Polyposis syndromes in children.

No conflict of interests to declare
From adult surgeons to paediatric gastroenterologists & surgeons
Objectives

- To examine the genetic basis for FAP and the nature of the APC gene
- How and when should adolescents undergo colonoscopic surveillance
- What are the surgical choices for patients with FAP and which procedure should we recommend for our patients.
Objectives contd

- Screening in Peutz Jeghers syndrome
- Role of endoscopic polypectomy versus laparoscopy in Peutz Jeghers
- Genotype/phenotype correlation in juvenile polyposis
Guidelines for the clinical management of familial adenomatous polyposis (FAP)

H F A Vasen,1 G Möslein,2 A Alonso,3 S Aretz,4 I Bernstein,5 L Bertario,6 I Blanco,7 S Bülow,8 J Burn,9 G Capella,10 C Colas,11 C Engel,12 I Frayling,13 W Friedl,4 F J Hes,14 S Hodgson,15 H Järvinen,16 J-P Mecklin,17 P Møller,18 T Myrhøi,5 F M Nagengast,19 Y Parc,20 R Phillips,21 S K Clark,21 M Ponz de Leon,22 L Renkonen-Sinisalo,16
Peutz–Jeghers syndrome: a systematic review and recommendations for management

Adenomatous polyposis syndromes

- Familial adenomatous polyposis
- Turcots syndrome

Hamartomatous polyps

- Solitary juvenile polyp
- Juvenile polyposis syndrome
- Peutz Jeghers syndrome
- Bannayan- Riley- Ruvalcaba
- Gorlin syndrome
- Cowden syndrome

Mixed polyposis syndrome
Clinical scenario

- A 7 year old from a family known to be affected by FAP comes to your clinic with infrequent rectal bleeding.

- Should you undertake a colonoscopy?
- Where is his gene mutation likely to lie on the APC gene?
- When should he undergo colectomy
- What surgery would you recommend
Early childhood presentation of FAP

- No FH
- Presents with rectal bleeding alone
- CHRPE
- Mutation codon 1309
- Youngest symptomatic FAP child

Symptomatic Polyposis in a Four-Year-Old: The Exception Proves the Rule
Will, Phillips, Hyer, Clark.
Dysmorphic syndromes and FAP
Desmoid disease - codon >1400
Screening for germline APC mutations in sporadic hepatoblastoma: is it worthwhile?

Harvey, Clark S, Hyer W, Hadzic N, Tomlinson I, Hinds R

This study does not support the need for routine germline APC mutation screening in sporadic HB.

Giardiello 1996: 8 affected children, codon 141-1230
Modifier genes

**COLORECTAL CANCER**

Explaining variation in familial adenomatous polyposis: relationship between genotype and phenotype and evidence for modifier genes


*Gut* 2002;51:420–423
Genotype – phenotype correlation

Does the location of the gene mutation impact on clinical care? - YES
Undergoing genetic testing

Family mutation known
- Counsel and genetic testing
  - Positive result
    - Full colonoscopy
  - Negative result
    - Discharge from follow up

Family mutation known
- Counsel and genetic testing
  - Positive result
  - Discharge from follow up

Family mutation not known
- No genetic testing
  - Annual sigmoidoscopy
Assess adenoma burden in the rectum
Assess polyp burden in the colon
Dye spray in FAP – identifying dysplasia & adenomas
We underestimate polyp burden
Which children had high adenoma burden?
Which children had high adenoma burden?

Both children had symptoms (bleeding or diarrhoea)
Both children codon 1309
Table 3  Proportion of FAP patients with CRC diagnosed at \( \leq 20 \) years of age*  

<table>
<thead>
<tr>
<th>Polyposis registry</th>
<th>Total number of CRCs</th>
<th>Number of CRCs (%) diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0–10 years</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>106</td>
<td>0</td>
</tr>
<tr>
<td>Denmark</td>
<td>190</td>
<td>0</td>
</tr>
<tr>
<td>Germany</td>
<td>524</td>
<td>0</td>
</tr>
<tr>
<td>St Mark’s</td>
<td>96</td>
<td>0</td>
</tr>
<tr>
<td>Finland</td>
<td>157</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1073</td>
<td>0</td>
</tr>
</tbody>
</table>

*Note: The data represents the proportion of FAP patients with colorectal cancer (CRC) diagnosed at or before 20 years of age.
Conclusion to screening

- Genetic and endoscopic screening from early teenage years
- Consider earlier screening if unfavourable gene mutation
- Consider any FAP related symptoms
  - Diarrhoea
  - Mucous PR
  - Blood PR
  - Abdominal pain
Surgical choice
Why choose an ileo-rectal anastomosis

- Straightforward and amenable to minimally invasive surgery.
- Preferable for the more mild phenotype
- Short hospital stay
- Excellent continence

- At risk of subsequent rectal stump polyposis and a lifetime 5% risk of CRC in the rectal stump.
- At 20 years, 12% risk of CRC
- 6 monthly rectal stump surveillance
- Might require conversion to IPAA later
Why chose an ileo – pouch – anal-anastomosis

- Treatment of choice if there are > 20 rectal adenomas.
- Risk of desmoid – impaired conversion from IRA – IPAA.
  - But these patients have a more mild phenotype
  - Delay surgery
- Technically challenging – limit surgery to experts
- Significantly reduced fertility in women – delay IPAA until after completed family.
- Still need annual examination of pouch
- Risk of incontinence, increased bowel frequency, and need for incontinence pads.
- Covering stoma
Colectomy in adolescents - IRA or IPAA?

Cancer risk

Complications and sequelae

IRA

IPAA

Genotype
Density of rectal polyps
Access to laparoscopy
Family experience
Perception of risk
Risk of desmoid
Schooling, relationships

< 20 rectal adenomas
< 1000 colonic adenomas

> 20 rectal adenomas
> 1000 colonic adenomas
Any rectal adenoma > 3 cms
Genetics – implication for choice of surgery

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Rectum Preserved</th>
<th>Rectum Removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>157</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>540</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>1060</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>1068</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>1309</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>1328</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>1464</td>
<td>0</td>
<td>1*</td>
</tr>
<tr>
<td>1528</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>23</td>
</tr>
</tbody>
</table>

* Patient choice, mild phenotype.

APC Genotype, Polyp Number, and Surgical Options in Familial Adenomatous Polyposis
The Cleveland Clinic Foundation, Cleveland, Ohio
Life expectancy after surgery

Cumulative probability (%)

Age groups

- No surgery
- Surveillance and IRA
- General population
Will the timing of surgery be delayed with use of NSAID?
THE EFFECT OF CELECOXIB, A CYCLOOXYGENASE-2 INHIBITOR, IN FAMILIAL ADENOMATOUS POLYPOSIS

GIDEON STEINBACH, M.D., PH.D., PATRICK M. LYNCH, M.D., J.D., ROBIN K.S. PHILLIPS, M.B., B.S., MARINA H. WALLACE, M.B., B.S., ERNEST HAWK, M.D., M.P.H., GARY B. GORDON, M.D., PH.D., NAOKI WAKABAYASHI, M.D., PH.D., BRIAN SAUNDERS, M.D., YU SHEN, PH.D., TAKASHI FUJIMURA, M.D., LI-KUO SU, PH.D., AND BERNARD LEVIN, M.D.

![Graph showing the effect of Celecoxib on percent change from baseline.](image-url)
Adenoma prevention with sulindac

The New England Journal of Medicine

PRIMARY CHEMOPREVENTION OF FAMILIAL ADENOMATOUS POLYPOSIS WITH SULINDAC

Francis M. Giardiello, M.D., Vincent W. Yang, M.D., Ph.D., Linda M. Hylland, B.S., R.N., Anne J. Krush, M.S., Gloria M. Petersen, Ph.D., Jill D. Trimbath, M.S., Steven Piantadosi, M.D., Ph.D., Elizabeth Garrett, Ph.D., Deborah E. Geiman, M.S., Walter Hubbard, Ph.D., G. Johan A. Offerhaus, M.D., M.P.H., Ph.D., and Stanley R. Hamilton, M.D.

Sulindac did not slow the development of adenomas
The Safety and Efficacy of Celecoxib in Children With Familial Adenomatous Polyposis

Patrick M. Lynch, MD, JD¹, Gregory D. Ayers, MS², Ernie Hawk, MD, MPH³, Ellen Richmond, RN, MSN³, Craig Eagle, MD⁴, Mabel Wolof, PhD⁴, James Church, MD⁵, Hennie Hasson, RN⁶, Sherri Patterson, RN⁷, Elizabeth Half, MD⁸ and Carol A. Burke, MD⁸

<table>
<thead>
<tr>
<th>Table 1. Celecoxib dose assignments by body weight and cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body weight</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>25.0–37.5 kg</td>
</tr>
<tr>
<td>37.6–50.0 kg</td>
</tr>
<tr>
<td>&gt;50.0 kg</td>
</tr>
</tbody>
</table>
Figure 2. Celecoxib dose–response relationship among pediatric patients with familial adenomatous polyposis. The number of polyps at baseline
Sue Clark & Professor Phillips
Warren Hyer, Jackie Hawkins, Chris Fraser
Polyposis Registry, St Mark’s Hospital
Medicines in children research network
Surgical choices for colectomy

- It is safe to monitor at regular colonoscopy
- Assess rectal burden
- Laparoscopic IRA
  - Enhanced recovery
  - Short admission
  - Good outcomes
  - Surveillance of rectum
- Not suitable if >20 rectal adenomas, >1000 colonic adenomas, or rectal polyp >3cms.
So what have we learnt together?
Now we know the answers.

- A 7 year old from a family known to be affected by FAP comes to your clinic with infrequent rectal bleeding.

- Should you undertake a colonoscopy? **YES**
- Where is his gene mutation likely to lie on the APC gene? **- Exon 15**
- When should he undergo colectomy. **Adenoma burden**
- What surgery would you recommend. **Depends on rectal adenoma burden**
Complications of Childhood Peutz-Jeghers Syndrome: Implications for Pediatric Screening

*R. Hinds, †C. Philp, ‡W. Hyer, and *J. M. Fell

*Department of Paediatric Gastroenterology, Chelsea and Westminster Hospital, London; and the †The Polyposis Registry, St. Mark’s Hospital, London, England
Imaging and protocols for PJS – time to change – perhaps the end of the barium contrast study

- Diagnosis made by phenotype or family history of PJS plus symptoms
  - Investigate relevant symptoms (e.g., pain or anemia by upper and lower endoscopy and barium FT/wireless capsule endoscopy)
  - Only small (< 5 mm) polyps present
  - Polyps > 10 mm; evaluate according to number
  - Large polyps > 1.5 cm: counsel endoscopy by polyp type with operative main bowel endoscopy
  - Refer for exploratory laparotomy with intraoperative endoscopy and polypectomy

- Depending on symptoms (e.g., anemia or pain), carry out upper and lower endoscopy and barium FT/wireless capsule endoscopy at intervals (e.g., every 2 years)
- Counsel parents; regular follow-up. Re-image according to symptoms
Capsule endoscopy
The end of the barium in PJS.....VCE is not perfect enough....

ABSTRACT

Video Capsule Endoscopy in the management of children with Peutz-Jeghers Syndrome: a blinded comparison with Barium Enterography for the detection of small bowel polyps.

Close correlation between MRI and capsule endoscopy in adults (and children) with PJS. Gut 2009 Postgate A et al (n=9)
What polyp is too big in a child?
Preventing perforation at polypectomy
Surgery in PJS
Realistic decisions about surgical/endoscopic choices
Double balloon enteroscopy in children

But how big a polyp can we resect without injury to the submucosa?

Lacking evidence and experience with DBE, and polypectomy in PJS in children

Adult case series/reports:

Small-Intestinal Peutz-Jeghers Polyps Resected by Endoscopic Polypectomy with Double-Balloon Enteroscopy and Removal Confirmed by Ultrasonography

Y. Matsumoto - N. Manabe - S. Tanaka - A. Fukumoto -
T. Yamaguchi - M. Shimamoto - M. Nakao -
Y. Mitsuoka - K. Chayama

Fig. 5 DBE image showed that the polyp was resected, and the ulcer was clipped
Conclusion for Peutz Jeghers

- Screening at an earlier age than FAP
- More early paediatric complications
- New imaging modalites

- These are meaty polyps
- Substantial and under reported risk of perforation
- Avoid laparatomies
  - Laparoscopy
  - DBE
Unwinding the Heterogeneous Nature of Hamartomatous Polyposis Syndromes

John M. Careyhers, MD

In any classic "who done it?" mystery, the goal of the investigator is to find and expose the guilty party. At the onset, there may be many suspects, some of whom may appear guilty. However, the shrewd investigator picks through those distractors to clearly eliminate them and focuses on specific details to finally identify the true culprit. The same approach holds for the recognition of the hamartomatous polyposis syndromes, many of which demonstrate phenotypic features that overlap with each other.

See also p 2465.

2005; Vol 294, No. 19 (Reprinted)
Unpicking the hamartomous syndromes – 21st century style

Genetics
Clinical phenotype
Pathology
Family history
Colonoscopic appearance

Cronkhite-Canada syndrome
Bannayan Riley Ruvalcaba syndrome

Juvenile polyposis syndrome
Cowdens syndrome
Juvenile polyposis Syndrome in infancy
What genetics?

- **LKB1**
  - PJS
- **PTEN**
  - 85% of Cowden
  - 65% of Bannayan Riley Ruvalcaba syndrome
  - JPS
- **SMAD 4**
  - 20-50% JPS
- **BMPRIA**
  - 20-40% of JPS
- **ENG**
  - JPS, HHT
No cancer risk in childhood with JPS

It is the anaemia and hypoalbuminaemia in the syndromic forms in infancy which create the clinical challenge.
Conclusion to screening in FAP

- Genetic and endoscopic screening from early teenage years
- Consider earlier screening if unfavourable gene mutation
- Consider any FAP related symptoms
  - Diarrhoea
  - Mucous PR
  - Blood PR
  - Abdominal pain
Surgical choices for colectomy in FAP

- It is safe to monitor at regular colonoscopy
- Assess rectal burden
- Laparoscopic IRA
  - Enhanced recovery
  - Short admission
  - Good outcomes
  - Surveillance of rectum
- Not suitable if >20 rectal adenomas, >1000 colonic adenomas, or rectal polyp >3cms.
Thank you

UK Polyposis team

- St Mark’s Hospital UK:
  - Polyposis Registry, UK
  - Professor Robin Phillips,
  - Kay Neale and Jo Rawlings, & Jackie Hawkins
  - Ms Sue Clark
  - Wolfson Academic Dept of Endoscopy,
  - Department of Colorectal Surgery

- And thank you to BSPGHAN and Mark Beattie