Colorectal Cancer

Hereditary colorectal cancer syndromes

- Diagnosis and management -

- **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	28%	§	Brustkrebs	32%
Lungenkrebs	12%		Dickdarmkrebs	10%
Dickdarmkrebs	11%		Lungenkrebs	10%
Schwarzer Hautkrebs (Melanom)	7%		Schwarzer Hautkrebs (Melanom)	7%
Blasenkrebs	4%		Gebärmutterkörperkrebs	5%

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- **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)

Die Krebsarten mit der grössten Sterblichkeit nach Geschlecht (Mortalität)

Männer			Frauen	
Lungenkrebs	21%	#	Brustkrebs	18%
Prostatakrebs	15%		Lungenkrebs	17%
Dickdarmkrebs	10%		Dickdarmkrebs	10%
Bauchspeicheldrüsenkrebs	7%		Bauchspeicheldrüsenkrebs	8%
Leberkrebs	5%		Eierstockkrebs	5%

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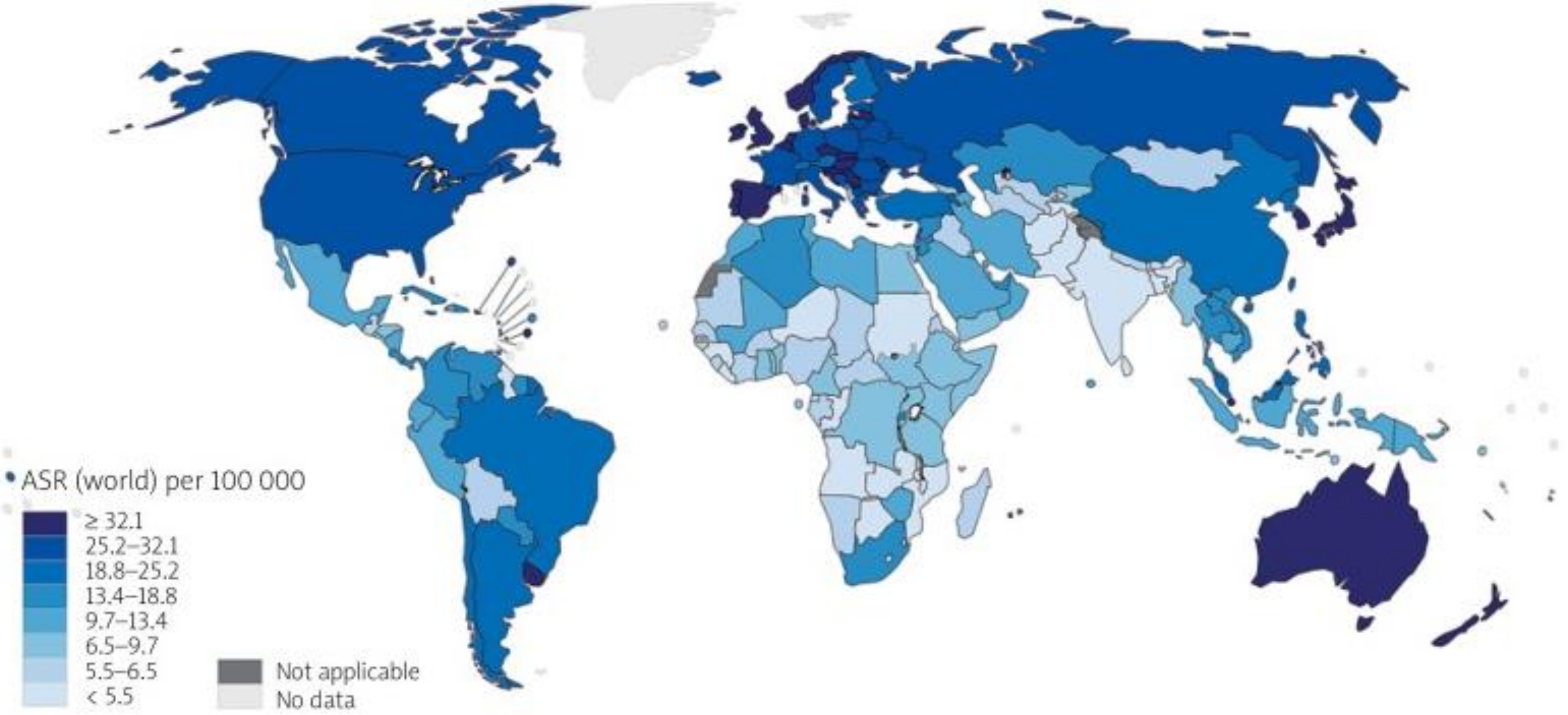
- **CRC** is the **second most deadly cancer worldwide** (about 881000 deaths estimated for 2018)
- About **1.8 million new cases of CRC** are estimated to be diagnosed **in 2018**
- **Developed countries** are at the **highest risk** of CRC
- Globally the incidence varies over 10-fold



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

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

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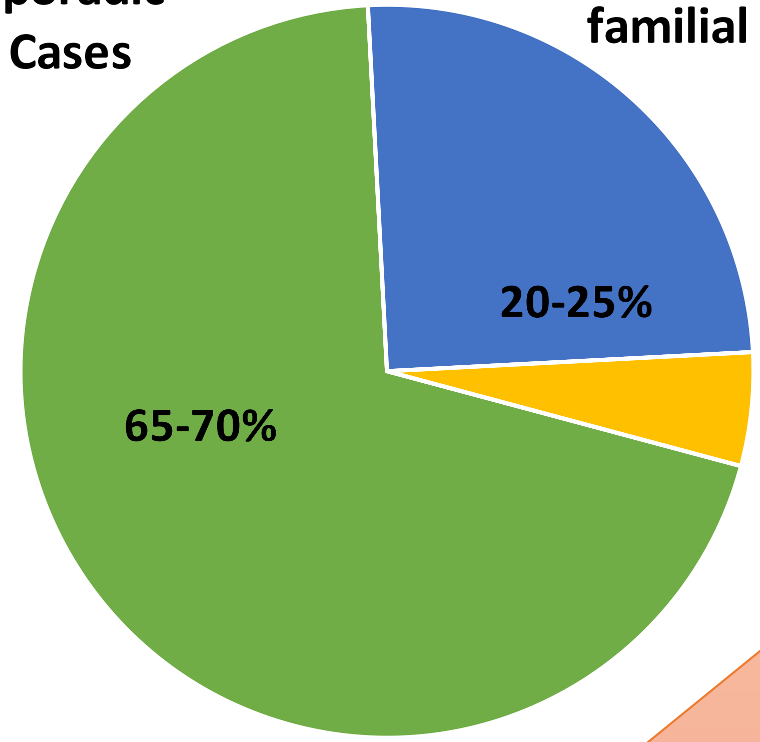
- **CRC results from** both **genetic and environmental factors** and their interaction

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

- **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

- **Hereditary CRC forms (7-10%;** Lynch-Syndrome and Polyposis 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 (2-5%)**
- **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)
- Polymerase-Proofreading-Associated-Polyposis (PPAP)

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

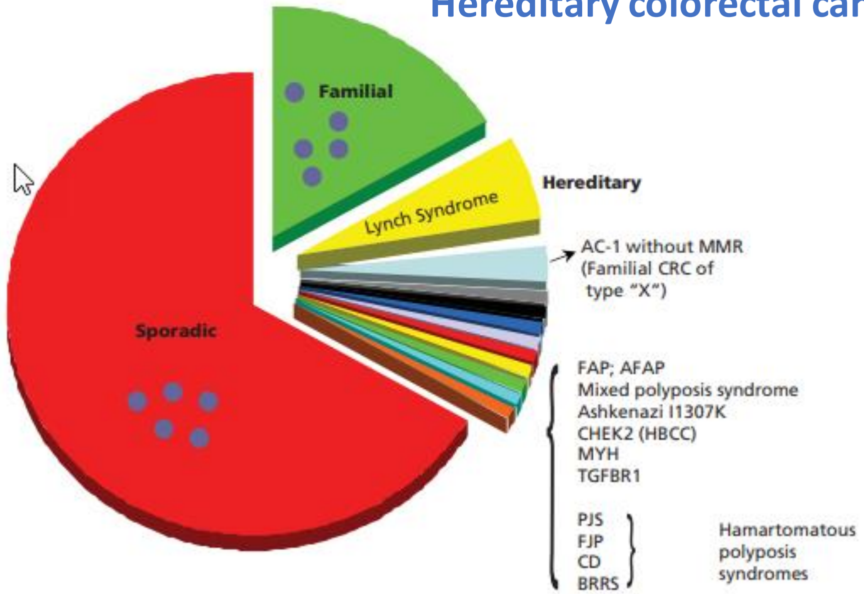
Hereditary colorectal cancer

Lynch syndrome (absence of colorectal polyposis)

Lynch Syndrome

- **Most common hereditary CRC syndrome**
- **Epidemiology**
  - Accounts for 3-5 % of CRCs
  - Prevalence: 1 in 440

Hereditary colorectal cancer

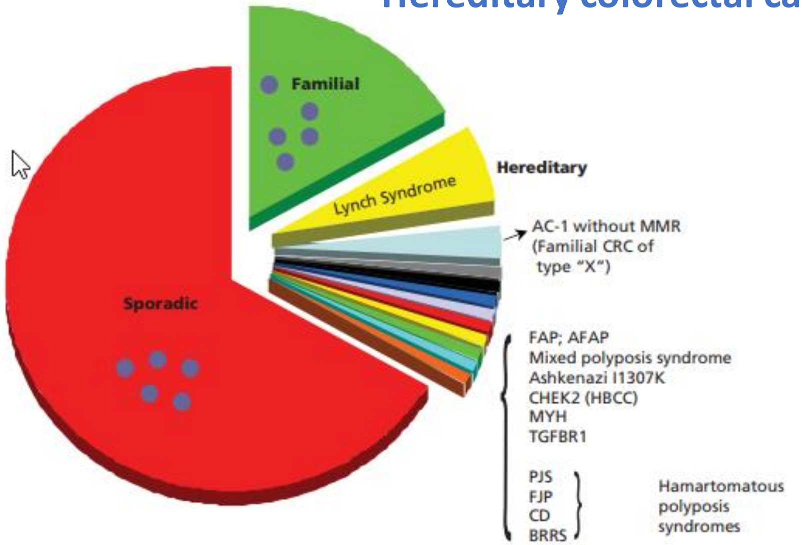


- **Genetics**
  - **Autosomal dominant** condition that occurs due to **dysfunction in a DNA mismatch repair (MMR) gene or EPCAM**
  - Caused my mutations in one of the **five genes**
    - **MLH1, MSH2** (70% of cases)
    - **MSH6** (14% of cases)
    - **PSM2** (<15% of cases)
    - **EPCAM** (1-3% of cases)

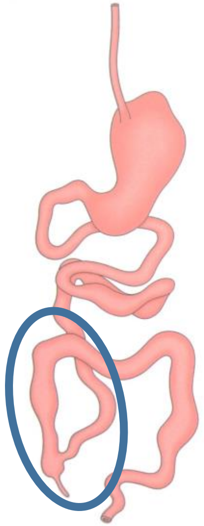
Epithelial **C**ell **A**dhesion **M**olecule

- Does not belong to the MMR gene family
- Germline deletion leads to inactivation of MSH2

Lynch Syndrome



- **Clinical manifestations**
  - Individuals with LS are at increased risk of
    - CRC
    - Several other malignancies
- **Colonic manifestations**
  - Individual with LS are at **increased risk for synchronous and metachronous CRSs**
  - **Lifetime risk of CRC** to age 70 years in LS varies from **10-90% depending on**
    - Sex
    - MMR gene mutation
  - **CRCs in** LS are predominantly **right sided** in location
  - **Adenoma**
    - Tend to **be larger and flatter**
    - Are mor likely to have **high grade dysplasia and/or villous histology**
  - The **adenoma-carcinoma sequence progresses much more rapidly** (35 month versus 10-15 years)



Lifetime cancer risk related to Lynch genotypes

Cancer site	MLH1			MSH2Δ			MSH6			PMS2		
	Female	Male	Both	Female	Male	Both	Female	Male	Both	Female	Male	Both
Any Lynch cancer	**71 to 81%**	**71 to 72%**	**71 to 90%**	**61 to 84%**	**52 to 75%**	**52 to 84%**	**62 to 65%**	**41 to 47%**	**58 to 73%**	–	–	**34 to 52%**
Colorectal	35 to 57%	39 to 78%	35 to 90%	26 to 68%	31 to 63%	52 to 84%	20 to 30%	12 to 69%	18 to 58%	12 to 15%	13 to 20%	12 to 52%
Endometrial	20 to 57%	–	–	21 to 71%	–	–	17 to 71%	–	–	13 to 15%	–	–
Gastric	3 to 15%	6 to 37%	Up to 37%	13 to 19%	5 to 20%	Up to 20%	1 to 4%	1 to 8%	Up to 8%	–	–	Unknown*
Ovarian	8 to 20%	–	–	12 to 38%	–	–	1 to 11%	–	–	3 to 5%	–	–
Ureter/kidney	2 to 5%	4 to 5%	Up to 5%	6 to 19%	6 to 18%	Up to 19%	1 to 5%	1 to 2%	Up to 5%	–	–	Up to 4%
Bladder	1 to 5%	4 to 11%	Up to 11%	3 to 8%	4 to 13%	Up to 13%	1 to 2%	1 to 8%	Up to 8%	–	–	Unknown*
Prostate	9 to 14%			24 to 30%			9 to 30%			Up to 5%		
Breast¶	Up to 19%			Up to 16%			Up to 14%			Up to 15%		
Brain	Up to 2%			Up to 8%			Up to 4%			–		
Small bowel	Up to 4%			Up to 8%			Up to 4%			Unknown*		
Pancreatobiliary	Up to 5%			Up to 5%			Unknown*			Unknown*		
Skin	Up to 4%			Up to 10%			Up to 4%			Unknown*		

* Data are insufficient to make a determination.

¶ There is ongoing debate as to whether breast cancer is a Lynch syndrome associated cancer.

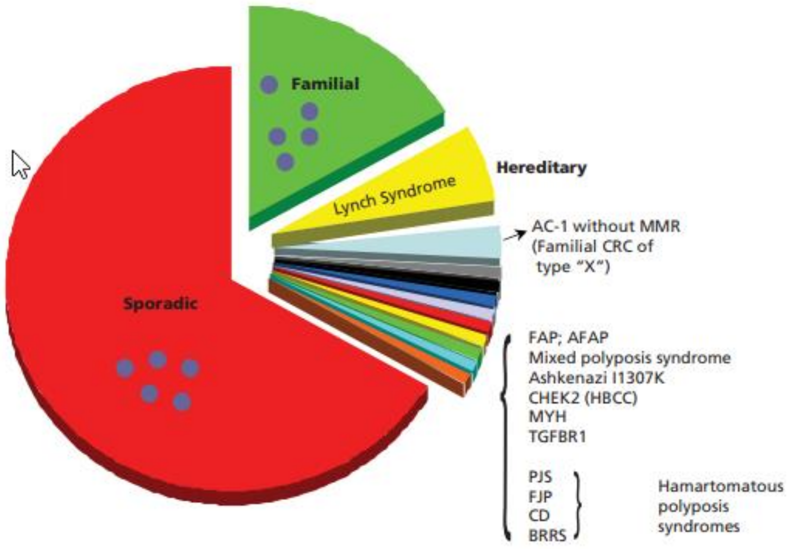
Δ Cancer risks in individuals with a pathogenic *EPCAM* variant are similar to those with a pathogenic *MSH2* variant.

Data from:
1. *Bonadona V, Bonaïti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 2011; 305:2304.*
2. *Dowty JG, Win AK, Buchanan DD, et al. Cancer risks for MLH1 and MSH2 mutation carriers. Hum Mutat 2013; 34:490.*
3. *Watson P, Vasen HF, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. Int J Cancer 2008; 123:444.*
4. *Joost P, Therkildsen C, Dominguez-Valentin M, et al. Urinary Tract Cancer in Lynch Syndrome; Increased Risk in Carriers of MSH2 Mutations. Urology 2015; 86:1212.*
5. *van der Post RS, Kiemeney LA, Ligtenberg MJ, et al. Risk of urothelial bladder cancer in Lynch syndrome is increased, in particular among MSH2 mutation carriers. J Med Genet 2010; 47:464.*
6. *Dominguez-Valentin M, Sampson JR, Seppälä TT, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med 2020; 22:15.*
7. *Senter L, Clendenning M, Sotamaa K, et al. The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology 2008; 135:419.*
8. *Ten Broeke SW, van der Klift HM, Tops CMJ, et al. Cancer Risks for PMS2-Associated Lynch Syndrome. J Clin Oncol 2018; 36:2961.*
9. *Ryan NAJ, Morris J, Green K, et al. Association of Mismatch Repair Mutation With Age at Cancer Onset in Lynch Syndrome: Implications for Stratified Surveillance Strategies. JAMA Oncol 2017; 3:1702.*
10. *Baglietto L, Lindor NM, Dowty JG, et al. Risks of Lynch syndrome cancers for MSH6 mutation carriers. J Natl Cancer Inst 2010; 102:193.*
11. *Choi YH, Cotterchio M, McKeown-Eyssen G, et al. Penetrance of colorectal cancer among MLH1/MSH2 carriers participating in the colorectal cancer familial registry in Ontario. Hered Cancer Clin Pract 2009; 7:14.*
12. *Capelle LG, Van Grieken NC, Lingsma HF, et al. Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in the Netherlands. Gastroenterology 2010; 138:487.*
13. *Engel C, Loeffler M, Steinke V, et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. J Clin Oncol 2012; 30:4409.*
14. *Ramsoekh D, Wagner A, van Leerdam ME, et al. Cancer risk in MLH1, MSH2 and MSH6 mutation carriers; different risk profiles may influence clinical management. Hered Cancer Clin Pract 2009; 7:17.*
15. *Harkness EF, Barrow E, Newton K, et al. Lynch syndrome caused by MLH1 mutations is associated with an increased risk of breast cancer: A cohort study. J Med Genet 2015; 52:553.*

Lynch Syndrome

- **Clinical manifestations**
  - Individuals with LS are at increased risk of
    - CRC
    - **Several other malignancies**
  - **Extracolonic manifestations**
    - **Endometrial cancer** is the **most common extracolonic tumor** in LS (lifetime risk 40-60%)
    - Individuals are also at increased risk of cancer of
      - Ovary (10-15%)
      - Urinary tract (1-12%)
      - Small intestine (4-8%)
      - Stomach (2-13%)
      - Pancreas (4%)
      - Prostata
      - Biliary tract
      - Skin
      - Brain
      - Breast (female)

Hereditary colorectal cancer



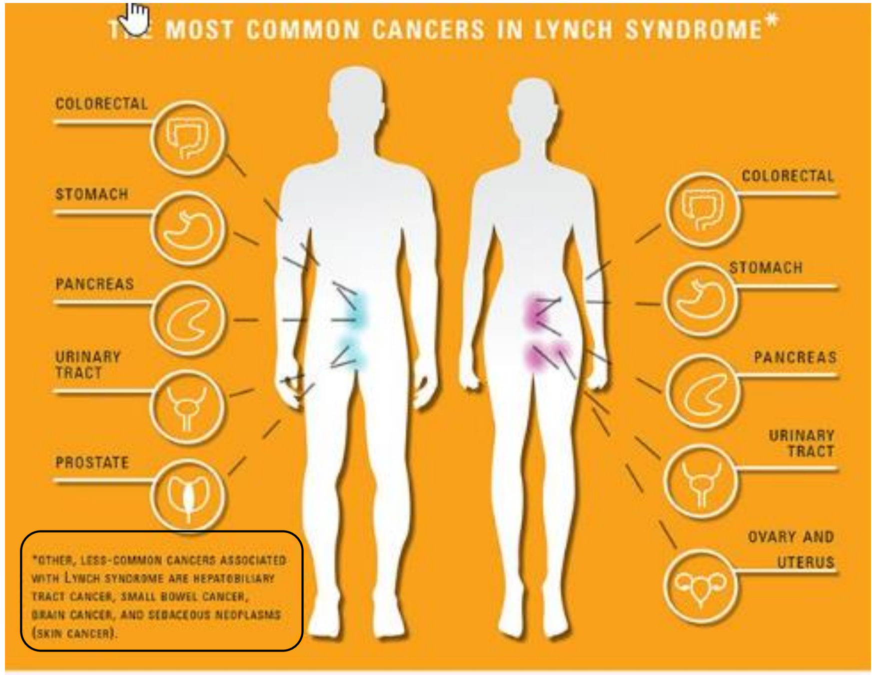


Table 7. **Cumulative risks of extracolorectal cancer in hereditary colorectal cancer syndromes**

Cancer site	General population risk[a]	Syndrome risk	Average age of diagnosis (years)	References
Lynch syndrome				
Endometrium				
General population	2.7%		65	SEER (328)
MLH1/MSH2		14–54%	48–54	(30,31,33,35,36,38)
MSH6		16–71%	53–54	(31,36,49)
PMS2		15%	49–50	(37)
Stomach	<1%	0.2–13%	49–55	(31,34,49,53–55,61,63,64)
Ovary	1.4%	3.4–22%	42–54	(31,36–38,49,53–55,63,64,67)
Hepatobiliary tract	<1%	0.02–4%	54–57[b]	(31,55,63,67)
Urinary tract	<1%	0.2–25.5%	52–57	(31,37,49,53–55,63,64,67)
Small bowel	<1%	0.4–12%	46–51	(31,34,53–55,64)
Brain/central nervous system	<1%	1.2–3.7%	50–55	(53,55,63,64)
Sebaceous neoplasm	<1%	9%[c]	51–54	(329–331)
Pancreas	1.5%	0.4–3.7%	51.5–56.5[b]	(33,53,271)
Prostate	15.3%	9–30%	59–60	(54,76,332)
Breast (female)	12.3%	1.5–18%	46–52	(53,54,75)

Hereditary colorectal cancer

MSH2 mutation carriers are at **higher risk of extracolonic cancers**

PMS2 mutation carriers are at **lower risk od CRC and endometrial cancer**

Lifetime cancer risk related to Lynch genotypes

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	Female	Male	Both	Female	Male	Both	Female	Male	Both	Female	Male	Both
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Ovarian	8 to 20%	–	–	12 to 38%	–	–	1 to 11%	–	–	3 to 5%	–	–
Ureter/kidney	2 to 5%	4 to 5%	Up to 5%	6 to 19%	6 to 18%	Up to 19%	1 to 5%	1 to 2%	Up to 5%	–	–	Up to 4%
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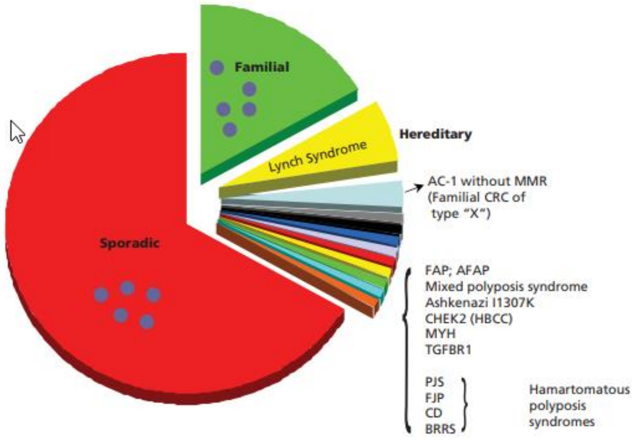
Lynch Syndrome

- **Diagnosis**
  - Due to the **high risk of developing CRC** (10-90%) **and extracolonic cancers** (risk of endometrial cancer up to 71%) **detection of patients with LS is critical**
  - **LS should be considered** in
    - **Individuals** whose personal and/or family history **fullfill the Amsterdam criteria, Bethesda Guidelines (**family history based strategies)
    - **Individuals whose tumors show evidence of MMR deficiency** (tumor-based strategies)
    - **Individuals** who **have a ≥2.5% risk of carrying a germline mutation** based on available **prediction models** (PREMM 5 Model)



Lynch Syndrome

Diagnosis

– Family history-based criteria
  - **Amsterdam criteria (I + II)**

Amsterdam I criteria
3-2-1 rule

- Three relatives with CRC
- CRC affecting more than one generation
- At least one CRC diagnosed before age 50y

Amsterdam I citeria were modified to include extracolonic LS assiciated malignancies

Amsterdam II criteria for Lynch syndrome

There should be at least three relatives with any Lynch syndrome-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis)
One should be a first-degree relative of the other two
At least two successive generations should be affected
At least one should be diagnosed before age 50
Familial adenomatous polyposis should be excluded in the colorectal cancer case(s), if any
Tumors should be verified by pathological examination

Adapted from Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) propose[...] [...]national Collaborative group on HNPCC. Gastroenterology 1999; 116:1453.

Graphic 59832 Version 7.0

Sensitivity and **specifity** for **diagnosis of LS**: 22% and 98%

Lynch Syndrome

Diagnosis

– Family history-based criteria
  - **Revised Bethesda criteria**

Revised Bethesda criteria

- Were **developed to identify individuals with CRC who should undergo** tumor **testing for MSI/MMR deficiency**
- Have largely been **replaced by universal LS screening for MMR deficiency** by immunhistochemistry a/o MSI testing in CRCs and endometrial cancers

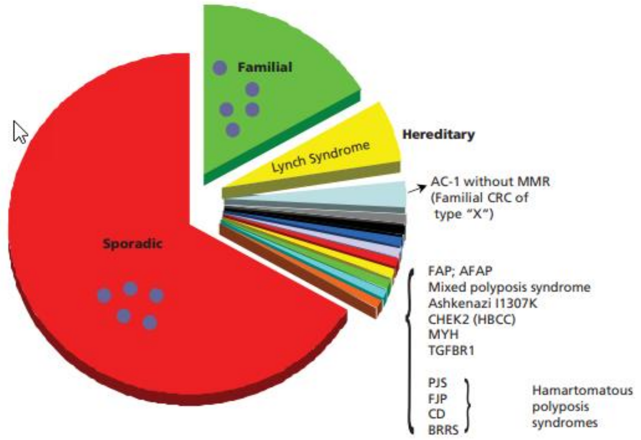
The revised Bethesda guidelines for testing colorectal tumors for microsatellite instability (MSI)

Tumors from individuals should be tested for MSI in the following situations:
1. Colorectal cancer diagnosed in a patient who is less than 50 years of age.
2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors*, regardless of age.
3. Colorectal cancer with the MSI-H¶-like histology$^{\Delta}$ diagnosed in a patient who is less than 60 years of age◊.
4. Colorectal cancer diagnosed in a patient with one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years.
5. Colorectal cancer diagnosed in a patient with two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

HNPCC: hereditary nonpolyposis colorectal cancer; MSI-H: microsatellite instability-high.

* HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratocanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

Lynch Syndrome



Diagnosis

– **Clinical prediction models** (PREMM 5)

PREMM 5 model

- Is a clinical prediction algorithm that estimates the cumulative probability of an individual carrying a germline mutation in the *MLH1, MSH2, MSH6, PMS2,* or *EPCAM* genes
- Variables included in the model include
    - proband sex
    - personal and/or family history (including age at diagnosis of CRC, endometrial cancer, or other Lynch-associated cancers)
- Genetic evaluation is recommended for individuals with a score of 2.5 percent or higher
- The PREMM5 model is available online (https://premm.dfci.harvard.edu)

PREMM5 MODEL | LYNCH SYNDROME

1 Patient information

Sex

- Male
- Female

Current age (years)

Has the patient had colorectal cancer?

- No
- Yes

Has the patient had any other Lynch syndrome-associated cancer?

Other Lynch syndrome-associated cancers include ovary, stomach, small intestine, urinary tract/bladder/kidney, bile ducts, brain, pancreas, and sebaceous gland skin tumors.

- No
- Yes

2 Relatives: First-degree

*First-degree relatives include **parents, siblings, children,** only from affected side of family*

How many first-degree relatives have had colorectal cancer?

- None
- One
- Two or more

+age/youngest age at diagnosis

How many first-degree relatives have had endometrial (uterine) cancer?

- None
- One
- Two or more

+age/youngest age at diagnosis

Have any first-degree relatives had other Lynch syndrome-associated cancers?

Other Lynch syndrome-associated cancers include ovary, stomach, small intestine, urinary tract/bladder/kidney, bile ducts, brain, pancreas, and sebaceous gland skin tumors.

- No
- Yes

3 Relatives: Second-degree

*Second-degree relatives are **grandparents, grandchildren, aunts, uncles, nieces, nephews,** only from affected side of family*

How many second-degree relatives have had colorectal cancer?

- None
- One
- Two or more

+age/youngest age at diagnosis

How many second-degree relatives have had endometrial (uterine) cancer?

- None
- One
- Two or more

+age/youngest age at diagnosis

Have any second-degree relatives had other Lynch syndrome-associated cancers?

Other Lynch syndrome-associated cancers include ovary, stomach, small intestine, urinary tract/bladder/kidney, bile ducts, brain, pancreas, and sebaceous gland skin tumors.

- No
- Yes

Calculate Probability

https://premm.dfci.harvard.edu

Development and Validation of the $PREMM_5$ Model for Comprehensive Risk Assessment of Lynch Syndrome

Fay Kastrinos, Hajime Uno, Chinedu Ukaegbu, Carmelita Alvero, Ashley McFarland, Matthew B. Yurgelun, Matthew H. Kulke, Deborah Schrag, Jeffrey A. Meyerhardt, Charles S. Fuchs, Robert J. Mayer, Kimmie Ng, Ewout W. Steyerberg, and Sapna Syngal

ABSTRACT

Purpose

Current Lynch syndrome (LS) prediction models quantify the risk to an individual of carrying a pathogenic germline mutation in three mismatch repair (MMR) genes: *MLH1*, *MSH2*, and *MSH6*. We developed a new prediction model, $PREMM_5$, that incorporates the genes *PMS2* and *EPCAM* to provide comprehensive LS risk assessment.

Patients and Methods

$PREMM_5$ was developed to predict the likelihood of a mutation in any of the LS genes by using polytomous logistic regression analysis of clinical and germline data from 18,734 individuals who were tested for all five genes. Predictors of mutation status included sex, age at genetic testing, and proband and family cancer histories. Discrimination was evaluated by the area under the receiver operating characteristic curve (AUC), and clinical impact was determined by decision curve analysis; comparisons were made to the existing $PREMM_{1,2,6}$ model. External validation of $PREMM_5$ was performed in a clinic-based cohort of 1,058 patients with colorectal cancer.

Results

Pathogenic mutations were detected in 1,000 (5%) of 18,734 patients in the development cohort; mutations included *MLH1* (n = 306), *MSH2* (n = 354), *MSH6* (n = 177), *PMS2* (n = 141), and *EPCAM* (n = 22). $PREMM_5$ distinguished carriers from noncarriers with an AUC of 0.81 (95% CI, 0.79 to 0.82), and performance was similar in the validation cohort (AUC, 0.83; 95% CI, 0.75 to 0.92). Prediction was more difficult for *PMS2* mutations (AUC, 0.64; 95% CI, 0.60 to 0.68) than for other genes. Performance characteristics of $PREMM_5$ exceeded those of $PREMM_{1,2,6}$. Decision curve analysis supported germline LS testing for $PREMM_5$ scores ≥ 2.5%.

Conclusion

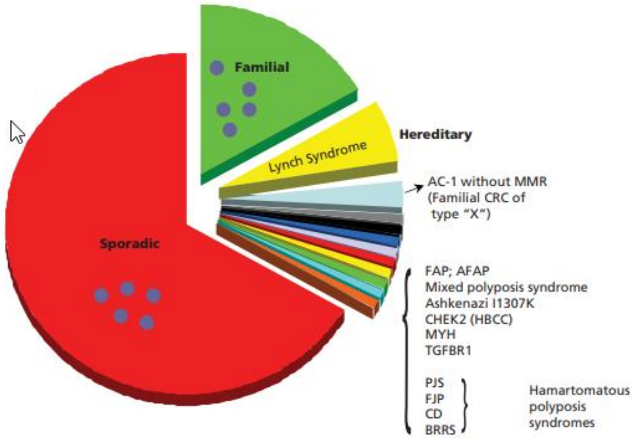
$PREMM_5$ provides comprehensive risk estimation of all five LS genes and supports LS genetic testing for individuals with scores ≥ 2.5%. At this threshold, $PREMM_5$ provides performance that is superior to the existing $PREMM_{1,2,6}$ model in the identification of carriers of LS, including those with weaker phenotypes and individuals unaffected by cancer.

J Clin Oncol 35:2165-2172.

Hereditary colorectal cancer

Lynch Syndrome

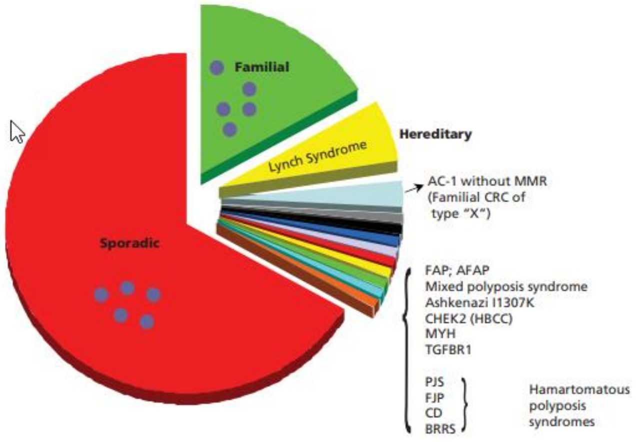
- **Diagnosis**
  - Due to the **high risk of developing CRC** (10-90%) **and extracolonic cancers** (risk of endometrial cancer up to 71%) **detection of patients with LS is critical**
  - **LS should be considered** in
    - **Individuals** whose personal and/or family history **fullfill the Amsterdam criteria, Bethesda Guidelines (**family history based strategies)
    - **Individuals** who **have a ≥5% risk of carrying a germline mutation** based on available **prediction models** (PREMM 5 Model)
    - **Individuals whose tumors show evidence of MMR deficiency** (tumor-based strategies)



Ideally, genetic evaluation for Lynch syndrome should begin with a patient affected with a Lynch syndrome cancer

Lynch Syndrome

Hereditary colorectal cancer



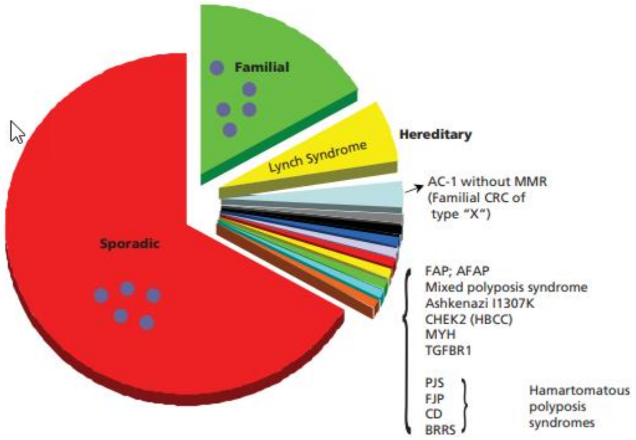
- **Diagnosis**
  - Family history based strategies
  - **Tumor-based strategies**
    - Tumor testing for evidence of defective DNA-Repair
      - **Immunhistochemistry (IHC)**
      - **Microsatellite instability testing (MSI)**
    - **Immunhistochemistry (IHC)**
      - Tumor tissue ist tested for lack of expression of MMR proteins
      - Sensitivity and specifity: 83 and 89%
      - Easily available, can be performed in biopsies, inexpensive
      - If IHC staining is abnormal, germline testing can be targeted to the gene associated with the absent protein
    - **Micosatellite instability testing**
      - MSI testing is performed using PCR
      - Sensitivity and specifity: of MSI testing for LS are 85 and 90%

Universal LS screening for MMR deficiency in all newly diagnosed CRCs and endometrial cancers by
- Immunhistochemistry (IHC) a/o
- MSI testing

MSI analysis and immunhistochemistry are equivalent for case finding regarding MMR tumor testing

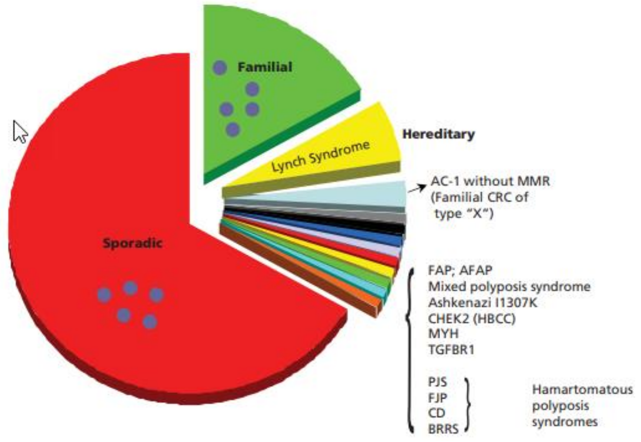
Lynch Syndrome

- **Diagnosis**
  - Due to the **high risk of developing CRC** (10-90%) **and extracolonic cancers** (risk of endometrial cancer up to 71%) **detection of patients with LS is critical**
  - **LS should be considered** in
    - **Individuals** whose personal and/or family history **fullfill the Amsterdam criteria, Bethesda Guidelines (**family history based strategies)
    - **Individuals whose tumors show evidence of MMR deficiency** (tumor-based strategies)
    - **Individuals** who **have a ≥2.5% risk of carrying a germline mutation** based on available **prediction models** (PREMM 5 Model)



Lynch Syndrome

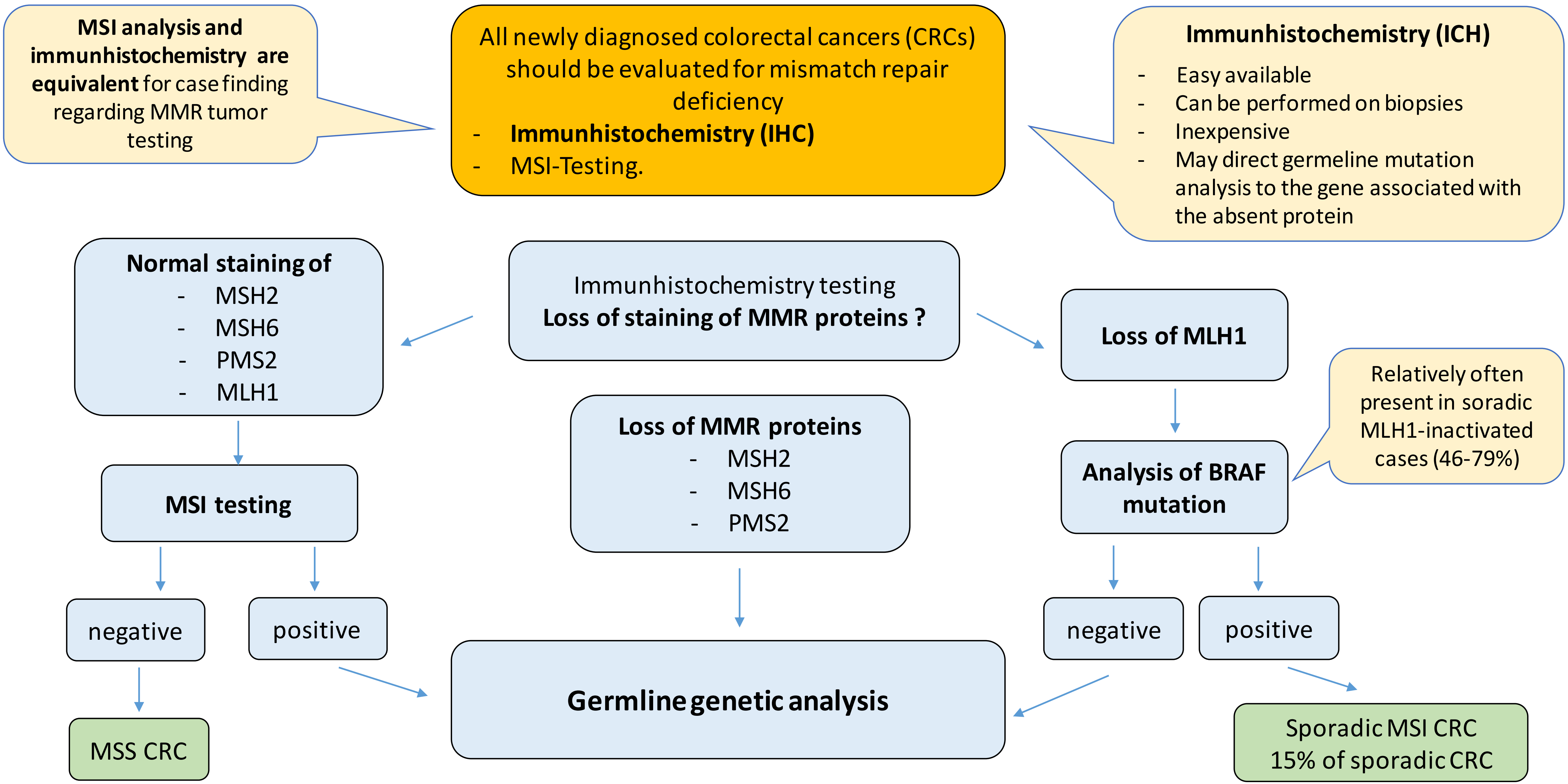
- **Diagnostic approach**
  - **Germline genetic evaluation for Lynch syndrome ?**
  - Ideally, genetic evaluation for Lynch syndrome should begin with a patient affected with a Lynch syndrome cancer



Germline genetic evaluation for Lynch syndrome in individuals with one of the following

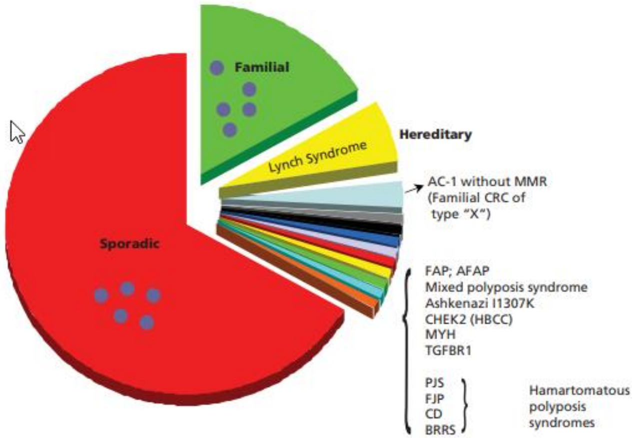
- **CRC** or endometrial cancer **prior to age 50 year**
- **CRC** or endometrial cancer **diagnosed at age >50 years with additional personal and family history suggestive of Lynch syndrome**
- **Identification of a pathogenic MMR variant** on somatic tumor testing in any tumor type
- **Unaffected** (no cancer**) individuals** with one of the following:
  - >2.5 percent chance of an MMR gene mutation by prediction models (PREMM 5)
  - Family cancer history meeting Amsterdam I or II criteria
  - First-degree or second-degree relative of those with known MMR/EPCAM gene mutation (predictive genetic diagnostics)

Lynch Syndrom - Tumor testing and indications for genetic testing



Lynch Syndrome

Screening and Surveillance of individuals with LS and their families (screening for LS-associated cancers)



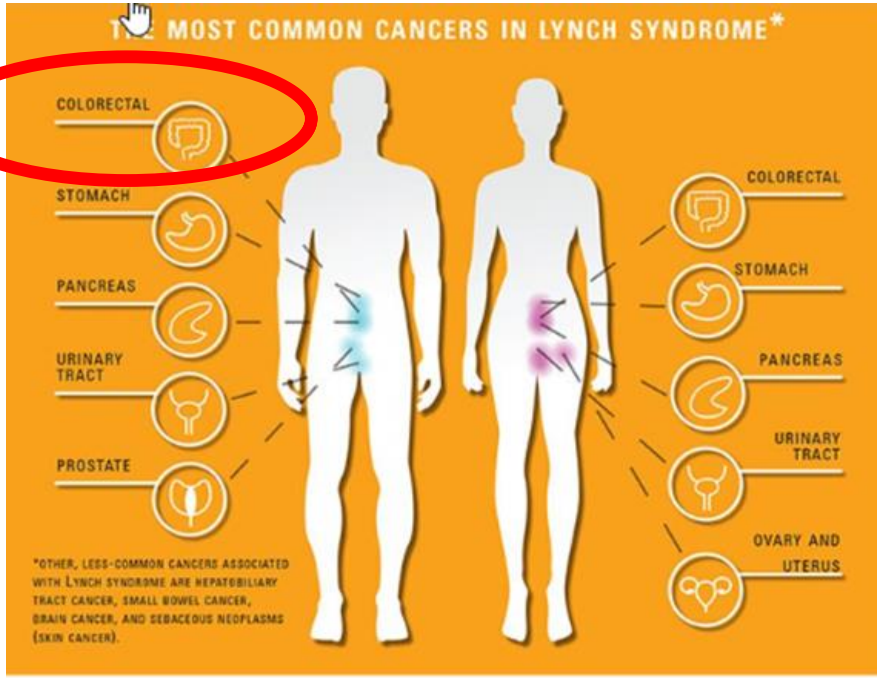
Candidates for screening

- Individuals with **germeline mutation in DNA MMR genes or EPCAM deletions** (can inactivate MSH2)
- **Individuals at risk for LS who have not undergone genetic evaluation**
  - Individuals in families meeting Amsterdam I or II criteria and individuals meeting revised Bethesda guidelines
  - Individuals with an elevated chance of an MMR gene mutation by prediction models (PREMM 5; threshold 2.5%)

Lynch Syndrome

Screening and Surveillance for CRC

- **Colonoscopy every one to two years** for individuals at risk or affected with LS
  - Beginnig at age 20 to 25 years, or
  - Two years prior to the earliest age of CRC diagnosis in the family (whicherver comes first)
- **Annual colonoscopy** should be considered **in confirmed mutation carriers**
- **Factors associated with increased risk od CRC**
  - Male sex
  - MLH1/MSH2 mutation
  - Age > 40
  - Adenoms identified at the index colonoscopy



Lifetime cancer risk related to Lynch genotypes

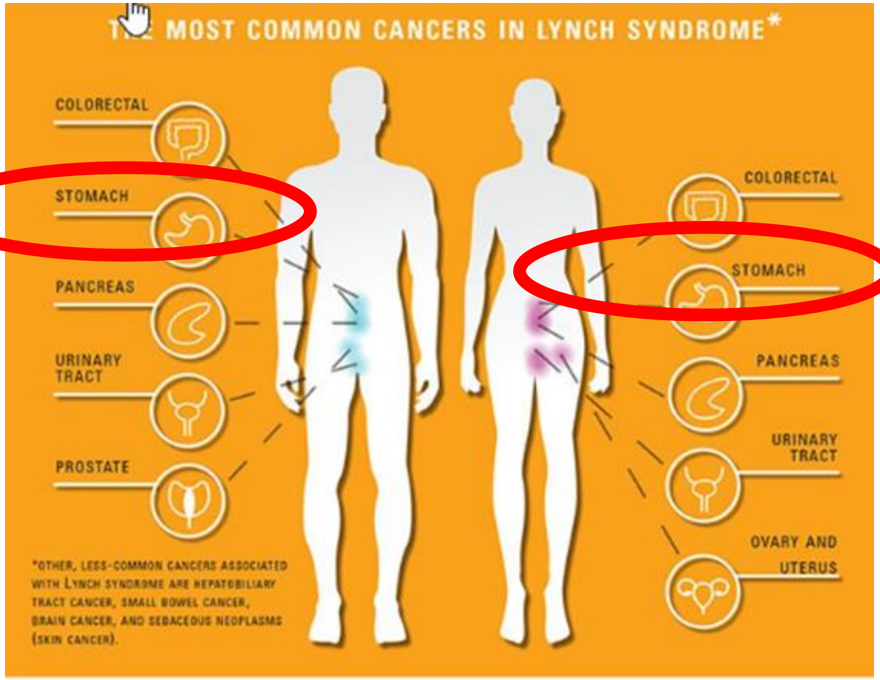
Cancer site	MLH1			MSH2Δ			MSH6			PMS2		
	Female	Male	Both	Female	Male	Both	Female	Male	Both	Female	Male	Both
Any Lynch cancer	**71 to 81%**	**71 to 72%**	**71 to 90%**	**61 to 84%**	**52 to 75%**	**52 to 84%**	**62 to 65%**	**41 to 47%**	**58 to 73%**	–	–	**34 to 52%**
Colorectal	35 to 57%	39 to 78%	35 to 90%	26 to 68%	31 to 63%	52 to 84%	20 to 30%	12 to 69%	18 to 58%	12 to 15%	13 to 20%	12 to 52%
Endometrial	20 to 57%	–	–	21 to 71%	–	–	17 to 71%	–	–	13 to 15%	–	–

Lynch Syndrome

Lifetime risk
2-13%

Screening and Surveillance for gastric cancer

- EGD and biopsy every 3 (-5) years starting at 30 to 35 years of age
- Treat for Helicobacter pylori infection if detected
- EGD can be performed more frequently if patient/family demonstrates features suggesting high risk
  - advanced atrophic gastritis
  - autoimmune gastritis
  - extensive or incomplete intestinal metaplasia
  - familiy history of gastric cancer



Screening and Surveillance for small intestinal cancer

- Screening for small intestinal cancer **is not routinely recommend** (lifetime risk for small inestinal cancer in LS is small, 4-8%)
- The majority of SB cancers in LS are located in the duodenum or ileum
- Optional for patients with family history including small bowel cancer; mutation carriers with unexplained abd. pain or iron deficiency anemia)

Lynch Syndrome

Screening and Surveillance for endometrial and ovarian cancer

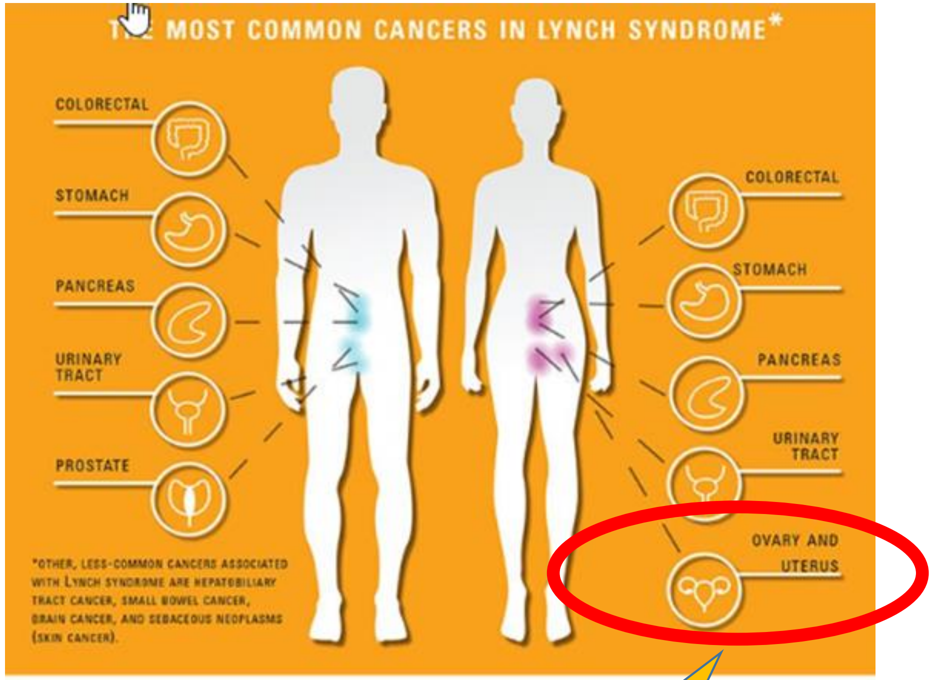
Endometial cancer screening

- **Yearly endometrial sampling** starting at age 30 to 35 or 5 to 10 years prior to the earliest age of Lynch-associated cancer in the family

Ovarian cancer screening

- Annual pelvic examination and **transvaginal ultrasound (TVUS)** examination with/without **CA 125** starting at age 30 to 35 or 5 to 10 years prior to the earliest age of Lynch-associated cancer in the family

For patients who have completed childbearing, risk-reducing total hysterectomy with bilateral salpingo-oohorectomy should be considered.



Lifetime risk for

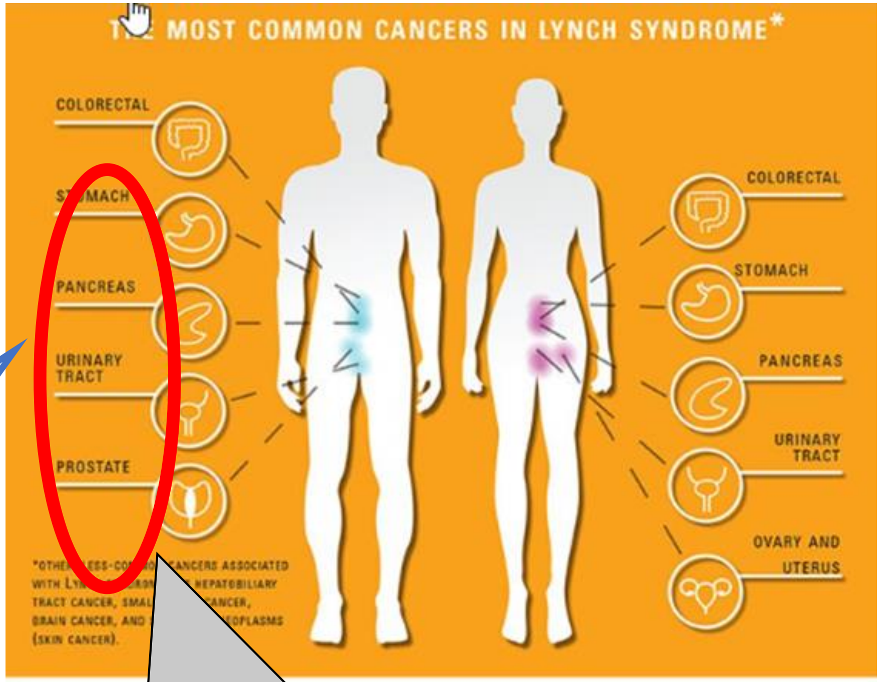
- Endometrial cancer 15-71%
- Ovarian cancer 3.4 -22%

Lynch Syndrome

Screening and Surveillance for cancers of

- Urinary tract
- Pancreas
- Prostate
- Breast
- Skin

Is **not recommended** unless there is a family history of specific cancers (conditional recommendation)



Pancreatic cancer

– The benefit of screening for PC in LS has not been evaluated.

– An international pancreas consensus panel recommended that, based on expert opinion, MMR gene mutation carriers with one affected FDR should be considered for annual PC surveillance with MRI or EUS

Urinary tract

– Annual cytological examination in addition to urine analysis can be considered

Lynch syndrome - Surveillance

Colorectal surveillance and management

Colon cancer surveillance by colonoscopy
- Starting at age 20-25 years
- Colonoscopy intervall: anually
- ESGE guideline recommends chromoendoscopy

Colectomy with ileorectal anastomosis (IRA) in patients with LS and
- CRC or
- Colonic neoplasia nit controllable by endoscopy

Extracolonic surveillance and management

Endometrian and ovarian cancer
- Pelvic examination and transvaginal US anually starting at age 30-35 years
- Endometrial biopsy anually starting at age 30-35 years

Gastric cancer/small intestinal cancer
- EGD (anually) starting at age 35 y
- Small intestinal cancer (lifetime risk 4-8%) in located in 35-50% in the duodenum
- Wireless capsule endoscopy ca be considered at 2-3 year intervalls **

Panceratic cancer
- Screening with EUS/MRI ist suggested in individuals with MMR mutation and a first degree relative with PC

Urinary tract cancer
- Annual cytological examination in addition to urine analysis can be considered

Skin/breat/prostate malignancies
- No standard screening recommendations

Hereditary CRC

- **7-10% of CRC cases**
- Two major subtypes
  - **Absence** of **colorectal polyposis** (2-5%)
  - **Presence** of **colorectal polyposis**

Lynch syndrome (LS)

Adenomatous polyposis syndromes

- Familial adenomatous poylposis (FAP)
- Attenuated FAP (AFAP)
- MUTYH-associated polyposis (MAP)
- Polymerase-Proofreading-Associated-Polyposis (PPAP)

Hamartomatous polyposis syndromes

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

Serrated polyposis syndrome (SPS)

Hereditary colorectal cancer

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)
- Polymerase-Proofreading-Associated-Polyposis (PPAP)

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

Serrated polyposis syndrome

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

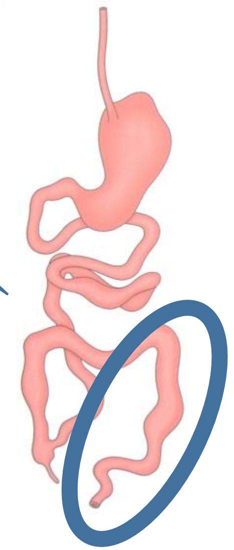
Table I. Common hereditary syndromes associated with CRC, genes involved, and pattern of inheritance

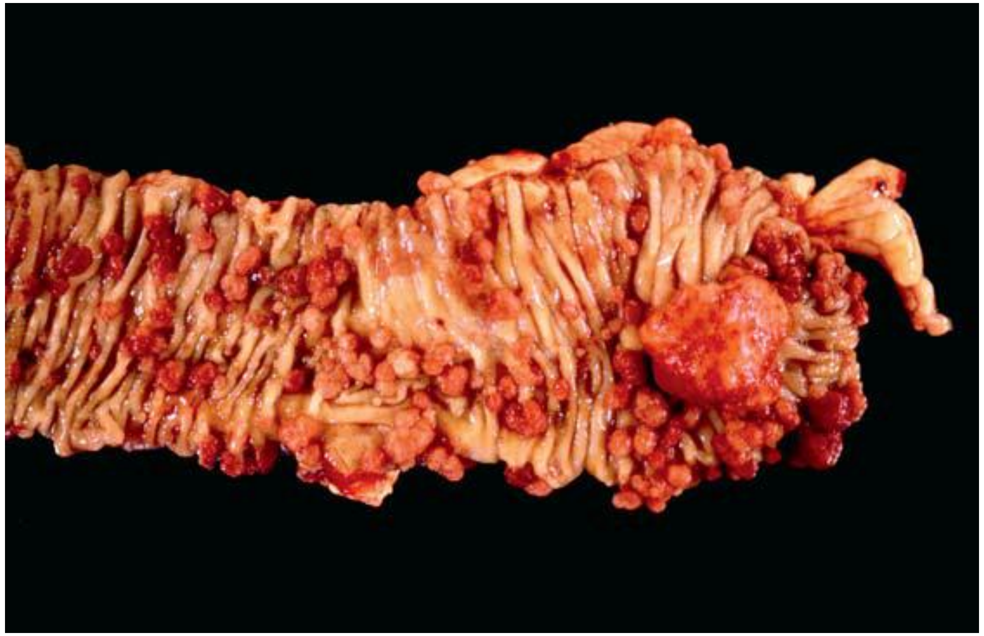
Lynch syndrome (absence of colorectal polyposis)

Familial adenomatous polyposis (FAP)

- **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

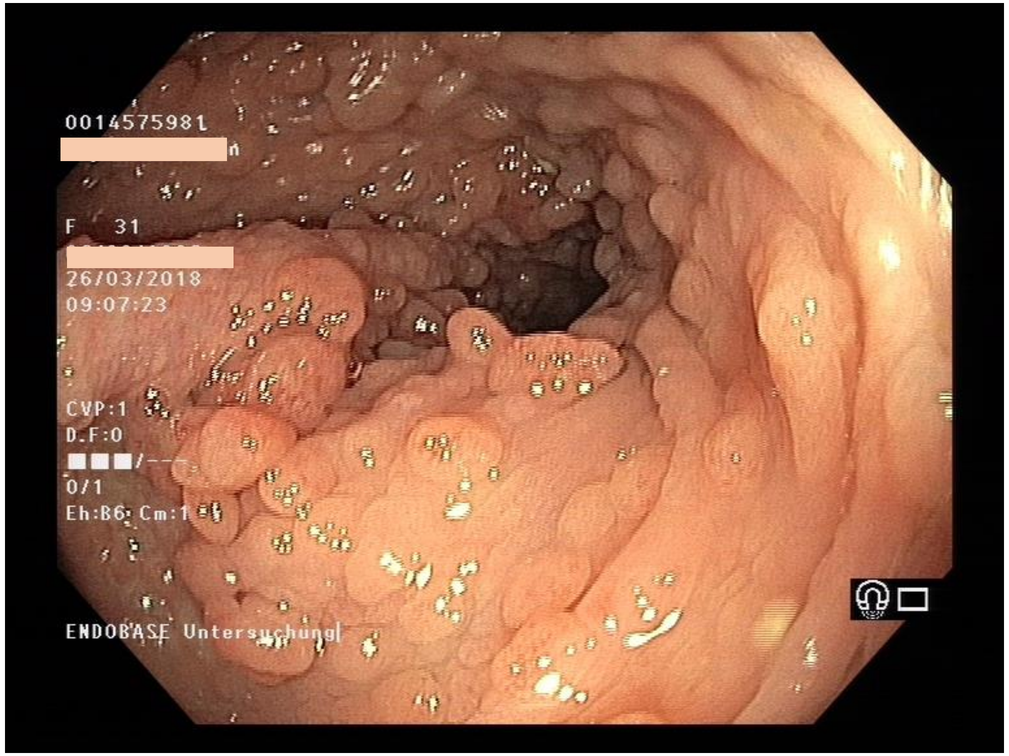
Left sided

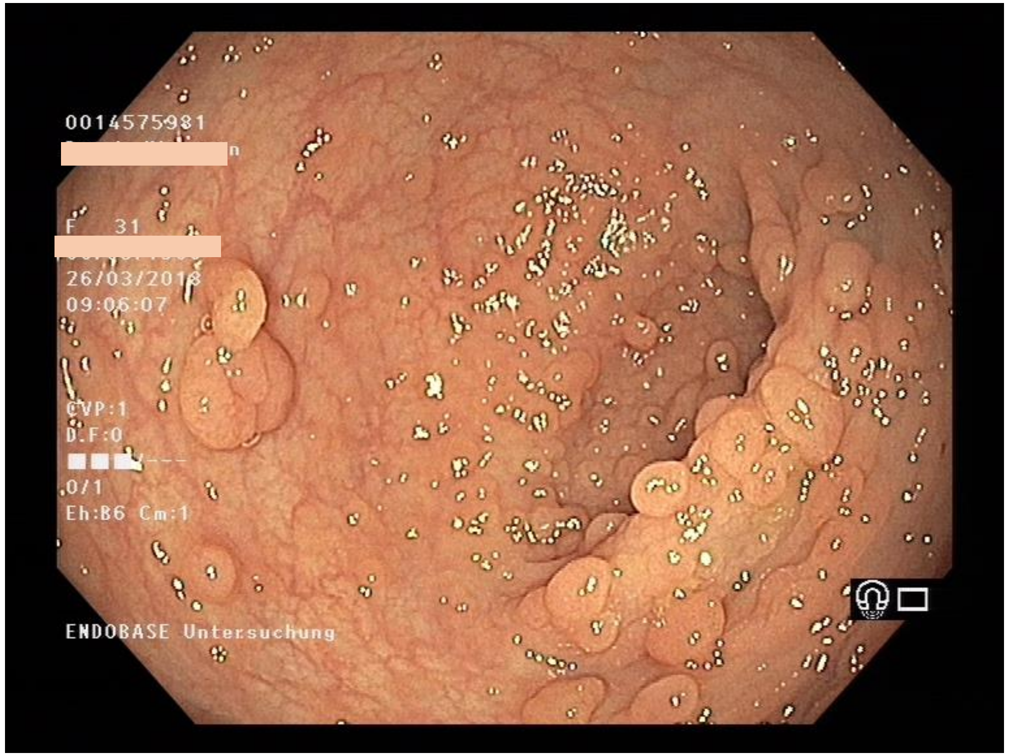


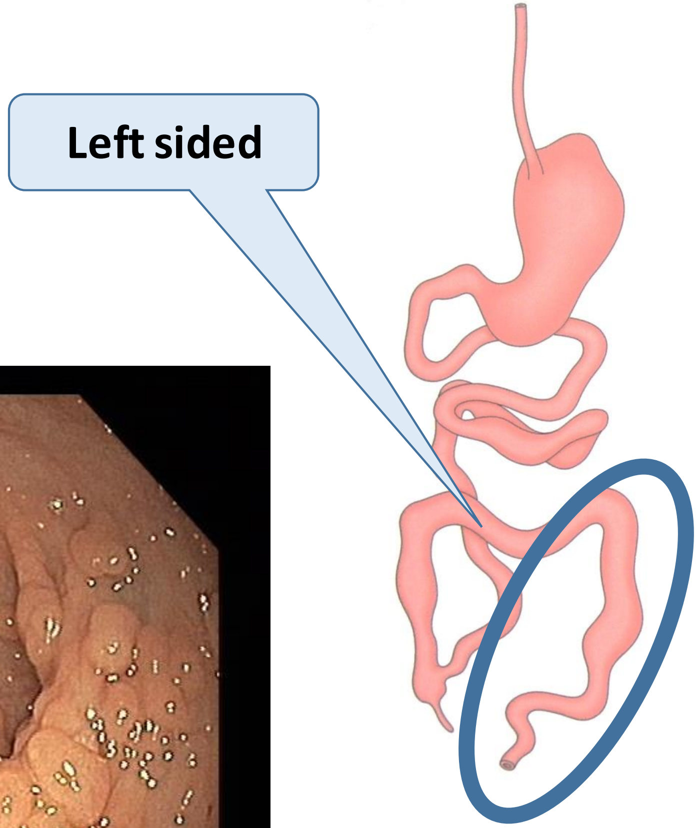


Familial adenomatous polyposis (FAP)

- **Clinical manifestations**
  - Colonic manifestations







Familial adenomatous polyposis (FAP)

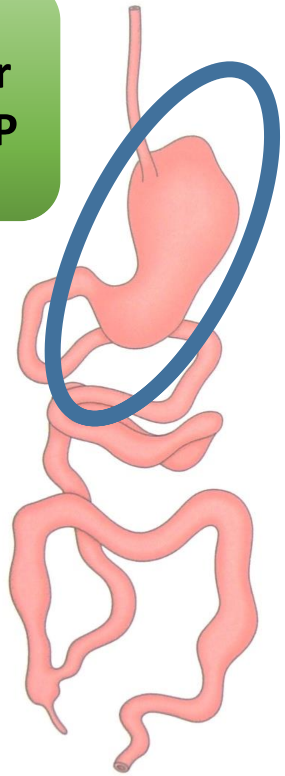
- **Clinical manifestations**
  - Colonic manifestations
  - Extracolonic manifestations

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

Familial adenomatous polyposis (FAP)

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

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

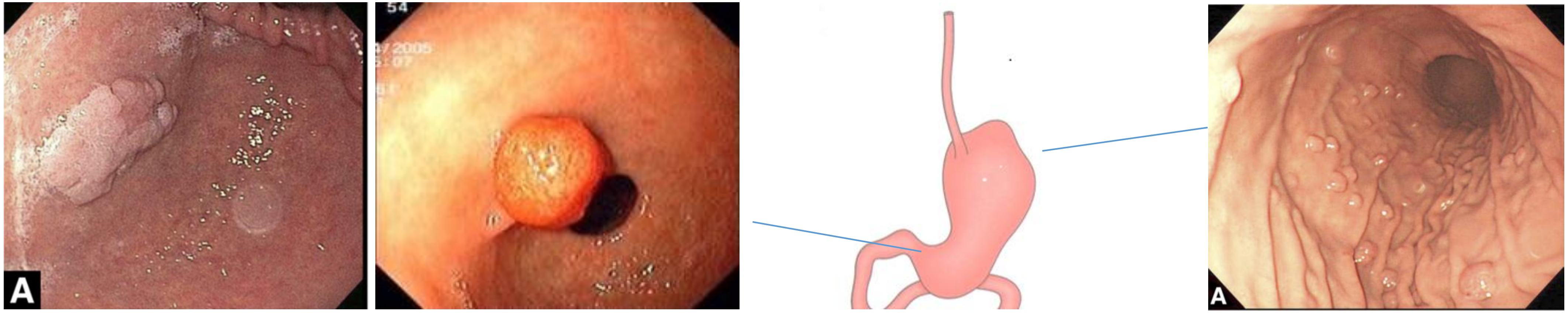


Fundic gland polyps

- 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**



Familial adenomatous polyposis (FAP)

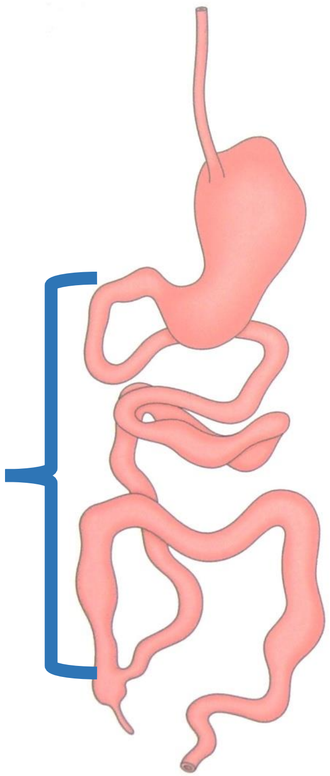
- **Extracolonic manifestations within the GI-tract**

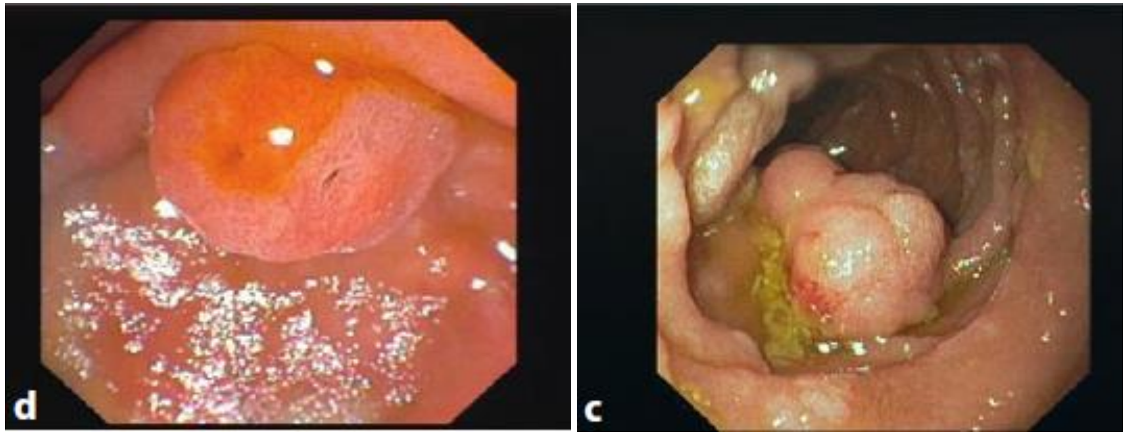
Duodenal adenomas

- 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)

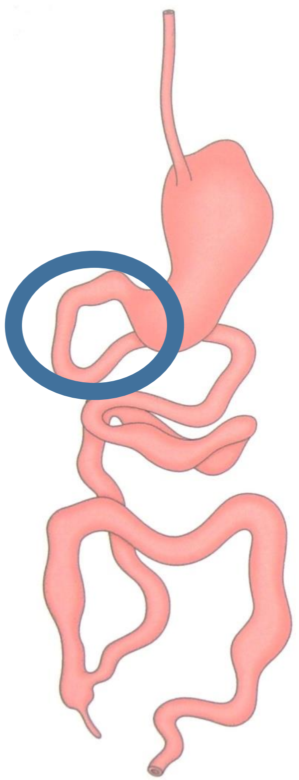
Table 3 Staging the duodenum and ampulla and recommended OGD surveillance intervals

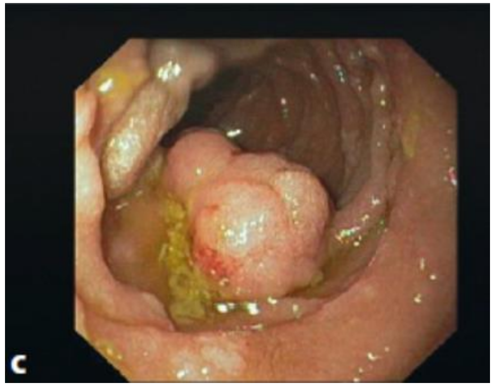
	Points allocated		
	1	**2**	**3**
Number of polyps	1–4	5–20	>20
Polyp size (mm)	1–4	5–10	>10
Histological type	Tubular	Tubulovillous	Villous
Degree of dysplasia	Mild	Moderate	Severe

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

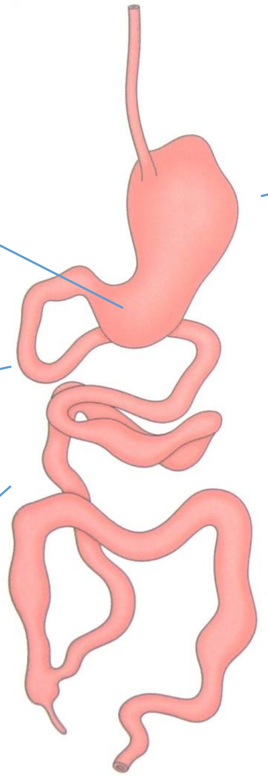
Familial adenomatous polyposis (FAP)

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

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

Duodenal adenomas
- 45-90% of pat.
- 5-10% 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

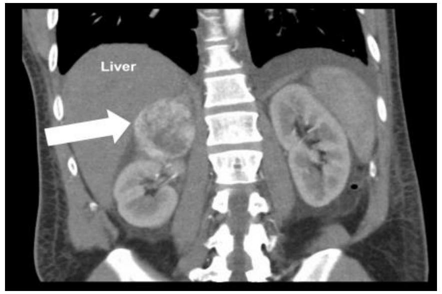
Polyps
- Left sided (80%)
- Nearly 100% risk of malignancy

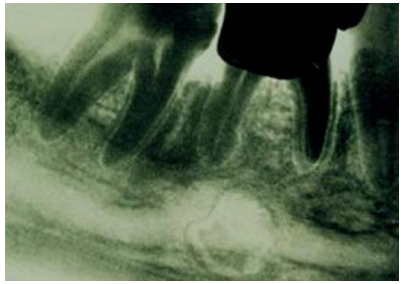
Familial adenomatous polyposis (FAP)

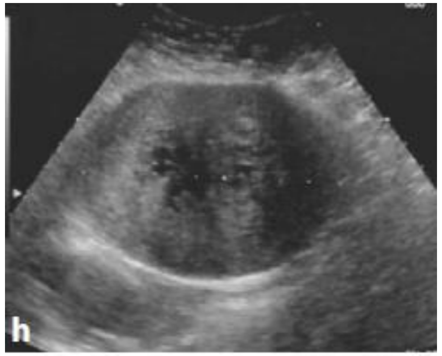
- **Extraintestinal manifestations of FAP**
  - Benigns extraintestinal manifestations
  - Malignant extraintestinal manifestations

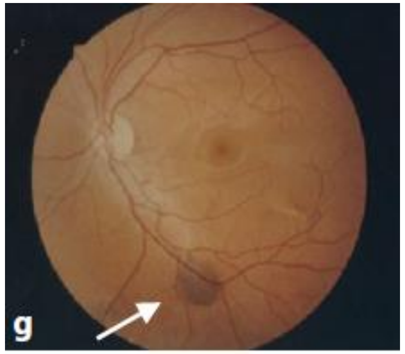
Familial adenomatous polyposis (FAP)

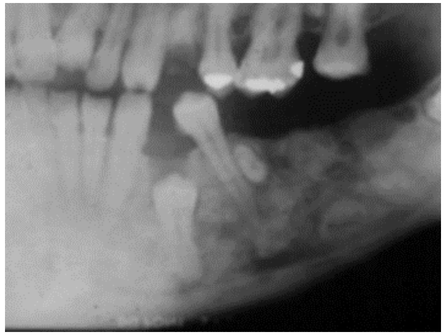
- **Benign extraintestinal manifestations ?**
  - **Cutaneous lesions**: fibromas, lipomas and epidermoid cysts
  - **Osteomas**
  - **Dental abnormilities**
  - **Congenital hypertrophy of the retinal pigment epithelium** (CHRPE; 58% of pat.)
  - **Desmoid tumors**
    - Solid tumors of the connective 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







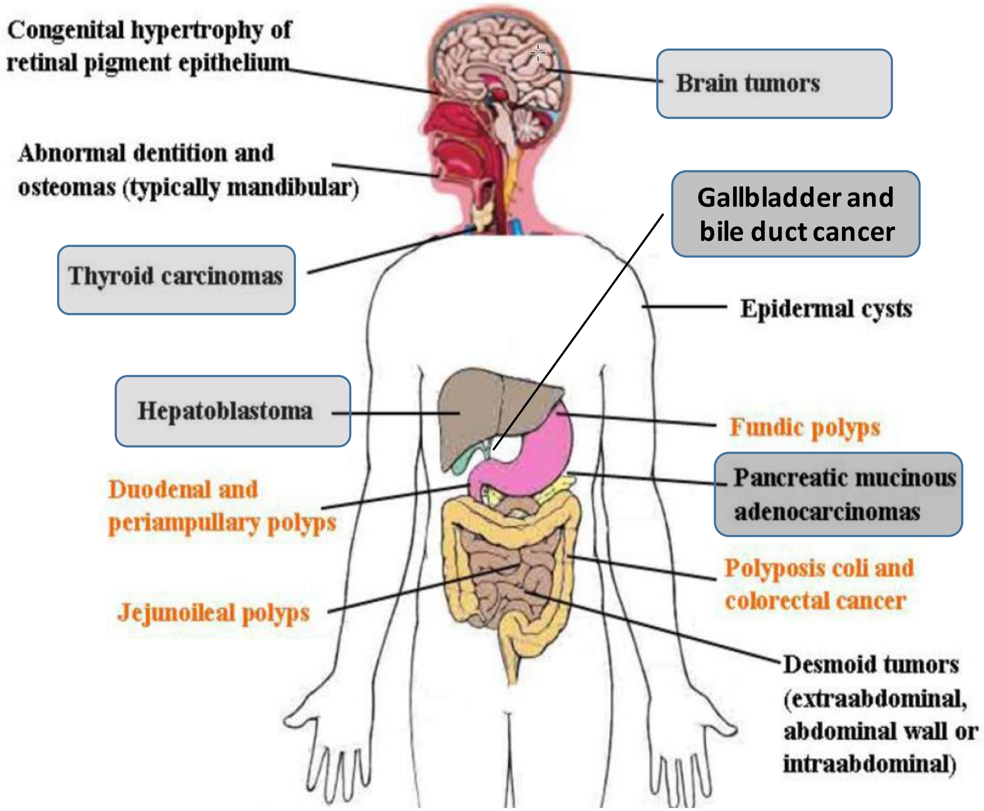




- Adrenal.com
- Allgemein-und Viszeralchirurgie up2date,2010, 277-295
- Onkologe 2021, 27:203-218

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

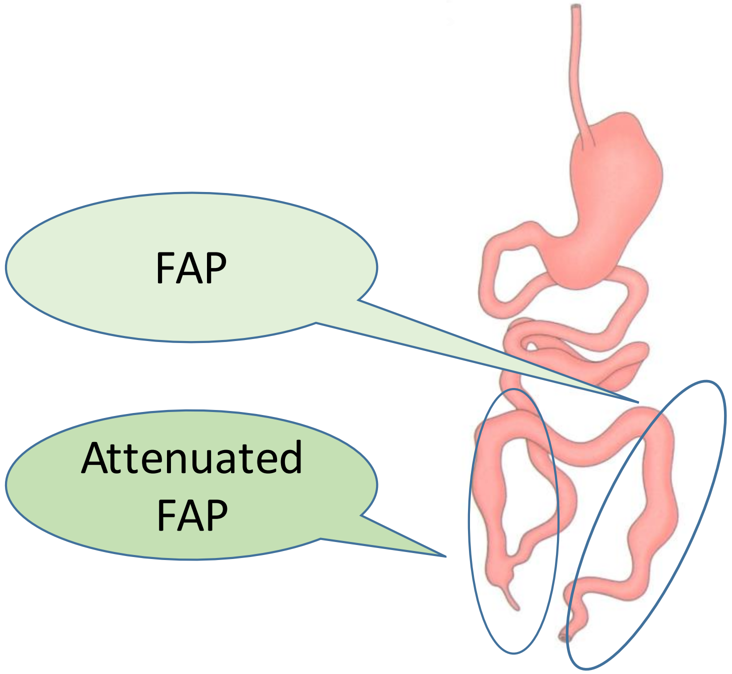
Brain tumor polyposis syndrome is a historical term that originally descriebed the a**ssociation of familial colon cancer and brain tumors**

Familial adenomatous polyposis (FAP)

- **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

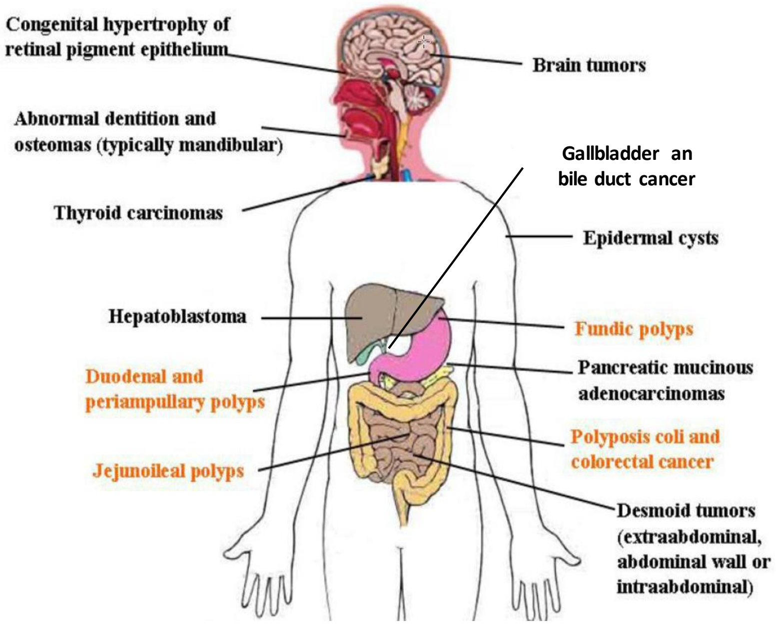
    - **Most predominant extracolonic findings**
      - Duodenal and gastric adenomas
      - Fundic gland polyps
      - Hepatoblastoma
      - Gastric and breast adenocarcinoma
      - Other extracolonic manifestations of FAP are rare

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



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

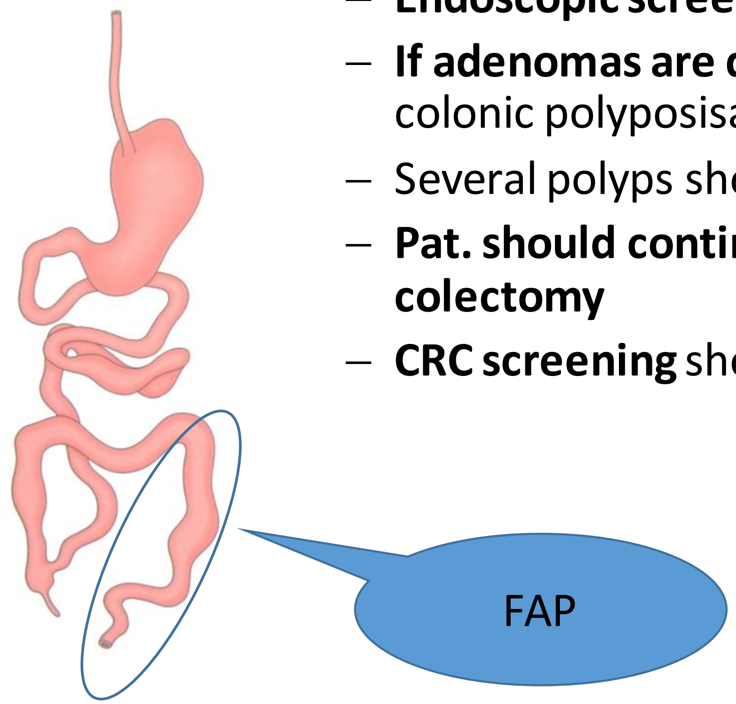
Individuals at-risk

- 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)

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

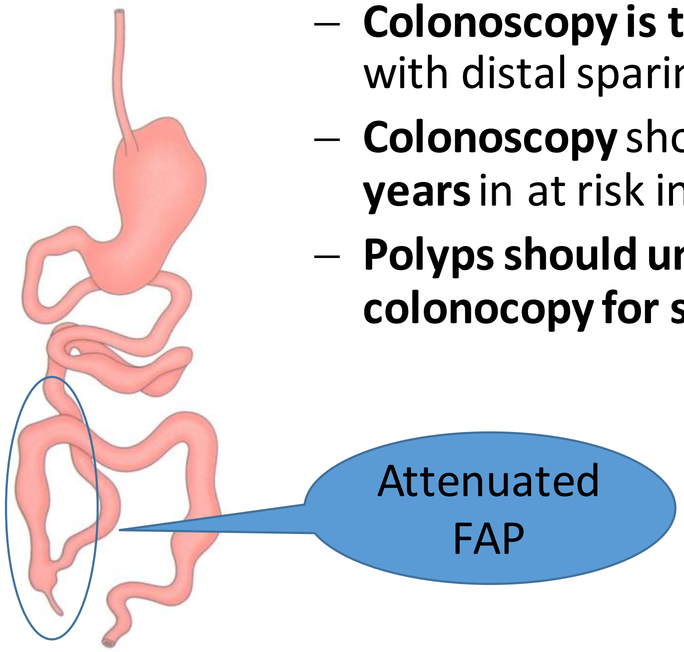
- **Screening** and management
  - **CRC screening and surveillance**
    - **Classic FAP**
      - **Endoscopic screening** with **sigmoidoscopy** should be **started** around age **10-12y**
      - **If adenomas are detected a full colonoscopy** should be performed to evaluate the extent of colonic 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**



Familial adenomatous polyposis (FAP)

Later age of adenoma appearance and fewer polyps

- **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**



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

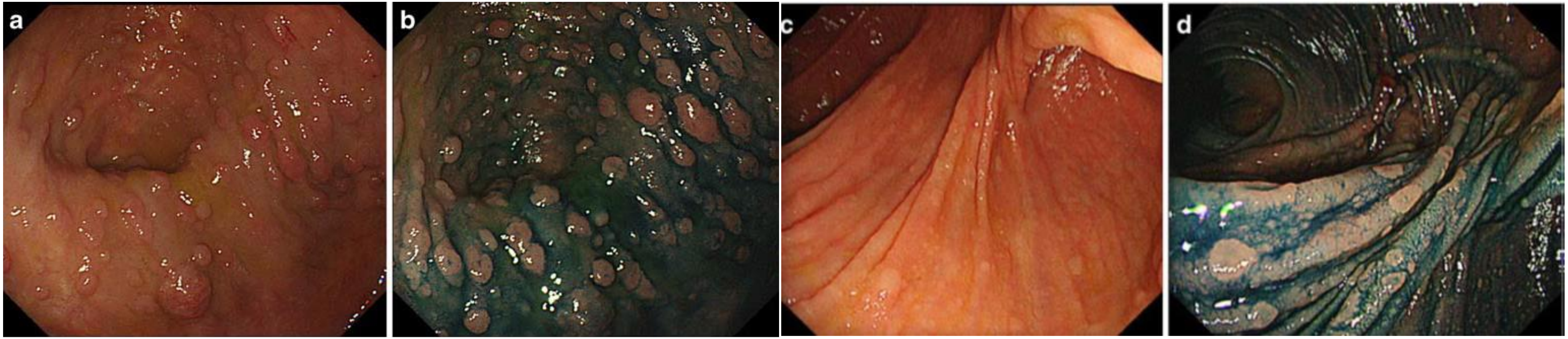
Nearly 100% of untreated patients will have malignancy by age 40-50y

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

- **Attenuated FAP**
  - If **endoscopic control** is feasible, surveillance can obviate or delay the need for colectomy

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)

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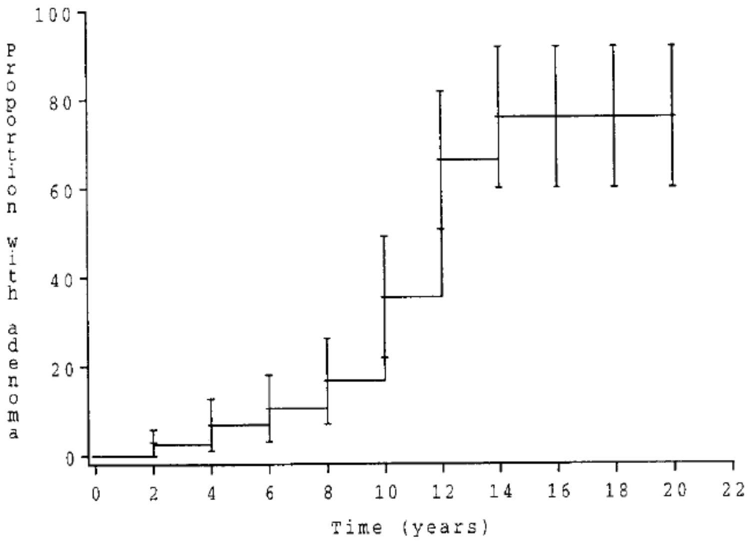


Figure 1. Risk curve to develop adenoma of the pouch after restorative proctocolectomy with construction of an ileal reservoir.

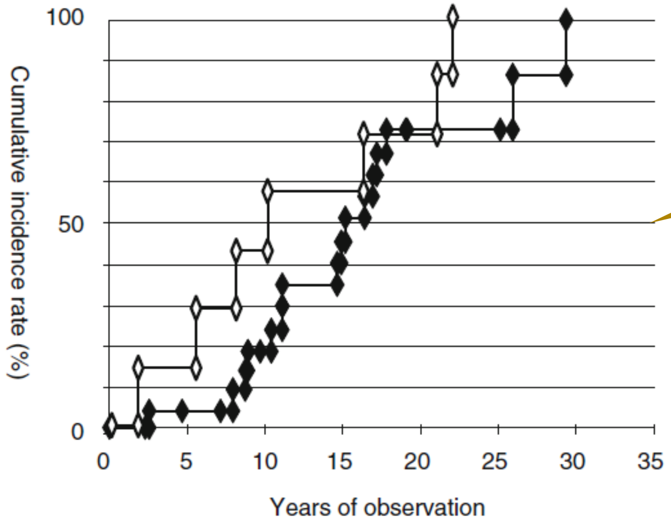
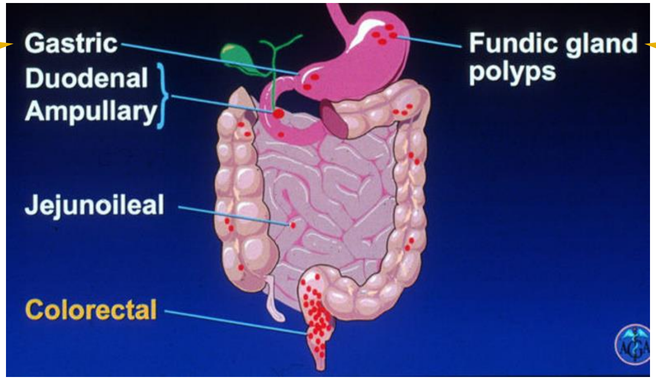


Figure 2 Cumulative incidence rate of adenomas in the ileal pouch after proctocolectomy with Kock and IPAA (*closed diamond*) and that of rectal adenomas after colectomy with IRA (*open diamond*).

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

Less commons

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



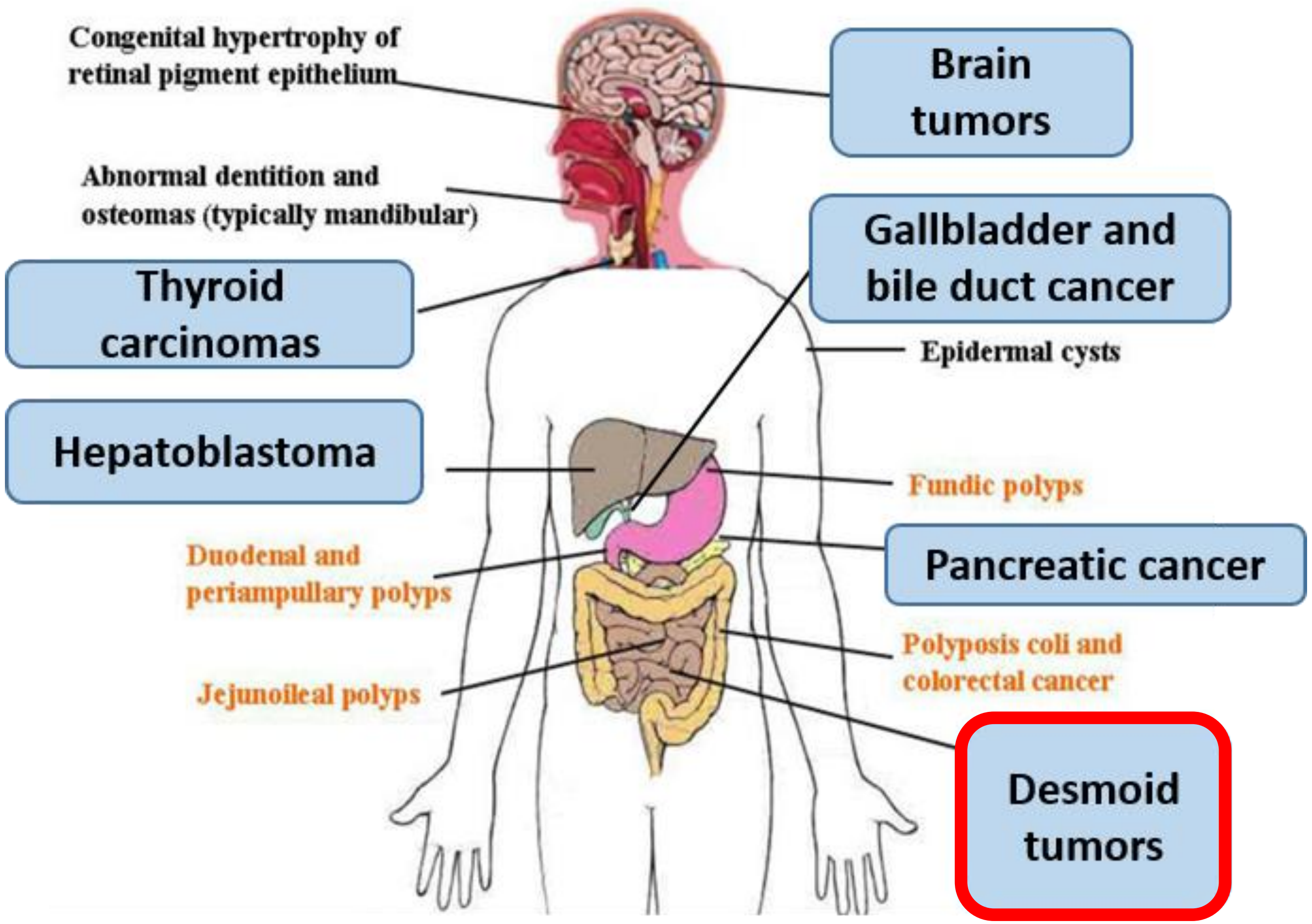
Most patients

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**
    - In patients **with duodenal adenomas follow-up due to Spigelmann stage**

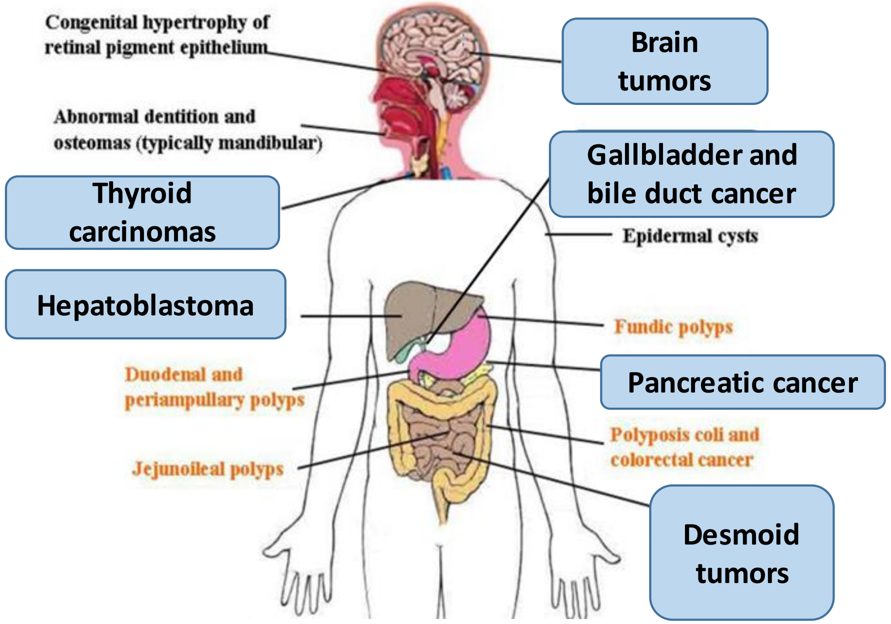
Familial adenomatous polyposis (FAP)

- **Extraintestinal malignancies ?**



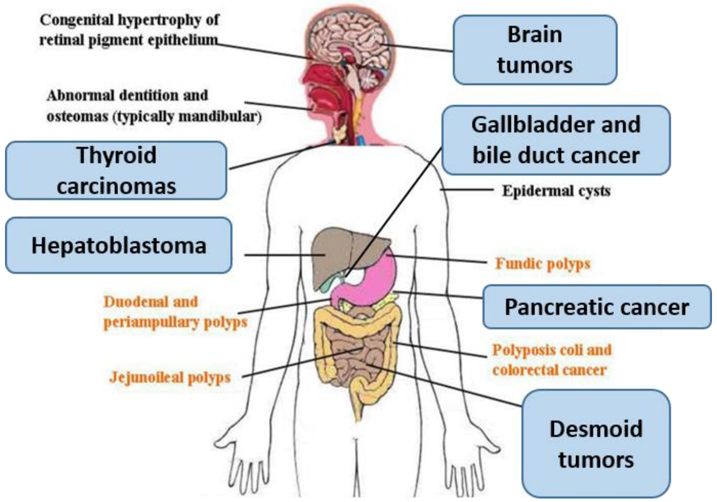
Familial adenomatous polyposis (FAP)

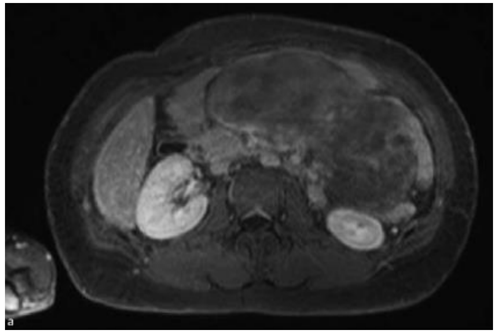
- **Screening and management**
  - **Extraintestinal malignancies**
    - **Thyroid cancer**
      - **Young women** are at particulary high risk (mean age 28y)
      - 80% of **FAP patients** have a nodular thyroid, **12% develop thyroid cancer**
      - **Screening:** annual US starting in the late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





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MUTYH-associated polyposis (MAP)

- **Second most common cancer syndrome associated with adenomatous polyposis5**
- First described in 2002

Epidemiology and Genetics ?

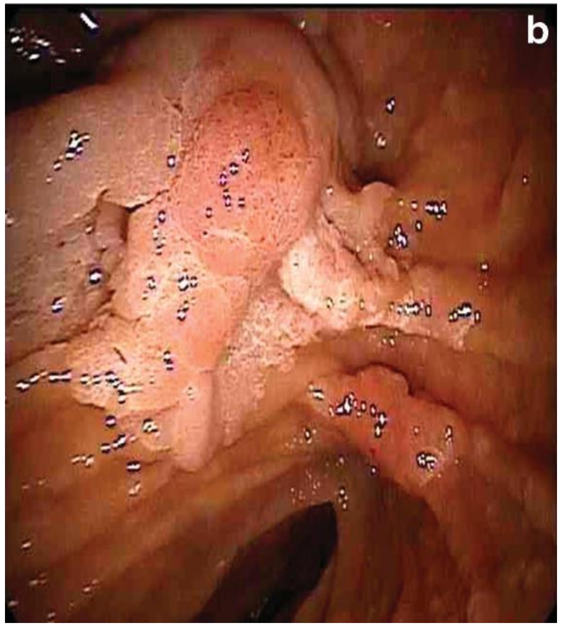
- **Epidemiology**
  - Monoallelic MUTYH mutations are found in 1-2 % of the general population
- **Genetics**
  - Autosomal recessive condition
  - MUTYH-gene: DNA base excision repair gene repairing DNA injury from oxidative stress

MUTYH-associated polyposis (MAP)

- **Clinical manifestations**
  - **Colonic manifestations**
    - Average age of onset around the mid-50s
    - Fewer than 100 adenomas
    - Additional serrated polyps are common
    - 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

Usually attenuated FAP phenotype

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



Am J Gastroenterol 2017; 112:1509–1525

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
    - continiued 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)

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

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

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

Polymerase-Proofreading-Associated-Polyposis (PPAP)

- **Epidemiology and Genetics**
  - very rare condition
  - PPAP is caused by a variants of one of the two DNA polymerase proofreading genes: **POLE and POLD1**
  - **Autosomal dominantly** inherited disorder
- **Clinical manifestations**
  - **Large** bowel **adenomas**
  - **Early onset CRC** (median age 45 y)
  - Risk of cancer may be lower with POLD1 variants (30% by 70 y) than with POLE variants (80% by 70 y)
  - **Significantly increased risk of endometrial cancer** in women with a pathogenic variant in **POLD1**.
  - **Other cancers** associated with PPAP: **breast, duodenal, ovarian and central nervous system.**

Polymerase-Proofreading-Associated-Polyposis (PPAP)

- **Management**
  - **Colonoscopy** should be **started** between **18- 20 years**, and repeated according to polyp burden
  - Through the endoscopic removal of polpys, many patients can be managed for many years, or even indefinitely
  - After surgery, any remaining large bowel or ileoanal pouch reconstruction requires regular endoscopic surveillance

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)
- Polymerase-Proofreading-Associated-Polyposis (PPAP)

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

Serrated polyposis syndrome

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

Hereditary colorectal cancer

Lynch syndrome (absence of colorectal polyposis)

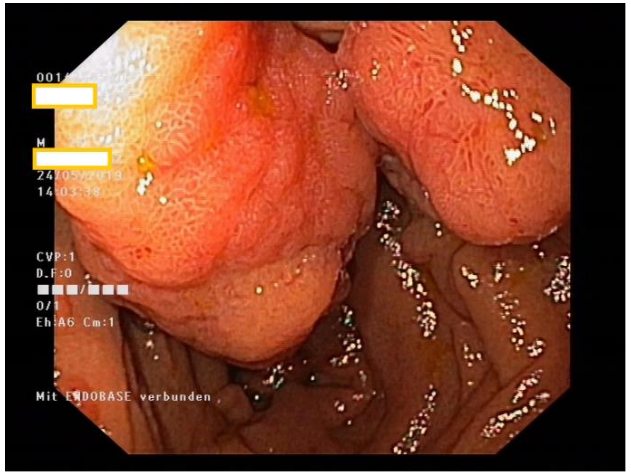
Peutz-Jeghers syndrome (PJS)

- **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

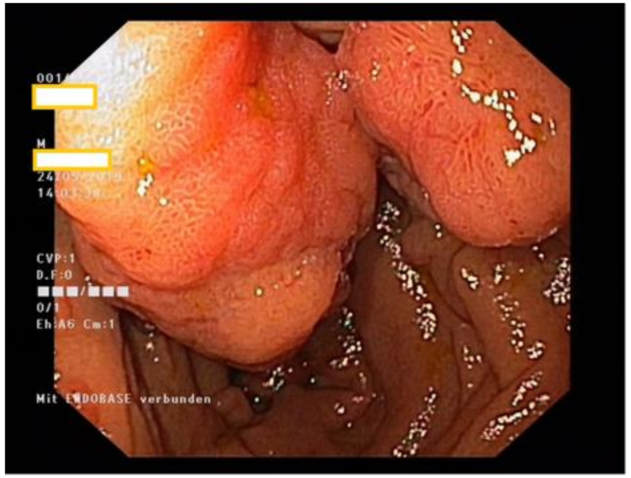


Peutz-Jeghers syndrome (PJS)

- **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 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?

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

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

Peutz-Jeghes syndrome (PJS)

- **Management ? Surveillance recommendations ?**

	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 commen
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

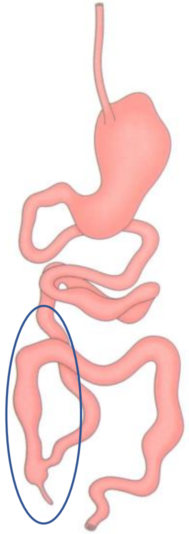
- **Start at age 8y** (polyp growth begins in first decade of life
- **If polyps present, repeat every 3y**
- **If no polyps, repeat at age 18, then every 3y**

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**

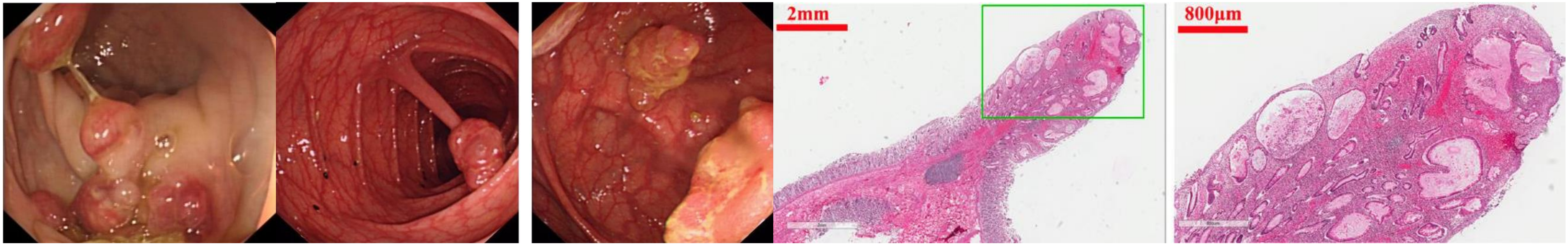
Juvenile polyposis syndrome (JPS)

- **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%



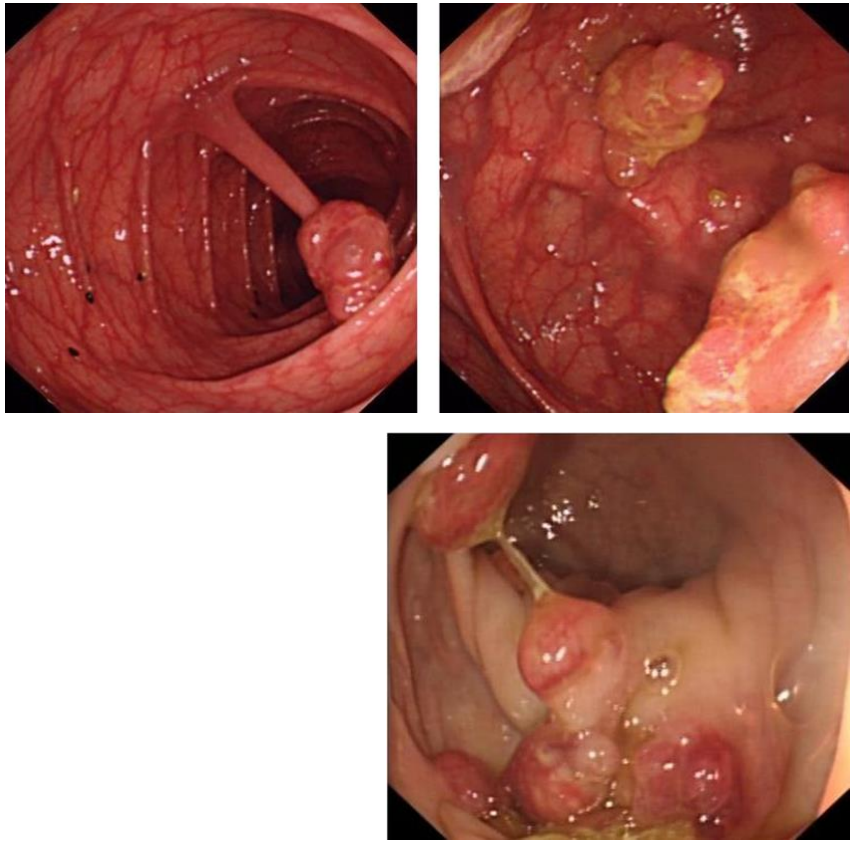
Gao et al. BMC Gastroenterology (2020) 20:167; https://doi.org/10.1186/s12876-020-01238-7

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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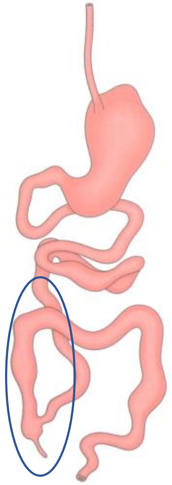
Juvenile polyposis syndrome (JPS)

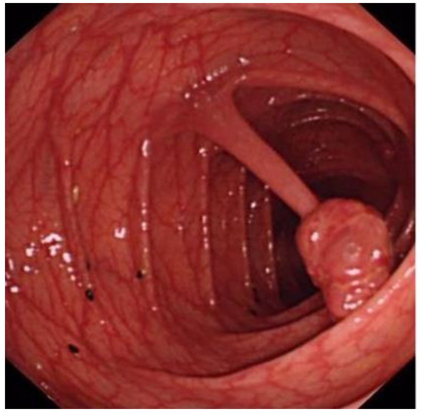
- **Genetic testing ?**

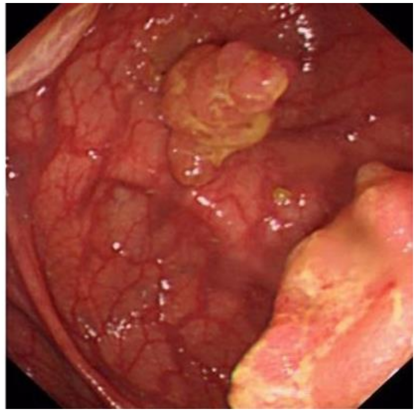
Individuals with

- ≥ 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

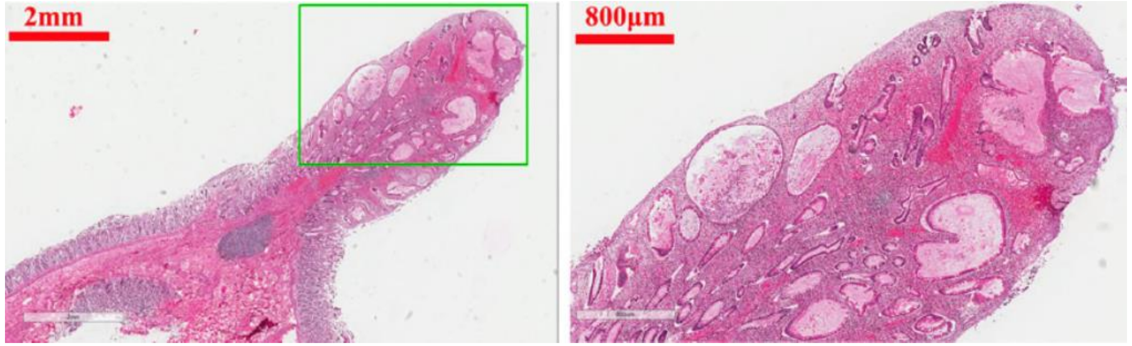






JPS polyps – frequency by segment

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



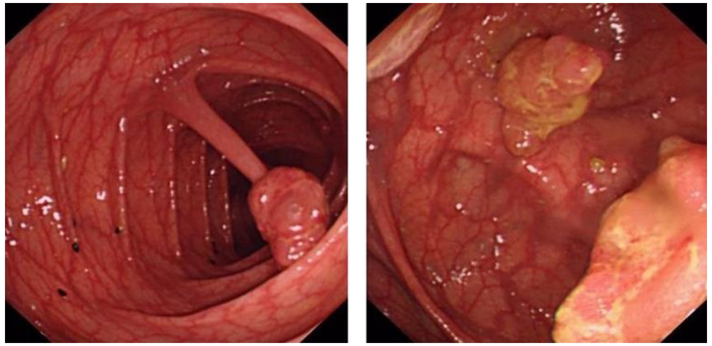
Juvenile polyposis syndrome (JPS)

- **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

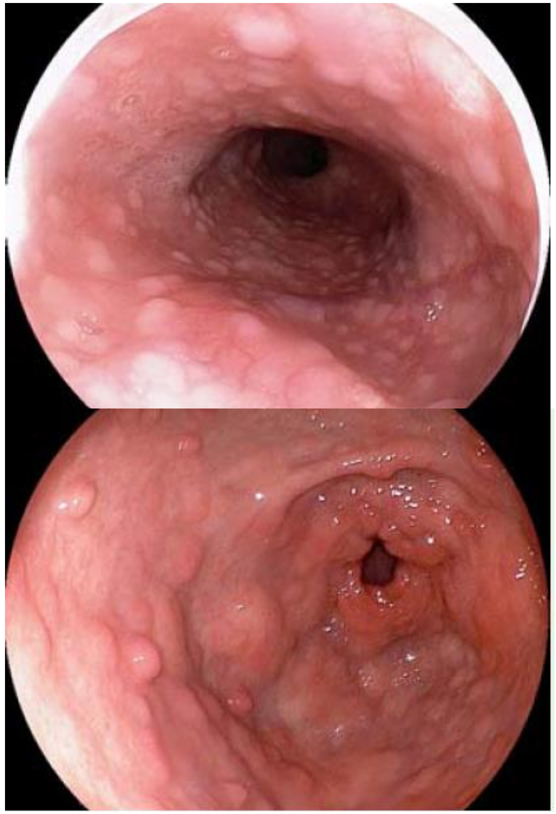
- **Diffuse glycogenic acanthosis** in the esophagus
- Frequent finding of multiple **hamartomatous polyps** in **stomach, duodenum** and the **small bowel**

- Extraintestinal manifestations

- Increased risk for extracolorectal cancer

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]



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

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