Polyposis Syndromes

Definition

- **Polyposis syndromes**
  - Are **hereditary disorders** characterized by the presence of **multiple and/or unusual polyps** distributed in the colon and rectum
  - Are associated with an **increased risk for colorectal cancer** and
  - Can be related with multiple **extracolonic manifestations**.

- **Polyposis syndromes** are t**ogether with** the **Lynch syndrome**/HNPCC **classified as hereditary CRC syndromes** which account for **7-10% of colorectal cancer.**

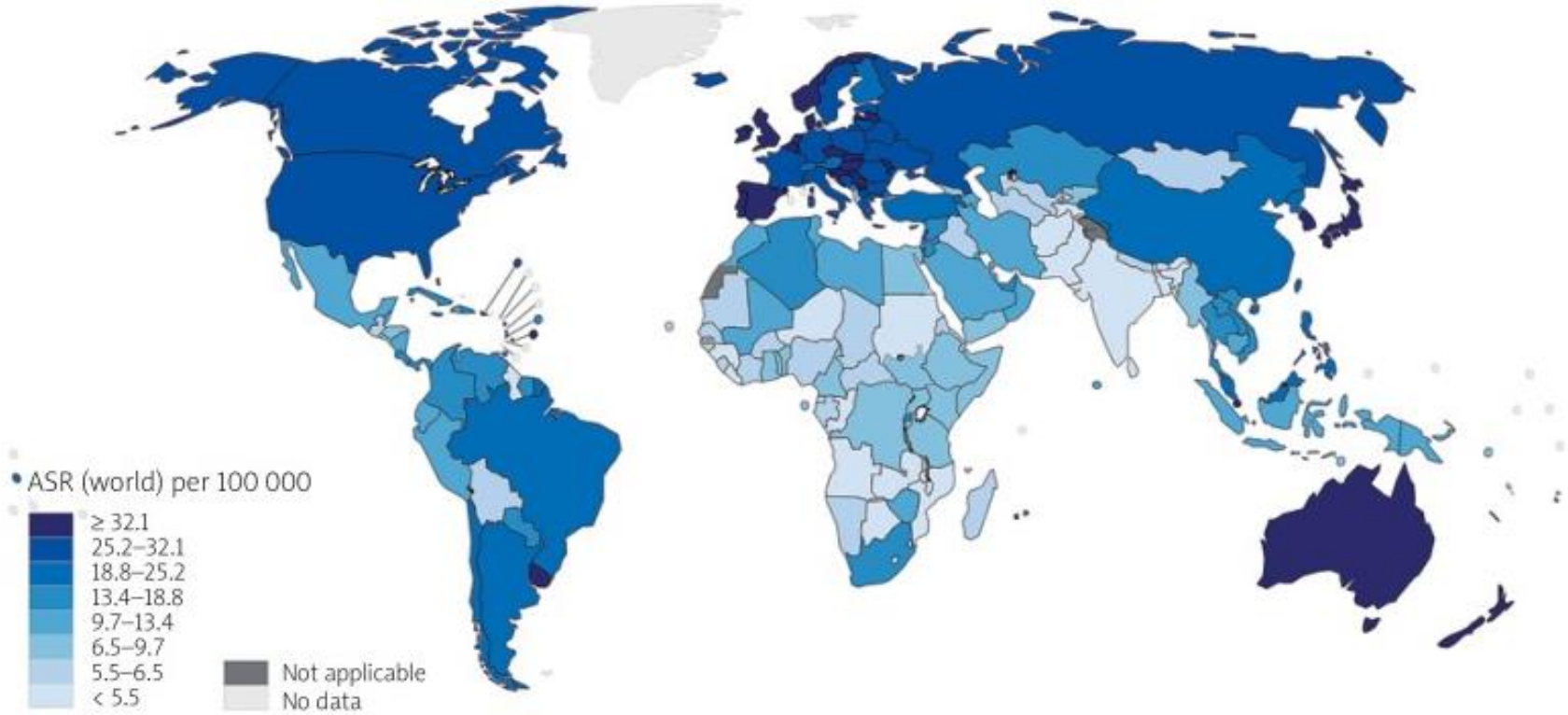
- **Colorectal cancer (CRC) is one of the most frequent neoplasms** and an important cause of mortality
- **CRC** is the **third most commonly diagnosed cancer in males** and the **second in females**

Die häufigsten Krebsarten nach Geschlecht (Inzidenz)

Männer		Frauen	
Prostatakrebs	27.5%	Brustkrebs	31.7%
Lungenkrebs	11.9%	Dickdarmkrebs	10.1%
Dickdarmkrebs	10.9%	Lungenkrebs	9.3%
Schwarzer Hautkrebs (Melanom)	6.6%	Schwarzer Hautkrebs (Melanom)	6.8%
Blasenkrebs	4.1%	Gebärmutterkörperkrebs	4.7%

www.krebsliga.ch

- **CRC ist more incident among men than women (**Age-standardised incidence rates per 100.000 of CRC in both sexes is 19.7, in males is 23.6, and in females is 16.3)
- **CRC** is the **second most deadly cancer worldwide** (about 881000 deaths estimated for 2018)
- About **1.8 million new cases of CRC** are estimated to be diagnosed **in 2018**
- **Developed countries** are at the **highest risk** of CRC
- Globally the incidence varies over 10-fold



Map showing estimated age-standardised incidence rates (world) in 2018, colorectum, both sexes, all ages (reproduced from http://globocan.iarc.fr/ [10])

Gastroenterology Rev 2019; 14 (2): 89–103
DOI: https://doi.org/10.5114/pg.2018.81072

Alle Krebsarten

Jährliche Krebsneuerkrankungen

42’500 neue Krebsfälle pro Jahr.

CRC

Legende –

- Leukämien (Blutkrebs)
- Non-Hodgkin-Lymphom
- Blasenkrebs
- Brustkrebs
- Dickdarmkrebs

Hautkrebs / Melanom (Schwarzer Hautkrebs)
Lungenkrebs
Mundhöhlenkrebs

Bauchspeicheldrüsenkrebs (Pankreaskarzinom)
Prostatakrebs
übrige Krebsarten

Frauen **19’500**

Männer **23’000**

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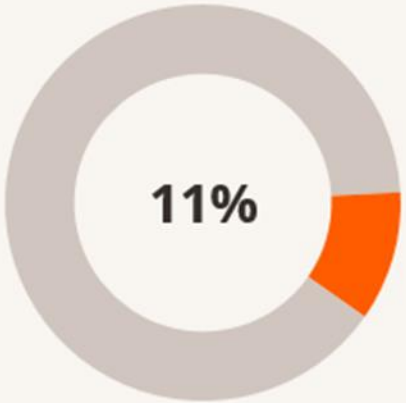
Dickdarmkrebs

‹ Übersicht

Jährliche Krebsneuerkrankungen



4'500 neue Fälle von **Dickdarmkrebs** pro Jahr.

Frauen
2'000

Männer
2'500

Anzahl Krebs-Neuerkrankungen pro Jahr in der Schweiz (Inzidenz)
Zeitperiode 2013-2017

Inzidenz (gerundete Zahlen, geordnet nach Häufigkeit)			
	Männer	**Frauen**	**Total#**
alle Krebsarten*	23'000	19'500	42'500
Brustkrebs	50	6'200	6'250
Prostatakrebs	6'400	0	6'400
Lungenkrebs	2'700	1'800	4'500
Dickdarmkrebs	2'500	2'000	4'500
Schwarzer Hautkrebs (Melanom)	1'500	1'300	2'800
Non-Hodgkin-Lymphom	900	700	1'600
Bauchspeicheldrüsenkrebs	750	750	1'500
Blasenkrebs	950	320	1'270
Krebs von Mundhöhle und Rachen	800	370	1'170
Leukämien	700	450	1'150
Nierenkrebs	700	310	1'010
Magenkrebs	600	340	940
Gebärmutterkörperkrebs	0	950	950
Leberkrebs	650	240	890
Schilddrüsenkrebs	240	550	790
Multiples Myelom	370	290	660
Hirntumore und Tumore des Rückenmarks	380	270	650
Eierstockkrebs	0	650	650
Speiseröhrenkrebs	450	140	590
Hodenkrebs	470	0	470
Krebs von Gallenblase und Gallengang	160	190	350
Weichteilkrebs (Weichteilsarkome)	170	130	300
Hodgkin-Lymphom	160	110	270
Kehlkopfkrebs	220	40	260
Gebärmutterhalskrebs	0	260	260
Dünndarmkrebs	150	110	260
Analkrebs	70	150	220
Malignes Mesotheliom (Brustfellkrebs)	170	30	200
Krebs von Nierenbecken und Harnleiter	120	70	190
Krebs von Knochen, Gelenken und Knorpeln	60	40	100
Augenkrebs	30	30	60
Andere Krebsarten (insgesamt)	650	800	1'450

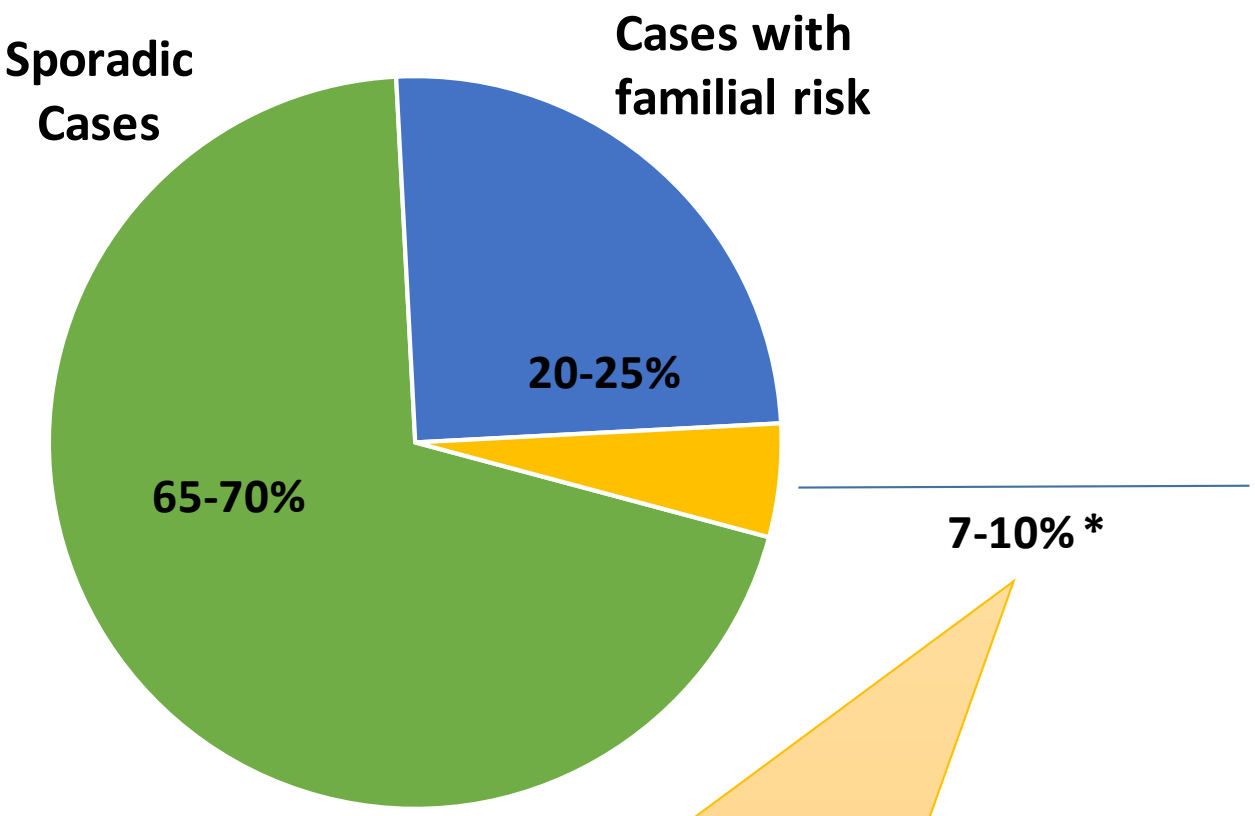
- **CRC results from** both **genetic and environmental factors** and their interaction

- **Sporadic disease** (**70% of CRCs)**
  - Most common over the age of 50y
  - Dietary and environmental factors (including diet, exercise, smoking, obesity) are etilogically implicated

- **Hereditary CRC forms (7-10%;** Lynch-Syndrome and Polyposis syndromes)

- **Familial CRC (25% of CRCs)**
  - Patients have a family history for CRC, but the pattern is not consistent with one of the known inherited syndromes

  - There are probably predisposing germeline mutations that have yet not been indentified
  - It is **likely** that the **amount of inherited syndromes is a little bit underestimated.**



Identifying those **patients** who have an inherited cancer predisposition syndrome has **significant benefit to** both the **patient and at-risk releatives with implications on**

- **Screening**
- **Management**
- **Surveillance strategies**

Hereditary CRC

- **Lynch Syndrome (2-4%)**
- **Polyposis Syndromes**
  - FAP/AFAP
  - Gardner`s syndrome
  - Turcot syndrome
  - MUTYH-associated polyposis (MAP)
  - Juvenile polyposis syndrome (JPS)
  - Peutz-Jeghers syndrome (PJS)
  - Polymerase proofreading-associated polyposis (PPAP)
  - PTEN hamartoma tumors syndrome (PHTS)
  - Cowden syndrome

*** 315 -450 newly diagnosed cases per year in CH**

Two subtypes of hereditary CRC

- Absence of colorectal polyposis
- **Presence of colorectal polyposis**

Adenomatous polyposis syndromes

- Familial adenomatous polyposis FAP)
- Attenuated FAP (AFAP)
- MUTYH associated polyposis (MAP)

Hamatomatous polyposis syndromes

- Peutz Jeghers Syndrome (PS)
- Juvenile polyposis syndrome (JPS)
- Cowden syndrome

Serrated polyposis syndrome

Familial cases of SPS **have been reported. Genetic etiology** has yet **not** been **defined**

Condition	Gene	Inheritance pattern
Familial adenomatous polyposis (FAP) (classic and attenuated FAP)	APC	Autosomal dominant
Gardner's syndrome (variant of FAP)	APC	Autosomal dominant
Turcot syndrome (variant of FAP)	APC, MLH1 or PMS2	Autosomal dominant or autosomal recessive
Hereditary non-polyposis colorectal cancer (HNPCC) syndrome (Lynch syndrome)	MLH1, MSH2, MSH6, EpCAM and PMS2	Autosomal dominant
MUTYH-associated polyposis (MAP)	MUTYH, APC	Autosomal recessive
Juvenile polyposis syndrome (JPS)	SMAD4 (MADH4), BMPR1A (ALK3)	Autosomal dominant
Peutz-Jeghers syndrome (PJS)	STK11 (LKB1)	Autosomal dominant
Polymerase proofreading-associated polyposis (PPAP)	POLE, POLD1	Autosomal dominant
PTEN hamartoma tumors syndrome (PHTS)	PTEN	Autosomal dominant
Cowden syndrome	PTEN	Autosomal dominant
Familial colorectal cancer type X	BRCA2, KRAS, APC, NTS, BRAF, BMPR1A, and RPS20	Autosomal dominant

Table I. Common hereditary syndromes associated with CRC, genes involved, and pattern of inheritance

Lynch syndrome (absence of colorectal polyposis)

Familial adenomatous polyposis (FAP)

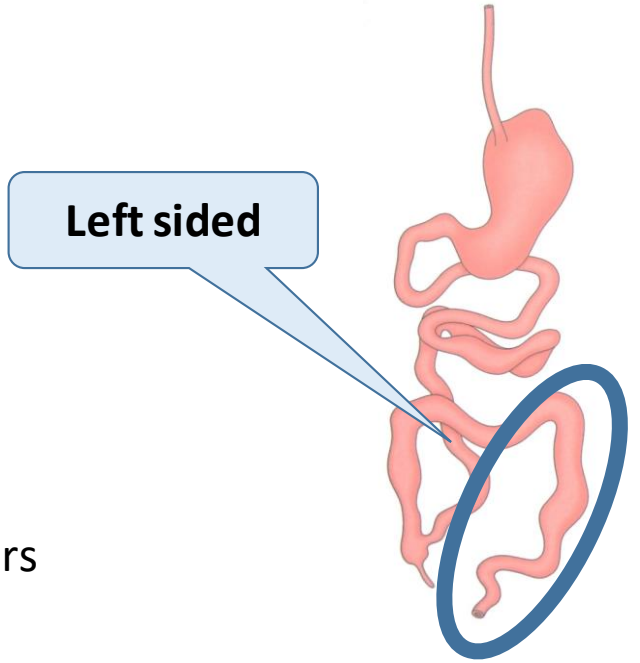
- Most common polyposis syndrome
- **Epidemiology**
  - Accounts for approximately 1% of all CRC cases
  - Prevalence: three cases per 100.000 individuals
- **Genetics**
  - Caused by **germeline mutations** in the **Adenomatous Polyposis Coli (APC) Gen** (tumor suppressor gene, located on chromosome 5)
  - **Autosomal dominant disease**
  - APC mutation in up to 90% of patients with FAP
  - **De novo mutations**
    - **Up to 25%** of FAP cases are due to new or de novo mutations

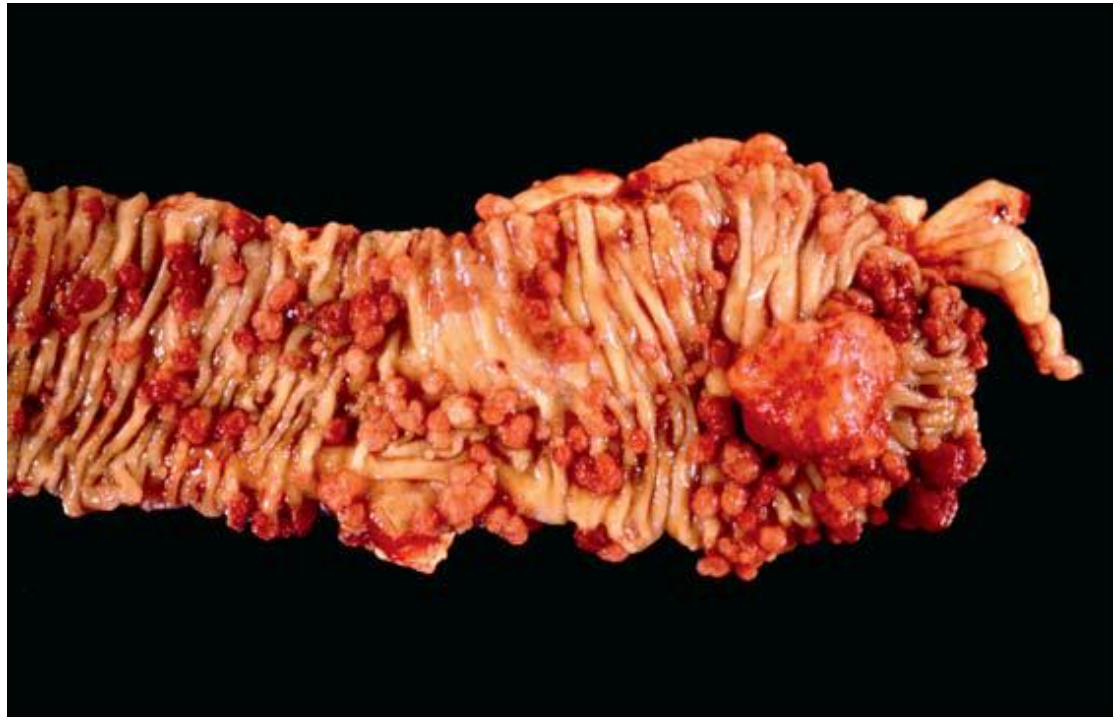
Familial adenomatous polyposis (FAP)

- **Clinical manifestations**
  - Colonic manifestations
  - Extracolonic manifestations

Familial adenomatous polyposis (FAP)

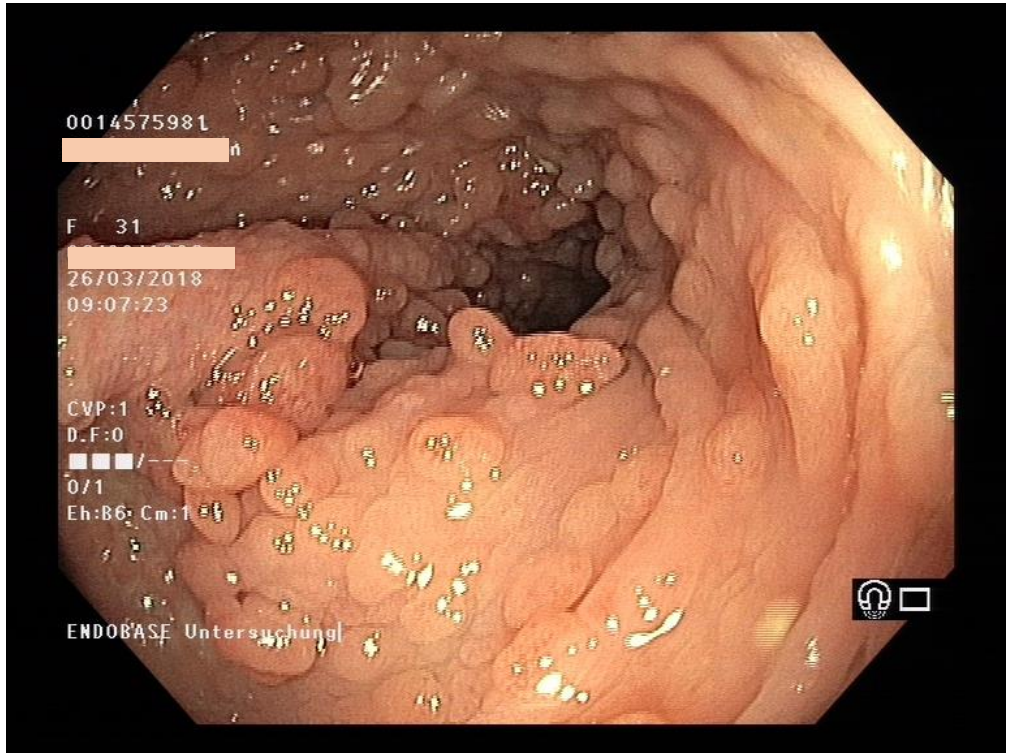
- **Clinical manifestations**
  - **Colonic manifestations ?**
    - Development of **100`s to 1000`s of adenomatous polyps**
    - **Polyps begin to develop** during the **second decade of life**
    - Nearly **100% of untreated patients will have malignancy** by age 40-50 years
    - Approx. 40% of individuals with CRC have **synchronous malignancies**
    - 80% of tumors are **left sided**
    - 90% of adenomas are **<0.5 cm**
    - < 1% of polyps > 1 cm

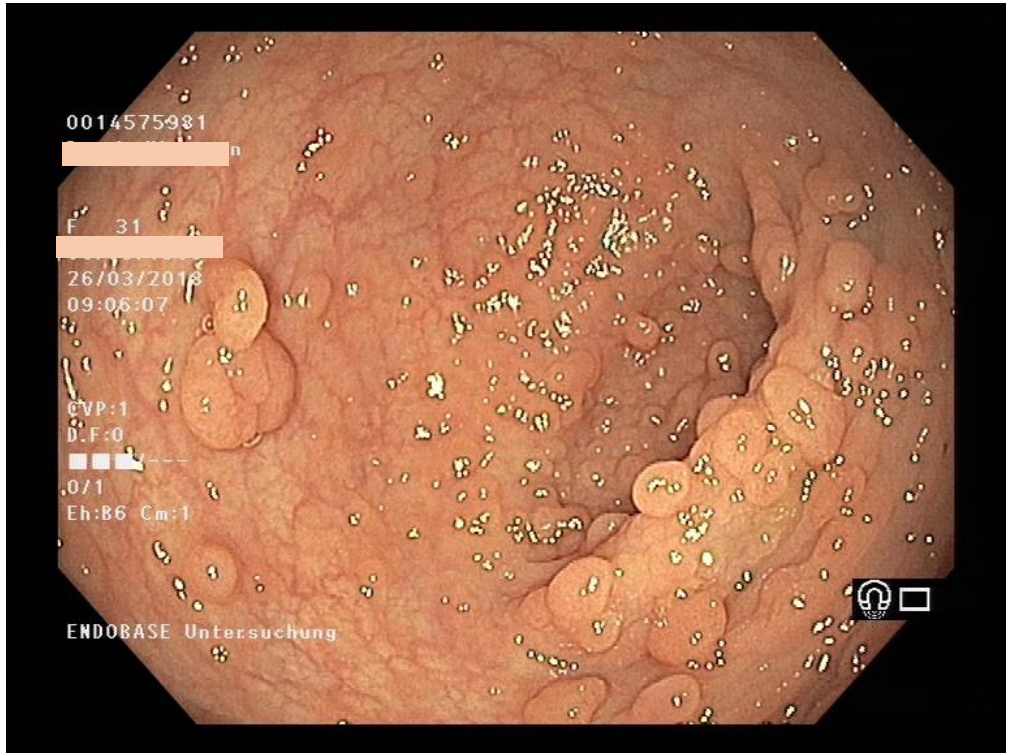


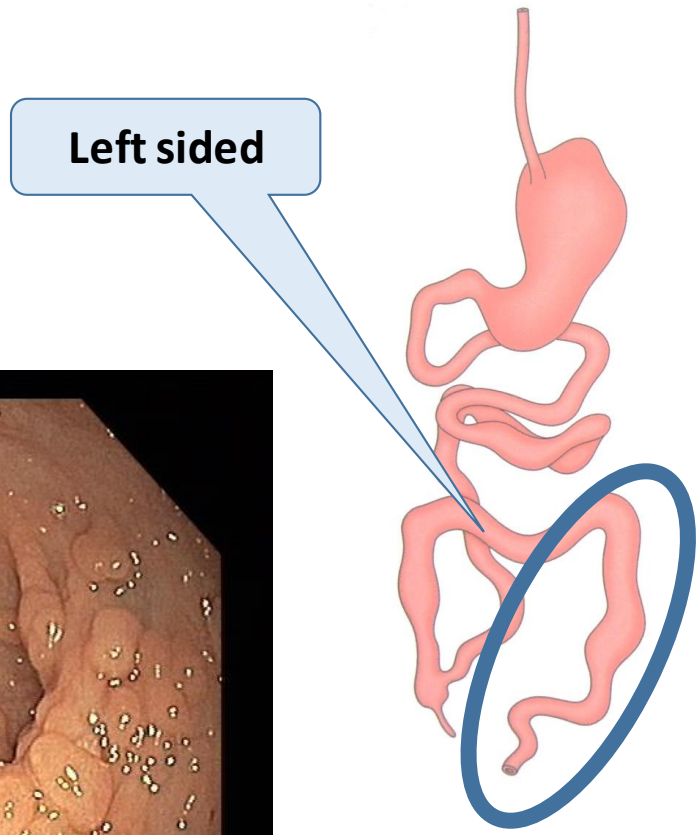


Familial adenomatous polyposis (FAP)

- **Clinical manifestations**
  - **Colonic manifestations**







Familial adenomatous polyposis (FAP)

- **Clinical manifestations**
  - Colonic manifestations
  - Extracolonic manifestations

- **Extracolonic manifestations within the GI-tract**
- **Extraintestinal manifestations**

Familial adenomatous polyposis (FAP)

- **Extracolonic manifestations within the GI-tract ?**

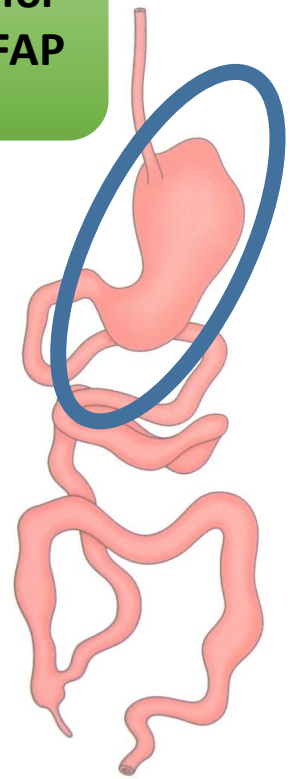
Fundic gland polyps

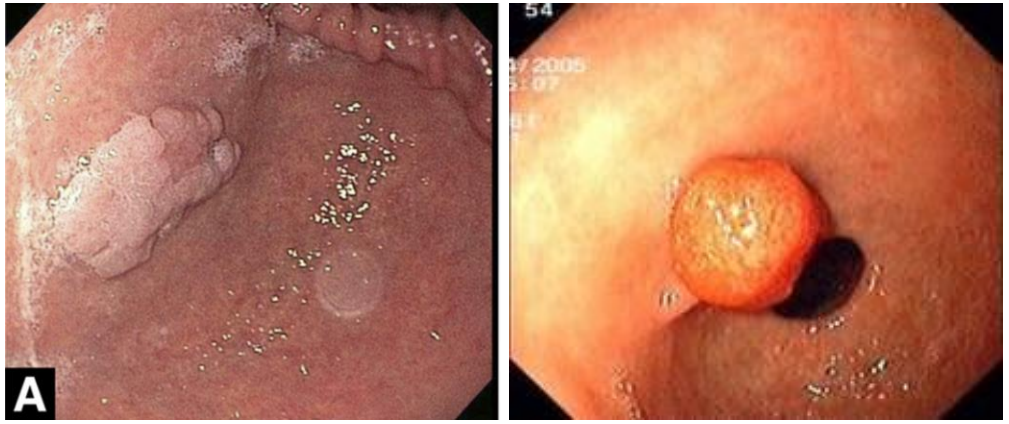
- Are found in **most patients** wit FAP (90% of pat.)
- **Low grade dysplasia** occurs **in nearly half of fundic gland polyps**, although they **rarely progress to cancer**

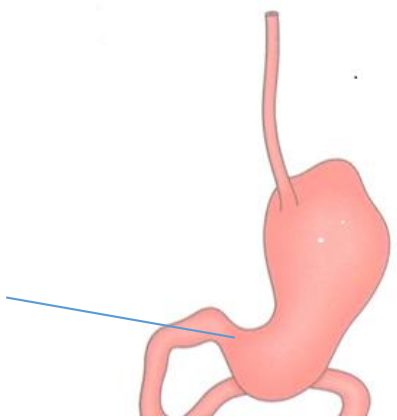
Gastric adenomas

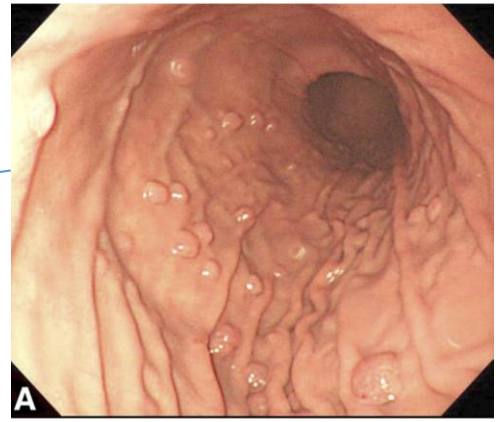
- Are much **less common than fundic gland polyps** (<10% of pat. with FAP)
- Are typically isolated, located in the **antrum**
- Are associated with a **relatively low risk of progression to cancer**

Lifetime risk of gastric cancer for patients with FAP <1%







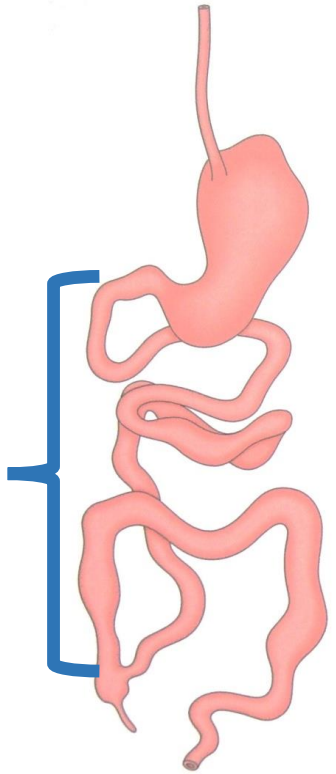


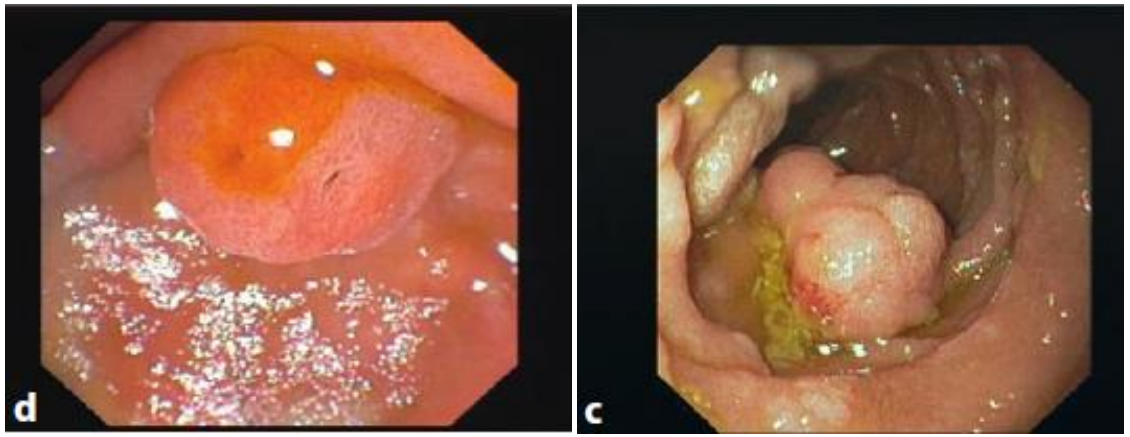
Familial adenomatous polyposis (FAP)

- **Extracolonic manifestations within the GI-tract**

  Duodenal adenomas
  - Occur in **45 to 90% of pat**. with FAP
  - Predilection for the **ampullary and periampullary region**
  - Can develop into **adenocarcinoma** with a **lifetime risk of 5-10%**

  Small bowel polyps
  - Rate of jejunal and ileal polyps: 30-75%
  - 50% of cases in the prox. Jejunum, 20% in term. Ileum
  - **Risk of malignancy is much lower compared duodenal adenomas**





Onkologe 2021 · 27:203–218

Familial adenomatous polyposis (FAP)

- **Extracolonic manifestations within the GI-tract**
  - Duodenal adenomas (found in 90% of pat.) – **Spigelmann classification** (Gold standard for the risk-stratification of duodenal cancer)

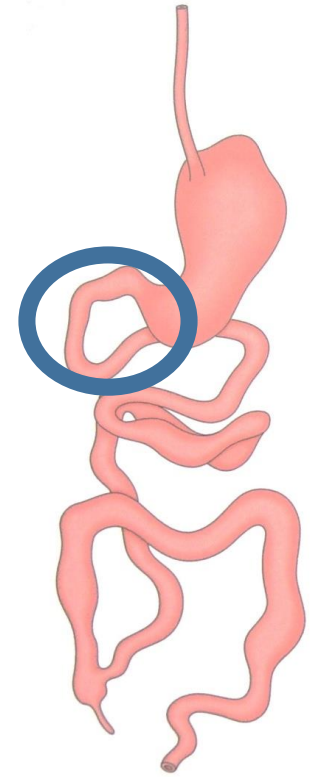
Table 3 Staging the duodenum and ampulla and recommended OGD surveillance intervals

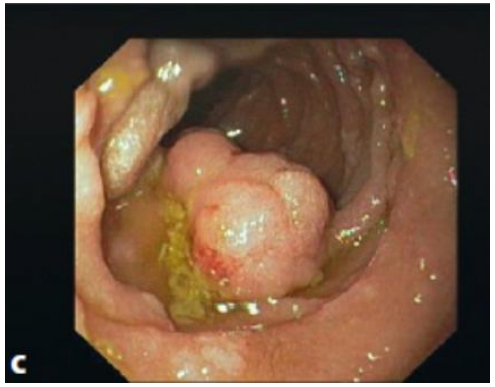
	Points allocated		
	1	2	3
Number of polyps	1–4	5–20	>20
Polyp size (mm)	1–4	5–10	>10
Histological type	Tubular	Tubulovillous	Villous
Degree of dysplasia	Mild	Moderate	Severe

OGD, oesophago-gastro-duodenoscopy.

Total points	Spigelman stage	Recommended follow-up interval
0	0	5 years
1–4	I	5 years
5–6	II	3 years
7–8	III	Annual and consider endoscopic therapy
9–12	IV	6–12 months and consider endoscopic or surgical therapy

Lifetime risk of adenocarcinoma 5-10%





Monahan KJ, et al. Gut 2020;**69**:411–444

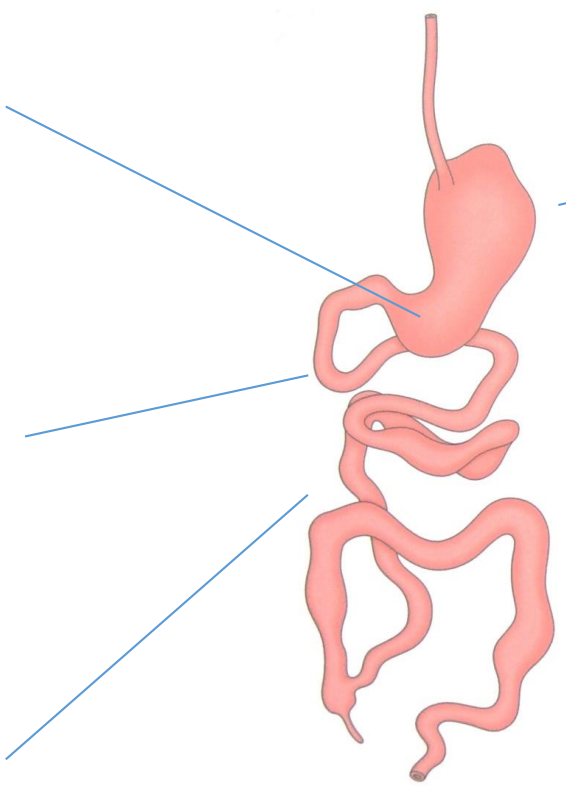
Familial adenomatous polyposis (FAP)

- **Colonic and extracolonic manifestations within the GI-tract**

Gastric adenomas
- <10% of patients
- isolated
- Low risk of malignancy

Duodenal adenomas
- 45-90% of pat.
- 4-10% risk of malignancy (Spigelmann class.)

Small bowel polyps
- 30-75% of pat.
- Low risk of malignancy

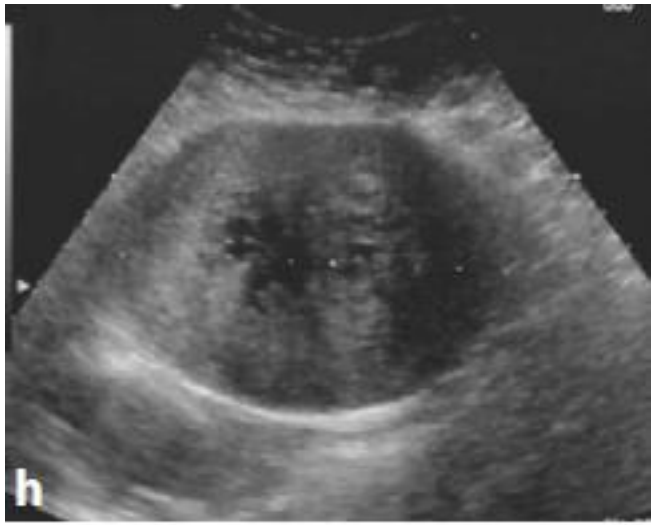


Fundic gland polyps
- Most patients
- 50% low grade dyplasia
- Rarely progress to cancer

Polyps
- Left sided (80%)
- Nearly 100% risk of malignancy

Familial adenomatous polyposis (FAP)

- **Extraintestinal manifestations of FAP**
  - Benigns extraintestinal manifestations
  - Malignant extraintestinal manifestations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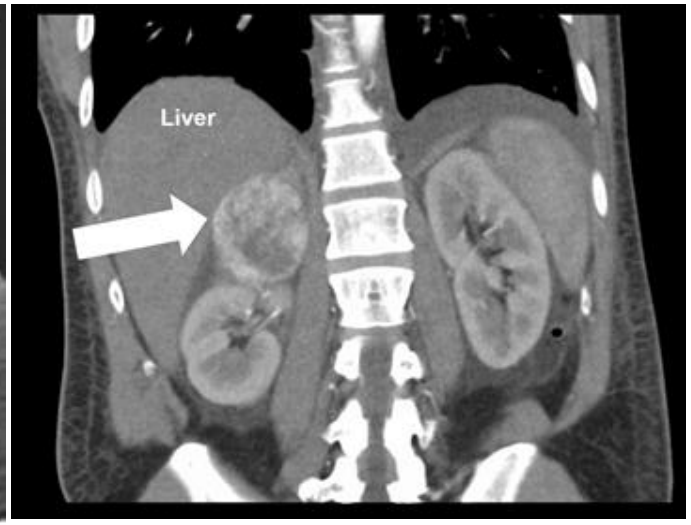
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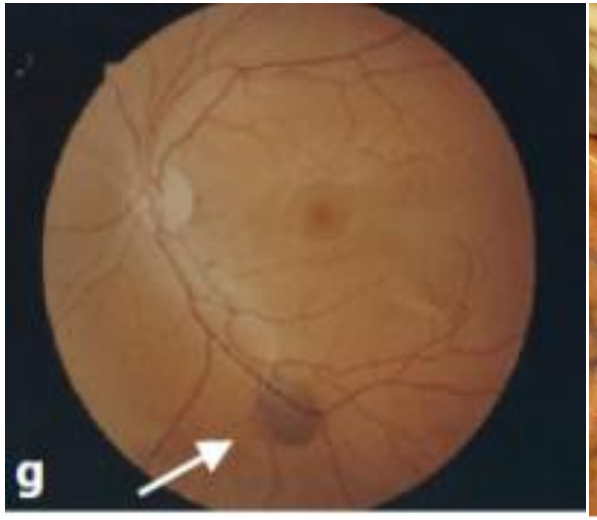
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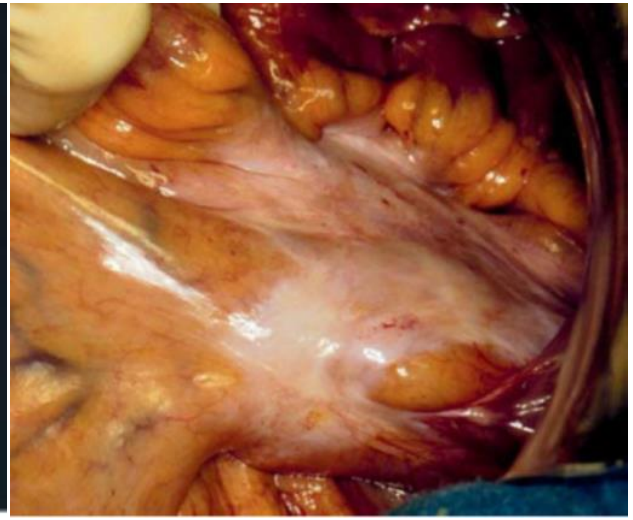

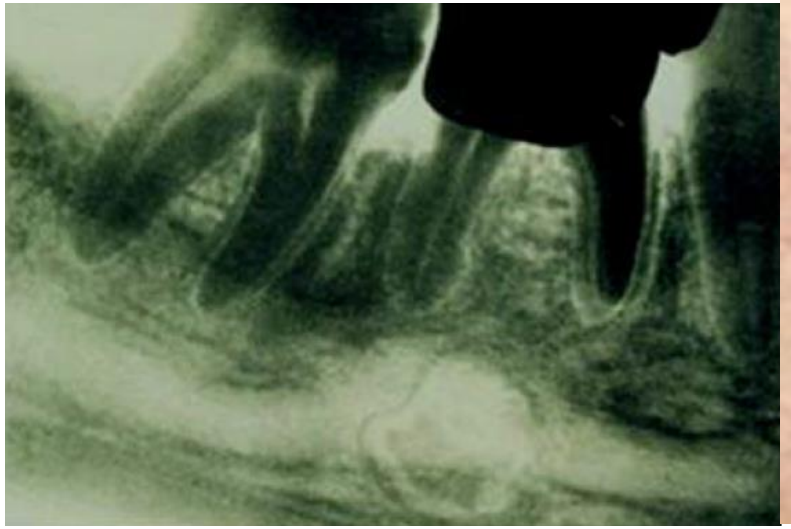

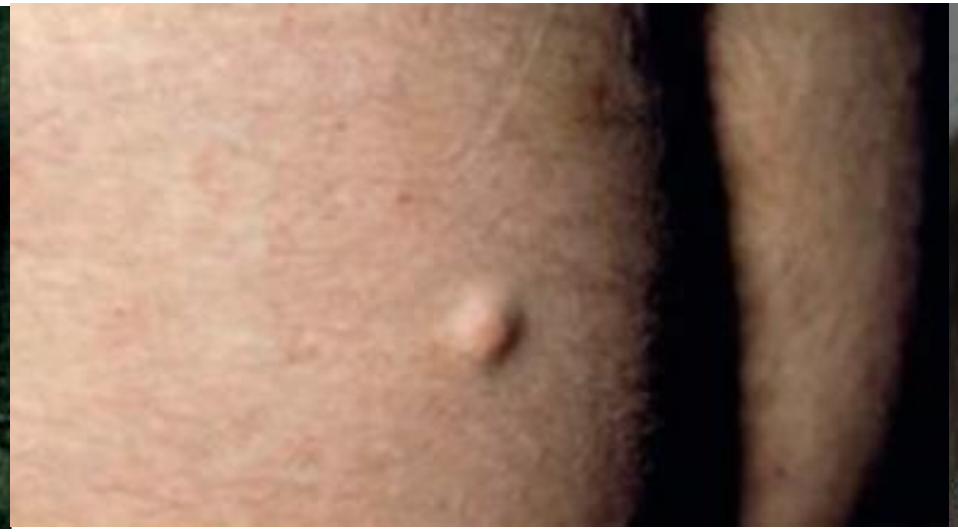

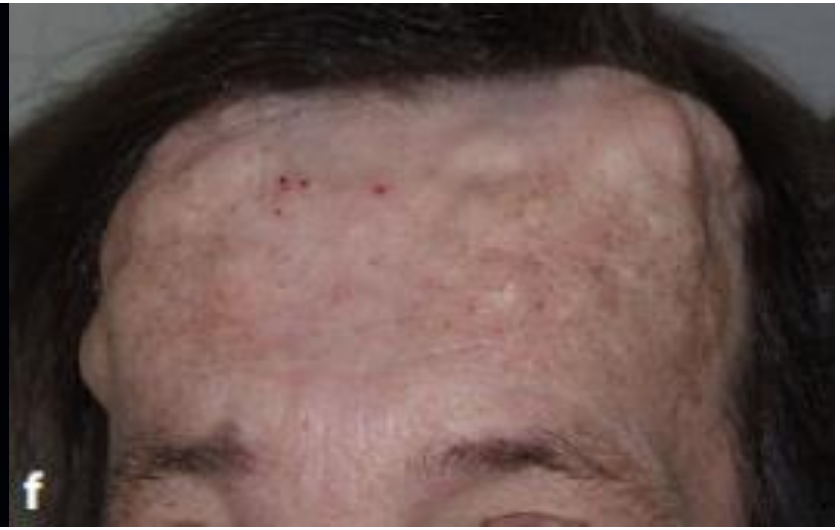
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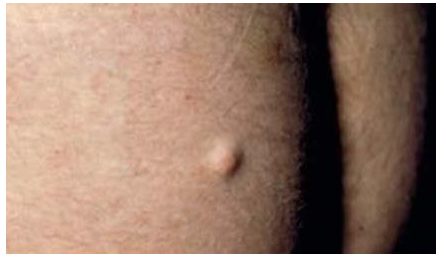
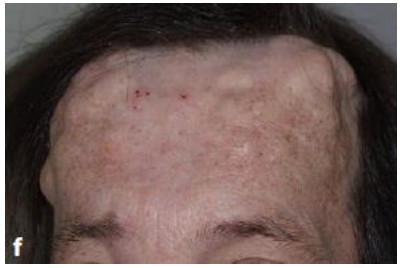
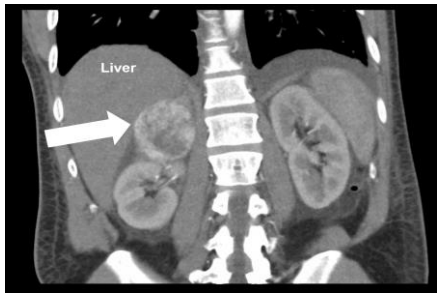
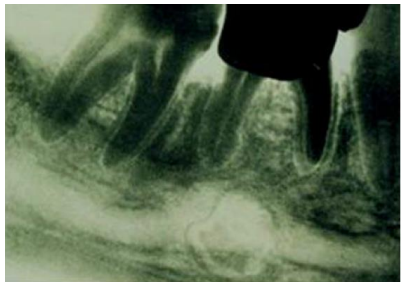
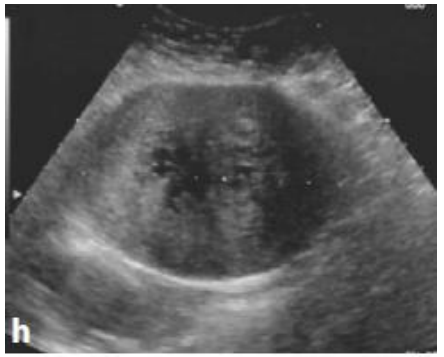
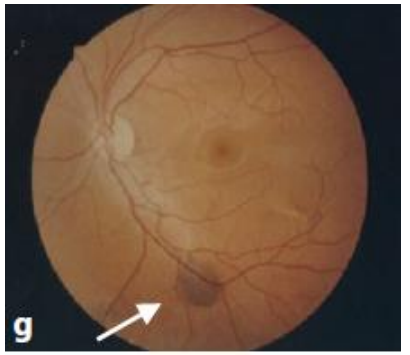
Familial adenomatous polyposis (FAP)

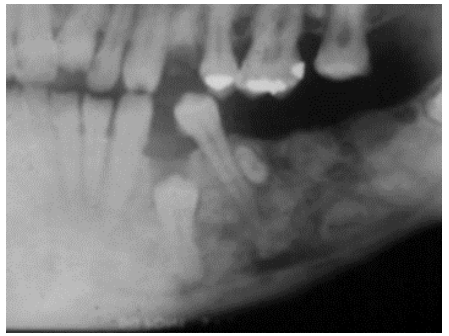
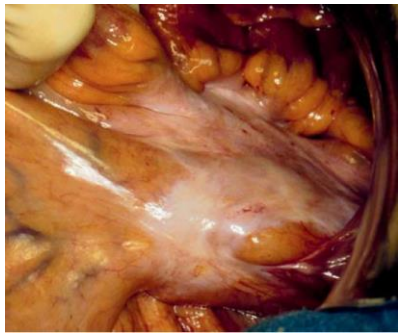
- **Benign extraintestinal manifestations ?**
  - **Cutaneous lesions**: fibromas, lipomas and epidermoid cysts
  - **Osteomas**
  - **Dental abnormilities**
  - **Congenital hypertrophy of the retinal pigment epithelium** (CHRPE; 58% of pat.)
  - **Desmoid tumors**
    - Solid tumors of the connective tissue
    - Approx. 20% of pat. wth FAP
    - Slow growing, do not metastasize
    - Can cause severe morbidity and mortality (enlargement with pressure on GI or urinary tract, local nervous or vascular system)
  - **Adrenal tumors**
    - Lifetime prevalence 7-13% in FAP pat.
    - Are rarely malignant, routine surveillance is not recommended



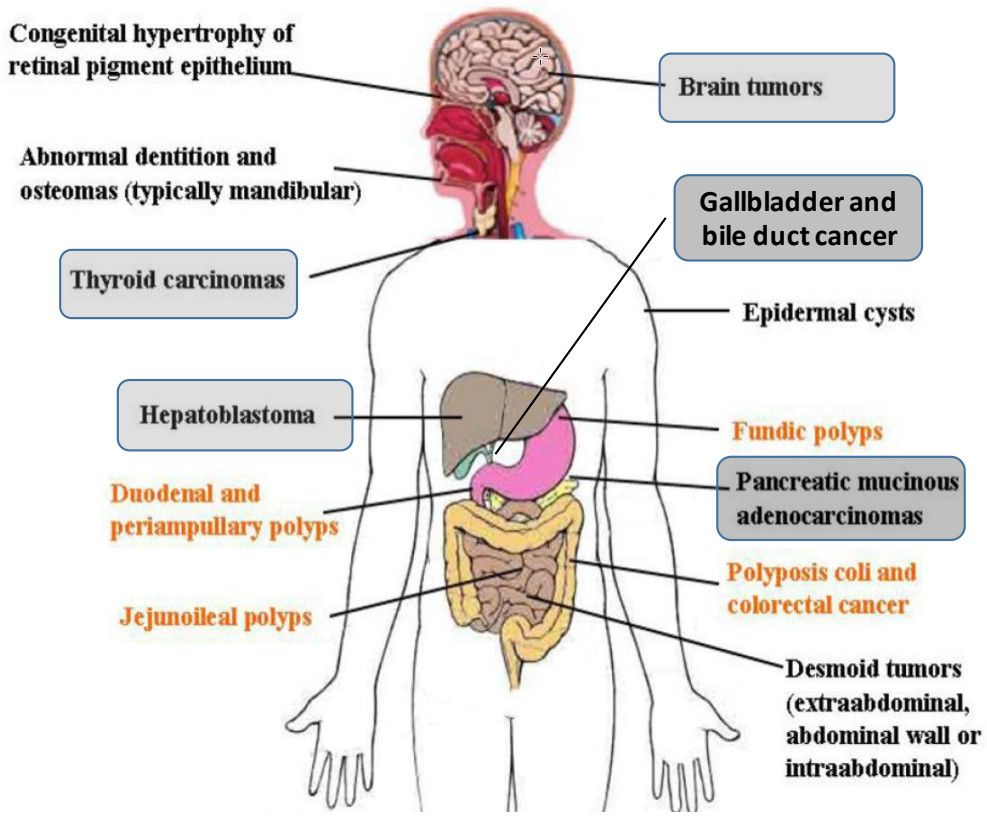


- Adrenal.com
- Allgemein-und Viszeralchirurgie up2date,2010, 277-295
- Onkologe 2021, 27:203-218

Familial adenomatous polyposis (FAP)

- **Malignant extraintestinal manifestations ?**
  - **Hepatoblastoma**
    - 1.6% of FAP patients
    - Male predominance
    - Most often occur in the first 5 y of life
  - **Brain tumors**
    - 1-2% of FAP patients
    - In 80% of cases medulloblastoma
  - **Thyroid cancer**
    - Up to 12% (2-12%) of FAP patients
    - Mean age of diagnose 28 y
    - Female predominance (90% of cases)
  - **Gallbladder, bile duct and pancreas cancer ?**
    - Adenomatous change and cancer have been reported
    - Pancreas cancer: 1.7% of pat. (gen. population risk 1.5%)



European Society of Radiology; www.myESR.org

Familial adenomatous polyposis (FAP)

- **FAP variants**
  - Gardner syndrome
  - Turcot syndrome
  - **Attenuated FAP**

Constellation of inherited colonic adenomatosis with extracolonic manifestations

Gardner, in the early 1950s, described a kindred with intestninal characteristics of familial adenomatous polyposis (FAP), but also with a number of extracolonic growths, including osteomas, epidermals cysts and fibromas. Dental abnormilities, desmoid tumors were later recognized as additional manifestations of the underlying genetic defect

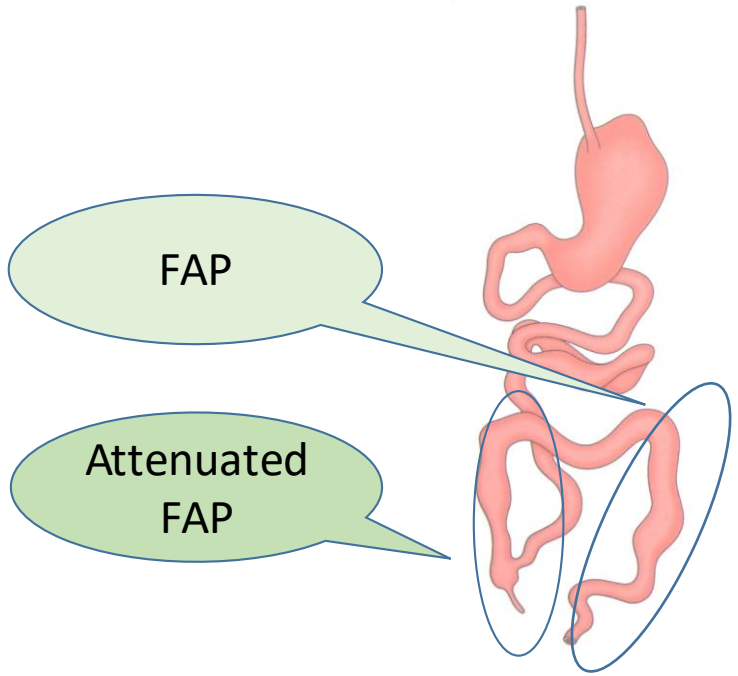
Brain tumor polyposis syndrome is a historical term that originally describbed the a**ssociation of familial colon cancer and brain tumors**

Familial adenomatous polyposis (FAP)

FAP
- Second decade of life
- Nearly 100% malignancy by age 40-50y

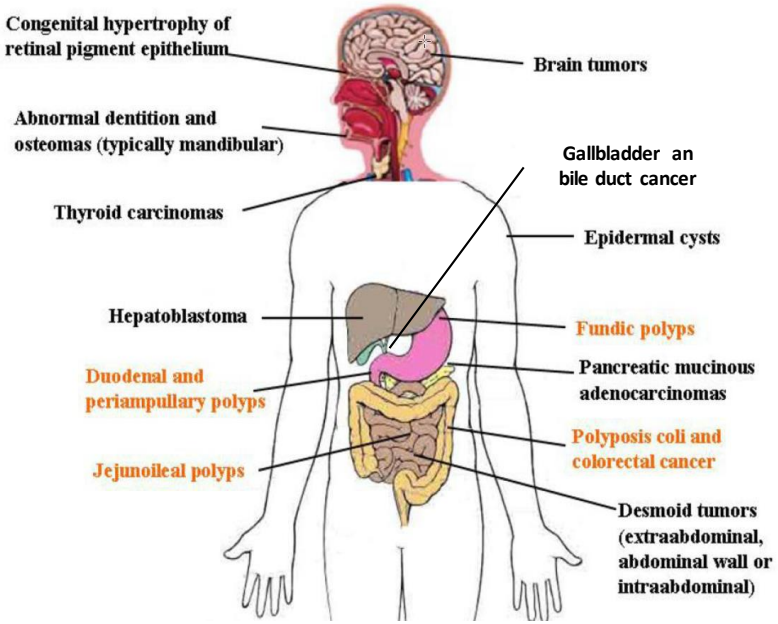
- **Attenuated FAP**
  - **Less aggressive variant** characterized by
    - **fewer** colorectal adenomatous **polyps** (usually 10-100)
    - **Later age of adenoms** appearance (mean age at diagnosis 44y) **and cancer** (56y)
    - Mainly **proximal colonic involvement**
    - **80% lifetime risk for CRC**
    - **APC mutation in 15-30% of patients** with AFAP

    - **Most predominant extracolonic findings**
      - Duodenal and gastric adenomas
      - Fundic gland polyps
      - Hepatoblastoma
      - Gastric and breast adenocarcinoma
      - Other extracolonic manifestations of FAP are rare



Familial adenomatous polyposis (FAP)

- **Diagnosis**
  - **FAP should be suspected ?**
    - In pat. with 10 or more cumulative colorectal adenomas
    - In pat. with a history of colorectal adenomas in combination with extracolonic features
  - **Genetic testing should be performed for ?**
    - **FAP and MUTYH-associated polyposis (MAP), overlapping clinical features**
    - **Other polyposis asscociated genes (**Mutationen in den Genen POLD1 und POLE; Polymerase-Proofreading-Associated Polyposis, PPAP)
  - **If APC mutation is identified, genetic testing should be offered to at-risk relatives**
    - All first-degree relatives (FDR) of the index case
    - All FDR of those found to have an APC mutation
    - Second-degree relatives when a family member declines genetic testing or has died



Familial adenomatous polyposis (FAP)

- **Screening and management**
  - **Candidates for screening**
    - **Individuals with a pathogenic APC mutation**
    - **Individuals at-risk for** APC who have **not undergone genetic testing** or have indeterminate genetic test results

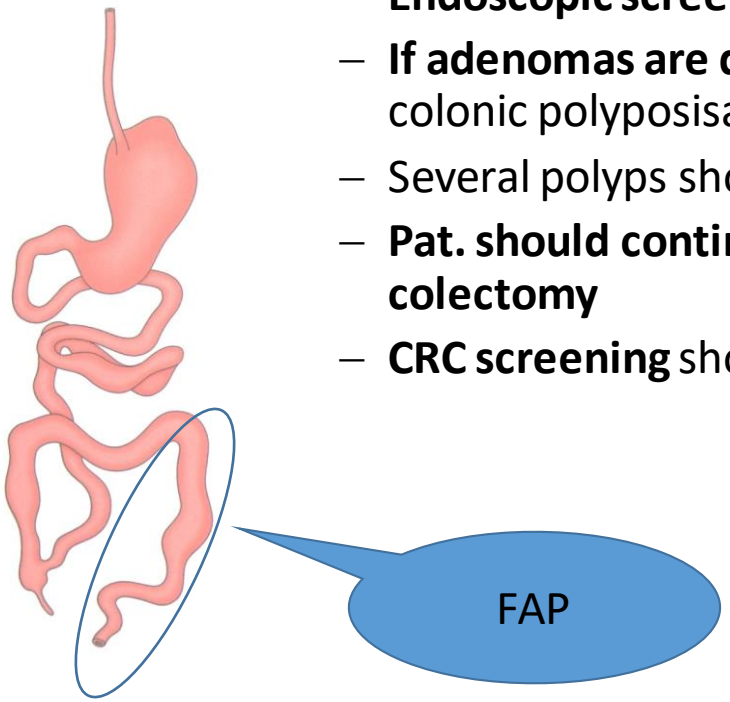
Individuals at-risk

- FDR of those with FAP
- Individuals with >10 cumulative colorectal adenomas
- Individuals with colorectal adenomas in combination with extracolonic features associated with FAP

Familial adenomatous polyposis (FAP)

- **Screening** and management
  - **CRC screening and surveillance**
    - **Classic FAP**
      - **Endoscopic screening** with **sigmoidoscopy** should be **started** around age **10-12y**
      - **If adenomas are detected a full colonoscopy** should be performed to evaluate the extent of colonic polyposisand for planing colectomy (number, size and distribution of polyps)
      - Several polyps should be sampled to confirm histology
      - **Pat. should continue to undergo annual colonoscopy** (CRC screening) **while awaiting colectomy**
      - **CRC screening** should be repeated **annually** and continued lifelong **in APC mutation carriers**

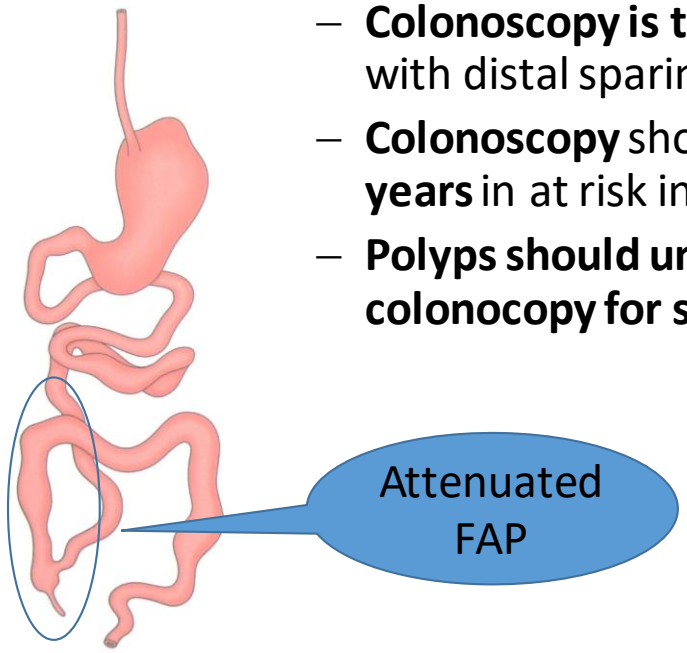
Nearly 100% of untreated patients will have malignancy by age 40-50y



Familial adenomatous polyposis (FAP)

- **Screening** and management
  - **CRC screening and surveillance**
    - **Attenuated FAP**
      - **Colonoscopy is the preferred CRC screening modality** (higher risk of proximal lesions with with distal sparing)
      - **Colonoscopy** should be **started at the age of 25y** and should be performed **every one to two years** in at risk individuals
      - **Polyps should undergo endoscopic resection** (all detected polyps) **followed be annual colonocopy for surveillance**

Later age of adenoma appearance and fewer polyps



Familial adenomatous polyposis (FAP)

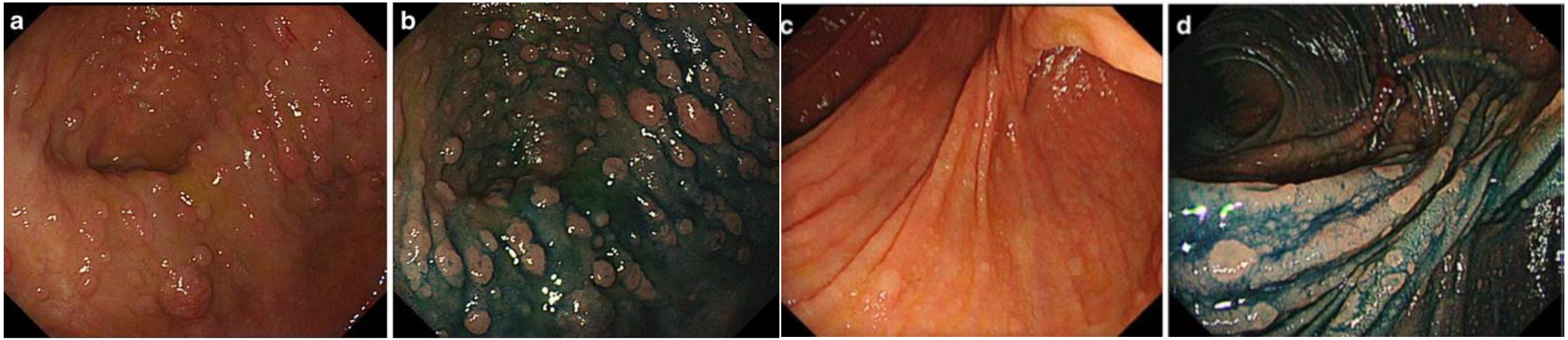
- Screening and **management**
  - **Classic FAP**
    - **Surgery**
      - Recommended for all patients
      - **Poctocolectomy with ileal pouch anal anastomosis (IPAA)**
        - More extensive surgery (pelvis dissection)
        - Reduction of fertility
        - Worse bowel function
      - **Total colectomy with ileorectal anastomosis (IRA)**
        - Complication rate is low
        - Bowel function is usually good
  - **Attenuated FAP**
    - If **endoscopic control** is feasible, surveillance can obviate or delay the need for colectomy

Nearly 100% of untreated patients will have malignancy by age 40-50y

Decision depends on
- Age
- Severity of polyposis
- Risk of developing demoids
- Wish to have children

Familial adenomatous polyposis (FAP)

- **Screening and management**
  - **Surveillance following colectomy ?**
    - Colectomy does not completely eliminates the risk for cancer
    - Adenomas/Tumors may arise from the anal transition zone or within the ileal pouch
    - **Endoscopic evaluation of the rectum or ileal pouch** should be performed **annually**



J Gastrointest Surg (2009) 13:1266–1273

Familial adenomatous polyposis (FAP)

- **Screening and management**
  - **Surveillance following colectomy ?**
    - Colectomy does not completely eliminates the risk for cancer
    - Adenomas/Tumors may arise from the anal transition zone or within the ileal pouch
    - **Endoscopic evaluation** of the **rectum or ileal pouch** should be performed **annually**

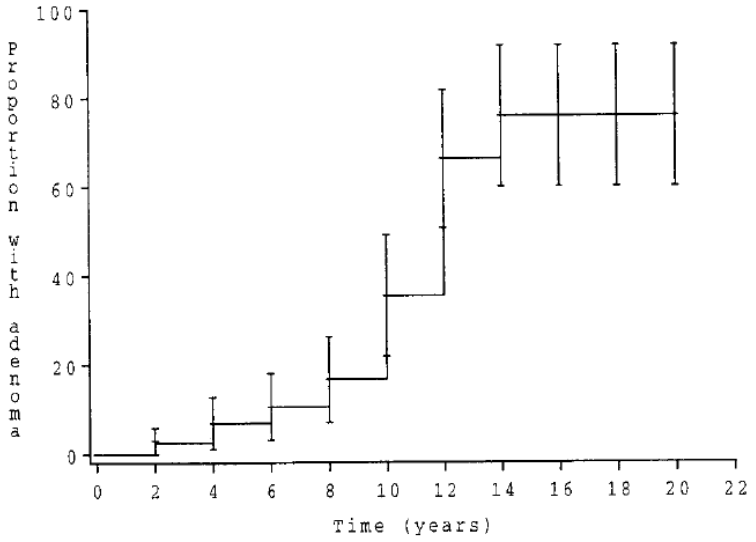


Figure 1. Risk curve to develop adenoma of the pouch after restorative proctocolectomy with construction of an ileal reservoir.

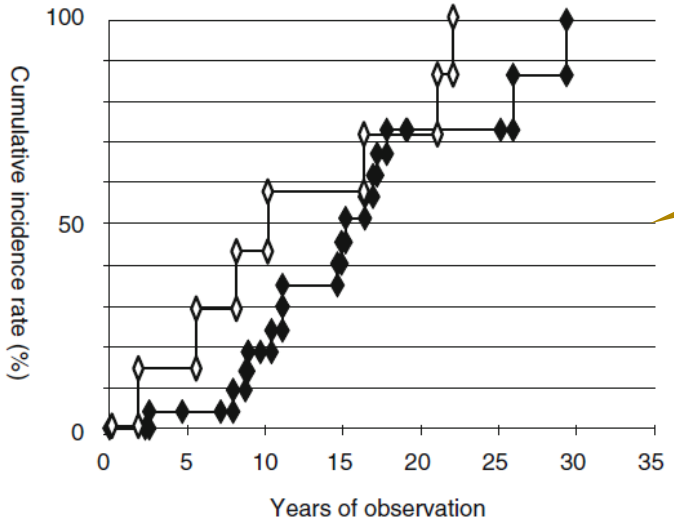
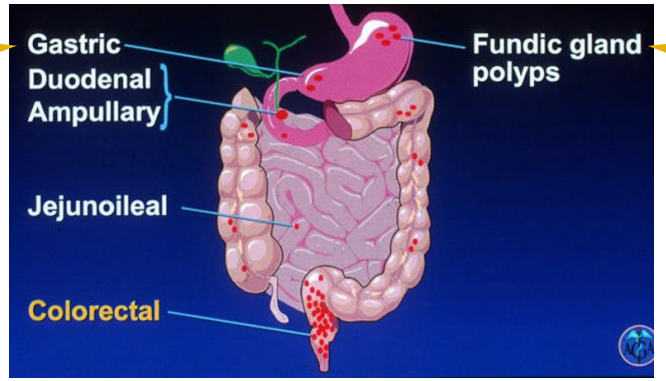


Figure 2 Cumulative incidence rate of adenomas in the ileal pouch after proctocolectomy with Kock and IPAA (*closed diamond*) and that of rectal adenomas after colectomy with IRA (*open diamond*).

Risk of adenoma in the **pouch** was **13%, 43%, and 72% at 5, 10, and 20 years** of follow-up

Familial adenomatous polyposis (FAP)



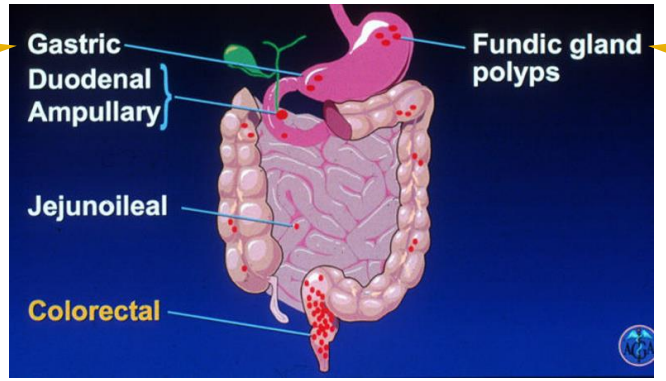
- **Screening and management**
  - **Upper gastrointestinal tumours**
    - **Duodenal adenomas** occur in **45-90% of pat.** with FAP with a **predilection** for the **ampullary and periampullary regions. Lifetime risk of 4-10% to develop into adenocarcinoma**
    - **Fundic gland polyps** (found in most pat. with FAP) **and gastric adenomas** (< 10% of pat.) are associated with a relatively **low risk of progression to cancer**
  - **Screening for upper GI tumors ?**
    - **Upper endoscopic screening** (forward- and side-viewing) should be **initiated in pat. with classic FAP and AFAP at the onset of colonic polyposis or around age 25-30y** (whichever comes first)
    - In patients **without duodenal adenomas upper endoscopy** should be repeated **every three years**

Familial adenomatous polyposis (FAP)

- Screening and **management**
  - **Upper gastrointestinal tumours**

Less commons

45-90% of pat. (risk of cancer)



Most patients

- **Fundic gland polyps**
  - Lage or irregular appearing polyps should be biopsied or resected
  - Surgery/endoscopic resection should be reserved for high grade dysplasia or cancer

- **Gastric adenomas**
  - Usually located in the antrum
  - Should be resected endosopically

Lifetime risk for adenocarcinoma 4-10%

- **Duodenal adenomas**
  - Polyps should be resected (>10 mm) or sampled
  - The frequency of upper endoscopic surveillance and treatment varies based on the severity of duodenal polyposis (Spigelmann 0 to IV)
  - Surgery should be performed in pat. with stage IV polyposis

- **Duodenal adenomas – Spigelmann classification** (gold standard for risk stratification of duodenal cancer

Table 3 Staging the duodenum and ampulla and recommended OGD surveillance intervals

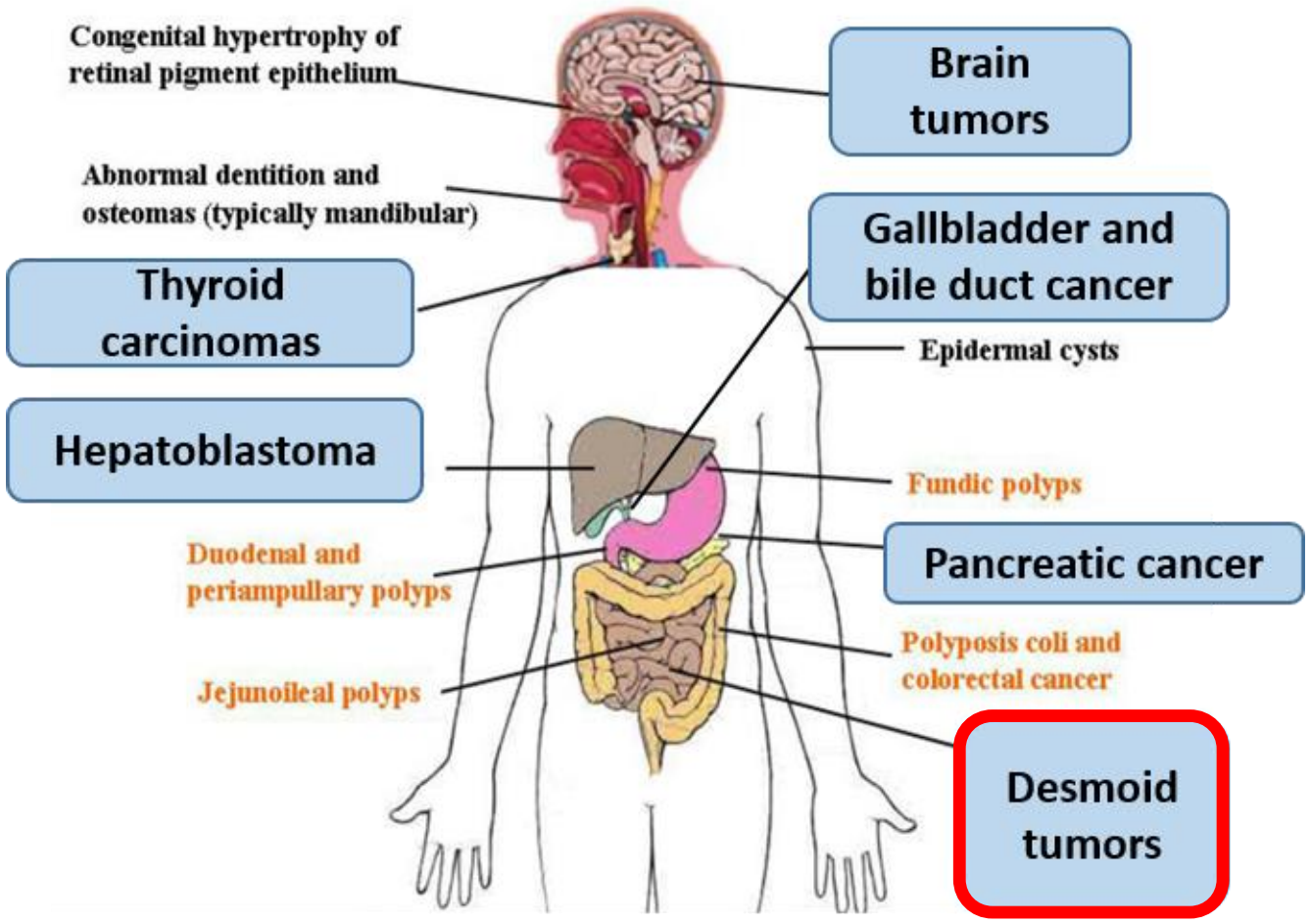
	Points allocated		
	1	2	3
Number of polyps	1–4	5–20	>20
Polyp size (mm)	1–4	5–10	>10
Histological type	Tubular	Tubulovillous	Villous
Degree of dysplasia	Mild	Moderate	Severe

OGD, oesophago-gastro-duodenoscopy.

Total points	Spigelman stage	Recommended follow-up interval
0	0	5 years
1–4	I	5 years
5–6	II	3 years
7–8	III	Annual and consider endoscopic therapy
9–12	IV	6–12 months and consider endoscopic or surgical therapy

Familial adenomatous polyposis (FAP)

- **Extraintestinal malignancies ?**



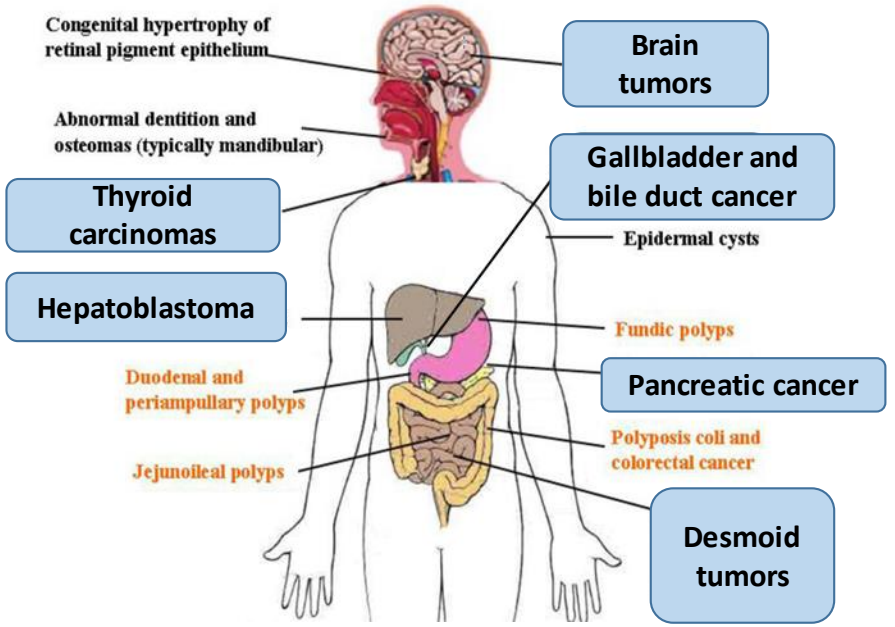
Familial adenomatous polyposis (FAP)

• Screening and management

– Extraintestinal malignancies

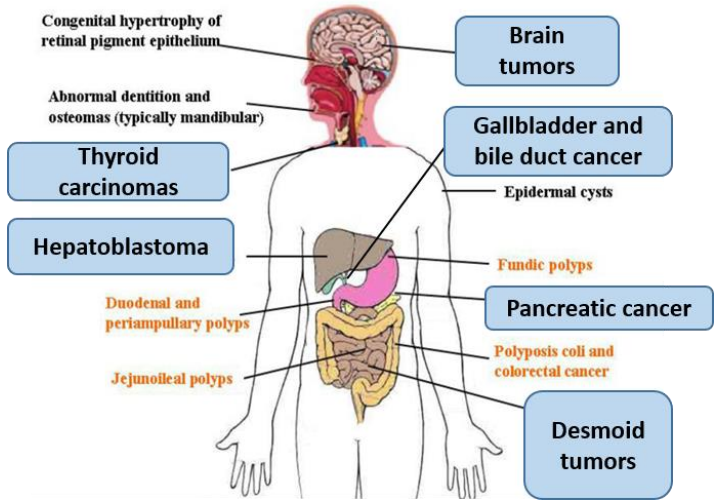
- **Thyroid cancer**
  - **Young women** are at particulary high risk (mean age 28y)
  - 80% of **FAP patients** have a nodular thyroid, **12% develop thyroid cancer**
  - **Screening:** annual US starting in the late teens

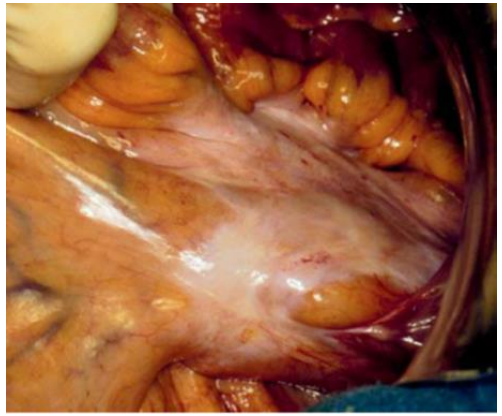
- **Hepatoblastoma**
  - Occur in 1.6% of pat. with FAP with male predelection
  - Are diagnosed at a mean age of 6 to 36 month
  - **Screening:** AFP an US from infancy untill 5 to 10y every 3-6 months

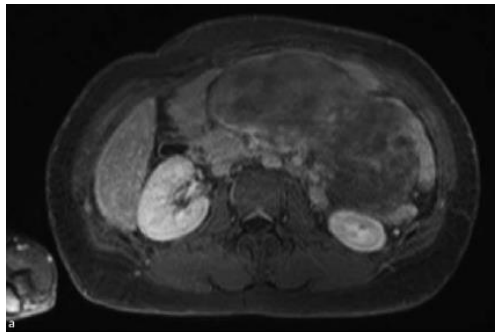


Familial adenomatous polyposis (FAP)

- **Screening and management**
  - **Extraintestinal malignancies**
    - **Desmoid tumors**
      - Approx. **8% of men and 13% of women** with FAP
      - Can cause severe morbidity and mortality (progressive enlargement and consequently pressure on gastrointestinal or urinary tarct, local nervous or vacular system)
      - **Screening** (periodic abdominal imaging) is **not recommended** in asymptomatic pat.
    - **Brain tumors, gallbladder, bile duct and pancreatic cancer**
      - **Surveillance strategies** are currently **not recommended**
      - Adenomatous change and cancer have been reported
      - Pancreas cancer: 1.7% of pat. (gen. population risk 1.5%)







MUTYH-associated polyposis (MAP)

- **Second most common cancer syndrome associated with adenomatous polyposis**
- First described in 2002

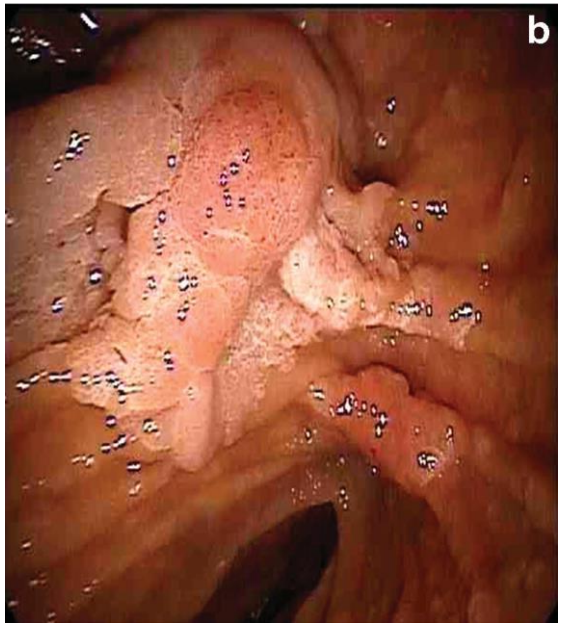
Epidemiology and Genetics ?

- **Epidemiology**
  - Monoallelic MUTYH mutations are found in 1-2 % of the general population
- **Genetics**
  - Autosomal recessive condition
  - MUTYH-gene: DNA base excision repair gene repairing DNA injury from oxidative stress

MUTYH-associated polyposis (MAP)

Usually attenuated FAP phenotype

- **Clinical manifestations**
  - **Colonic manifestations**
    - Average age of onset around the mid-50s
    - Fewer than 100 adenomas
    - High penetrance with a lifetime CRC risk of 70-80%
  - **Extracolonic manifestations**
    - Increased risk of duodenal polyposis (20%) and carcinoma (4%)
    - Cancers of
      - Ovaries and endometrium
      - Bladder
      - Skin
      - Breast



Am J Gastroenterol 2017; 112:1509–1525

It is still **not clear weather** the **lifetime risk** for these malignancies **is increased**

MUTYH-associated polyposis (MAP)

- **Diagnosis**
  - **MAP** should be **suspected in patients with 10 or more** cumulative colorectal **adonemas**
  - **Genetic testing** should be performed **for MAP and FAP** (overlapping clinical features)

- **Screening**
  - **Colonoscopy**
    - Starting at age 25-30y
    - repeated every 2-3 years if negative
    - continuied lifelong
  - **EGD**
    - Starting at age 30-35y (NCCN recommendation)
    - Including an EDG with side-viewing instrument
    - Future screening dependant on findings (Spigelman stage), at least every 3 y

Average age of onset around the mid-50s

The **risk for duodenal cancer** in MAP is **similar to** that of **AFAP** and **FAP**

MUTYH-associated polyposis (MAP)

- **Lifetime CRC risk 70-80%**
- **Fewer than 100 adenomas**
- **Average age of onset mid-50s**

- **Treatment**
  - **Colorectal management**
    - Endoscopic polypectomy
    - Surgical treatment (IPAA/IRA)
      - patients with unmanageable adenomas
      - If cancer deveolpes
  - **Duodenal adenomas:**
    - Usually managed as in FAP (Spigelmann Classification)

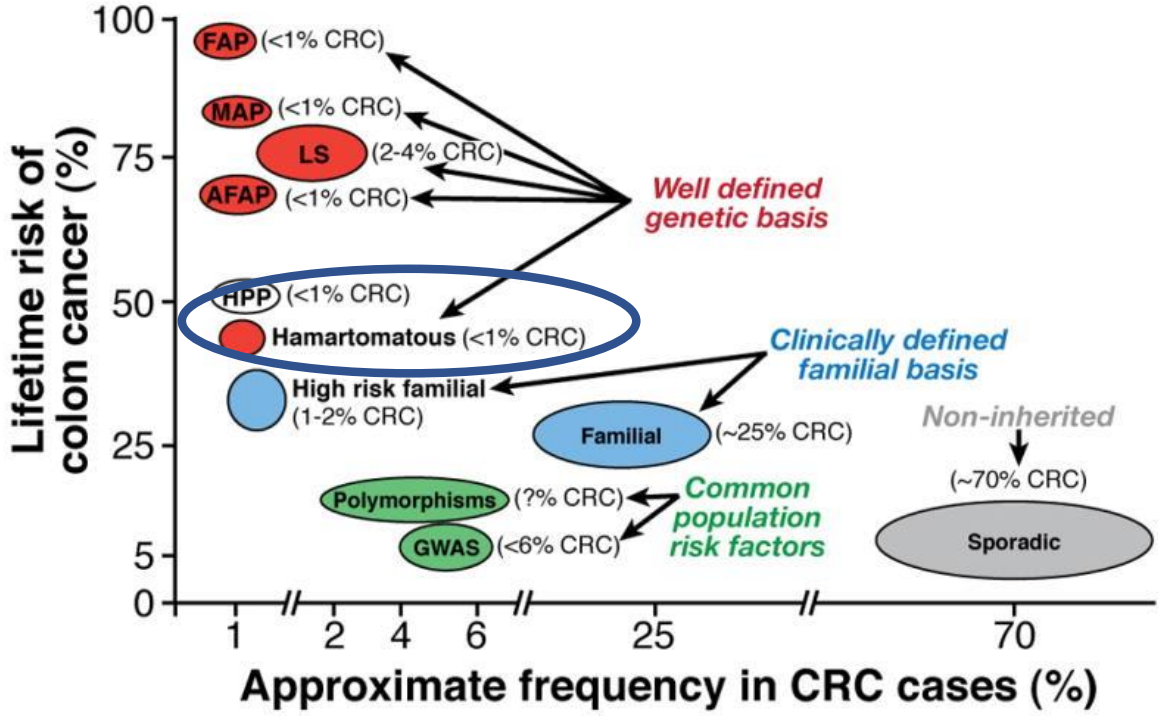
Duodenal adenomatosis
Spigelman staging system (gold standard for risk stratification)

- **Surveillance**
  - **Colorectal**
    - **Endoscopy anually**
      - after colectomy
      - in patients managed with endoscopic polypectomy
  - **Duodenal adenomatosis**
    - Usually managed as in FAP (Spigelmann Classification)

Hereditary CRC

Two major subtypes

- Absence of colorectal polyposis
- Presence of colorectal polyposis



Gastroenterology. 2010 June ; 138(6): 2044–2058. doi:10.1053/j.gastro.2010.01.054

Lynch Syndrome (LS)

Adenomatous polyposis syndromes

- Familial adenomatous polyposis (FAP) √
- Attentuated (AFAP) √
- MUYTH-associated polyposis (MAP) √

Hamartomatous polyposis syndromes

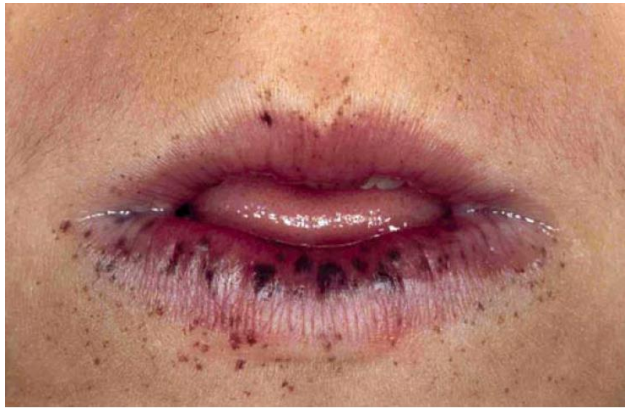
- Peutz-Jeghers syndrome (PJS)
- Juvenile polyposis syndrome (JPS)
- Cowden syndrome

Serrated polyposis syndrome (SPS)

Peutz-Jeghers syndrome (PJS)

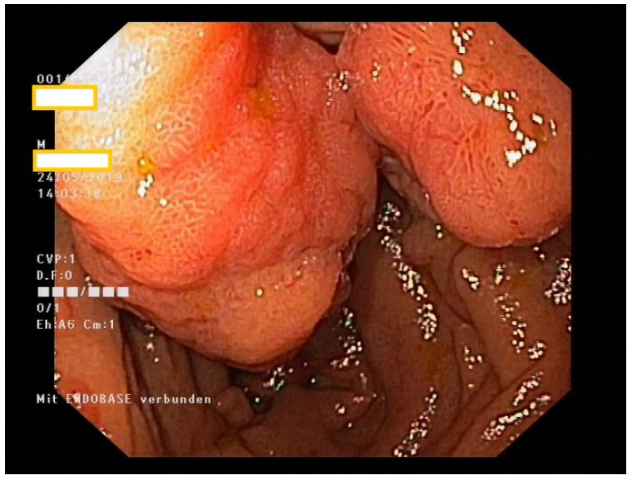
- **Epidemiology**
  - Prevalence 1:80000 to 1:120.000 births
- **Genetics**
  - Autosomal-dominantly inherited syndrome
  - PJS arises from mutations of the STK11 gene (tumor suppr. seronine/threonine kinase gene; 94% of pat.)
  - 25% de novo mutations
- **Clinical manifestations**
  - Mucocutaneous melanin pigment spots in > 95%
  - Multiple harmatomatous GI polyp
  - Growth begins in first decade of life
  - **Symptoms ?**

    Symtoms arise from larger polyps in second/third decade
    - Bleeding
    - Obstruction
    - Intussusception



PJS polyps – frecuency by segment

Stomach	24%
Small bowel	**96%**
Colon	27%
Rectum	24

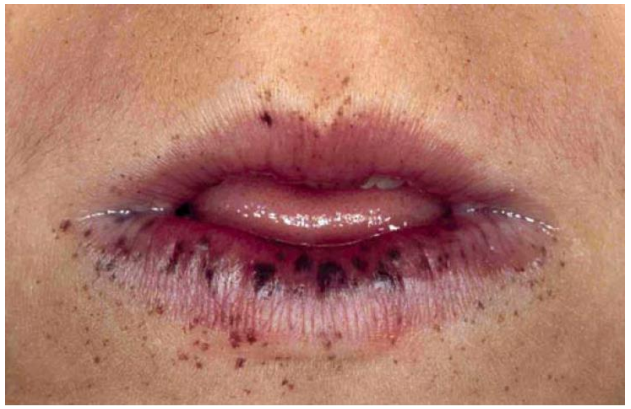


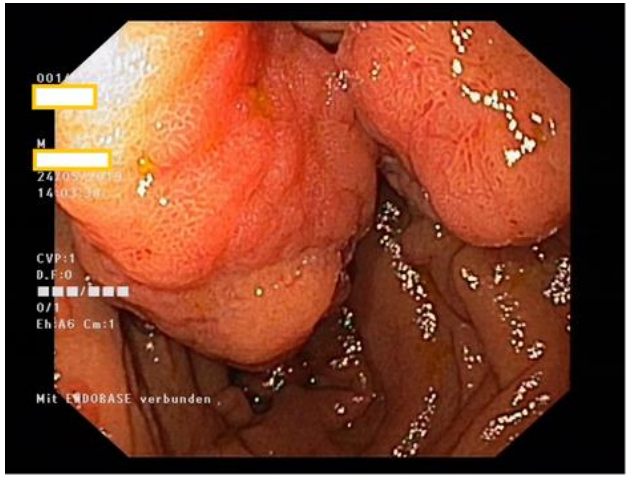
Peutz-Jeghers syndrome (PJS)

- **Genetic testing ?**

Evaluation for PJS

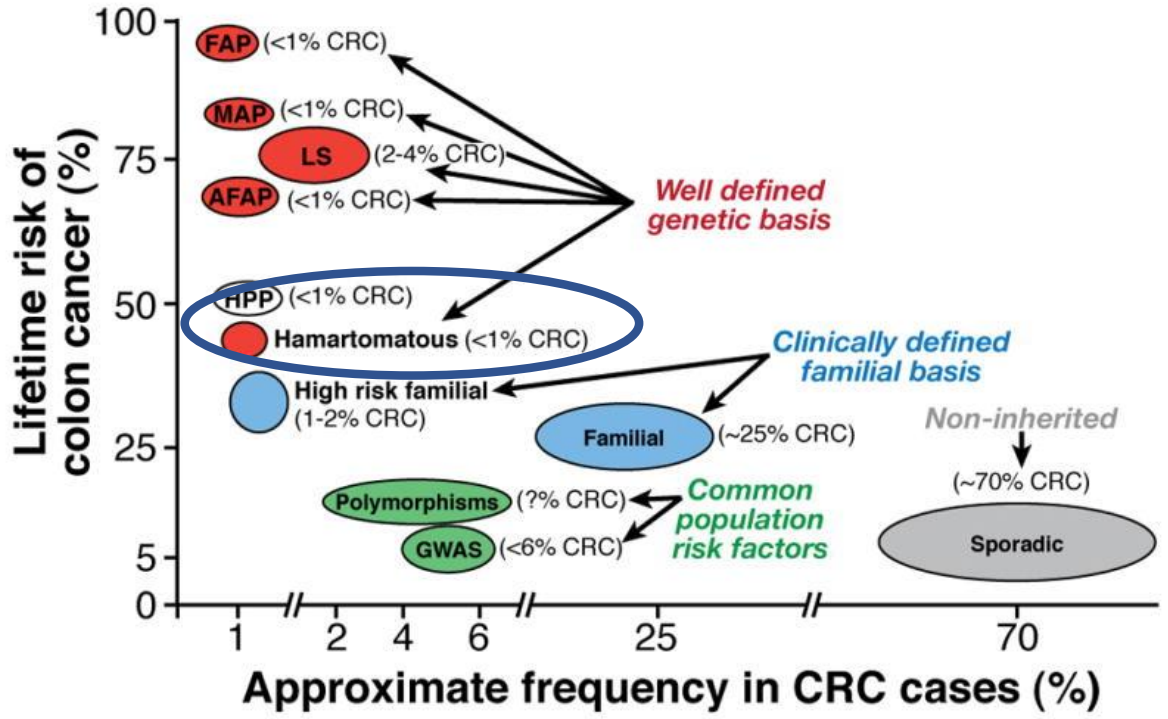
- Individuals with perioral or buccal pigmentation a/o
- ≥ 2 histologically characteristic GI hamartomatous polyps or
- A family history of PJS





Peutz-Jeghers syndrome (PJS)

- **High risk of gastrointestinal** (CRC, extracolonic) **and extraintestinal cancer** in PJS



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Peutz-Jeghers syndrome (PJS)

High risk of gastrointestinal (CRC, extracolonic) **and extracolorectal cancer** in PJS

Risk of CRC ?

Table 5. Cumulative risks of colorectal cancer in hereditary colorectal cancer syndromes

Syndrome	Gene	Risk	Average age of diagnosis (years)
Peutz–Jeghers syndrome	*STK11*	39%	42–46

Risk of extracolorectal cancer?

Table 7. Cumulative risks of extracolorectal cancer in hereditary colorectal cancer syndromes

Cancer site	General population risk[a]	Syndrome risk	Average age of diagnosis (years)
Peutz–Jeghers syndrome			
Stomach	<1%	29%	30–40
Small bowel	<1%	13%	37–42
Pancreas	1.5%	11–36%	41–52
Breast	12.4%	32–54%	37–59
Ovarian (mostly SCTAT (sex cord tumor with annular tubules))	1.6%	21%	28
Uterus	2.7%	9%	43
Cervix (adenoma malignum)	<1%	10%	34–40
Testicular (Sertoli cell tumor)	<1%	9%	6–9
Lung	6.9%	7–17%	47

Overall risk of developing **any cancer at age 70y is 81%**

Peutz-Jeghes syndrome (PJS)

- **Management ? Surveillance recommendations ?**

- **Start at age 8y** (polyp growth begins in first decade of life
- **If polyps present, repeat every 3y**
- **If no polyps, repeat at age 18, then every 3y**

	Gen.pop. risk (%)	Syndrome risk (%)
Colon		39%
Stomach	<1%	29%
Small bowel	<1%	13%
Pancreas	1.5%	11-36%
Breast	12.4%	32-54%
Ovarian	1.6%	21%
Endometrial	2.7%	9%
Cervix	<1%	10%
Testicular	<1%	9%
Lung	6.9%	7-17%

Table 10. Surveillance recommendations for hereditary gastrointestinal (GI) cancer syndromes

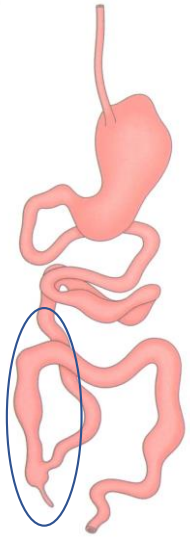
Site	Age to begin surveillance (years)	Surveillance interval (years)	Surveillance procedures and comments
Peutz–Jeghers syndrome			
Colon	8, 18[d]	3	Colonoscopy[d]
Stomach	8, 18[d]	3	Esophagogastroduodenoscopy[d]
Small bowel	8, 18[d]	3	Video capsule endoscopy[d]
Pancreas	30	1–2	Magnetic resonance cholangiopancreatography or endoscopic ultrasound
Breast	25	1	Annual self-exam starting age 18, annual breast MRI, and/or mammogram starting at age 25
Ovarian	25	1	Pelvic exam and pelvic or transvaginal ultrasound, CA-125 probably not helpful
Endometrial	25	1	Pelvic exam and pelvic or transvaginal ultrasound
Cervix (adenoma malignum)	25	1	Pap smear
SCTAT (sex cord tumor with annular tubules)	25	1	Same as uterine and ovarian; almost all women develop SCTAT, but 20% become malignant
Testicular (Sertoli cell tumor)	Birth to teenage years	1	Testicular exam, ultrasound if abnormalities palpated or if feminization occurs; 10 to 20% of benign Sertoli cell tumors become malignant
Lung	—	—	Provide education about symptoms and smoking cessation

Juvenile polyposis syndrome (JPS)

- **Epidemiology**
  - Incidence 1/100.000 to 1/160.000
- **Genetics**
  - **Autosomal-dominantly** inherited syndrome
  - JPS occurs as a result of **mutations of** the **SMAD4 gene or** the **BMPR1A gene** (tumor supressor genes; involved in the the TGF-beta signaling pathway)
  - **Up to 60% of individuals** with clinically defined JPS exhibits mutations of SMAD4 gene or the BMPR1A gene (approx. 40% of JPS pat. have no germline mutation)
  - Approxim. 25% of newly diagnosed cases are **de novo mutations**

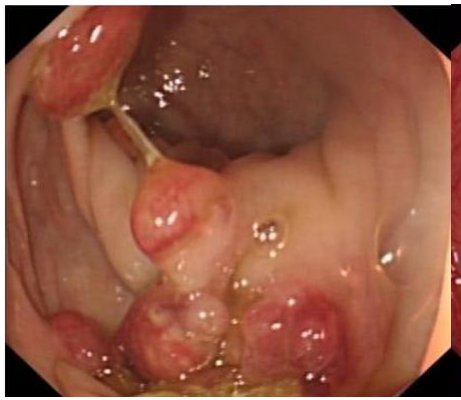
Juvenile polyposis syndrome (JPS)

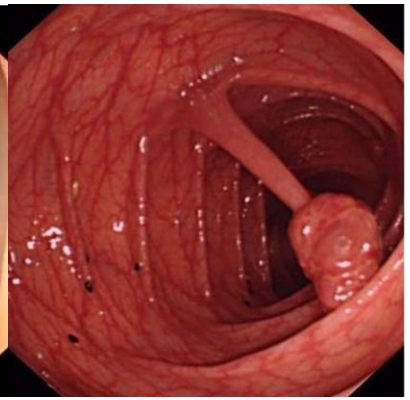
- **Clinical manifestations**
  - Polyposis involves the entire GI-tract
  - **70% of polyps** occur in the **proximal colon**
  - **Polyps begin to spear** in the **first decade**
  - Average age at diagnosis 18.5 y
  - **Juvenile polyps** (endoscopic and histologic features)
    - vary in size from small sessil to large pedunculated lesions
    - Smooth, reddish colored, often white exudate on the surface
    - Histopathology; elongated and cystically dilated glands

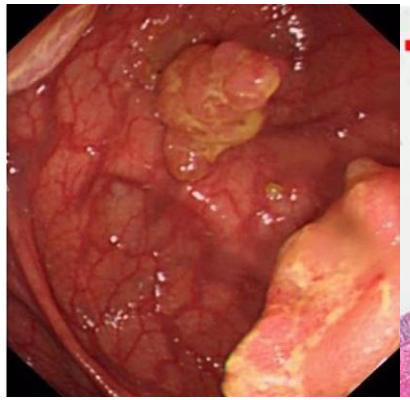


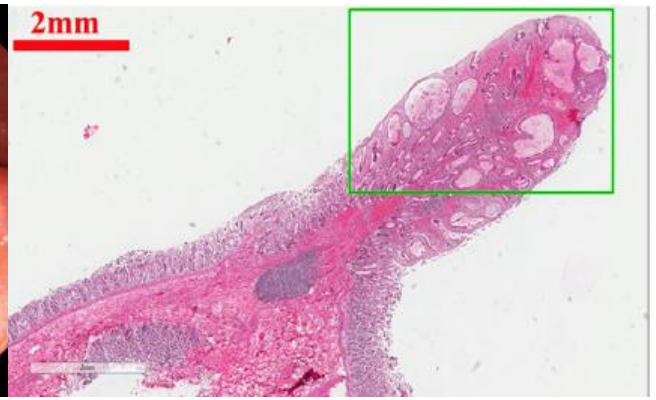
JPS polyps – frequency by segment

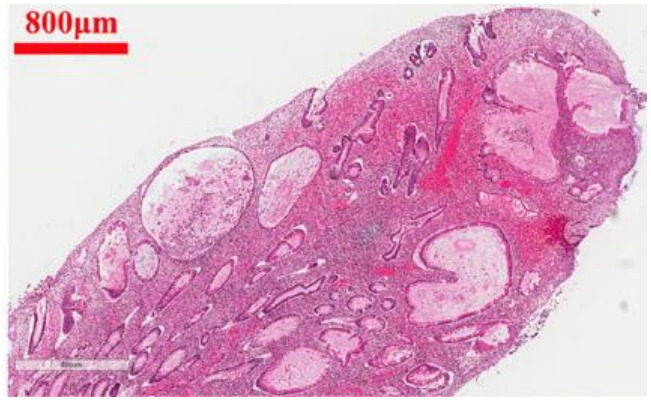
Colorectum	**98%**
Stomach	14%
Jejunum/Ileum	7%
Duodeum	7%











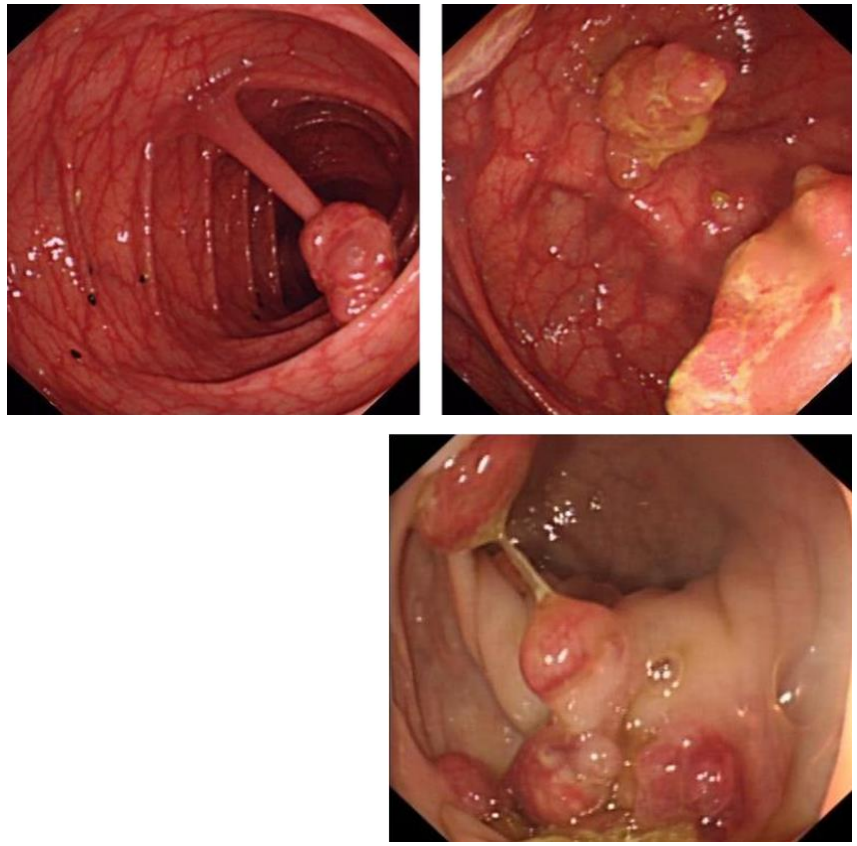
Gao et al. BMC Gastroenterology (2020) 20:167; https://doi.org/10.1186/s12876-020-01238-7

Juvenile polyposis syndrome (JPS)

- **Clinical manifestations**

  - Symptoms

  - Most patients are symptomatic by age 20y
  - Overall, **90 percent of pat. present with** rectal **bleeding or anemia**
  - Pain
  - Diarrhea (due to protein losing enteropathy)
  - Intussusception



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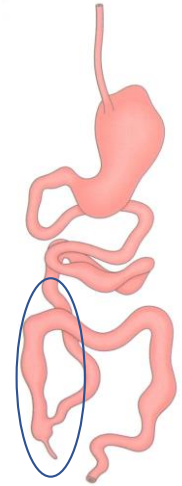
Juvenile polyposis syndrome (JPS)

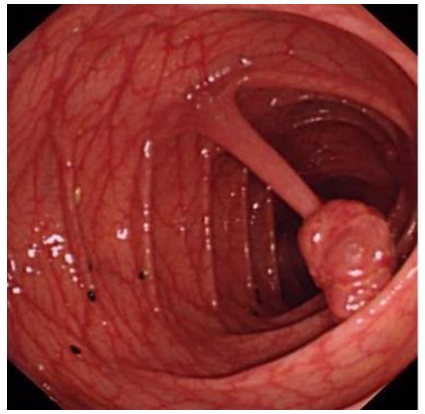
- **Genetic testing ?**

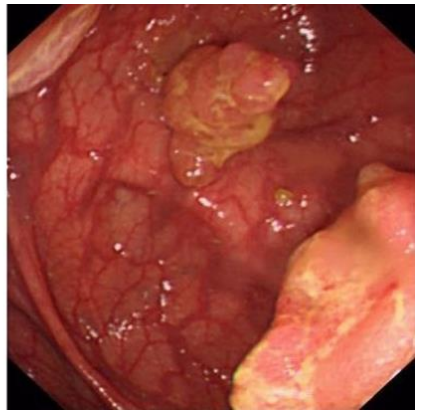
Individuals with

- ≥ 5 JP in the colorectum
- Any juvenile polyps in other parts of GI tract
- First degree relatives of individuals with JPS

Autosomal-dominantly inherited syndrome







JPS polyps – frequency by segment

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Stomach	14%
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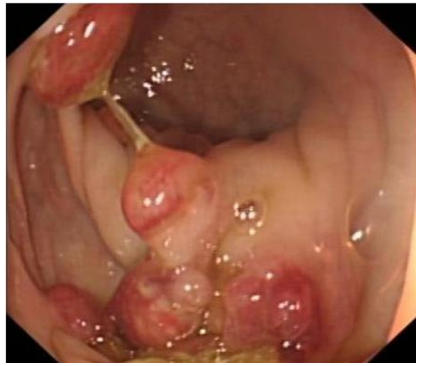
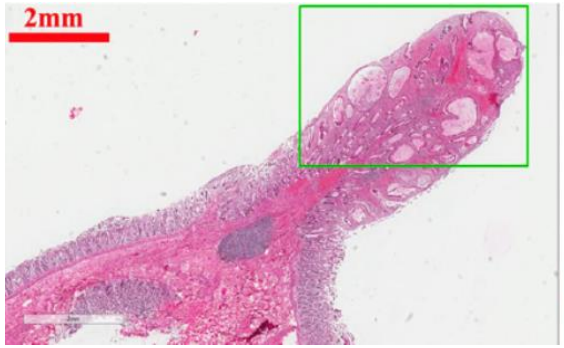
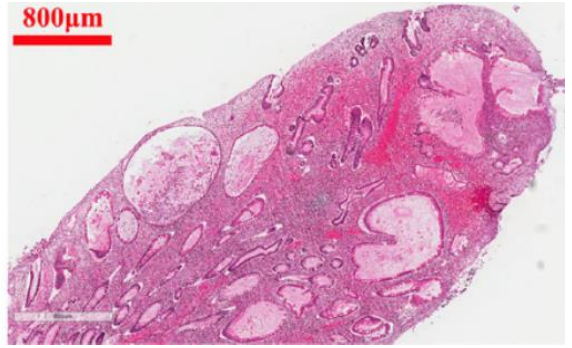
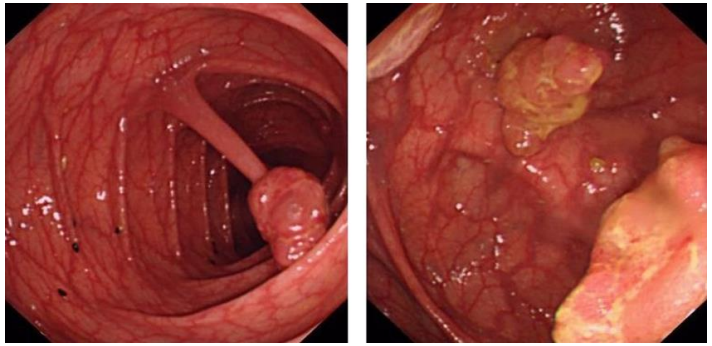






Juvenile polyposis syndrome (JPS)



- **Cancer risk of JPS mutation carriers**

High risk for CRC

Table 5. Cumulative risks of colorectal cancer in hereditary colorectal cancer syndromes

Syndrome	Gene	Risk	Average age of diagnosis (years)
Juvenile polyposis	*SMAD4* *BMPR1A*	38–68%	34–44

Risk for CRC approaches **68%** **by age 60y**

Extracolonic malignancies ?

- **Increased risk** for **gastric**, **duodenal** and **pancreatic cancers**

Table 7. Cumulative risks of extracolorectal cancer in hereditary colorectal cancer syndromes

Cancer site	General population risk[a]	Syndrome risk	Average age of diagnosis (years)
Juvenile polyposis			
Upper gastrointestinal (GI) cancer (stomach, pancreas, and small bowel)	—	21%[c]	54

– Greater risk of gastric cancer in *SMAD4* mutations carriers

Juvenile polyposis syndrome (JPS)

- **Surveillance recommandations**

Table 10. Surveillance recommendations for hereditary gastrointestinal (GI) cancer syndromes

Site	Age to begin surveillance (years)	Surveillance interval (years)	Surveillance procedures and comments
Juvenile polyposis syndrome			
Colon	12–15	1–3	Colonoscopy[e]
Stomach	12–15	1–3	Esophagogastroduodenoscopy[e]
Small Intestine	—	—	Rare, undefined lifetime risk. Periodic enteroscopy, capsule endoscopy, and/or CT enterography
Pancreas	—	—	Rare, undefined lifetime risk. No screening recommendations given
HHT (hereditary hemorrhagic telangiectasia)	Within first 6 months of life	—	Undefined lifetime risk. In individuals with SMAD4 mutations, screen for vascular lesions associated with HHT

Small bowell should peridically surveilled (enteroscopy, VCE, CT/MR enterography) **depending on initial findings**

JPS polyps – frequency by segment

- **Colorectum 98%**
- Stomach 14%
- Jejunum/Ileum 7%
- Duodeum 7%

- **Polyps begin to spear in** the **first decade**
- Average age at diagnosis is 18.5y

- **Management**
  - Endoscopic resection of polyps ≥ 5mm
  - Colectomy and IRA/proctocolectomy with IPAA if polyps can not be managed endoscopically

Cowden syndrome (CS)

- **Epidemiology**
  - Incidence < 1 in 200000
- **Genetics**
  - Autosomal dominant disorder
  - CS is caused by mutations in the PTEN gene
- **Clinical manifestations**
  - **Colorectal manifestations**
    - **Colonic polyps** are found in **up to 95%** of pat.
    - **Lifetime risk** for **CRC 9-16%**
    - The majority of CS patients have **multiple synchronous histologic types of polyps**
      - Hamartomatous polyps (most common)
      - Adenomas
      - Ganglionuromas, inflammtory polyps
      - Hyperplastic polyps
    - **Polyps may occur at young age**

Cowden syndrome (CS)

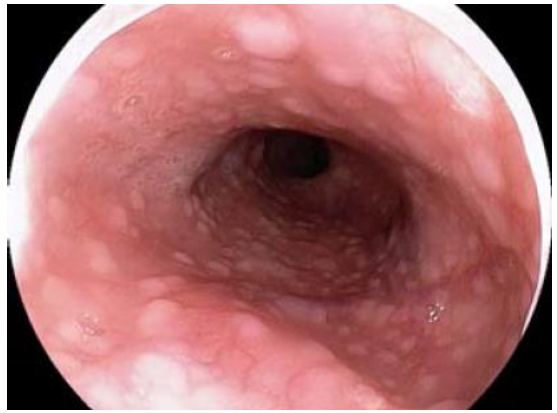
- **Clinical manifestations**

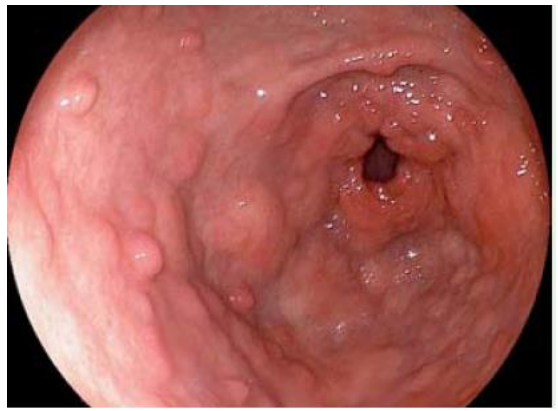
  - Extracolorectal manifestations

  - **Diffuse glycogenic acanthosis** in the esophagus
  - Frequent finding of multiple **hamartomatous polyps** in **stomach**, **duodenum** and the **small bowel**

  - Extraintestinal manifestations

  - Increased risk for extracolorectal cancer





Coriat et al., Endoscopy 2011; 43:723-726

Table 7. Continued

Cancer site	General population risk[a]	Syndrome risk	Average age of diagnosis (years)
Cowden syndrome			
Breast	12.4%	25–85%	38–46
Thyroid	1.1%	3–38%	31–38[b]
Endometrium	2.7%	5–28%	25[d]
Kidney (renal cell)	1.6%	15–34%	40[d]
Melanoma	2	6%	3[e]

Cowden syndrome (CS)

- **Surveillance recommendations**

Recommendations are all **expert opinion based** rather than evidence based

Polyps may occur **at young age**

Table 10. **Surveillance recommendations for hereditary gastrointestinal (GI) cancer syndromes**

Site	Age to begin surveillance (years)	Surveillance interval (years)	Surveillance procedures and comments
Cowden syndrome			
Colon	15	2	Colonoscopy, intervals may increase or decrease, depending on findings
Upper GI tract and small bowel	15	2–3	Esophagogastroduodenoscopy. If duodenal polyposis is present, repeat depending on number of polyps
Thyroid	Adolescence	1	Thyroid exam and baseline ultrasound
Breast	25 30–35	Monthly 1	Self-breast exam Mammography and breast magnetic resonance imaging
Uterine	30–35	1	Annual endometrial sampling or vaginal ultrasound
Renal cell	18	1	Urine analysis with cytology and possibly renal ultrasound
Melanoma	By 18	1	Physical cutaneous examination

Serrated polyposis syndrome (SPS)

- **WHO diagnostic criteria**
- **Epidemiology**
  - Incidence
    - 1/100.000 (N Engl J Med. 2006;355(18):1863-72)
    - 1/151 (Gut.2013;62(3):475)
- **Genetics**
  - Genetic etiology has yet not been defined
  - Familial cases of SPS have been reported
- **Surveillance and management**
  - Complete clearance of all polyps ≥ 10 mm
  - Surveillance colonoscopy every 1-3 years, depending on
    - number and size of polyps
    - number of concurrent adenomas

Diagnostic criteria for SPS

- **At least 5 serrated polyps proximal** of the **sigmoid** colon **with ≥2 of these being >10 mm**
- **Any number of serrated polyps proximal** to the **sigmoid** colon **in an individual who has FDR with SPS**
- **> 20 serrated polyps** of any size distributed throughout the large intestine

Serrated polyposis syndrome (SPS)

- **Surveillance for individuals with a family history of SPS ?**

  NCCN recommends colonoscopy of FDRs at the earliest of the following
  - Age 40 years
  - Same age of the youngest SPS diagnosis in the family
  - 10 years before CRC in the family in a patient with SPS

Diagnostic criteria for SPS

- **At least 5 serrated polyps proximal** of the **sigmoid** colon **with ≥2 of these being >10 mm**
- **Any number of serrated polyps proximal** to the **sigmoid** colon **in an individual who has FDR with SPS**
- **> 20 serrated polyps** of any size distributed throughout the large intestine