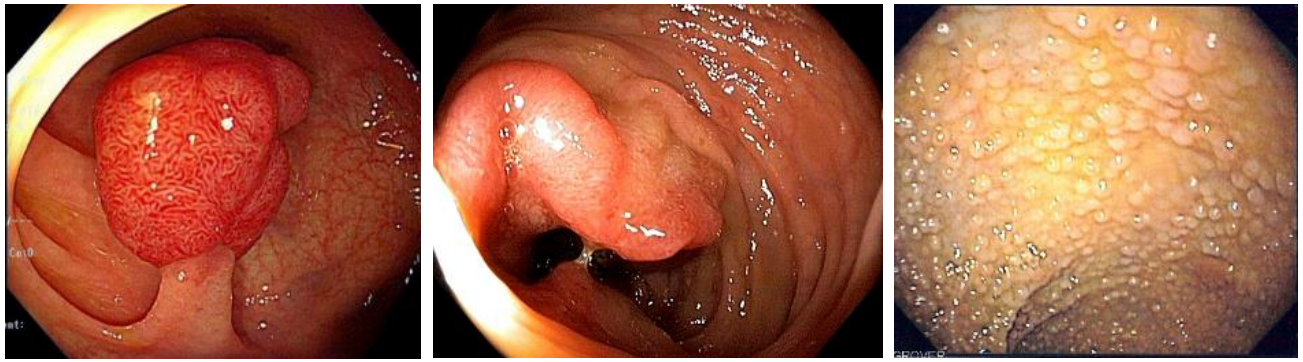
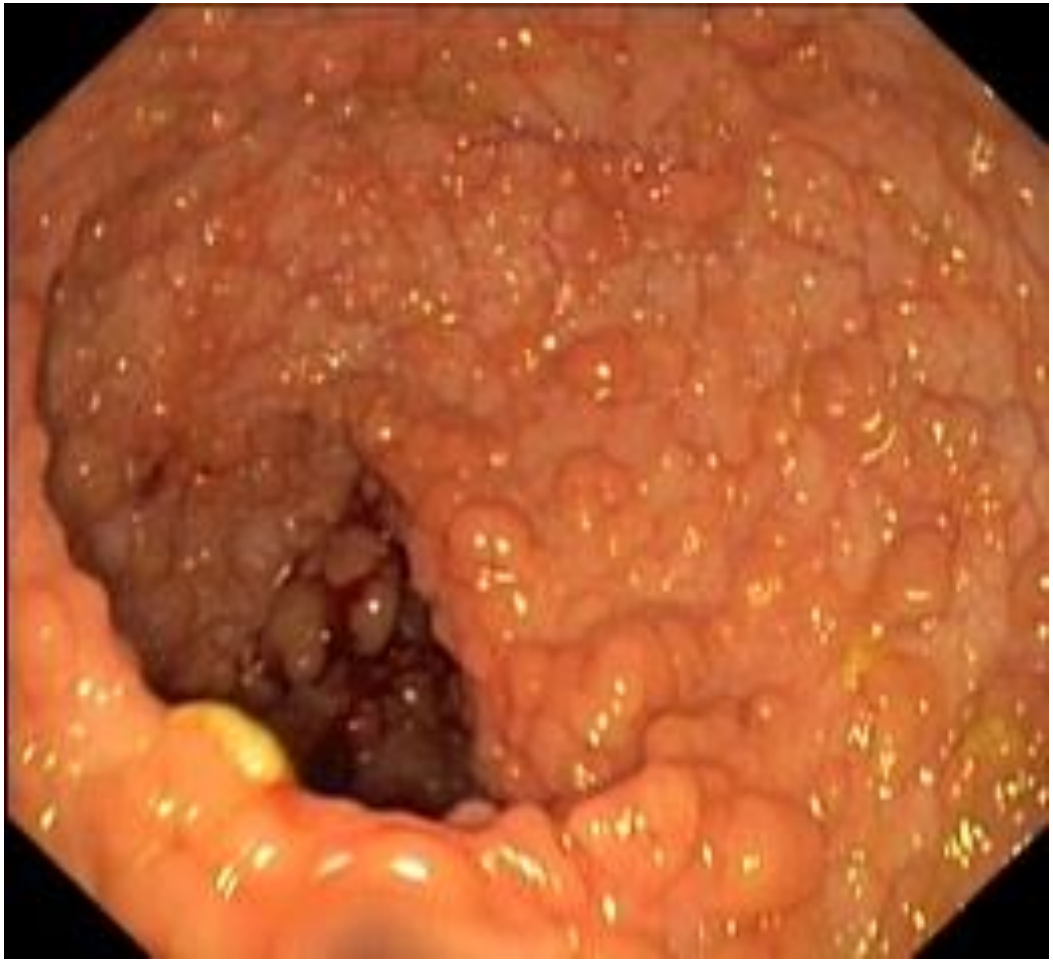
INSELSPITAL
Universitätsklinik für
Viszerale Chirurgie und Medizin

Familial polyposis syndromes



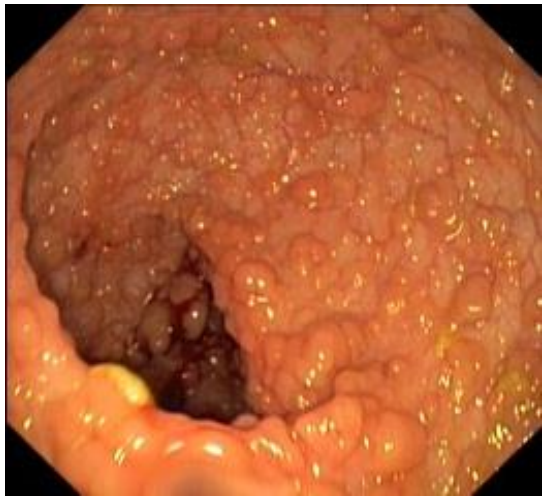
Benjamin Misselwitz, 17th of April 2019

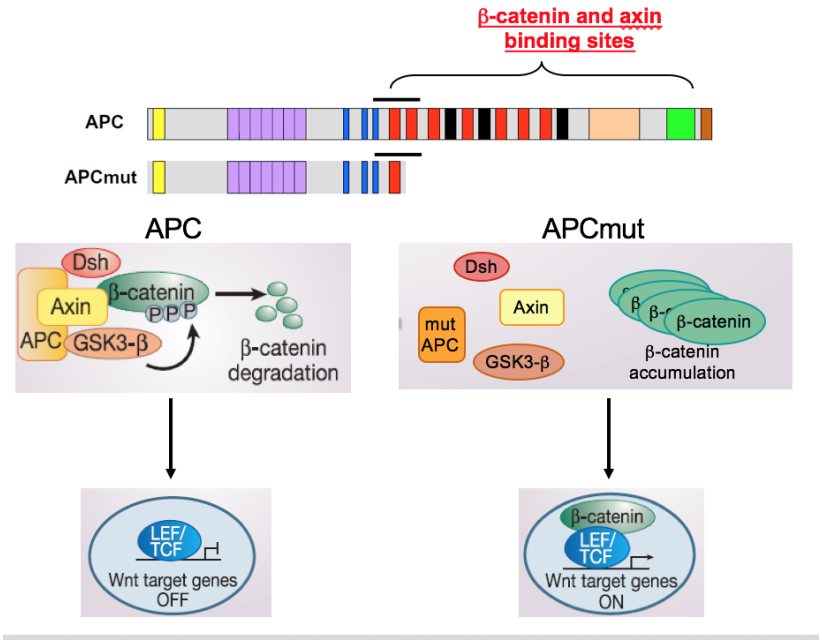
Bauchzentrum
BERN



Familial adenomatous polyposis (FAP)

- ≤1% of all colorectal carcinomas
- Frequency 1:100'000
- **Mutation of APC gene**, **autosomal-dominant**, but:
  25% new mutations (no family history)!
- Diffuse proliferation of colorectal polyps (100->5000) in 2nd and 3rd decade (average 16 years)
- 100% penetrance for colonic polyposis





FAP: mutated APC gene
→ 2nd hit: mutation of other allele
→ No catenin degradation
→ Wnt pathway is active
→ Cell proliferation

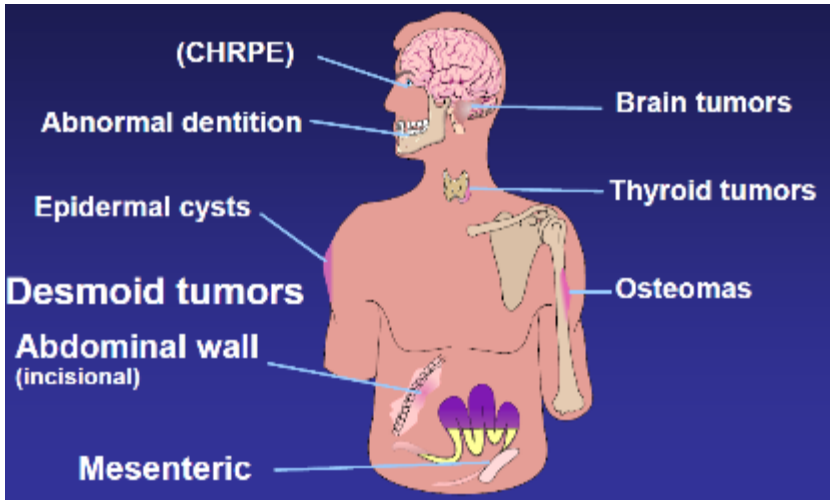
Giardiello Gastroenterol 2001;121:198; Grady Gastroenterology 2003; 124:1574 ; Burt. Gastroenterol 2005;128:1696; www.memorangapp.com

Attenuated FAP

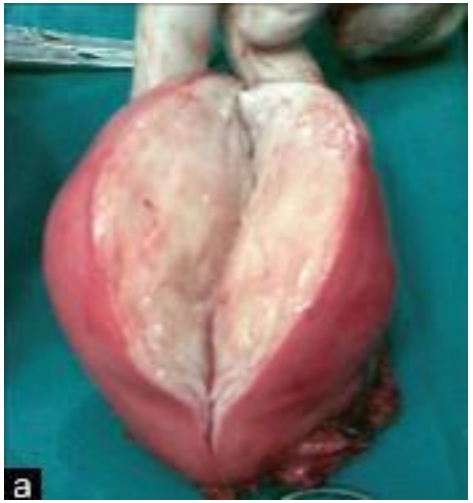
- «oligopolyposis» – 10-99 adenomas
- Carcinomas later in life (44 -58 years)
- **Life time carcinoma risk ~80%**

Extracolonic manifestationen

- Duodenal adenomas
- Gastric adenomas/ fundic gland polyps
- Desmoids (15%) – occasional bowel obstruction
- 80% «nodular thyroid» - 12% thyroid cancer
- Brain tumors (medulloblastoma)



Desmoid tumor



Life time risk in FAP

Type	%
Colon	100
Duodenum/ Periampullary	4-12
Pancreas	2
Thyroid	1-12
Liver	1-2
Stomach	< 1
CNS	< 1

AFAP

Type	%
Colon	70
Duodenum/ Periampullary	4-12

Giardiello. Gastroenterol 2001;121:198 / Grady Gastroenterology 2003;124:1574 / Burt. Gastroenterology 2005;128:1696

Duodenal lesions in FAP

- 2nd most common site of polyp development
- 15 years after colon polyps, life time adenoma risk ~100%
- Around/ distal of papilla of Vater (bile acid exposure?)
- Endoscopic treatment advanced lesions (>1cm, villous)
- Duodenal carcinoma: 5% (life-time); OR: 200-300

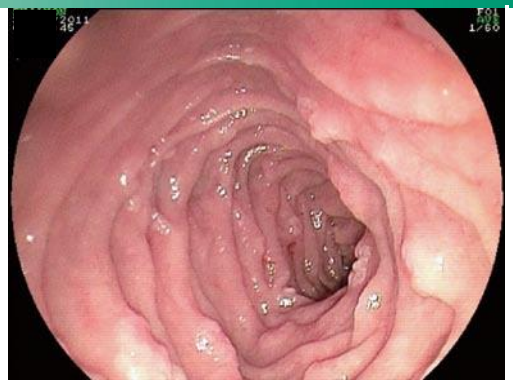
Spigelman classification

Criterion	1 point	2 points	3 points
Polyp number	1–4	5–20	>20
Polyp size (mm)	1–4	5–10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild*	Moderate*	Severe†

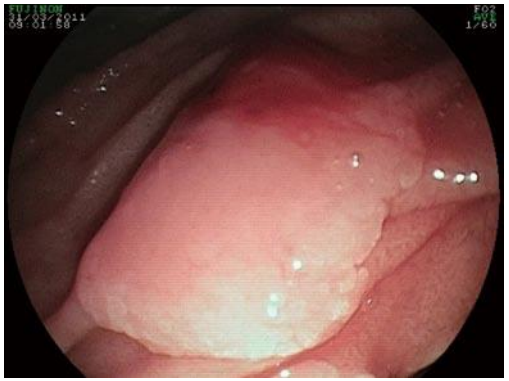
Stage 0, 0 points; stage I, 1–4 points; stage II, 5–6 points; stage III, 7–8 points; stage IV, 9–12 points.
*A low degree of dysplasia according to current classification.
†A high degree of dysplasia.

Surveillance intervals

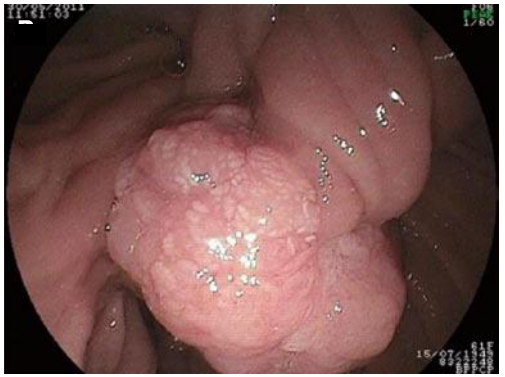
Spigelman classification	Surveillance interval (years)
0/I	5
II	3
III	1–2
IV	Consider surgery



10-20 white numerous flat adenomas



Papilla of Vater with solitary adenoma



Carcinoma of papilla of Vater

Campos World J Gastroenterol 2015; 7:950

FAP - Surveillance

Surveillance

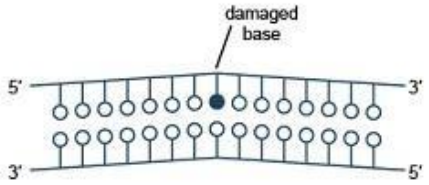
Test	*Start (Y)*	*Interval (Y)*	*Remarks*
Colonoscopy	*FAP 10-12*	*1-2* *	*Sigmoidoscopy until 1st adenoma detected*
	AFAP 18-20		
EGD	*20-25*	*3 or according Spigelman stage*	
Small bowel			*No recommendations*
Thyroid US	*10-12*	*1*	
Abdominal US	*FAP 10-12*	*1*	
	AFAP 18-20		

*prophylactich colectomy, if polyps not «manageable»

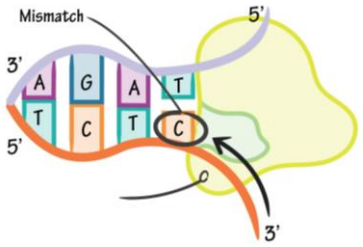
Vasen, Möslein, Gut 2008;57:704–713
Giardiello FM, Gastroenterology. 2001;121:198–213
Jasperson KW. Gastroenterology 2010

MUTYH associated polyposis (MAP)

- MUTYH
  - Autosomal recessive
  - Base excision repair enzyme
  - 10-100 adenomas by 5th to 6th decade of life
  - Extracolonic features
    - Gastric and duodenal polyps, bladder cancer, ovarian cancer…
    - Osteomas, dental cysts, desmoids…

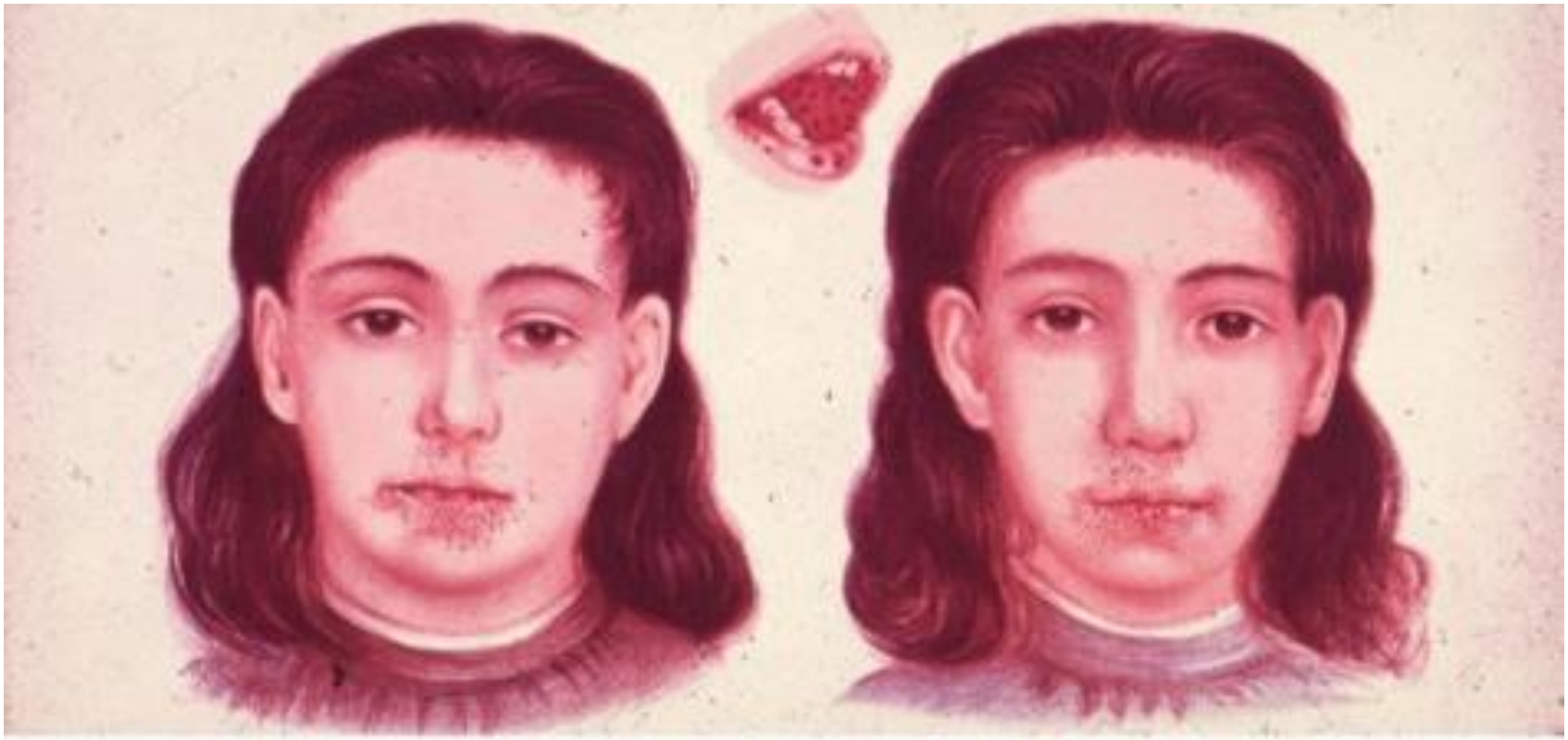


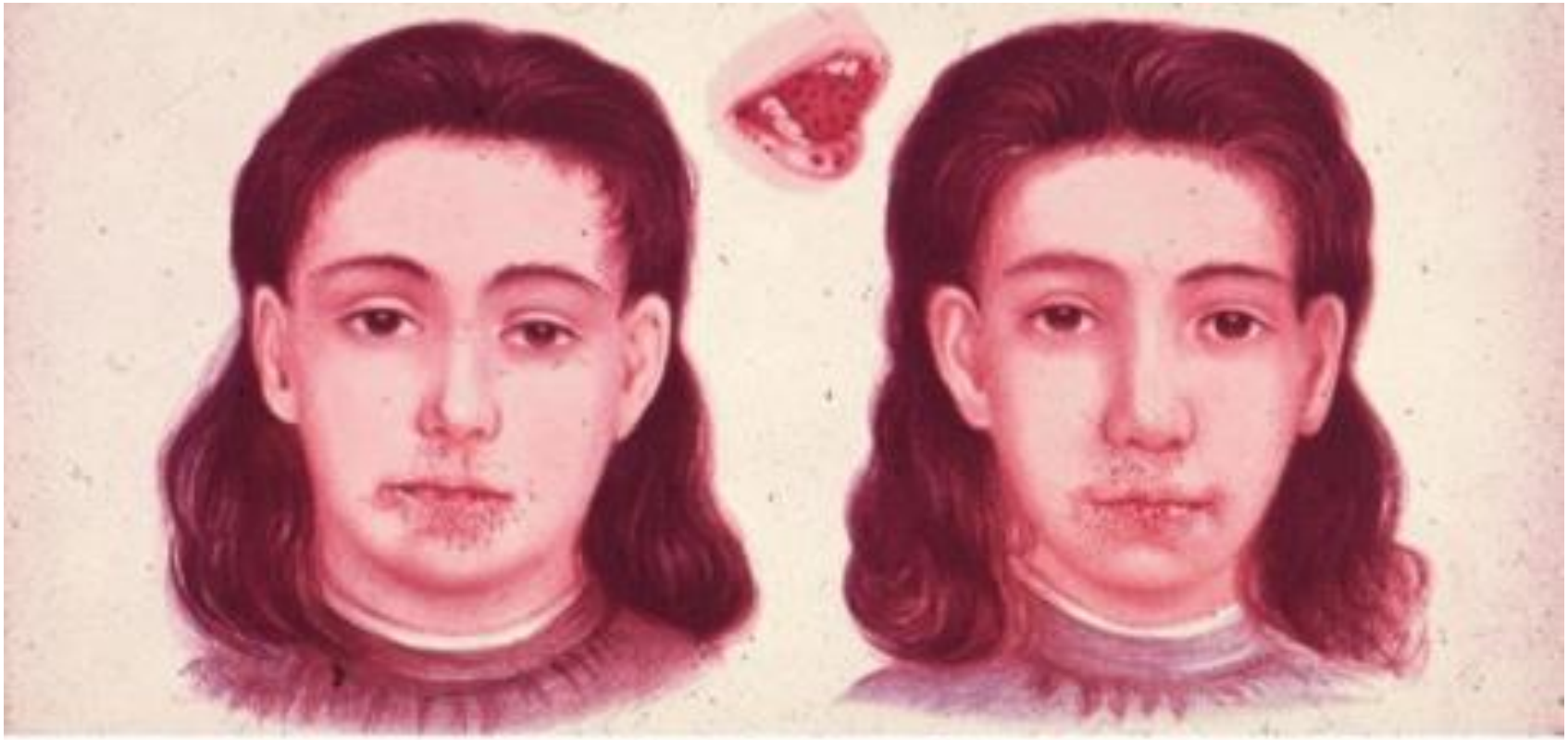
- Polymerase proofreading enzymes (POLE, POLD1)
  - Autosomal dominant, rare
  - Oligoadenomatous polyposis, colorectal cancer
  - Endometrium cancer



- Surveillance
  - Colonoscopy at 18-25 years of age

Farrington SM, Am J Hum Genet. 2005 Jul; 77(1):112-9
Vasen HF, Gut. 2008;57:704–713



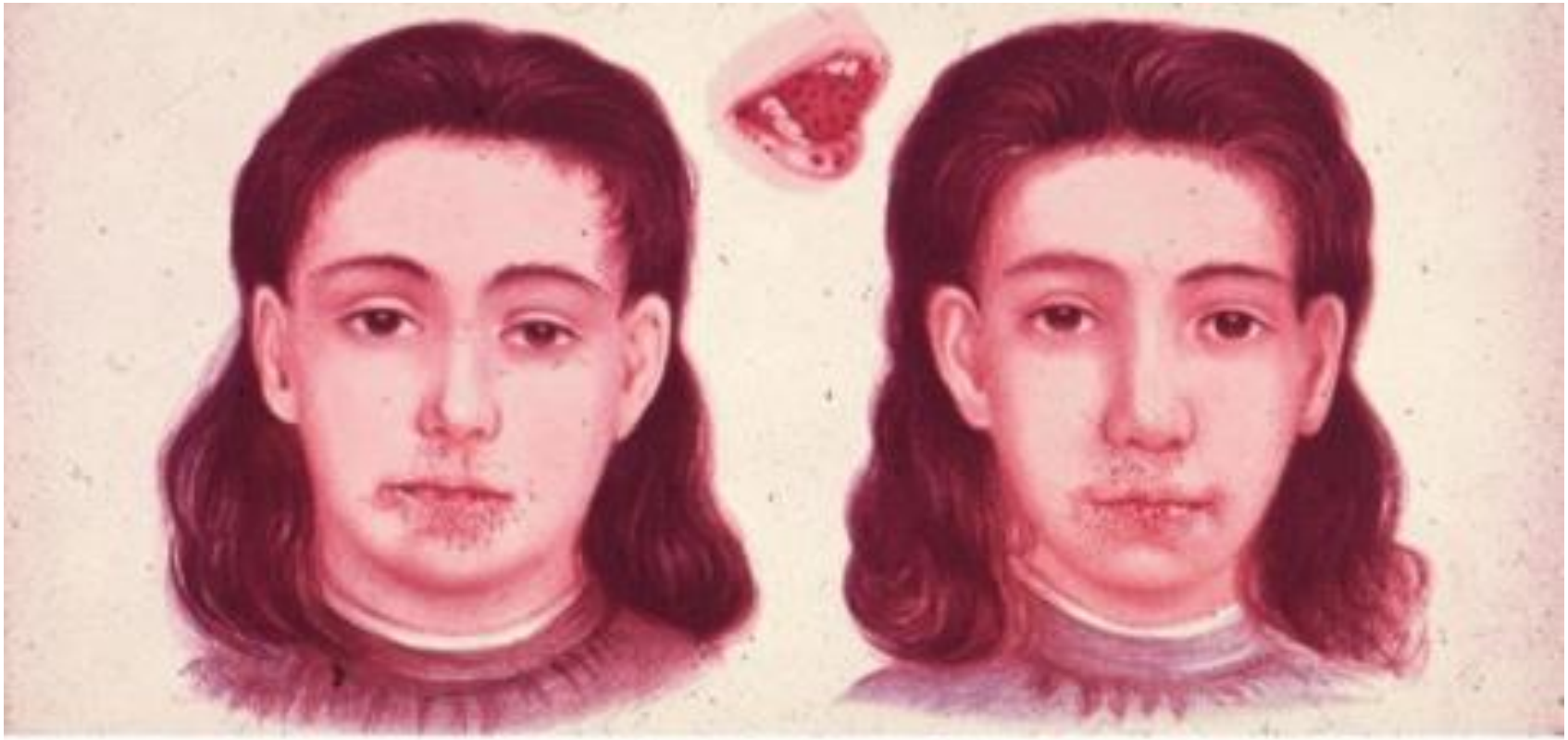


"Dr. J. T. Connor showed two cases of Pigmentation, of the Lips and the Mouth, in twins, both girls, aged twelve years, of dark complexion and anaemic. The pigment spots, which were only noticed two years ago, were ink black in colour, mostly of very small size and scattered over the lips, (especially the lower), gums, hard palate, and not on the tongue."

One twin died of intussusception at age 20, the other of breast cancer at age 52.

Connor et al., *Lancet* 1895; 2:1169

Peutz-Jeghers-Syndrome (PJS)



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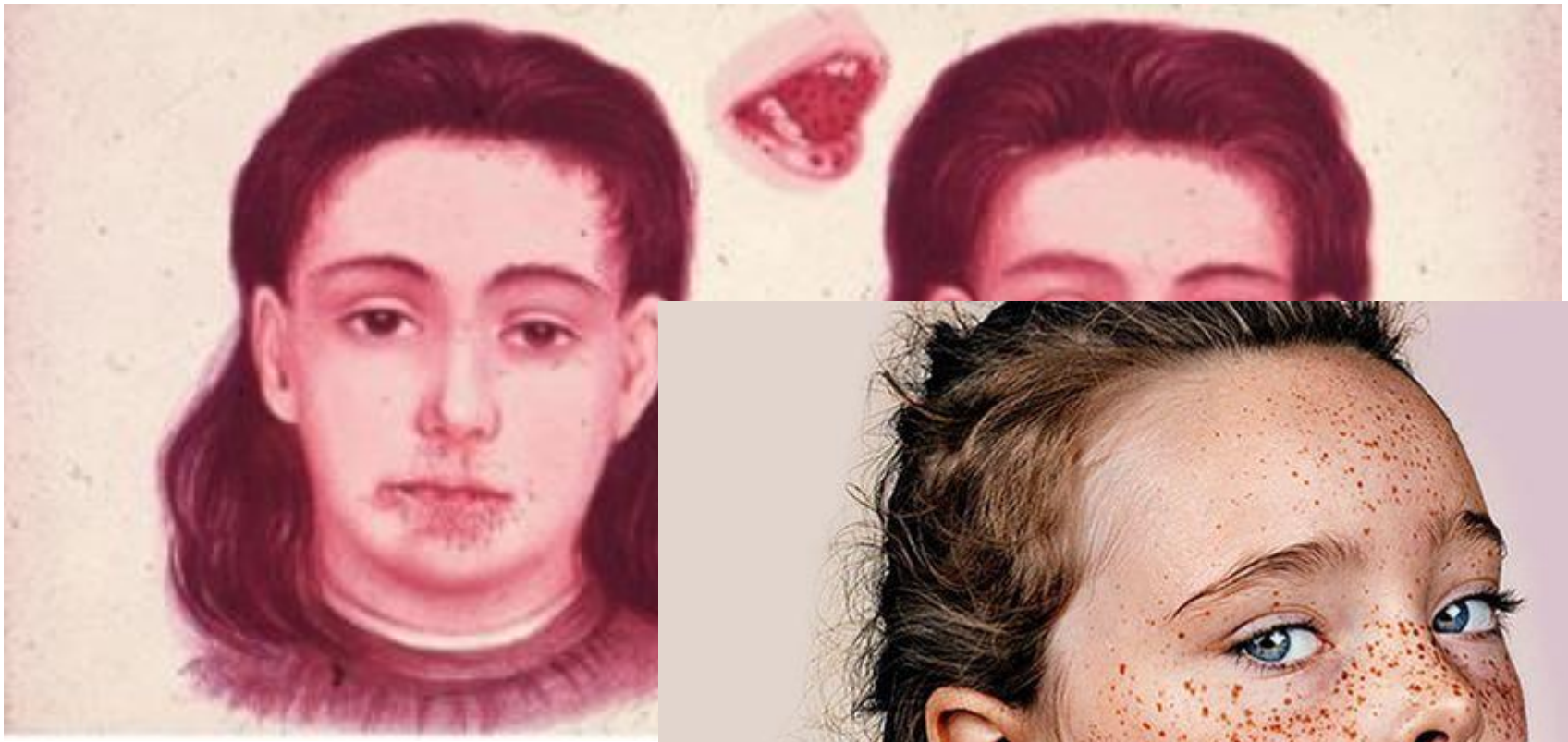

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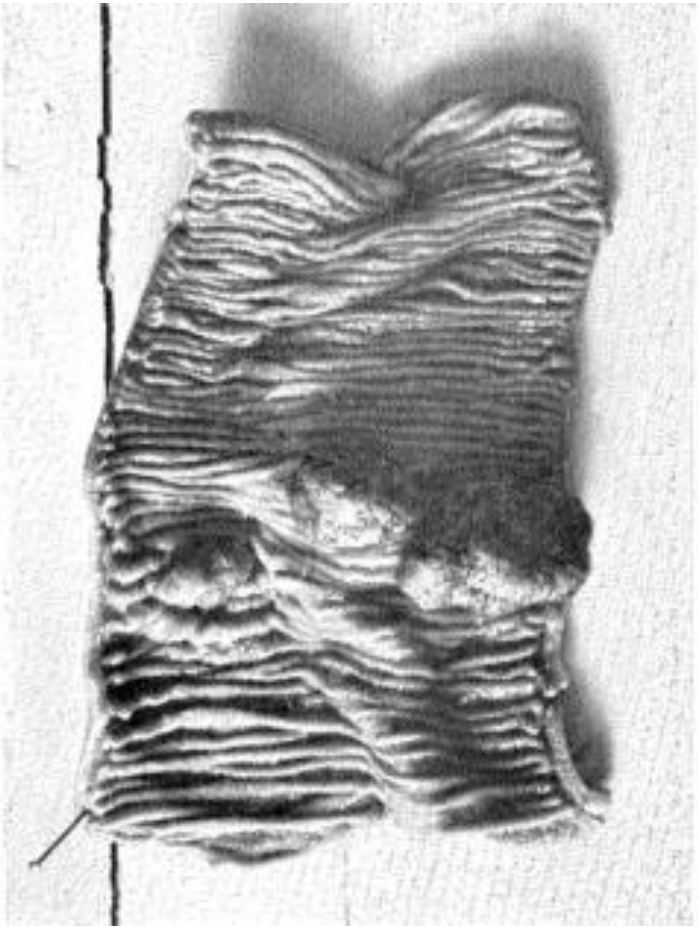
Peutz-Jeghers: *Ephilides inversae*

Connor et al., Lancet 1895; 2:1169

Peutz-Jeghers-Syndrome (PJS)

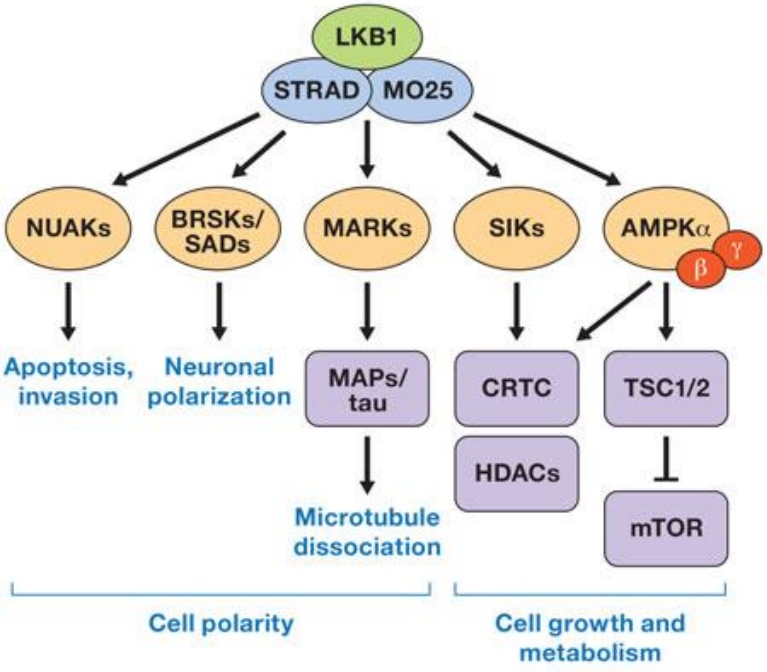


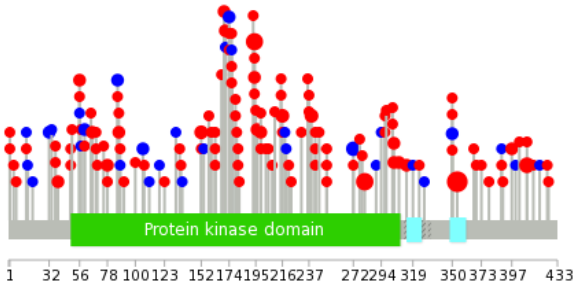
"Concerning the unusual syndrome of familial polyposis of the gastrointestinal mucosa with that of the nasal cavity also in combination with strange pigmentation of the skin and mucosa."

Peutz et al., Nederl Maandschr Geneesk. 1921; 10:134
Jeghers et al., N Engl J Med 1949; 241:1031

Peutz-Jeghers-Syndrome (PJS)

- Prävalenz 1:25‘000-200`000
- **Autosomal dominant,** 70% familiär, 30% sporadisch
- STK11/LKB1-Mutation (Ser/Thr kinase 11/ liver kinase B1
- The first kinase acting as a tumor suppressor gene
- Involved in regulation **cell polarity**, **cell growth** → STK11 activates 11 additional kinases

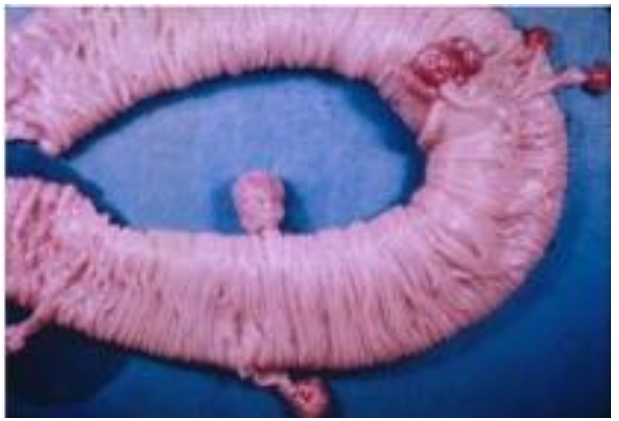


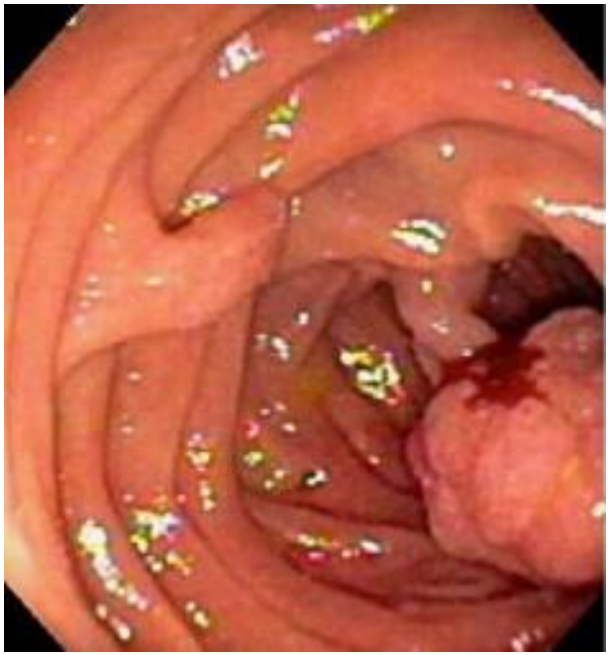


An & Brognard IUBMB Life 2018

Polyps in Peutz-Jeghers-Syndrome

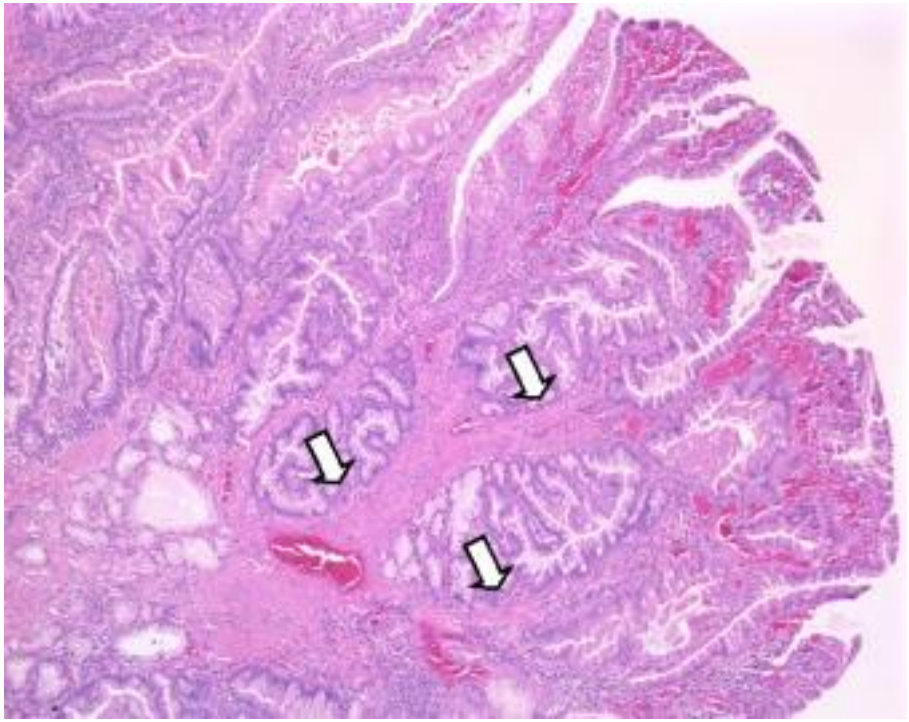
- **Intestinal polyps**
  - Jejunum
  - Ileum
  - Colon
  - Rectum
  - Stomach
  - Duodenum
  - Appendix
  - Esophagus
- **Nasal polyposis (15%)**
- **Gallbladder, bile duct polyps (4%)**



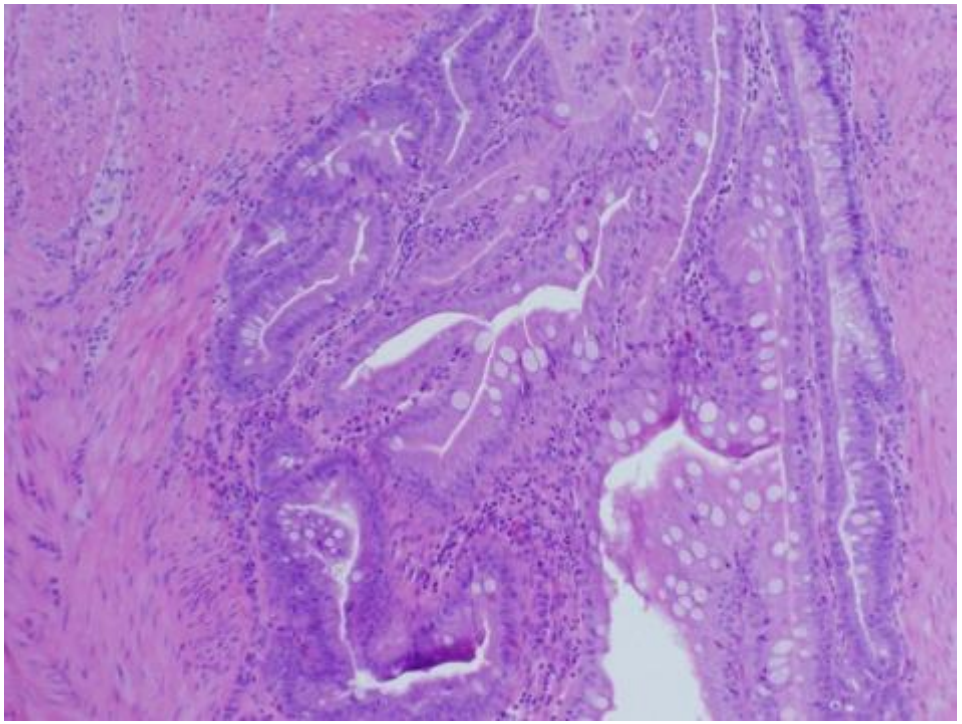


Riegert-Johnson et al., Cancer Syndromes [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2009

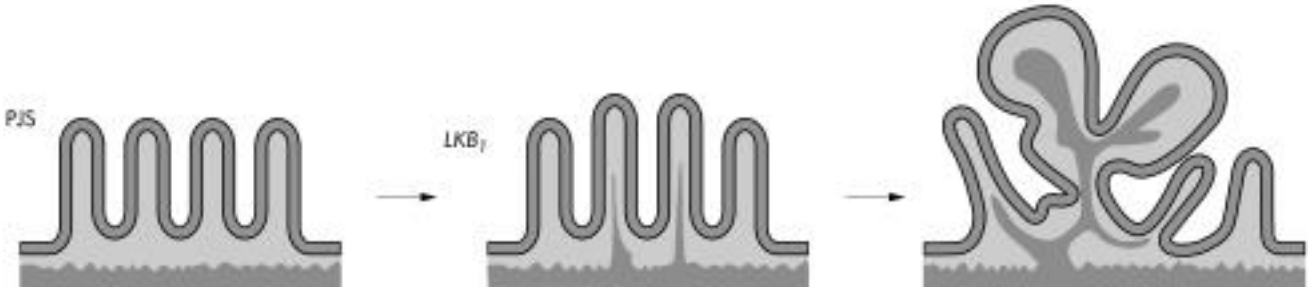
Peutz-Jeghers-Syndrome (PJS)



Hamartomatous polyp

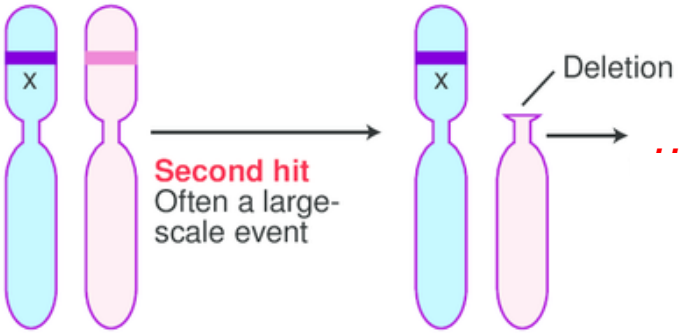


Pseudoinvasion



Riegert-Johnson et al.; 2009
Jansen et al., 2006 Gut; 55:1

Carcinogenesis in PJS



Loss of heterozygosity

…Adenoma …Carcinoma

144 PJS patients

792 Hamartomas

11 dysplastic hamartomas (1.4%) — 60% LOH (3/5) in dysplastic areas; 0% LOH in non-dysplastic areas

24 malignancies (17%) — 50% LOH (3/6)

There is no “absolute” hamartoma → carcinoma sequence.
Pathogenesis of hamartomas and carcinomas might be independent.

→ Hamartomas in small intestine, carcinoma in colon, pancreas

→ Low incidence of SI carcinoma despite high hamartoma load

Korsse et al., Carcinogenesis 2013; 34:1611

MAYO CRITERA

A diagnosis of PJS can be made in patients without a family history of PJS if either of the following are present

- Characteristic melanotic macules and one or more intestinal polyps with PJS-type histology, or
- Two intestinal polyps with PJS-type histology

In patients with a family history of PJS in a parent or sibling, if any of the following are present

- Characteristic melanotic macules, or
- One intestinal polyp with PJS-type histology, or
- *LKB1* mutation

TOMLINSON AND HOUSTON

A diagnosis of PJS can be made if there are

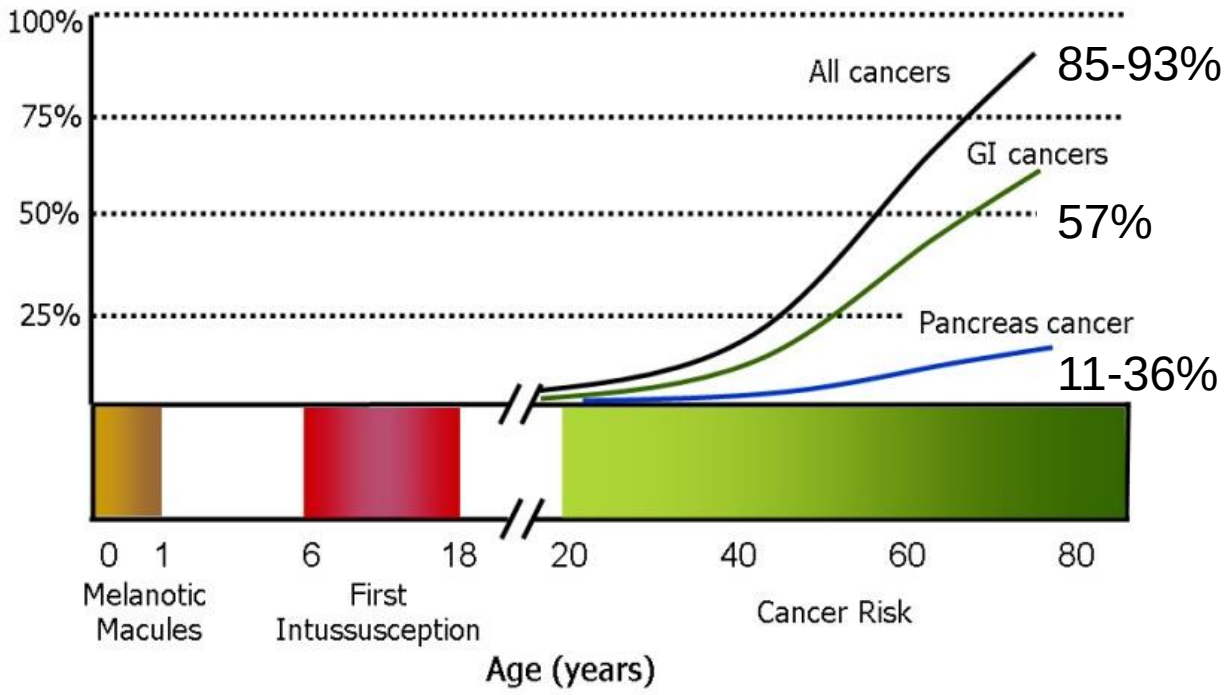
- Two or more intestinal polyps with PJS histology, or
- One intestinal polyp with PJS-type histology with either typical melanotic macules or a family history of PJS, or
- A family history of PJS and characteristic melanotic macules

→ Diagnosis mostly clinical, genetic testing generally not necessary
negative in 25% of cases, does not change management
no genotype – phenotype relation

Tomlinson J Med Genet. 1997; 34:1007

Clinical course and carcinoma incidence in PJS

Cumlative risk at age 70 years:



Site	Cumulative risk from age 15 to 64
All cancers	93%
Esophagus	0.5%
Stomach	29%
Small intestine	13%
Colon	39%
Pancreas	36%
Lung	15%
Testes	9%
Breast	54%
Uterus	9%
Ovary	21%
Cervix	10%

Riegert-Johnson et al., Cancer Syndromes [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2009
Giardiello. Gastroenterology. 2000;119:1447
Postgate J Pediatr Gastroenterol Nutr. 2009

Surveillance in PJS

Test	Start (Y)	Interval (Y)	Remarks
History "routine blood tests"	*birth*	*1*	
Colonoscopy	*12-20*	*1-3*	*Yearly with polyps*
EGD	*8-12*	*2-3*	*Yearly with polyps*
Small bowel	*8-12 ???*	*2-3 ???*	*CT/MR-Sellink or Capsule endoscopy or Double balloon*
Pancreas MRCP/EUS	*18-30*	*1-2*	*Benefit unclear!!*
Breast MRI/Rx	*18-25*	*1*	
Ovarian/Cervix/Uterus	*18*	*1*	*Pelvic exam, pap smear, transvaginal US*
Testicular US	*10*	*1*	

Goal: prevention of intussusception + carcinoma

Cave: no evidence! Only few cancers are detected by surveillance (1/96; 2/34)…

Friedl W. Dtsch Arztebl. 1999;96:A 2285–A 2291; McGarrity TJ. Cell Mol Life Sci. 2006;63:2135–2144; Jasperson KW. Gastroenterology 2010; Haerle N. Clin Cancer Res 2006;12:3209; Riegert-Johnson et al., Cancer Syndromes [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2009

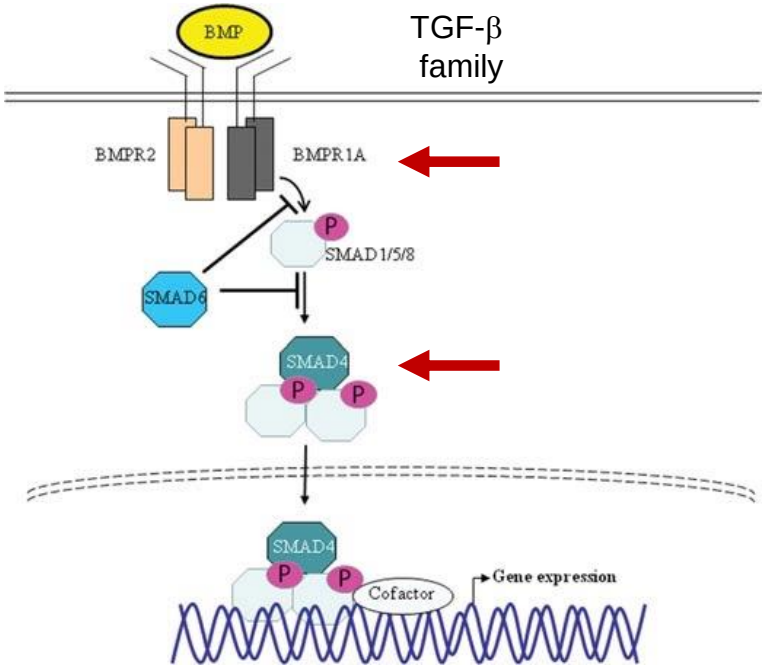
Juvenile Polyposis Syndrome (JPS)

- **Hamartomatous Polyposis**
  1:100‘000 – 1:160’000
  25% new mutations

- **DD: Solitary hamartomatous (juvenile) polyp**
  - 90% of all juvenile polyps
  - Rectal bleeding
  - no carcinoma risk

- **Diagnostic criteria JPS**
  - ≥5 hamartomatous polyps within the colon or rectum
  - Hamartomatous polyps in other parts of the GI tract
  - Any number of hamartomatous polyps with positive family history of JPS

- **Genetic**
  - Autosomal-dominant
  - Mutations found in 40-60% of cases
    - SMAD4
    - BMPR1A

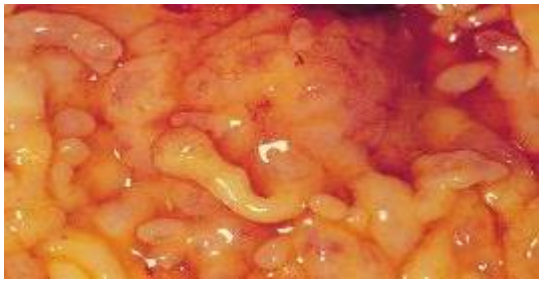


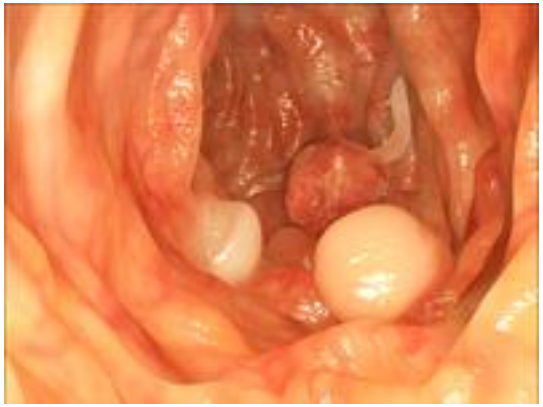
tumor suppression

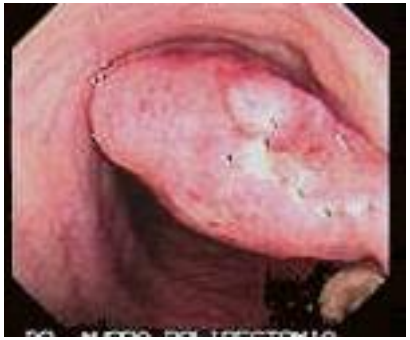
Cohen et al., JPGN 2019; 68:3
Tan et al. Human Mutation, 2012; 33:720

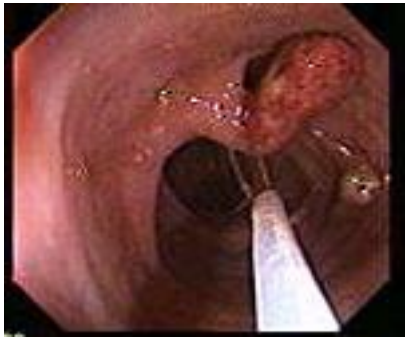
Juvenile Polyposis Syndrome (JPS)

- Polyps since first decade of life
  - Colorectum (98%)
  - Stomach (14%)
  - Duodenum (7%)
  - Jejunum & ileum (7%)
- Bleeding, diarrhea, protein loosing enteropathy
- Increased carcinoma risk:
  - Colorectal carcinom at young age (median 34 years)
    - 35 years: 17-22%
    - 60 years: 68%
  - Gastric carcinoma (median 58 years)
    - Life time risk: 30-30
- SMAD4
  → Overlap with hereditary hemorrhagic teleangiectasia (HHT)
  = Osler-Weber-Rendu disease
- BMPR1A
  → overlap with PTEN (adjacent genes)
  → juvenile polyposis of infancy
  more aggressive phenotype









Cohen et al., JPGN 2019; 68:3
https://ghr.nlm.nih.gov/condition/juvenile-polyposis-syndrome
http://www.altcancer.com/images/polyposis.jpg

Juvenile Polyposis Syndrome (JPS)

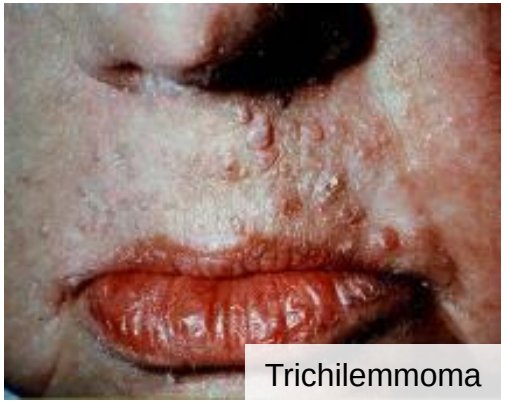
Associated conditions

Cardiac:	12–13%
Mitral valve prolapse	
VSD + pulmonary stenosis bicuspid aortic valve	
Vascular/skin:	9–56%
Telangiectasia, pigmented nevi, splenic artery aneurysm	
Bilateral iliac artery aneurysm, pulmonary AVM	
Cranial/skeletal:	12–70%
Macrocephaly, hydrocephalus, cleft palate, polydactyly, hypertelorism	
Thyroid disease, ADHD/autism	9%
Neurology: epilepsy	22%
Undescended testes	17%
Ocular abnormalities	4%

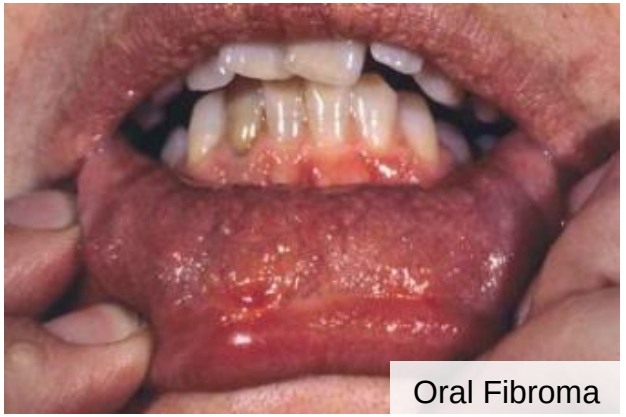
Test	Start (Y)	Interval (Y)	Remarks
Colonoscopy	*12-15*	*1-5*	*Earlier if symptomatic Yearly if polyps found*
EGD	*12-25*	*1-3*	*Earlier if symptomatic*
Small bowel	*Baseline in teenage years f/u according to findings*		*Earlier if symptomatic*

Cave: no evidence for surveillance schedule!

Cohen et al., JPGN 2019; 68:3

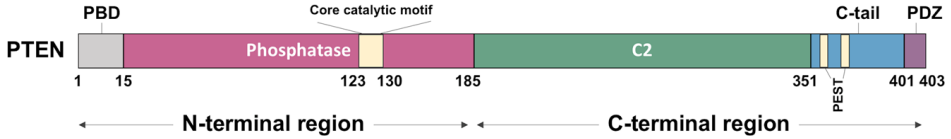


Trichilemmoma



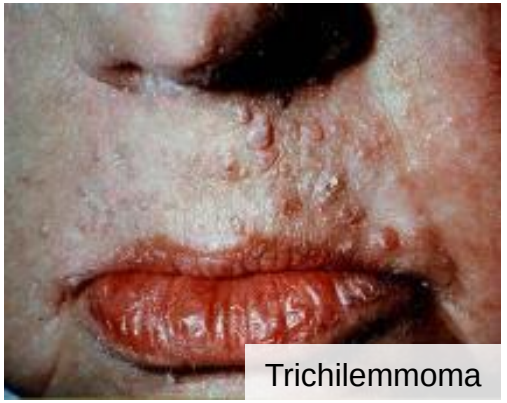
Oral Fibroma

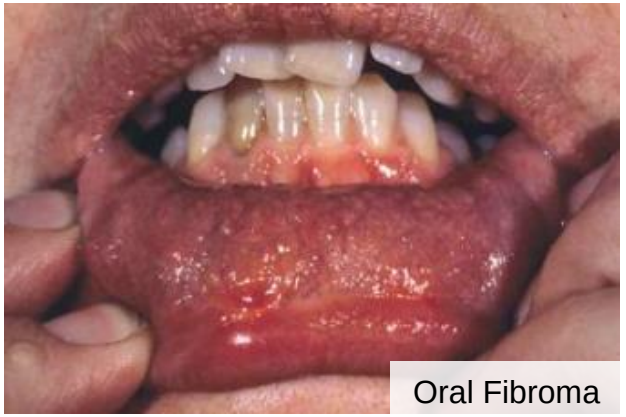
PTEN hamartoma tumor syndrome (PHTS) =Multiple Hamartoma Syndrome



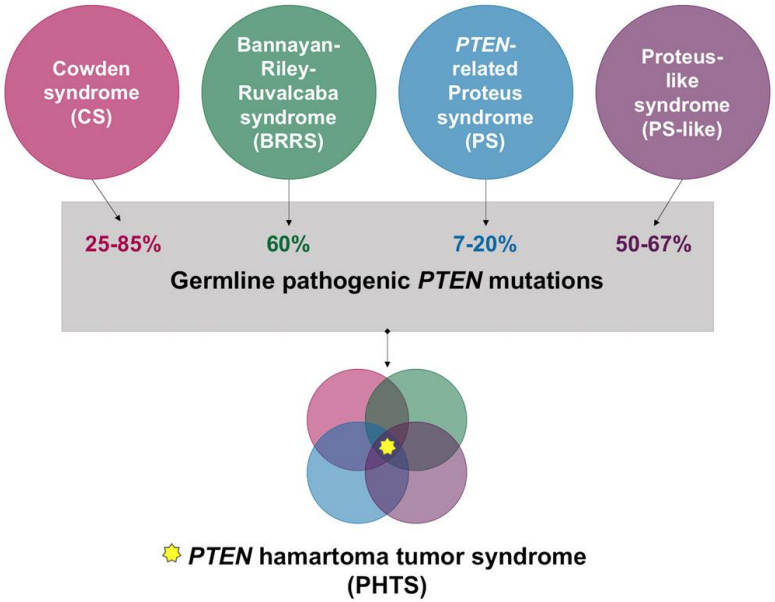
PTEN = Phosphatase and tensin homologue

- **Cowden syndrome**
  - Trichilemmomas
  - Oral fibromas
  - Palmoplantar keratoses
- Bannayan-Riley-Ruvalcaba
  - Subcutaneous lipomas
  - Macrocephaly
- Adult Lhermitte-Duclos disease
  - Hamartomatous outgrowth of cerebellum
- Proteus/ proteus like syndrome
  - Segmental overgrowth, lipomatosis, AV-malformation, Nevus
- Autism with macrocephaly


Trichilemmoma


Oral Fibroma

Gustafson S,. Semin Oncol. 2007;34:428–434
Melbärde-Gorkusa, Hered Cancer Clin Pract 2012
Tan MH, Clin Cancer Res 2012 Jan 15;18(2):400-7
Yehia & Eng, Endocrine related cancer (2018); 25:T121



PTEN hamartoma tumor syndrom (PHTS) = Multiple Hamartoma Syndrome

- Prevalence < 200`000
  Autosomal dominant
- Unique mutations in families
- Complex diagnostic criteria (major + minor)

GI-manifestations

- Esophageal glycogenic acanthosis
- Gastric and duodenal polyps (66-100%)
  - Hamartomas, hyperplastic polyps, ganglioneuromas, adenomas, inflammatory polyps
- Colon polyps (93%)!!!
  - Hamartomas, inflammatory polyps, hyperplastic polyps, ganglioneuromas, adenomas, leiomyomas, lipomas
  - Multiple synchronous pathologies
- GI-malignancy
  - Colon carcinoma (9-17%)
  - Gastric cancer (rare)

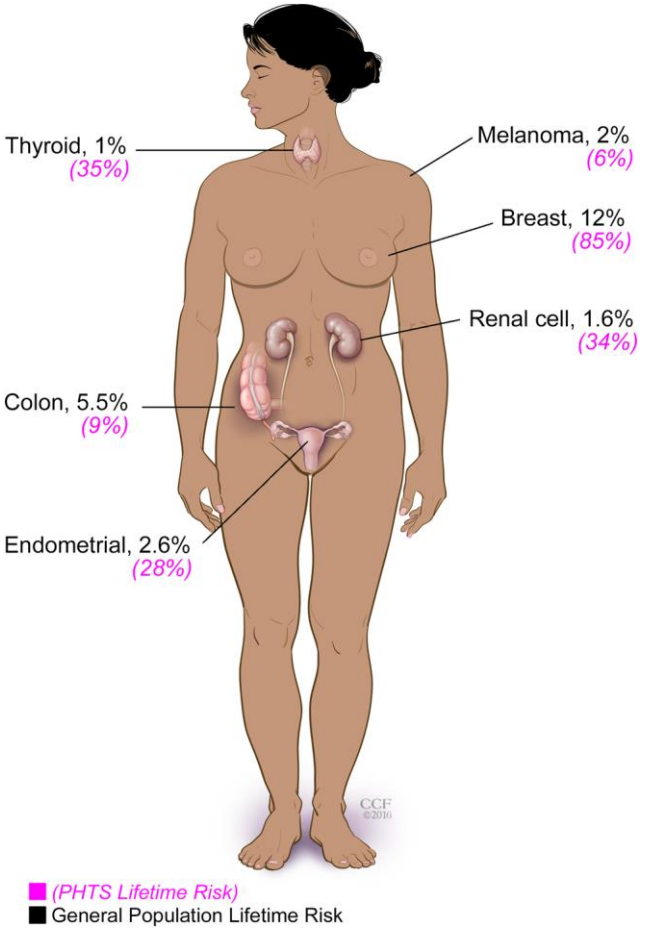
Yehia & Eng, Endocrine related cancer (2018); 25:T121
Pilarski et a., J Natl Cancer Inst 2013; 105:1607

PTEN hamartoma tumor syndrome (PHTS) Management

Cancer surveillance

Cancer	Screening recommendations
Breast (female)	Starting at age 30 years: annual mammogram; breast MRI
Thyroid	Annual ultrasound
Endometrial	Starting at age 30 years: annual endometrial biopsy or transvaginal ultrasound
Renal cell	Starting at age 40 years: renal imaging every 2 years
Colon	Starting at age 40 years: colonoscopy every 2 years
Melanoma	Annual dermatologic examination

35 y.???



The same guidelines apply to all PHTS conditions

Yehia & Eng, Endocrine related cancer (2018); 25:T121

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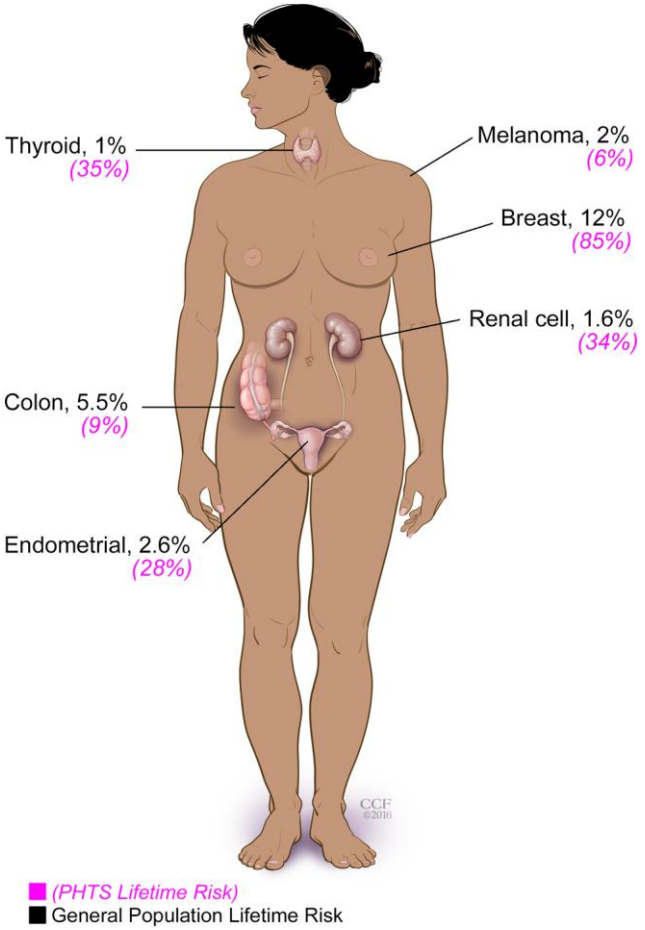

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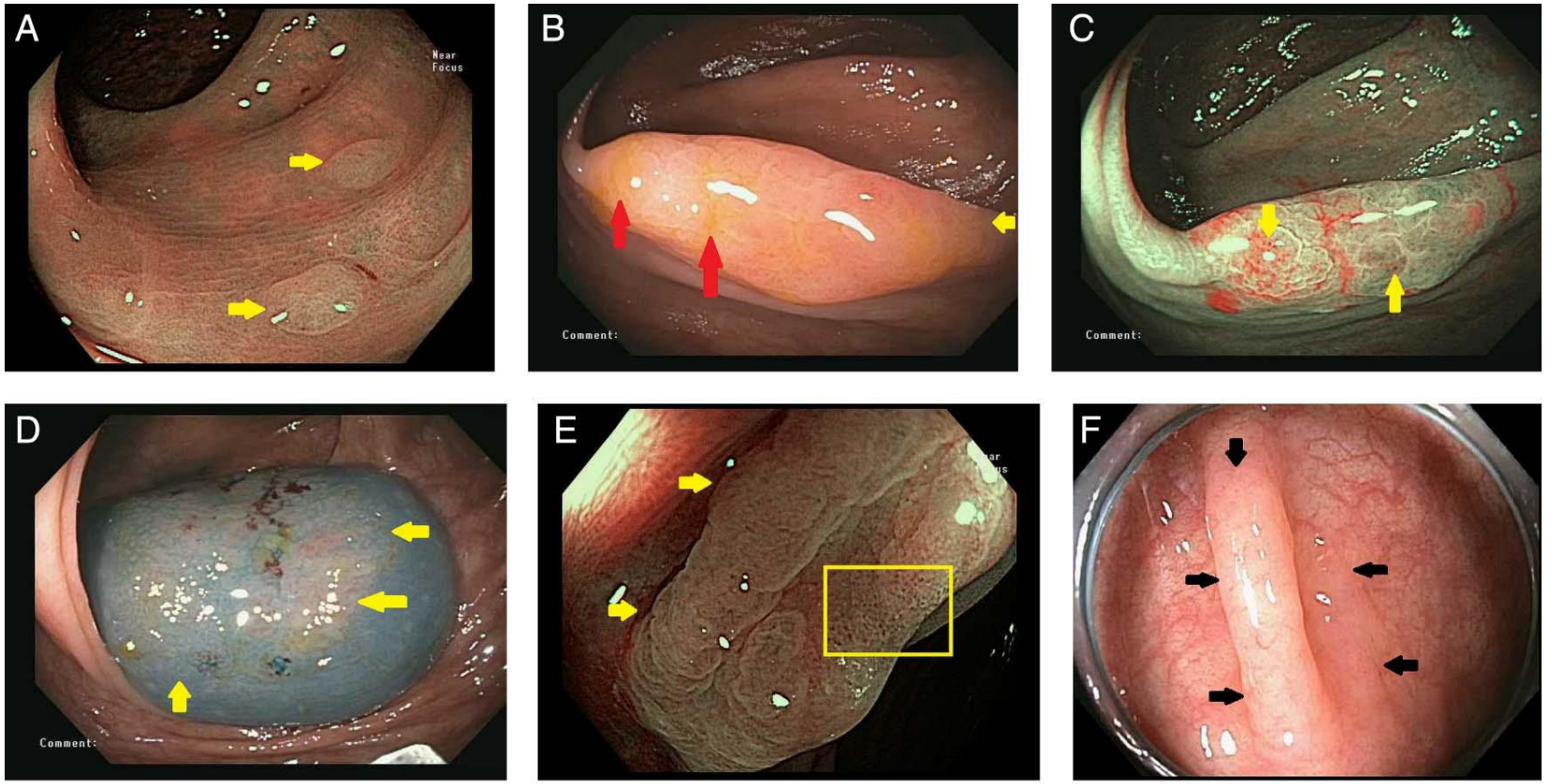
Hyperplastic and Serrated Polyps



Compared to hyperplastic polyps serrated polyps are/ have:

- Larger, distributed toward the proximal colon,
- Cloud-like or bossellated surface
- irregular surface, a mucus cap, indistinct edges
- Large black pits predict SSP over HP

East et al. Gut 2015; 64:991

Hyperplastic Polyps and Serrated Polyposis Syndrome (SPS)

- **15-30% of CRC arise via the serrated adenoma pathway**
  - Hyperplastic polyps
  - Sessile serrated polyp
  - Sessile serrated polyp without cytological dysplasia
  - Sessile serrated polyp with cytological dysplasia
  - Traditional serrated adenoma
- WHO-criteria for Serrated Polyposis Syndrome **(SPS):**

  1) >20 hyperplastic polyps distributed throughout the whole colon

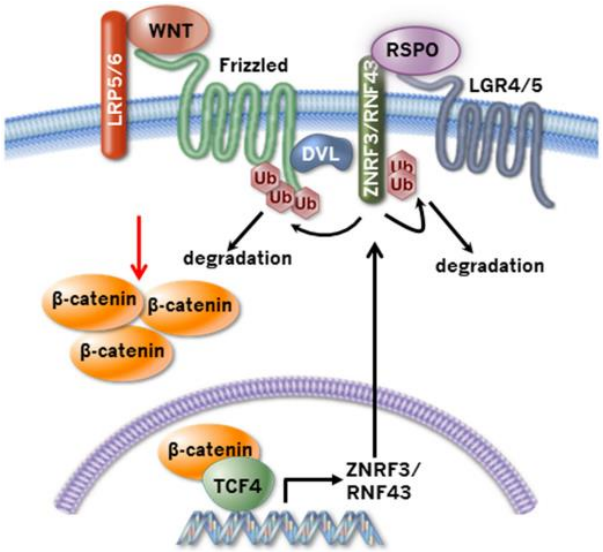
  2) ≥5 hyperplastic polyps proximal to the sigmoid colon with ≥2 being >1cm

  3) ≥1 serrated polyp proximal to the sigmoid colon in an individual with a first degree relative with SPS
- **Prevalence of SPS**
  - 1:2'000 in individuals referred for colonoscopy screening
  - 1:300 in individuals with positive FOBT/ FIT

East et al. Gut 2015; 64:991

Snover et al. WHO classification of tumours of the digestive system. Lyon, 2010. 160–5.

Genetics of Serrated Polyposis Syndrome (SPS)



Wnt – β-catenin pathway for cellular proliferation
RNF43 ubiquitinates FZD → marked for degradation
= negative feedback.

Lesion	Total number	RNF43 Loss of Heterozygosity
Serrated polyp Hyperplastic, serrated, traditional serrated acenoma	16	14 (87.5%)
Adenoma Tubular, villous	5	4 (80%)
Adenocarcinoma	1	1 (100%)

In 1 out of 4 SPS families an RNF43 mutation was found

→ 2nd hit mutations in serrated polyps, adenomas and CRC

→ RNF34 might be one genetic factor for SPS and the serrated adenoma pathway

Yan et al., Gut 2017;66:1645
Hao et al., Cancers 2016, 8:54

Personalized surveillance for Serrated Polyposis Syndrome (SPS)

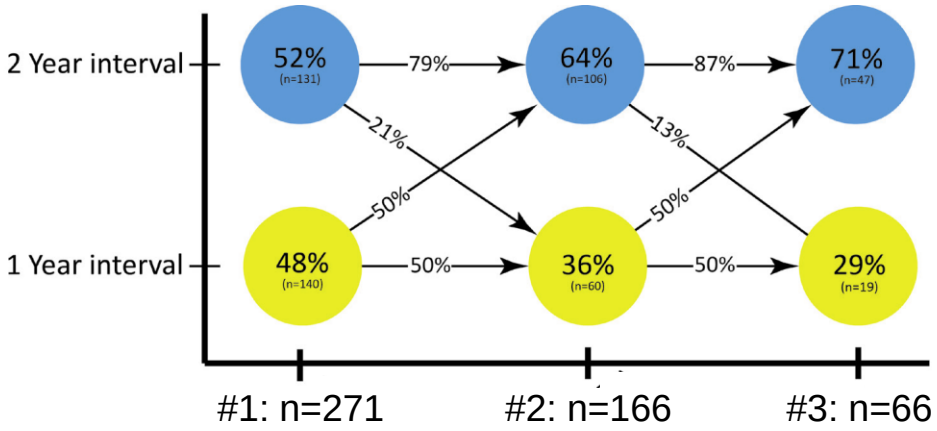
271 SPS patients. Clear colon. f/u for 3.6 years

Apply surveillance criteria:

- ≥ 1 advanced serrated adenoma or adenoma
- ≥ 5 serrated lesions
- Surgery needed

yes → 1 year surveillance

no → 2 year surveillance



2 carcinomas

- 1 after 2 years surveillance
  - Late recurrence after surgery
- 1 after 1 years surveillance
  - After piece meal resection

→ 2 year surveillance schedule seems save
surveillance colonoscopies reduced by 40%

Blejenberg et al., Gut 2019 *in press*


GAME OVER
CONTINUE
END