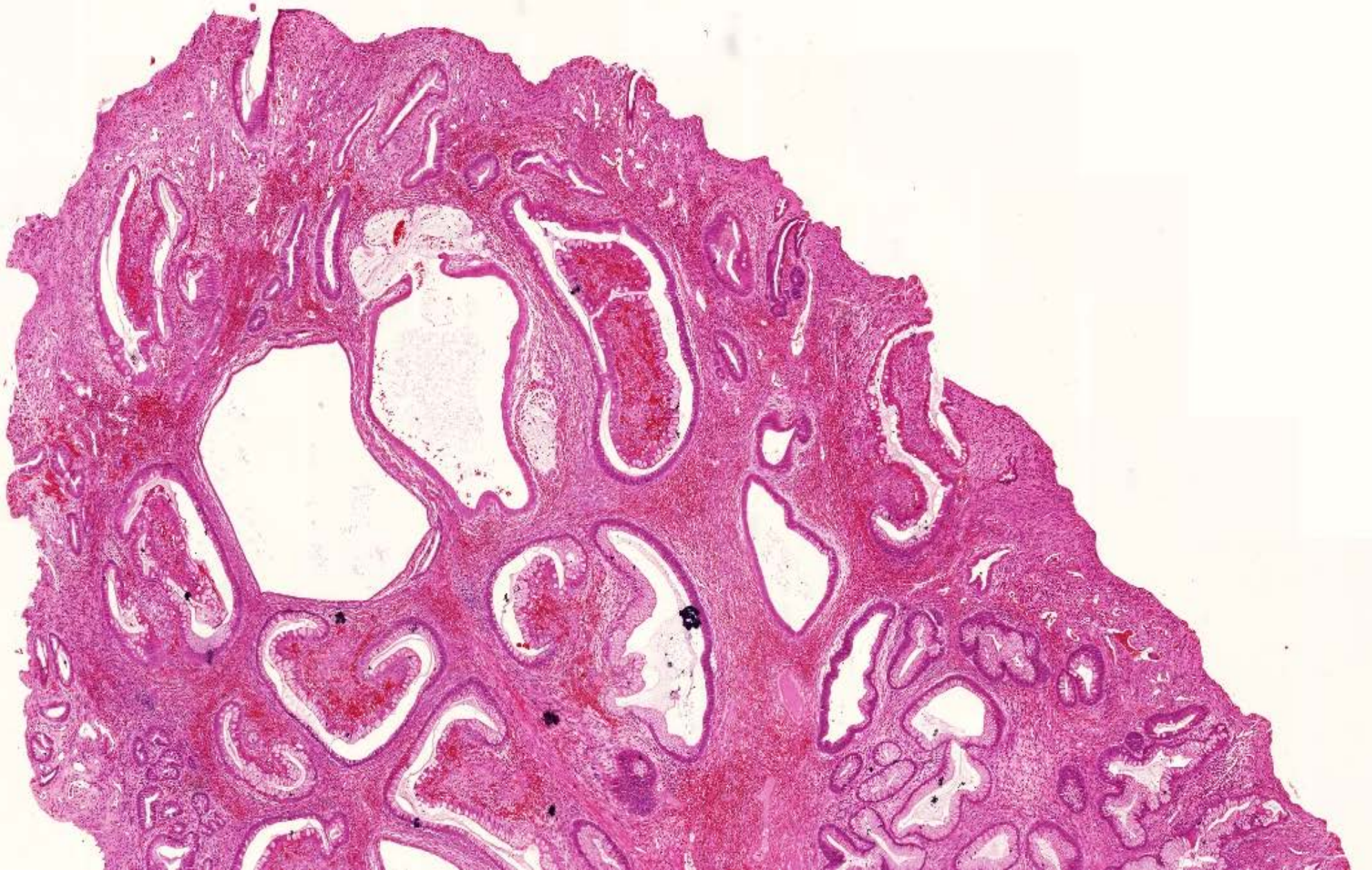
- 1: 100000 (en sık)
- 50-200 polip
- Kolorektum > mide > ince barsak
- Malignite riski %20-70
- İnfantil form: diffüz GI polipozis, fatal seyreder
- Ekstraintestinal: Konjenital kraniofasiyal, kardiak anomaliler
  - TGF-B sinyal arayolundaki tümör supresör genler
  - SMAD4 / MADH4(18q21.1) ya da BMPR1A/ALK3(10q22.3)
  - MADH4 mutasyonları masif gastrik polipozis, gastrik CA ve HHT
  - 10q23 mikrodelesyonlarında agresif polipozis + KRK

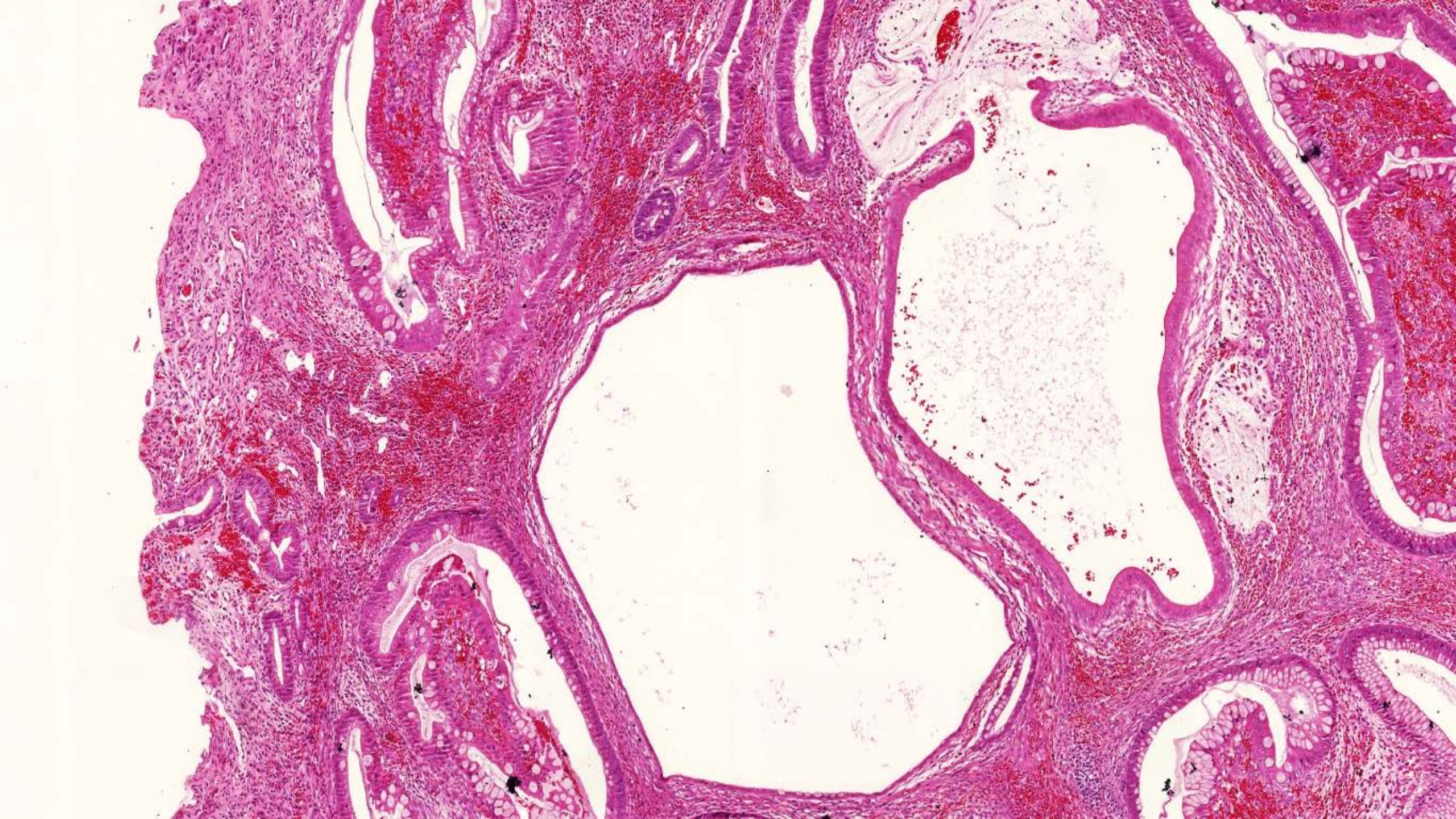
Juvenil polip

- Düzgün, parlak yüzey
- 1cm çap, 2cm uzunlukta sap
- Yüzey erode, kistik glandlar, ödemli, inflame stroma
- Musinöz retansiyon kistine yol açabilir
- Displazi görülebilir









PTEN-Hamartoma Tümör Sendromu

- Cowden Sendromu
- Bannayan-Riley-Ruvalcaba Sendromu (BRRS)
- Proteus Sendromu

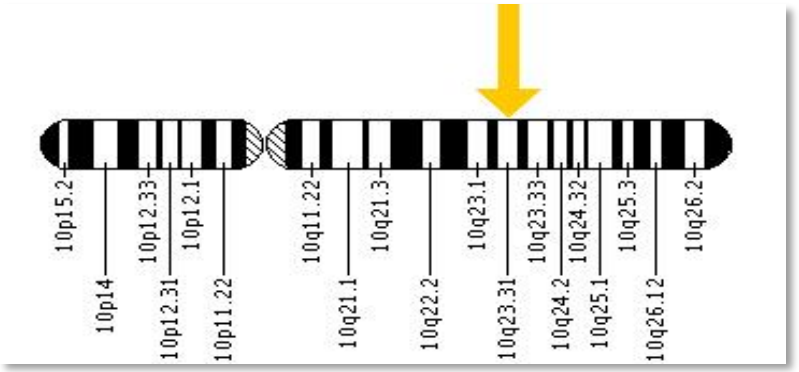
- Polipler hamartomatöz, juvenil ya da inflamatuar

Table 2 Colon findings from the *PTEN* hamartoma tumor syndrome cohort and systematic review

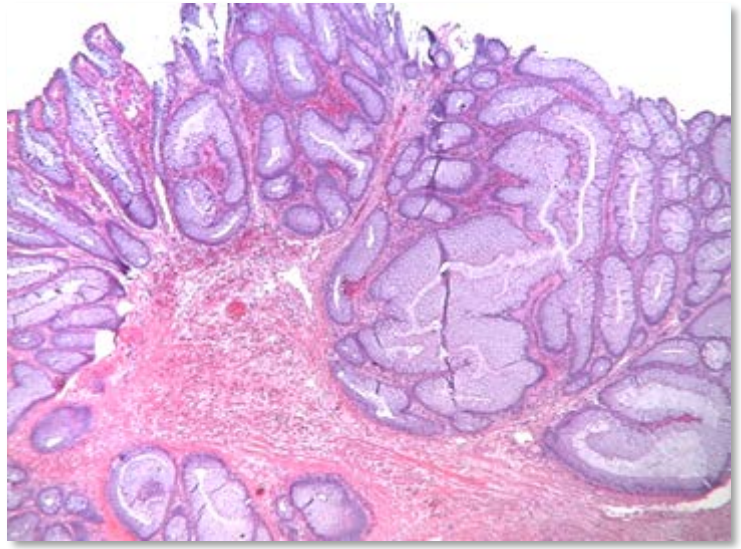
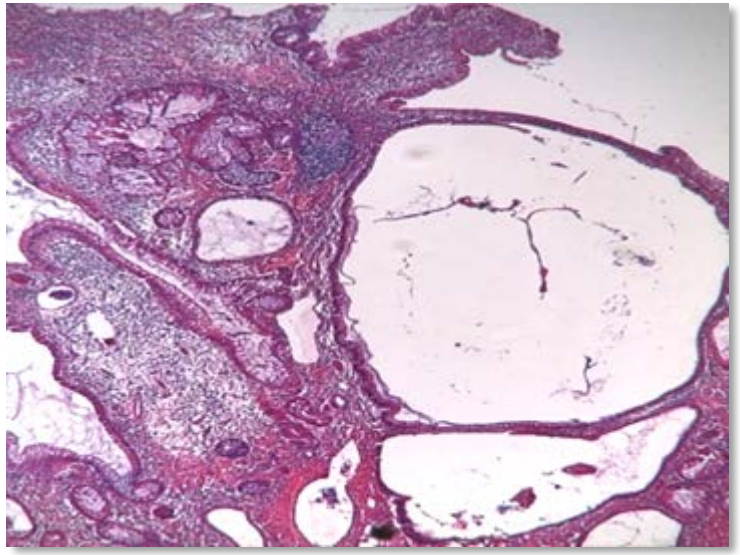
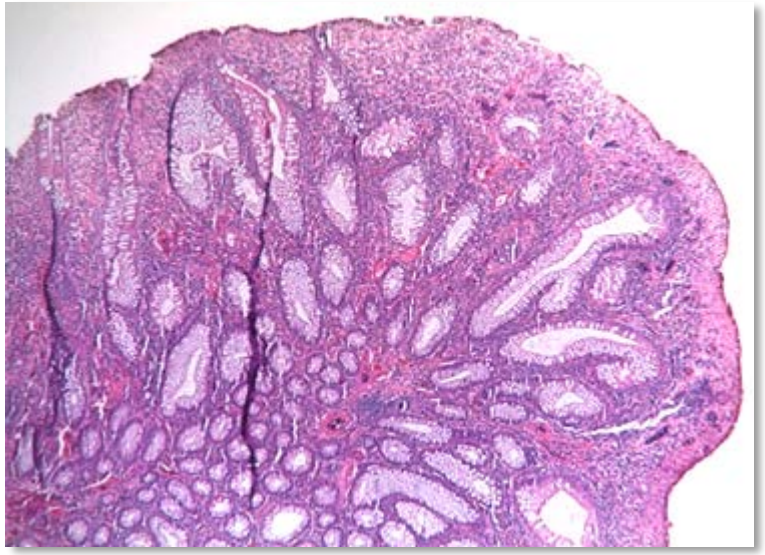
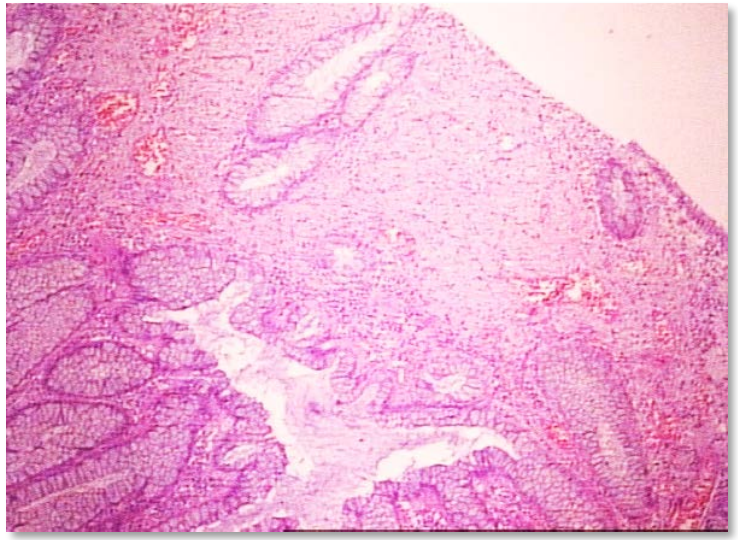
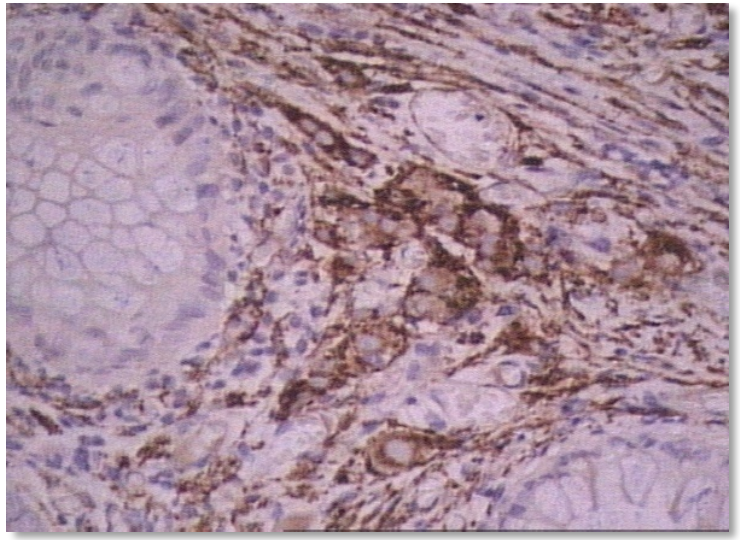
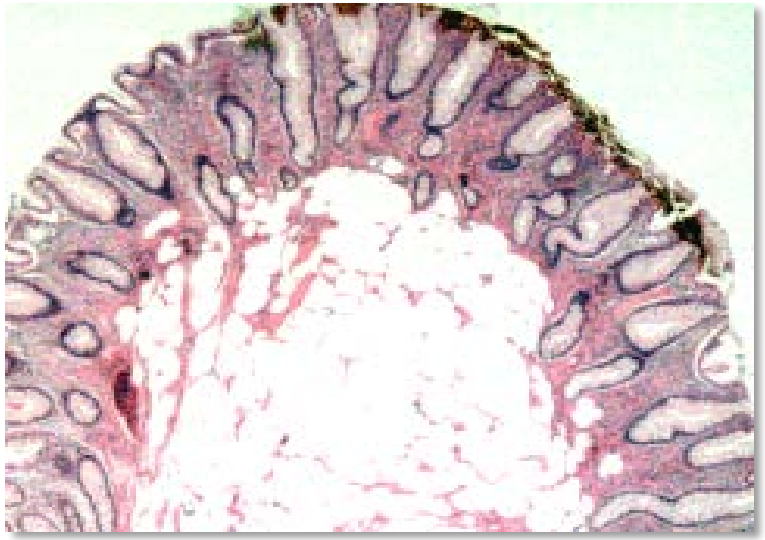
Author	OSU cohort	Levi *et al*[19]	Coriat *et al*[18]	Stanich *et al*[16]	Heald *et al*[14]	Kim *et al*[17]	Total, all patients	Percentage	Total, + *PTEN* mutation	Percentage
n, with colonoscopy	5	10	10	10	67	5	107		88	
PTEN mutation	4	10	NR	5	67	2	88	82%	88	100%
Age (yr), mean	45.8	31.7	37	48	36.4	34	37.4		36.9	
# of colonoscopies, mean	4.2	2.4	3.1	2	NR	NR	2.7		2.9	
Patients with colon polyps	5	8	10	9	62	5	99	92.5%	81	92%
> 50 polyps	1	NR	8	7	NR	NR	16	64%	5	55.6%
Pancolonic location	3	7	7	8	NR	NR	25	71.4%	14	73.7%
Left-sided location	2	1	NR	1	NR	NR	4	16%	3	15.8%
n, with colonic pathology	4	8	10	11	56	5	94		75	
Adenocarcinoma	0	1	0	2	9	0	12	12.8%	12	16%
Adenoma	2	3	10	6	16	1	38	40.4%	24	32%
Ganglioneuroma	1	3	5	6	16	0	31	33%	23	30.7%
Hamartoma	0	5	6	7	18	0	36	38.3%	27	36%
Hyperplastic	2	8	0	4	27	0	41	43.6%	39	52%
Inflammatory	0	0	0	7	11	5	23	24.5%	18	24%
Juvenile	1	2	0	2	0	0	5	5.3%	5	6.7%
Lymphoid hyperplasia/polyp	0	0	0	0	4	1	5	5.3%	5	6.7%
Sessile serrated polyp	0	0	0	0	2	0	2	2.1%	2	2.7%
1 polyp type	2	1	NR	2	29	3	37	44%	32	42.7%
2 polyp types	2	4	NR	2	16	2	26	31%	25	33.3%
⩾ 3 polyp types	0	3	NR	7	9	0	19	22.6%	16	21.3%

Cowden Sendromu

- 1:200000
- %60 GI polipozis, deri tm, tiroid kanseri, fibrokistik hastalık, SSS anomalileri
- hamartomatöz, inflamatuar, lipomatöz, ganglioneuromatöz, ender adenomatöz
- mide, duodenum, ince barsak ve kolon
- %80 dermatolojik malignite
- Kanser riski ?



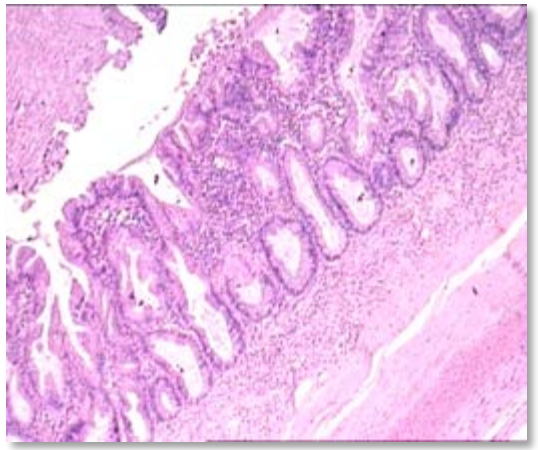
- Germline PTEN (10q23) mutasyonları sonucu kontrolsüz büyüme

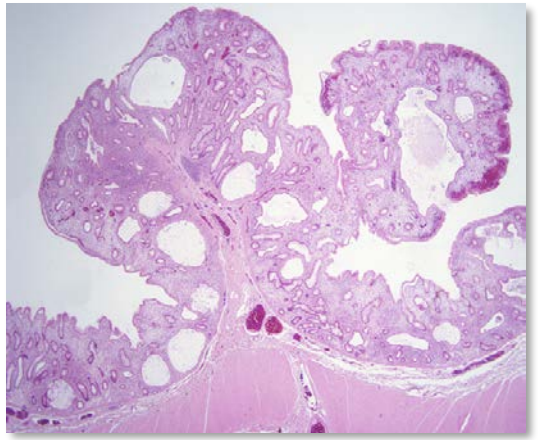
Non-herediter Polipozis Sendromları

- Serrated Polipozis Sendromu
- Cronkhite-Canada Sendromu
- İnflamatuar «cap» polipozis
- Lenfomatoid polipozis
- Nodüler lenfoid hiperplazi
- Pnömatozis sistoides intestinalis
- Kolitis sistika profunda

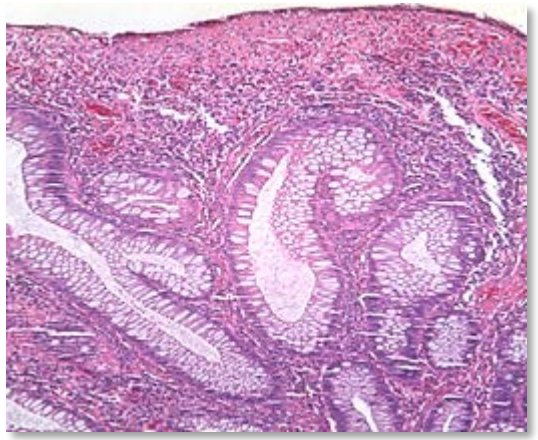
Serrated polip



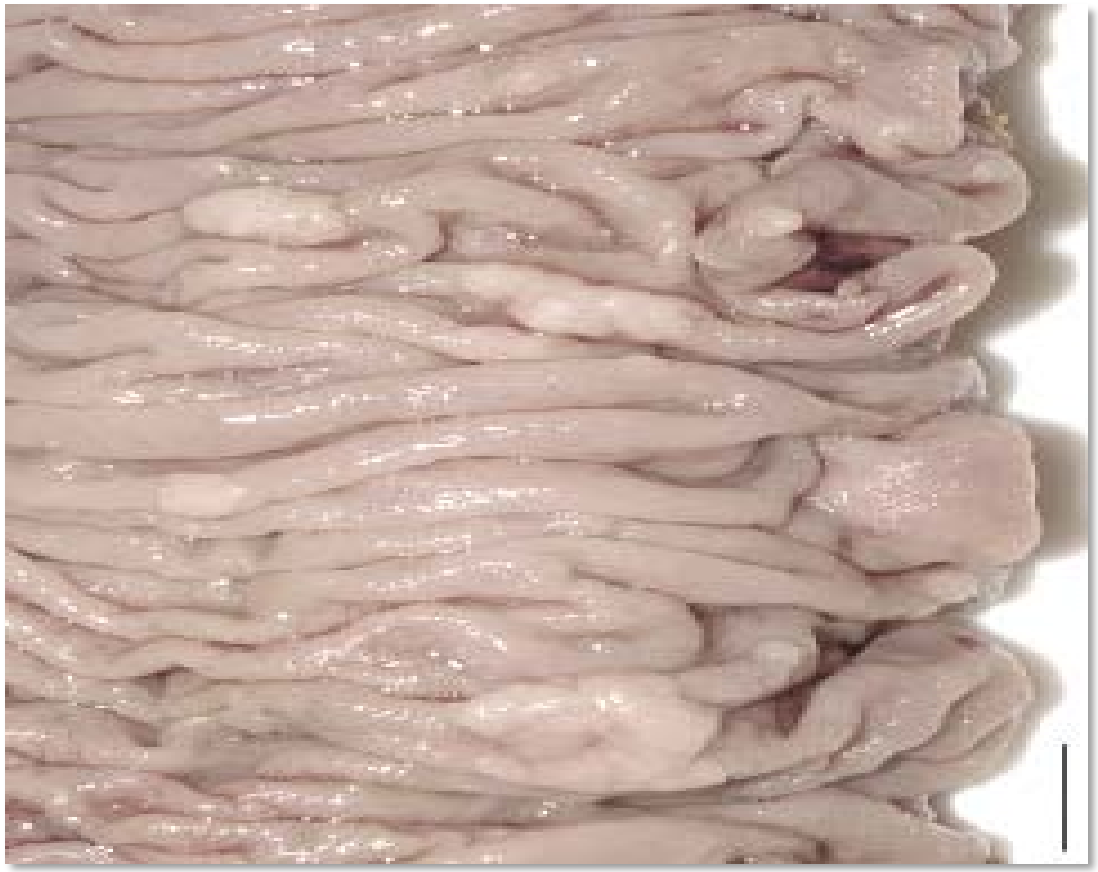
CC polibi



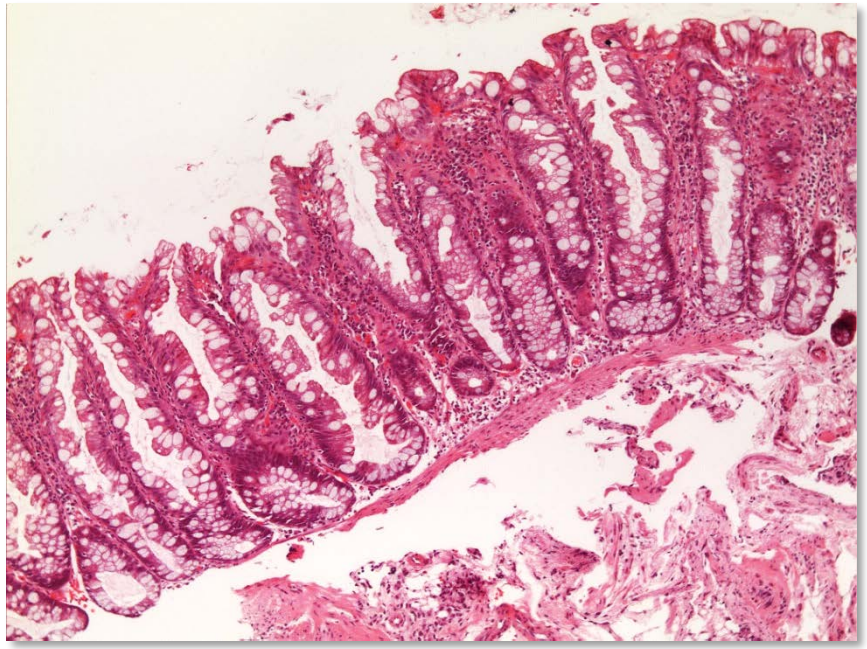
İnflamatuar polip



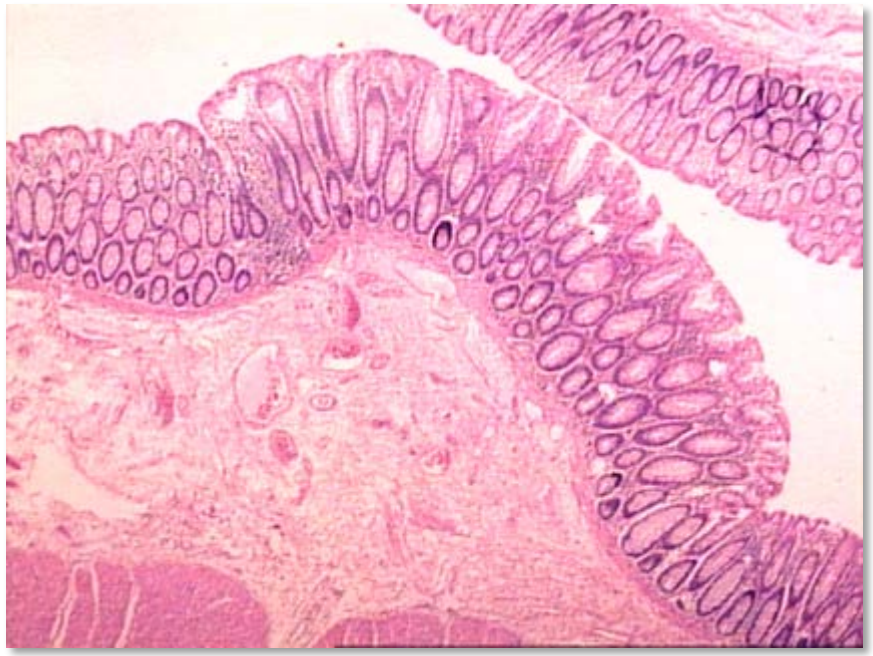
“Serrated” polipozis



Tip 1 SPS
- Multipl SSA/P
- Büyük çaplı
- Proksimal kolonda sık
- Ca riski ↑
- BRAF mutasyonu sık



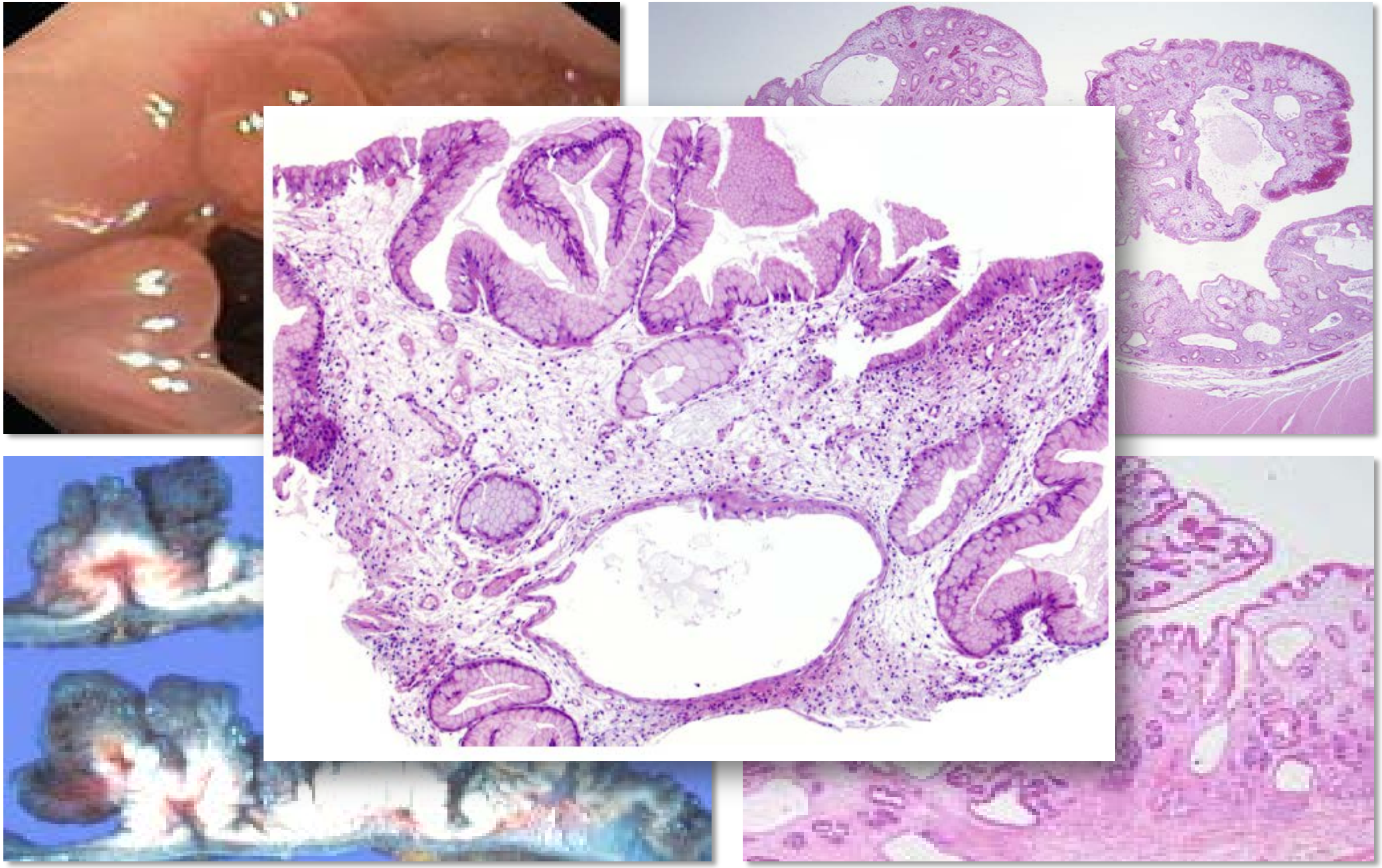
Tip 2 SPS
- Sayısız HP
- <5mm
- Tüm kolonda yaygın
- Ca riski Ø / düşük
- KRAS mutasyonu sık



Cronkhite-Canada Syndrome

- Otoimmün inflamatuar (IgG4-assosiye) hastalık
- Mide > kolon > duodenum > ileum > jejunum
- Juvenil ya da hamartomatöz polip
- Çevre mukoza anormal-hiperplastik dev pililer
- Malign transformasyon ender
- Malabsorpsiyon ve protein-kaybettiren enteropati

- Ektraintestinal: Alopesi, deri pigmentasyonu, tırnak anomalileri



Syndrome	Colonoscopy		EGD		Small bowel		Complementary examinations
	Start (age)	Intervals (years)	Start (age)	Intervals (years)	Start (age)	Intervals (years)	
FAP	10–12	1–2*[2]	30*[3]	3*[4]	n.p.	n.p.	Thyroid and abdominal US every year from age 10–12*[5]
AFAP	18–20*[6]	1–2	30*[3]	3*[4]	n.p.	n.p.	Thyroid US every year from age 10–12*[5] and abdominal US from age 18–20
MAP	18–20	1–2	25–30*[3]	3*[4]	n.p.	n.p.	None
PJS	8–20	2–3	8–12	2–3	8–12	2–3	Screen for breast cancer every 1–3 years from age 25; screen for testicular and ovarian tumors from birth
JPS	10–15	1–3	10–15	1–3	?	?	Monitor blood values and abdominal symptoms; possibly screen for vascular malformations
CS	50	10*7	n.p.	n.p.	n.p.	n.p.	Every year: screen for breast cancer from age 25, thyroid cancer from age 18, endometrial cancer from age 30–40, pancreatic cancer from age 30, among others
HP	20	1–3	n.p.	n.p.	n.p.	n.p.	None

Patoloğun rolü

- Ayrıntılı makroskopik değerlendirme yapmak
- Polip sayı ve dağılımını kaydetmek
- Poliplerin makroskopik özelliklerini kaydetmek (sesil/ saplı)
- En büyük polibin çapını vermek
- Poliplerin histolojik tipini belirlemek – dominant polip tipi
- Eşlik eden maligniteyi raporlamak
- «Swiss roll» ya da striplerle örneklemek
- >1cm polipleri total takibe almak
- Bu bilgileri içeren, klasifiye eden ve genetik danışmanlık ve moleküler testleri öneren rapor hazırlamak

nefrete inat SEVGİ...
savaşa inat BARIŞ...
HEMEN ŞİMDİ!