Major histological types of polyposis coli syndromes

1. Adenomatous polyposis syndromes
   1. Familial adenomatous polyposis (FAP)
   2. Attenuated familial adenomatous polyposis (AFAP)
   3. MUTYH-associated adenomatous polyposis (MAP)
   4. Colonic adenomatous polyposis syndrome of unknown etiology (CPUE)

2. Hamartomatous polyposis syndromes
   1. Peutz-Jeghers syndrome (PJS)
   2. Juvenile polyposis (JP)
   3. PTEN-associated hamartoma tumour syndromes
      Cowden syndrome (CS)
      Bannayan –Riley-Ruvalcaba syndrome (BRRS)
   4. Cronkite-Canada syndrome (CCS)

3. Serrated polyposis syndrome (SPS)

4. Mixed polyposis syndromes (HMPS)
Clinical relevance of polyposis coli syndromes:

1. Malignant potential
2. Extragastrointestinal manifestations
3. Genetic abnormalities (diagnosis, surveillance, follow-up)
Familial adenomatous polyposis (FAP)

Prevalence: 1:10000

Clinical importance: high risk of CRC increases with age - at age 20-7%, at age 50-93%, untreated 100% risk of CRC, account for ~1% colorectal cancer

Phenotype of classical FAP?

Colonic manifestations:
- presence of >100 polyps (sufficient for diagnosis) or fewer polyps at younger ages (2nd decade of life), esp. in a family known to have FAP (usually starting in the distal colon)

Extracolonic manifestations in the GI tract:
- Duodenal and other small bowel adenomas (in duodenum 20-100%, in the periampullary region >50%) with cancer risk of 4-12%
- Gastric fundic gland polyps in the 3rd decade (30-40%) with low potential for malignant transformation (<1%)
- Pancreatic cancer (1-2%)

Extraintestinal manifestations
- Abdominal desmoid tumours (10-30%) locally invasive, aggressive and difficult to treat
- Epidermoid cysts (30-50%): e.g. in Gardner syndrome
- Osteomas and fibromas
- Dental abnormalities (supernumerary/impacted teeth)
- Congenital hypertrophy of the retinal pigment (CHRPE)
- Non-GI cancers: thyroid (1-2%), hepatoblastoma (1-2%), central nervous system (<1%, medulloblastoma, e.g. Turcot sy.)
Familial adenomatous polyposis (FAP)

Phenotype of attenuated FAP (AFAP)?

Colonic manifestations:
- presence of 10–100 polyps (average 30 polyps), delayed onset (at age 35 to 40 or older), frequent right-sided distribution of polyps

Extracolonic manifestations in the GI tract:
- upper GI findings, duodenal cancer risk are similar to classical FAP

Extraintestinal manifestations
- unusual (incl. desmoids and CHRPE)
- thyroid cancer risk is similar to classical FAP
Genetics of FAP/AFAP?

Mutation of **adenomatous polyposis coli (APC)-gene (5q21-22)** detected **in 90% of FAP patients**
- AD-inherited mutation in 60%
- „de novo“ somatic mutation in 30%
- no mutation detected (CPUE)

Note: APC mutation detected only in **20-30% of AFAP patients**!
Making a correct diagnosis

- Personal history of classical/attenuated FAP
  
  **APC genetic testing is recommended**
  
  1. To confirm the diagnosis
  2. To allow for mutation-specific testing in other family members
  3. To predict the severity of polyposis, rectal involvement and desmoid tumours

- Family history of classical/attenuated FAP

  **Affected:** see above

  **Unaffected (no symptoms/findings), 1st degree relative of an affected individual, known family mutation**

  **APC genetic testing for familial mutation is recommended**

  - **APC positive**
    - **FAP/AFAP**
  - **APC negative**
    - regard as **FAP/AFAP**

  - **APC positive**
    - **FAP/AFAP**
  - **APC negative**
    - not affected (average risk)
Making a correct treatment

• Personal history of classical FAP (phenotype+genotype)
  
  Proctocolectomy w/ end ileostomy or w/ ileal pouch-anal anastomosis
  Colectomy w/ ileorectal anastomosis
  
  Pt <18 y of age with mild polyposis/ or w/o FH of early cancer or w/o severe genotype can be individualized, annual colonoscopy essential if surgery delayed

Making a correct surveillance  (S3 German guidelines)

<table>
<thead>
<tr>
<th></th>
<th>colonoscopy</th>
<th>EGD + side-viewing duodenoscopy</th>
<th>Abdominal MRI/CT scan</th>
<th>Abdominal US</th>
<th>Thyroid gland US</th>
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<tbody>
<tr>
<td></td>
<td>Start</td>
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<td>Start</td>
<td>interval</td>
<td>Start</td>
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<td>FAP</td>
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<td>interval</td>
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<td>After colectomy (10y)</td>
<td>12 mo</td>
<td>Rectoscopy 6-12mo</td>
<td>Ileoscopy 1-3y</td>
<td>At Dx (25-30y)</td>
<td>Spiegelman’s Stage 0</td>
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<td>10-12y</td>
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*consider prophylactic colectomy when >20 adenomas, >1 cm of size or advanced histology
** Surgical evaluation

No current evidence to support screening for other related cancers (pancreas, CNS)
Spiegelman`s classification

<table>
<thead>
<tr>
<th>Duodenal polyp</th>
<th>Score</th>
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<td>1</td>
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<tr>
<td>Number of polyp(s)</td>
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<tr>
<td>Polyp size</td>
<td>1-4</td>
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<tr>
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<td>tubular</td>
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<tr>
<td>Intraepithelial neoplasia</td>
<td>Low grade</td>
</tr>
</tbody>
</table>

Stage 0: 0  
Stage I: 1-4  
Stage II: 5-6  
Stage III: 7-7  
Stage IV: 9-12
Making a correct treatment/surveillance

- Personal history of attenuated FAP (phenotype+genotype)

**<21 y with small adenoma burden**
Colonoscopy every 1-2 yrs (note frequency of proximal colonic adenomas!)

**≥21 y with small adenoma burden**
Colonoscopy every 1-2 yrs + Consider colectomy w/ IRA

**Significant polyposis not manageable w/ endoscopy**
Colectomy w/ IRA preferred, Consider proctocolectomy

<table>
<thead>
<tr>
<th></th>
<th>Rectoscopy</th>
<th>EGD + side-viewing duodenoscopy</th>
<th>Physical exam</th>
<th>Thyroid gland US</th>
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<tr>
<td>Start interval</td>
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<td>AFAP</td>
<td>18-20y</td>
<td>25-30y</td>
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<tr>
<td>After colectomy</td>
<td>6-12 mo</td>
<td>4y</td>
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<td>12 mo</td>
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<td>At dx</td>
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<td>3-6mo**</td>
<td>1y</td>
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</table>

*small adenoma burden: <20 adenomas, <1 cm of size and no advanced histology

** Surgical evaluation

No current evidence to support screening for other related cancers (pancreas, CNS)
MUTYH-associated adenomatous polyposis (MAP)

Prevalence: <1:10000

Phenotype of MAP
Clinical characteristics of MAP are similar to AFAP in average number, proximal distribution, age at onset of adenomas and cancers, duodenal polyps/cancer (~5%) but...

- High prevalence of serrated polyps (47%, hyperplastic, sessile serrated, traditional serrated)
- Higher risk of colorectal cancer (50% of patients with CRC w/o polyp(s)!)  
- Increased risk for ovarian, bladder and skin cancer
- More frequent negative family history
Genetics of MAP

2002 Al-Tassan: Autosomal recessive-inherited mutations of the MUTYH-gene (1p35-36)

Two typical mutations (Tyr179Cys, Gly396Asp) in 85% of MAP cases

Biallelic mutation in MUTYH can be identified in 10-20% with APC-mutation-negative polyposis

Monallelic mutations in MUTYH are found in 1-2% of general population
Making a correct diagnosis

- Personal history of colorectal polyposis

**MUTYH genetic testing is recommended if:**

1. Patients with multiple (>10) adenomatous or serrated GI polyps (Pt with MAP may also meet the criteria for serrated polyposis syndrome!)
2. Have FH of adenomatous polyps or CRC compatible with an AR inheritance/sporadic
3. No APC-mutation is detected
4. Young onset CRC diagnosis w/o MMR-mutations (MSS, no change in IHC)
5. Siblings of biallelic mutation carriers

- Family history of MAP

Unaffected (no symptoms/findings), 1st degree relative/sibling of an affected individual, known family mutation  

**MUTYH genetic testing for familial mutation is recommended**
Making a correct treatment/surveillance

- Personal history of MUTYH-associated adenomatous polyposis (phenotype+genotype)/
- Sibling of a pt with MAP

<table>
<thead>
<tr>
<th>&lt;21 y with small adenoma burden</th>
<th>Colonoscopy every 1-2 yrs (note frequency of proximal colonic adenomas!)</th>
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<tbody>
<tr>
<td>≥21 y with small adenoma burden</td>
<td>Colonoscopy every 1-2 yrs + Consider colectomy w/ IRA</td>
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<tr>
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<table>
<thead>
<tr>
<th></th>
<th>Colonoscopy/Rectoscopy</th>
<th>EGD + side-viewing duodenoscopy</th>
<th>Physical exam</th>
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<tr>
<td></td>
<td>Start</td>
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<td>Start</td>
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<td>MAP</td>
<td>25-30y</td>
<td>1-2y</td>
<td>30-35y</td>
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<td>Spiegelman’s</td>
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<td>Stage IV</td>
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<tr>
<td>*small adenoma burden: &lt;20 adenomas, &lt;1 cm of size and no advanced histology</td>
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<tr>
<td>** Surgical evaluation</td>
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<tr>
<td>No current evidence to support screening for other related cancers (pancreas, CNS)</td>
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Peutz-Jeghers syndrome

Prevalence: 1:25,000-200,000

1. **multiple hamartomas throughout the GI tract**
   with predilection for the small bowel: jejunum (64%), colon (60%), stomach (49%), rectum (32%)

2. **mucocutaneous melanotic pigmentation** (lip, buccal mucosa and digits) in 95% of patients

3. association with **GI malformations** „hamartoma-carcinoma sequence“
   (colon, pancreas, stomach, small intestine, pancreas)

4. association **with extraintestinal malformations** (breast, ovary, lung, uterus, testis)

5. increased life-time **general malignancy risk** of 50-90% (15x risk the general population)

**Symptoms:**
1. **abdominal pain** (small bowel obstruction/intussusception)
2. **GI bleeding** (iron-deficiency)
Peutz-Jeghers syndrome

Making the diagnosis (diagnostic criteria):

Any of the followings:
1. $\geq 3$ histologically confirmed Peutz-Jeghers polyps
2. characteristic, prominent mucocutaneous pigmentation and family history of PJS
3. any number of Peutz-Jeghers polyps and a family history of PJS
4. $\geq 1$ Peutz-Jeghers polyp and characteristic, prominent, mucocutaneous pigmentation
Familial juvenile polyposis

Prevalence: 1:15,000-100,000

1. up to **hundreds of hamartomas throughout the GI-tract** since childhood
typical localization: colorectum (98%), stomach (13%), small bowel (6%)

2. **solitary** (in 2% of children) with no neoplastic potential
   vs. **multiple** juvenile polyps (as polyposis sy.) with **50% risk of malignancy**

3. symptoms: **hematochezia, abdominal pain** (intussusception, obstruction)

Making the diagnosis (diagnostic criteria):

Any of the followings:

1. ≥3 juvenile polyps of the **colorectum**
2. Multiple juvenile polyps **throughout the GI-tract** (at least one in the upper, one in the lower GI-tract)
3. ≥1 juvenile polyp in an individual with a **family history** of JPS
PTEN-associated hamartomatous polyposis syndrome(s)

Prevalence: 1:200.000

1. Cowden syndrome
2. Bannayan-Riley-Ruvalcaba syndrome

same disease with variable expression and age-related penetrance

Clinical characteristics

GI hamartomas +

1. Multiple polyps of different types/ mixed phenotype in the colon/stomach: inflammatory, adenomatous, hyperplastic, sessile serrated, lymphoid hyperplasia

2. Glycogenic acanthosis in the esophagus

3. Mucocutaneous lesions:
   hamartomas of the face (appear typically by late 20s), abnormal skin/mucous membranes (gingiva, bucca), pigmented maculas of glans penis

4. Pulmonary hamartomas
5. Macrocephaly
6. Lipomatosis
7. Increased risk of various cancers: breast, thyroid, endometrium
Cowden syndrome

Making the diagnosis (diagnostic criteria):

**Major criteria:**

1. Multiple hamartomas
2. Nonmedullary thyroid cancer
3. Breast cancer
4. Endometrial cancer
5. Mucocutaneous lesions
   (trichilemmoma, palmo-plantar keratosis, facial papulas, oral mucosal papillomatosis, macular pigmentaton of glans penis)
6. Macrocephaly

**Minor criteria:**

1. Single GI hamartoma/ganglineurinoma
2. Thyroid adenoma/multinodular goiter
3. Fibrocystic disease of the breast
4. Mental retardation/autism
5. Fibromas
6. Renal cell carcinoma
7. Uterine fibroids
8. Lipomas

Any of the following:

1. ≥2 major criteria (including macrocephaly)
2. ≥3 major criteria (w/o macrocephaly)
3. 1 major and ≥3 minor criteria
4. ≥4 minor criteria
Making the genetic testing of hamartomatous polyposis syndromes

Clinical characteristics of hamartomatous polyps

- ≥ 2 hamartomatous polyps
- - mucocutaneous hyperpigmentation
- - family history of PJS

- ≥ 3 juvenile colorectal polyps
- - multiple juvenile polyps in the stomach/small intestine/colon
- - family history of FJP

- - multiple hamartomatous polyps in the GI tract
- - mucocutaneous lesions
- - personal/family history of breast, thyroid gland or endometr. cancer

Peutz-Jeghers’ syndrome?

Search for STK1 gene germline mutation (~90%)

Juvenile polyposis syndrome?

Search for SMAD4/BMPR1 gene germline mutation (~60%)

Cowden syndrome?

Search for PTEN gene germline mutation (~80%)
Making a correct surveillance

<table>
<thead>
<tr>
<th></th>
<th>colonoscopy</th>
<th>EGD + side-viewing duodenoscopy</th>
<th>MRI/CT enterography</th>
<th>Abdominal MRI/EUS</th>
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<tr>
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<td>Start</td>
<td>Interval</td>
<td>Start</td>
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<td>PJS*</td>
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<td>35y</td>
<td>Annual</td>
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</tbody>
</table>

*PJS: Annual palpation of testes by 10y/annual pelvic examination and Pap smear beginning, consider transvaginal US by 18-20y

**Cowden sy: Annual transvaginal US + endometrium biopsy by 35y, annual thyroid gland palpation+US by 35y
Serrated polyposis syndrome

Multiple/large serrated polyps throughout the colon
Frequent co-occurrence with adenomatous polyps
Number of hyperplastic/serrated polyps positively correlates with CRC incidence
Less is known about genetic factors
(«serrated pathway» predominates over WNT pathway, sporadic CIMP-H CRC, epigenetic silencing of hMLH1 gene w/ or w/o BRAF mutation)

Prevalence: 1:100.000

Making the diagnosis (diagnostic criteria):

Any of the following:
1. ≥20 cumulative serrated polyps of any size distributed throughout the colon
2. ≥5 serrated polyps proximal to the sigmoid colon with ≥2 being >10 mm
3. ≥1 serrated colonic polyp with a 1st-degree relative with SPS

Langner et al: Dig Dis 201533:28-37
Serrated polyposis syndrome

Making the correct treatment/surveillance

**Affected person**

- Endoscopic polypectomy until all polyps ≥5 mm are removed, then follow-up colonoscopy every 1-3y

- Repeat every 1-3 yrs if normal

- Consider surgery if
  - colonoscopy treatment/surveillance inadequate
  - high-grade dysplasia

**Family member (1st degree)**

- Begin colonoscopy at age 40 or at same age as youngest Dx of SPS if uncomplicated by cancer
- 10 yrs before earliest diagnosis in family of CRC complicating serrated polyposis

- Repeat every 5 yrs if normal
- Consider 1-3yrs interval if proximal serrated polyps or multiple adenomas
**Colonic adenomatous polyposis of unknown etiology (no mutation found)**

- **Personal Hx of ≥100 adenomas**
  - Manage as FAP

- **Personal Hx of >10-<100 adenomas**
  - Small adenoma burden
  - Colonoscopy and polypectomy every 1-2y
  - Dense polyposis or large polyps not manageable by polypectomy
  - Subtotal colectomy/proctocolectomy depending on:
    - adenoma density
    - adenoma distribution

- **Family Hx of ≥100 adenomas diagnosed at age <40y in a FDR**
  - Begin colonoscopy at age 10-15y
    - then every 1y until age 24 y
    - every 2y from 24 to 34 y
    - every 3y from 34 to 44 y
    - every 3-5y thereafter
  - If polyposis detected, follow FAP/AFAP or MAP testing pathway

- **Family Hx of ≥100 adenomas diagnosed at age ≥40y in a FDR**
  - Colonoscopy and polypectomy every 2-3y starting at age 40y if uncomplicated by cancer

- **Family Hx of >10-<100 adenomas in a FDR**
  - Colonoscopy and polypectomy every 3-5y starting at the same age as youngest Dx of polyposis in the family if uncomplicated by cancer or by age 40 whichever earliest