GASTROINTESTINAL POLYPOSIS SYNDROMES

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DISCLOSURE OF INTEREST

I have no conflict of interest to declare
COLORECTAL CANCER (CRC) SPORADIC, FAMILIAL, HEREDITARY

- Sporadic: 75%
  - Familial clustering: 20-25%
  - Monogenic: 5%
- Lynch syndrome / HNPCC
- Polyposis syndromes
- Other tumour syndromes (LFS, CMMRD)
- Unknown / unsolved
COLORECTAL POLYPS

- 70 years of age: adenoma in ~ 50%
- CRC: ~ 10% of adenomas
- CRC lifetime risk: ~ 6%
UNTREATED: HIGH RISK COLORECTAL CANCER (CRC)
HOW IS A COLORECTAL POLYPOSIS DEFINED?

- **Adenomatous polyposis:**
  ≥ 10 synchronous adenomas

- **Juvenile polyposis:**
  ≥ 5 juvenile polyps

- **Peutz-Jeghers syndrome:**
  2 PJ polyps

- **Serrated polyposis:**
  20-30 serrated polyps

- 1° relative with confirmed polyposis

- Pathogenic germline mutation


**NCCN:** [www.nccn.org](http://www.nccn.org)
**GASTROINTESTINAL POLYPOSIS SYNDROMES**

<table>
<thead>
<tr>
<th>Polyposis form</th>
<th>Gene</th>
<th>Inheritance</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial adenomatous polyposis (FAP)</td>
<td>APC</td>
<td>AD</td>
<td>30-90 %</td>
</tr>
<tr>
<td>MUTYH-associated polyposis (MAP)</td>
<td>MUTYH</td>
<td>AR</td>
<td></td>
</tr>
<tr>
<td>Polymerase-associated polyposis (PPAP)</td>
<td>POLE, POLD1</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>NTHL1-associated polyposis (NAP)</td>
<td>NTHL1</td>
<td>AR</td>
<td></td>
</tr>
<tr>
<td>Unexplained adenomatous polyposis</td>
<td>?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome (PJS)</td>
<td>STK11</td>
<td>AD</td>
<td>&gt; 90 %</td>
</tr>
<tr>
<td>Juvenile polyposis syndrome (JPS)</td>
<td>SMAD4, BMPR1A</td>
<td>AD</td>
<td>60-80 %</td>
</tr>
<tr>
<td>Cowden / BRR / PHT syndrome (CS)</td>
<td>PTEN</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>Serrated polyposis syndrome (SPS)</td>
<td>RNF43, ?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganglioneuromatous polyposis</td>
<td>RET, PTEN, NF1, ?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cronkhite-Canada syndrome (CCS)</td>
<td>?</td>
<td></td>
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</tbody>
</table>

**Frequency:**
- 1:10,000 to < 1:200,000
the primary diagnosis of a polyposis syndrome is based on clinical and histologic findings

- Result endoscopy
- Polyp histology
- extraintestinal symptoms
- Family history
Polyp Histology

- Adenoma
- Hyperplastic polyp
- Juvenile polyp
- Juvenile polyp mit focal low-grade intraepithelial neoplasia
- Cowden polyp mit Ganglion cells
- Sessile serrated adenoma
- Peutz-Jeghers polyp
- Cronkhite-Canada polyp
- Fundic gland cysts (FAP)
### Mixtures of Different Polyp Types are Common

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Polyp histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenomatous polyposis (AP)</td>
<td>Serrated / hyperplastic polyps</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome (PJS)</td>
<td>Adenomas</td>
</tr>
<tr>
<td>Juvenile polyposis syndrome (JPS)</td>
<td>Hyperplastic polyps, adenomas, inflammatory (pseudo-)polyps</td>
</tr>
<tr>
<td>Serrated polyposis syndrome (SPS)</td>
<td>Hyperplastic-adenomatous polyps, adenomas</td>
</tr>
</tbody>
</table>
EXTRAINTESTINAL MANIFESTATIONS

- Developmental delay
- Bone tumours
- Skin lesions
- Fat tissue tumours
- Pigmentary changes
- Gingiva proliferation
- Vascular malformations
- Macrocephaly
- Disturbed nail development
EXTRAINTESTINALE MALIGNANCIES

- Thyroid cancer
- Medulloblastoma
- Skin cancer
- Breast cancer
- Hepatoblastoma
- Renal cancer
- Pancreas cancer
- Ovarian cancer
- Desmoids
- Endometrial cancer
DOMINANT INHERITANCE PATTERN

recurrence risk 50 %
RECESSIVE INHERITANCE PATTERN

recurrence risk 25 % for sibs
FAMILY HISTORY
DIFFERENTIAL DIAGNOSIS ADENOMATOUS POLYPS

Lynch syndrome
(MHL1, MSH2, MSH6, PMS2)

FAP
(APC)

MAP
(MUTYH)

PPAP
(POLE/D1)

NAP
(NTHL1)

“mixed“ Polyposis
NON-ADENOMATOUS / HAMARTOMATOUS POLYPS

- **PJS (STK11)**
- **JPS (SMAD4; BMPR1A)**
- **CS / PHTS (PTEN)**
- **SPS**

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Gastrointestinal Polyposis Syndromes

Lugano, 26.04.2019
OVERLAPPING EXTRAINTESTINAL TUMOUR SPECTRUM

Lynch syndrome
MMR genes
(MLH1, MSH2, MSH6, PMS2)

Sebaceous gland
Endometrium
Urinary tract
Ovaries

MAP
(MUTYH)

Vogt et al., Gastroenterology 2009
HIGH AND LOW PENETRANT GENES

Colorectal cancer
- Adenomatous polyposis
  - APC
  - MUTYH
  - POLE
  - POLD1

Non-polyposis CRC
- Lynch syndrome
  - MLH1
  - MSH2
  - MSH6
  - PMS2
  - EPCAM

Hamartomatous polyposis
- PTEN
- SMAD4
- BMPR1A
- STK11

Breast/ovarian cancer
- BRCA1
- BRCA2
- PALB2

Various
- Stomach
- Pancreas
- Sarcoma
- Melanoma

*Darker shading represents higher penetrance
bSize approximates population prevalence

Stoffel et al. Gastroenterology 2018
GENETIC GERMLINE DIAGNOSTICS

Multi gene analysis (Gene panels)

**Adenomatous polyposis**
APC, BUB1B, MSH3, MUTYH, NTHL1, POLD1, POLE

**Hamartomatous polyposis**
BMPR1A, PTEN, SMAD4, STK11, TP53

**Polyposis, unclear histology**
APC, BMPR1A, MSH3, MUTYH, NTHL1, POLD1, POLE, PTEN, RNF43, SMAD4, STK11, TP53
PROCEDURE GENETIC DIAGNOSTICS

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Gastrointestinal Polyposis Syndromes
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Patient with gastrointestinal polyps

Clinical evaluation:
Polyp number, histology, distribution

Clinical evidence for polyposis?

- Suspicous family history:
  - Clustering of tumours in family / relative?
  - Unusual early-onset disease?
  - Relative with polyposis?

- Genetic counselling

- Genetic diagnostics

- Genetic counselling and predictive testing

Genetic diagnostics
Pathogenic mutation identified?

no

yes

no

yes

Keine weitere Abklärung erblicher Darmkrebs

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Gastrointestinal Polyposis Syndromes
Lugano, 26.04.2019

Aretz / Steinke-Lange
### CANCER SURVEILLANCE RECOMMENDATIONS

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Tumor risk</th>
<th>Pediatric surveillance</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAP</td>
<td>Colorectum</td>
<td>Flexible sigmoidoscopy or colonoscopy</td>
<td>Starting at age 10–15; annually until surgery.</td>
</tr>
<tr>
<td></td>
<td>Thyroid</td>
<td>Cervical palpation</td>
<td>Starting at age 15–19; annually.</td>
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<tr>
<td></td>
<td>Liver</td>
<td>Abdominal ultrasonography and serum AFP (see discussion)</td>
<td>Starting early infancy; every 4–6 months until age 7.</td>
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<tr>
<td></td>
<td>(hepatoblastoma)</td>
<td></td>
<td>Following colectomy or other surgery; 1–3 years, then lengthen time frame to 5–10 years.</td>
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<tr>
<td></td>
<td>Desmoid</td>
<td>Annual physical examination</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Abdominopelvic MRI (for individuals with positive family history of desmoids)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medulloblastoma</td>
<td>Annual physical examination</td>
<td>Starting at childhood; annually.</td>
</tr>
<tr>
<td>Attenuated FAP</td>
<td>Colorectum</td>
<td>Colonoscopy</td>
<td>Starting at age 15–19; every 3 years until adenomas arise, then yearly.</td>
</tr>
<tr>
<td>Peutz–Jeghers syndrome</td>
<td>Gastric/duodenum</td>
<td>Upper gastrooduodenal endoscopy</td>
<td>Starting at age 8, baseline; every 3 years if polyps are found. In absence, repeat at age 18.</td>
</tr>
<tr>
<td></td>
<td>Stomach</td>
<td>Gastroduodenal endoscopy</td>
<td>Starting at age 8; every 2–3 years.</td>
</tr>
<tr>
<td></td>
<td>Small bowel</td>
<td>Capsule endoscopy</td>
<td>Starting at age 8; every 2–3 years.</td>
</tr>
<tr>
<td></td>
<td>Ovary and cervix</td>
<td>Annual physical examination</td>
<td>Starting at childhood; annually.</td>
</tr>
<tr>
<td></td>
<td>Testes</td>
<td>Annual physical examination</td>
<td>Starting at childhood; annually.</td>
</tr>
<tr>
<td>Juvenile polyposis</td>
<td>Colorectum</td>
<td>Colonoscopy</td>
<td>Starting at age 12–15; every year until no polyps are found, then lengthen interval to every 3 years.</td>
</tr>
<tr>
<td></td>
<td>Stomach</td>
<td>Gastroduodenal endoscopy</td>
<td>Starting at age 15; every 1–2 years.</td>
</tr>
<tr>
<td></td>
<td>Small bowel</td>
<td>Capsule endoscopy</td>
<td>Starting at age 15; every 1–2 years.</td>
</tr>
</tbody>
</table>

Successful example of individualized medicine
GERMLINE MUTATIONS ADENOMATOUS POLYPOSI S (2001)

FAP

? ~ 50%

APC ~ 50%
GERMLINE MUTATIONS ADENOMATOUS POLYPOSION (2016)

- MSH3
- CMMRD
- NAP NTHL1
- PPAP POLE + POLD1
- MAP
- APC mosaics
- GAPPS
- Intronc APC Promoter 1B deletions
- MUTYH ~10%
- ~ 7%
- ~ 20%
- APC ~60%

FAP

GERMLINE MUTATIONS ADENOMATOUS POLYPOSION

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Gastrointestinal Polyposis Syndromes
Lugano, 26.04.2019
APC MUTATION SCREENING IN MULTIPLE ADENOMAS

Patient 5 – APC:c.4127_4128delAT;p.Tyr1376Cysfs*9

Leukocyte DNA: 0 % mutant reads (Multiplicom: coverage = 2650)

Adenoma DNA: 17-92 % mutant reads

Spier et al. JMG 2016

Leukocyte

Adenoma 1

Adenoma 2

Adenoma 3

Adenoma 4

Sanger (reverse)

3 additional adenomas

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Gastrointestinal Polyposis Syndromes

Lugano, 26.04.2019
NON APC ADENOMATOUS POLYPOsis SYNDROMES

**Dominant** (heterozygous germline mutations)
**PPAP** = Polymerase Proofreading-associated polyposis (POLE, POLD1)

**Recessive** (biallelic germline mutations)
**MAP** = MUTYH-associated polyposis (MUTYH)
**NAP** = NTHL1-associated polyposis (NTHL1)
**MSH3AP** = MSH3-associated polyposis (MSH3)
**CMMRD** = Constitutional Mismatch Repair Deficiency (MSH6, PMS2)

Caused by germline mutations in DNA repair genes
Attenuated course of adenomatous polyposis
Broad extraintestinal tumour spectrum
Using mutational signatures to determine the NTHL1-related tumour spectrum in patients with biallelic germline mutations in NTHL1
POLYPOSIS: SUMMARY AND CONCLUSIONS

• Diagnostics primarily based on endoscopic findings and histology
• Clinical differential diagnosis often challenging
• Multi-gene / panel testing increasingly important in routine diagnostics
• Dominant types of hereditary cancer more common (because easier to identify with previous methods)
• Novel monogenic subtypes identified by exome sequencing: recessively inherited and caused by DNA repair genes
• Increased risk of extracolonic tumors, in particular endometrial cancer