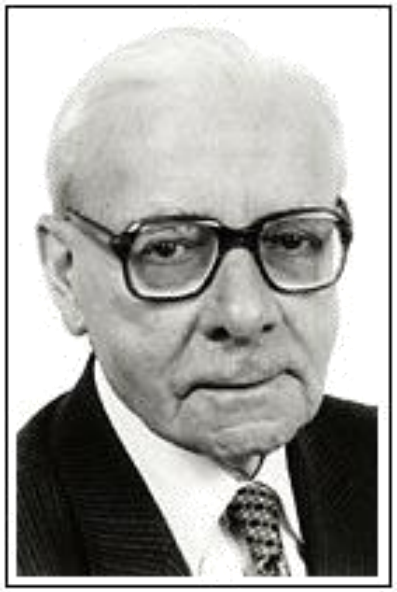
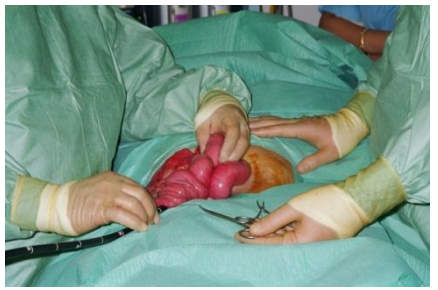
Dr Warren Hyer
Consultant Paediatric Gastroenterologist
St Mark's Hospital, UK

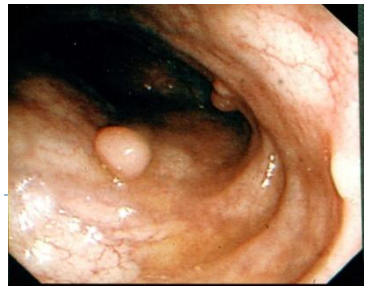
Polyposis syndromes in children.

No conflict of interests to declare

From adult surgeons to paediatric gastroenterologists & surgeons







St MARK'S HOSPITAL

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

Current guidelines

Gut 2008;**57**:704–713.

Guidelines

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

A D Beggs,[1] A R Latchford,[2] H F A Vasen,[3] G Moslein,[4] A Alonso,[5] S Aretz,[6] L Bertario,[7] I Blanco,[8] S Bülow,[9] J Burn,[10] G Capella,[11] C Colas,[12] W Friedl,[6] P Møller,[13] F J Hes,[14] H Järvinen,[15] J-P Mecklin,[16] F M Nagengast,[17] Y Parc,[18] R K S Phillips,[19] W Hyer,[19] M Ponz de Leon,[20] L Renkonen-Sinisalo,[15] J R Sampson,[21] A Stormorken,[22] S Tejpar,[23] H J W Thomas,[24] J T Wijnen,[14] S K Clark,[19] S V Hodgson[1]

- Adenomatous polyposis syndromes
  - *Familial adenomatous polyposis*
  - *Turcots syndrome*

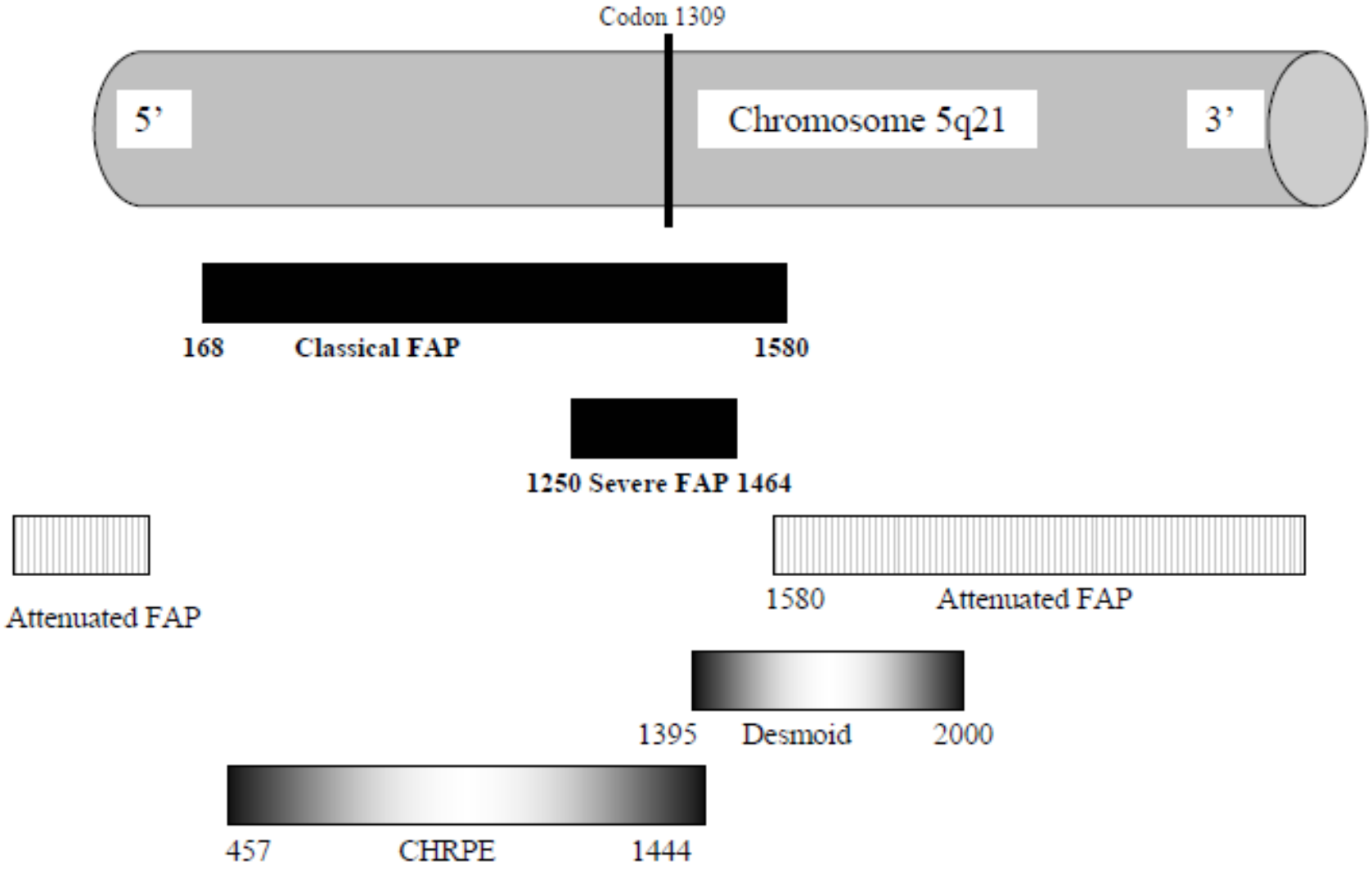
- Hamartomatous polyps
  - *Solitary juvenile polyp*
  - *Juvenile polyposis syndrome*
  - *Peutz Jeghers syndrome*
  - *Bannayan- Riley- Ruvalcaba*
  - *Gorlin syndrome*
  - *Cowden syndrome*

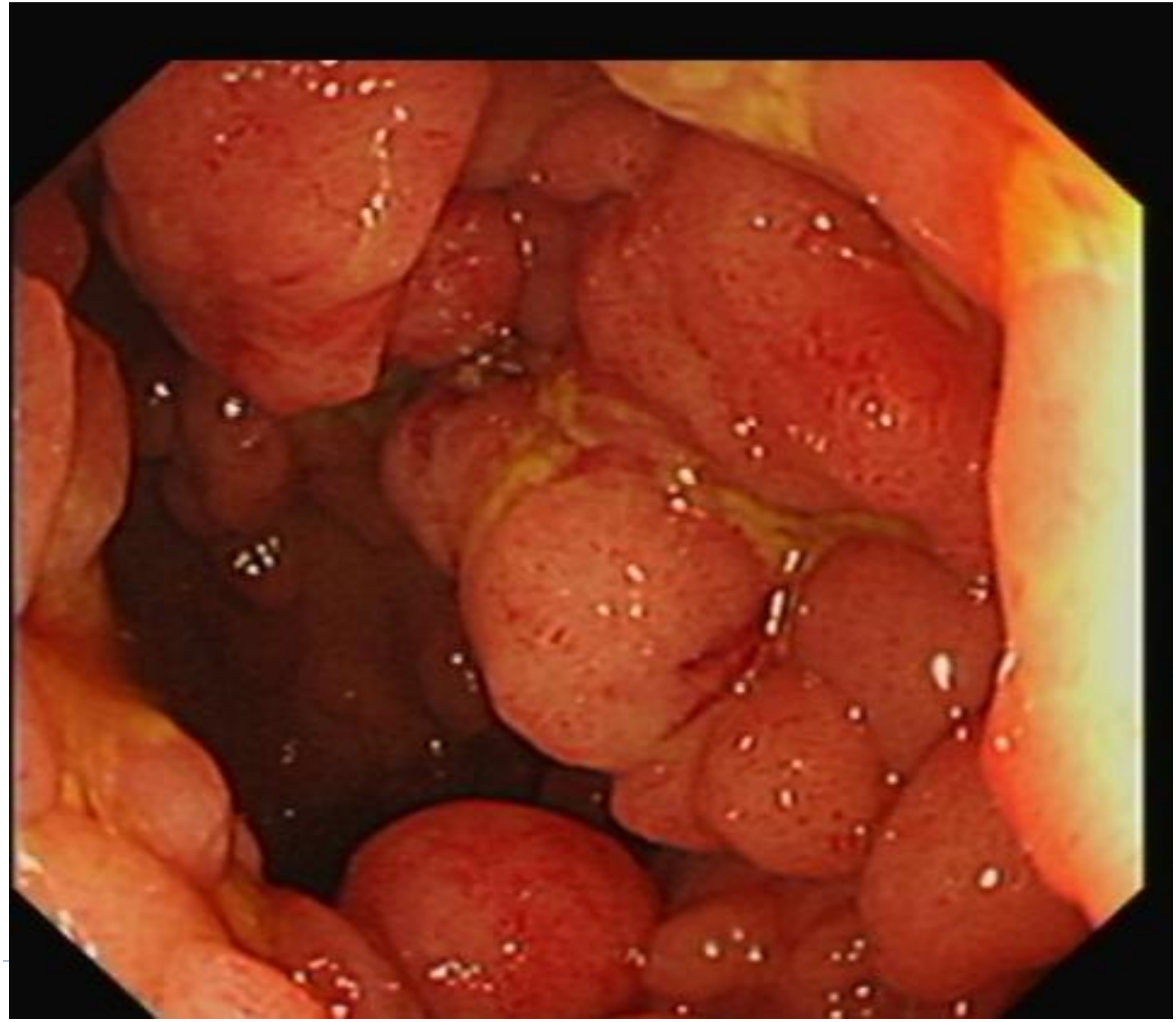
- Mixed polyposis syndrome

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


Codon 1309
5'
Chromosome 5q21
3'
168
Classical FAP
1580
1250 Severe FAP 1464
Attenuated FAP
1580
Attenuated FAP
1395
Desmoid
2000
457
CHRPE
1444

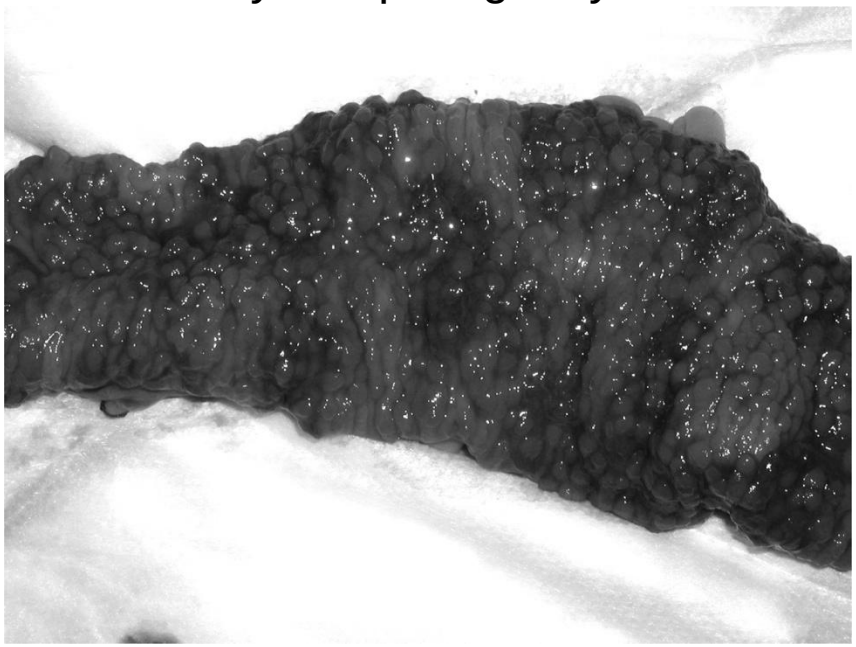


Early childhood presentation of FAP

- No FH
- Presents with rectal bleeding alone
- CHRPE
- Mutation codon 1309

- Youngest symptomatic FAP child

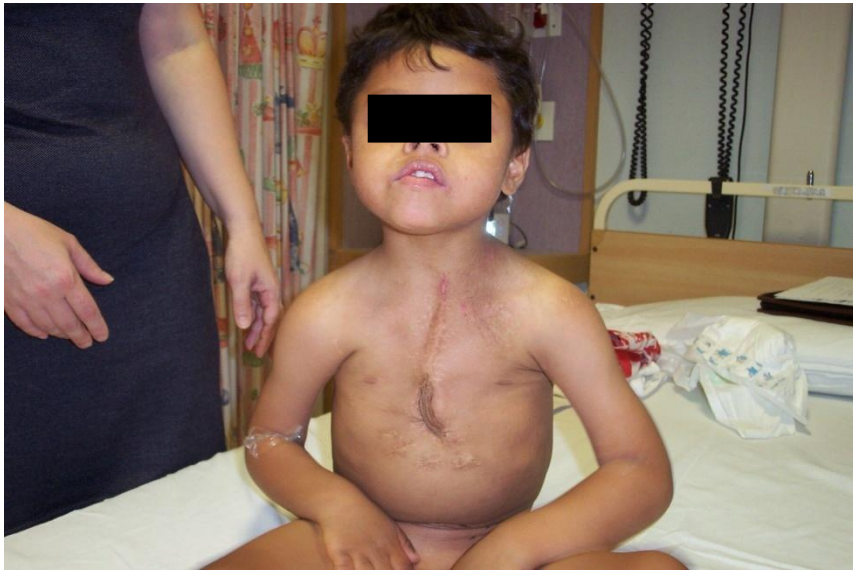
Colectomy sample age 4 years

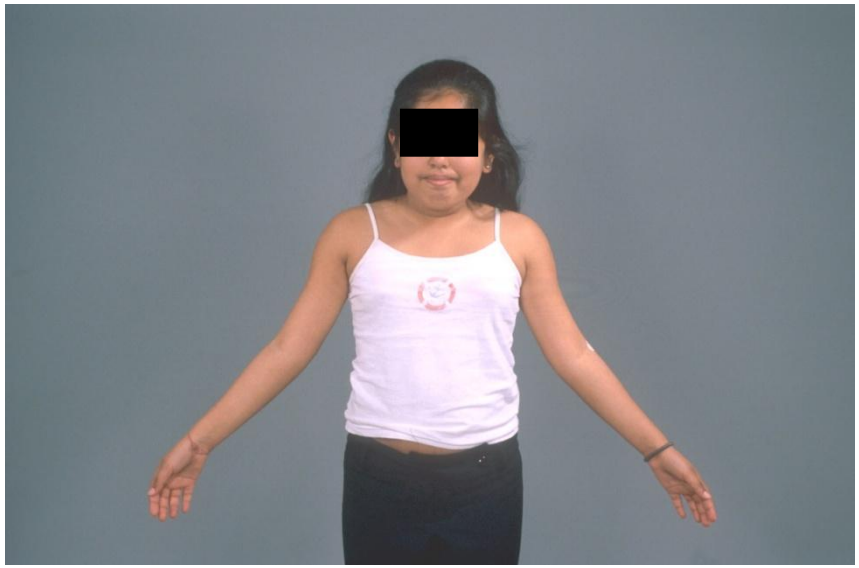


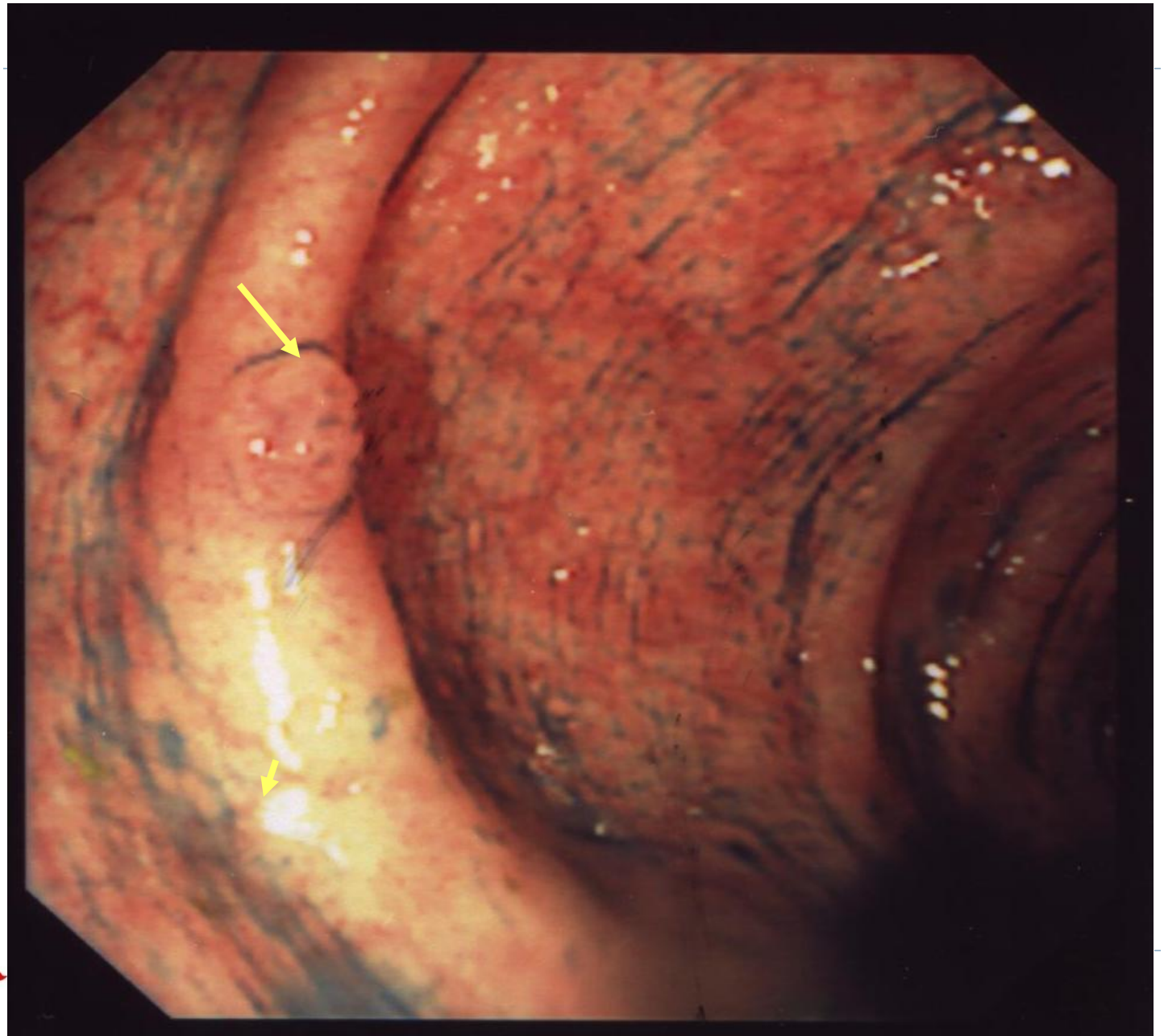
Symptomatic Polyposis in a Four-Year-Old: The Exception Proves the Rule
Will, Phillips, Hyer, Clark.

St MARK'S HOSPITAL

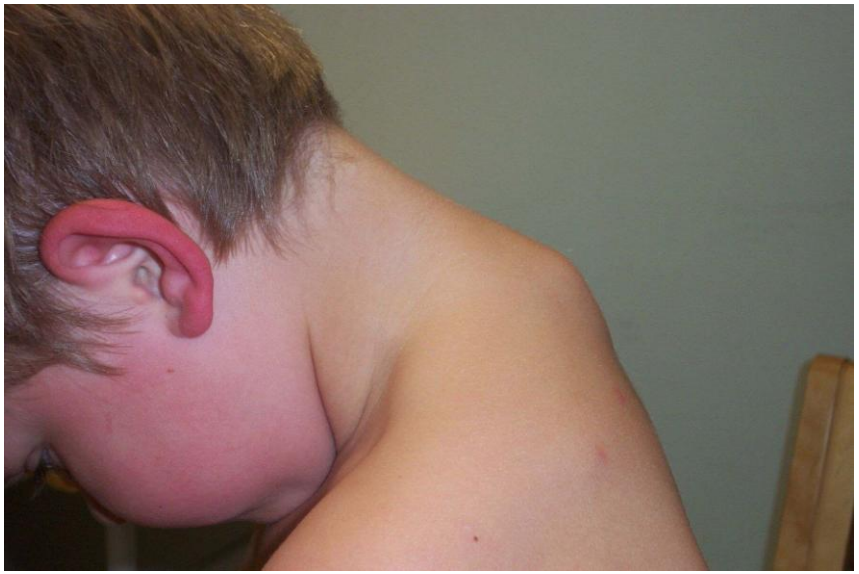
Dysmorphic syndromes and FAP

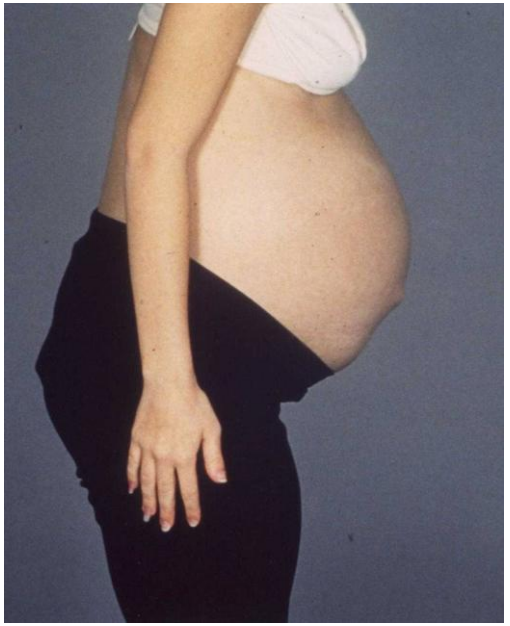


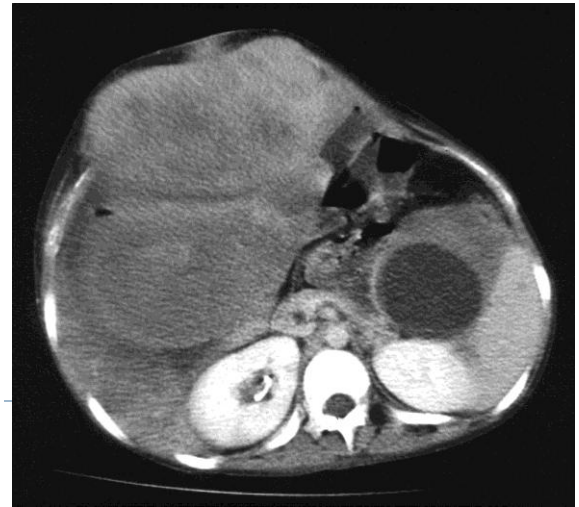




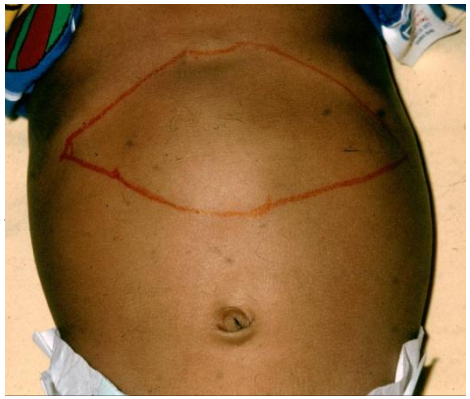
Desmoid disease- codon >1400







Hepatoblastoma and FAP.



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

St MARK'S HOSPITAL

Modifier genes

COLORECTAL CANCER

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

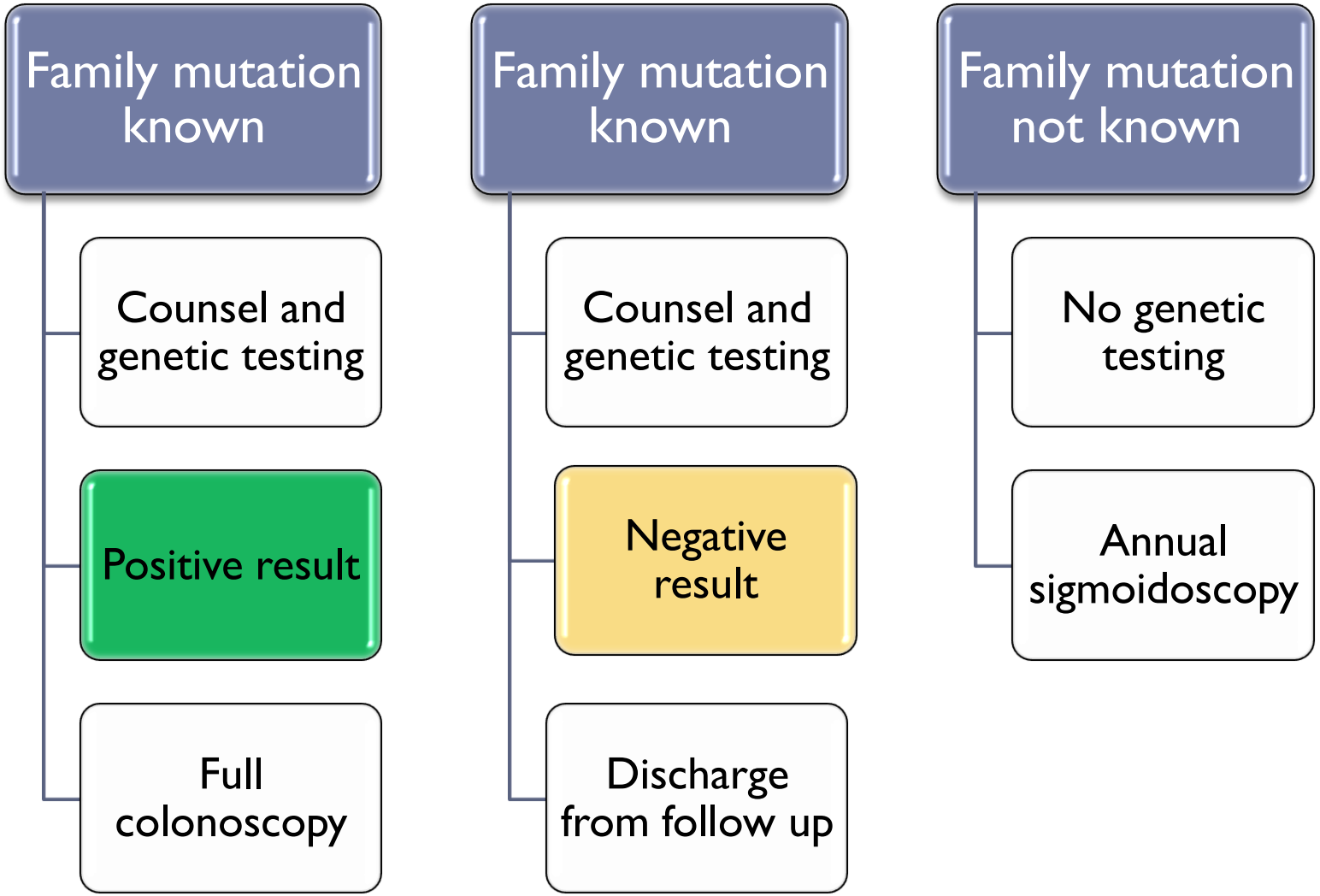
M D Crabtree, I P M Tomlinson, S V Hodgson, K Neale, R K S Phillips, R S Houlston

Gut 2002;**51**:420–423

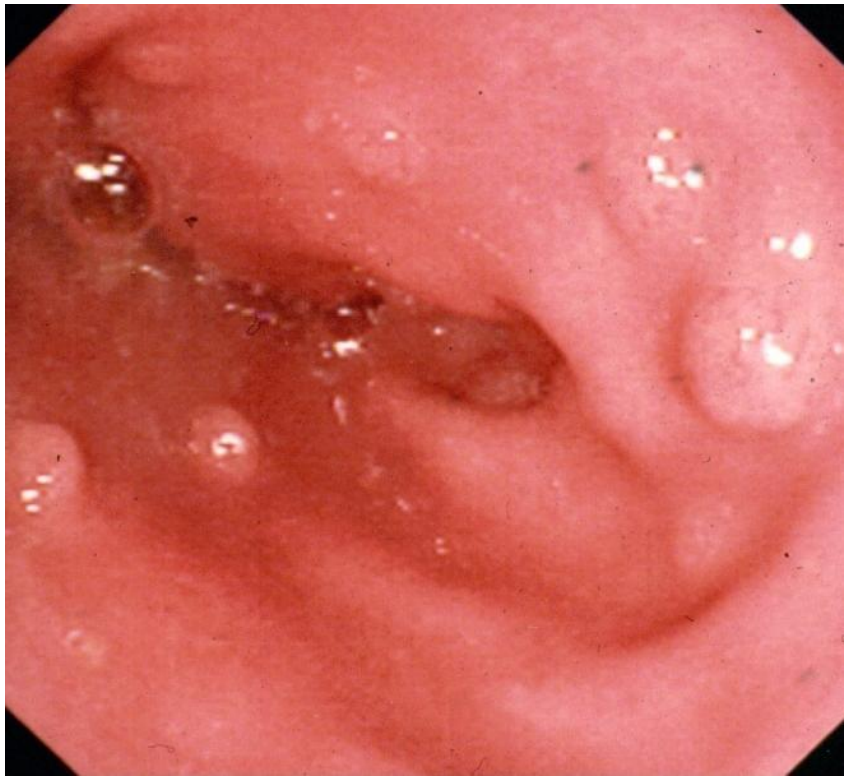
Genotype – phenotype correlation

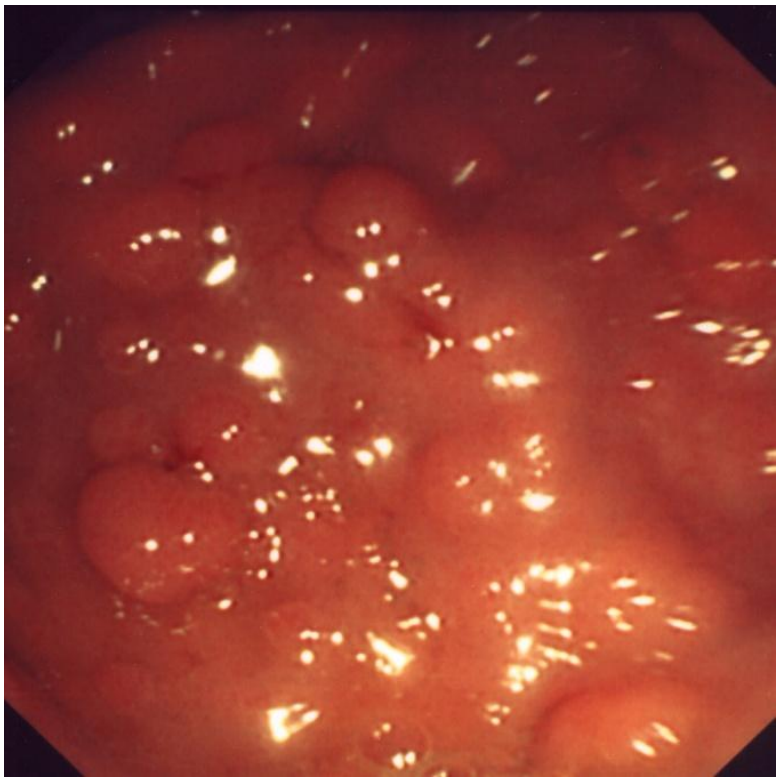
Does the location of the gene mutation impact on clinical care? - YES

Undergoing genetic testing

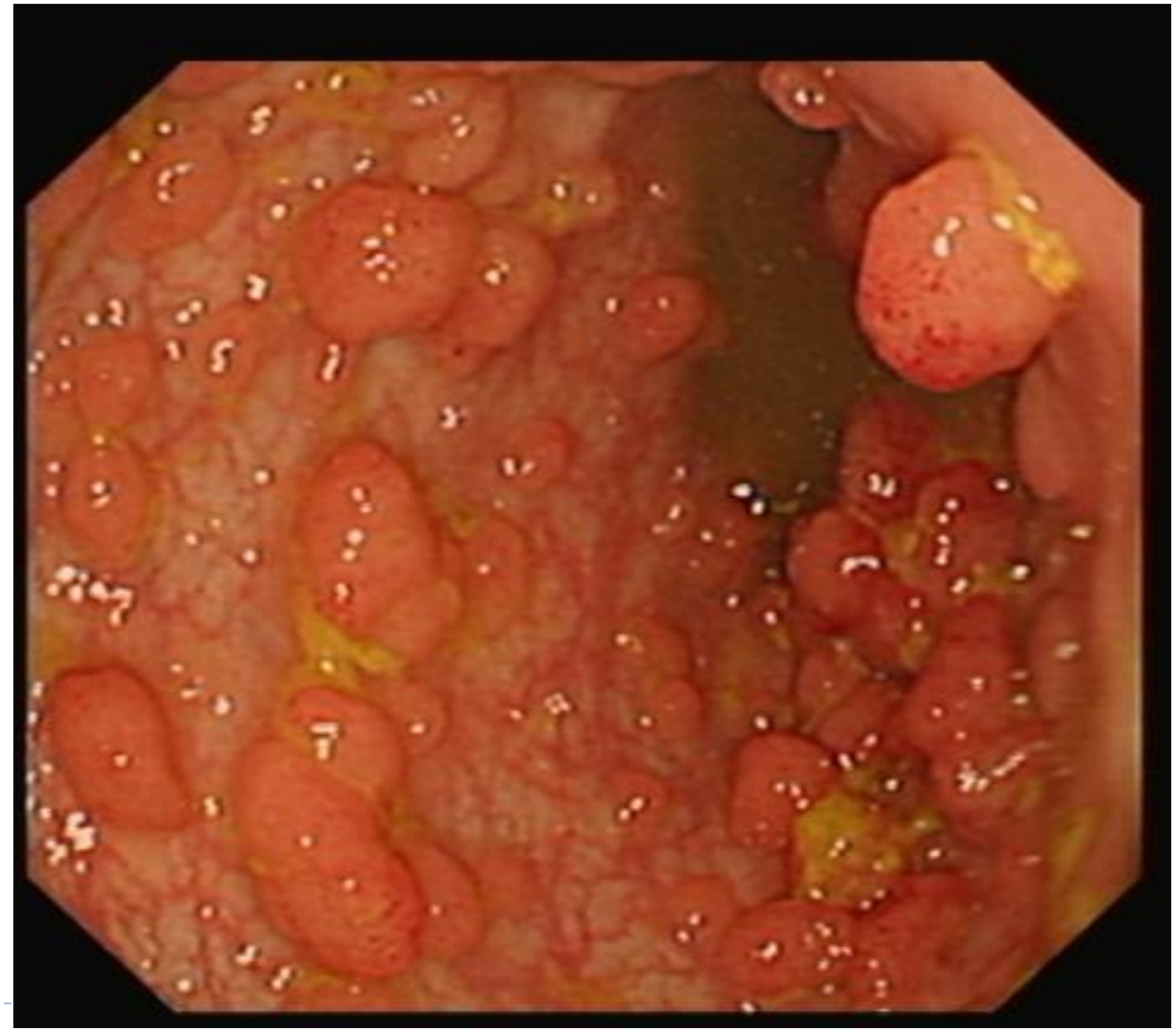


Assess adenoma burden in the rectum

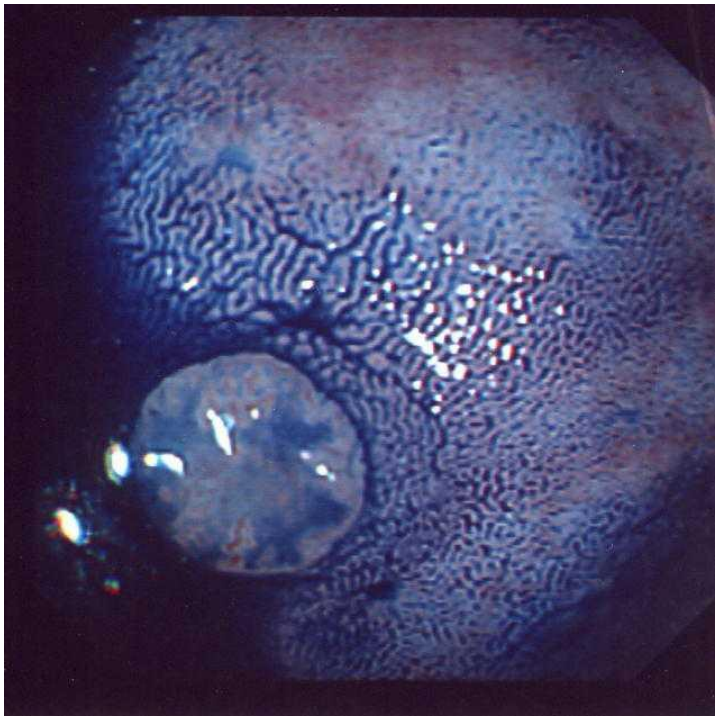


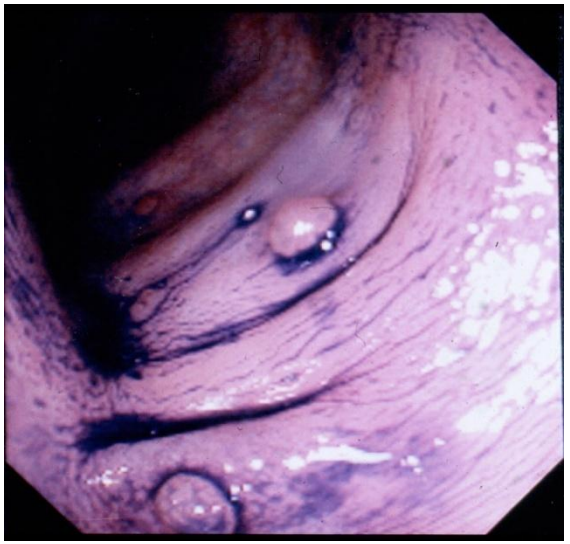


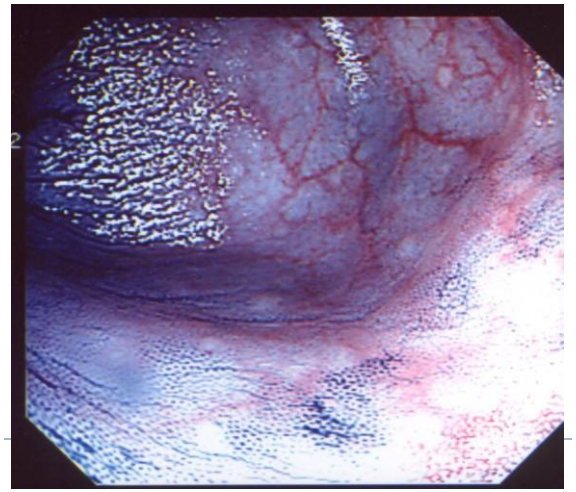
Assess polyp burden in the colon



Dye spray in FAP – identifying dysplasia & adenomas

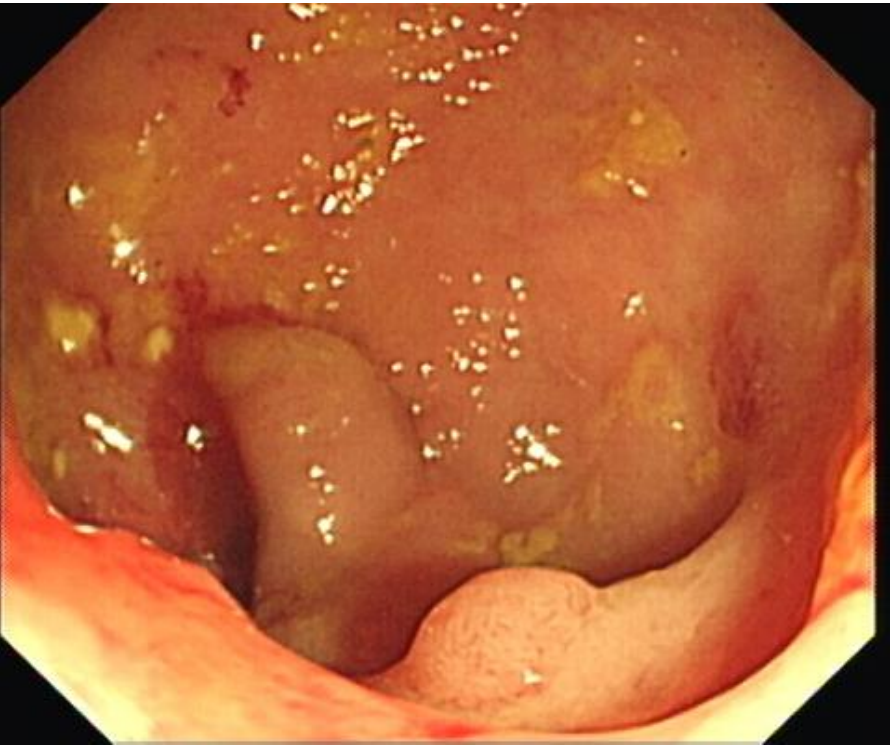


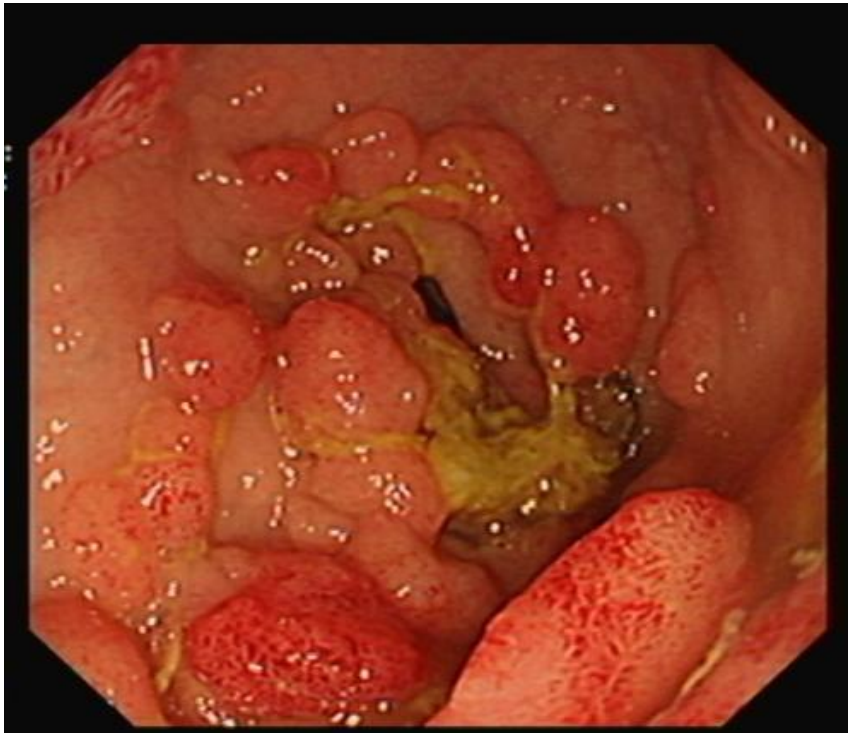




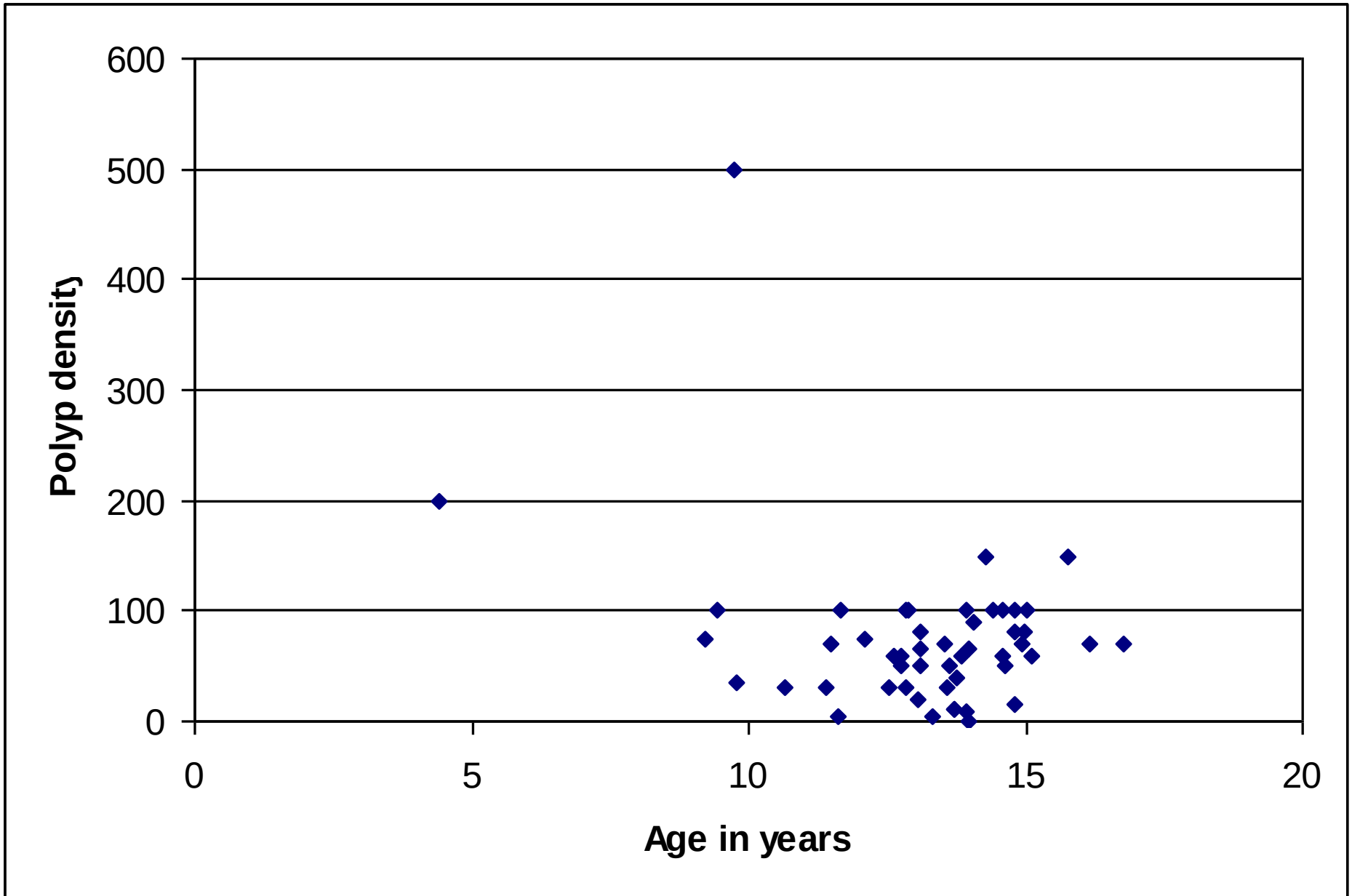
St MARK'S HOSPITAL

We underestimate polyp burden

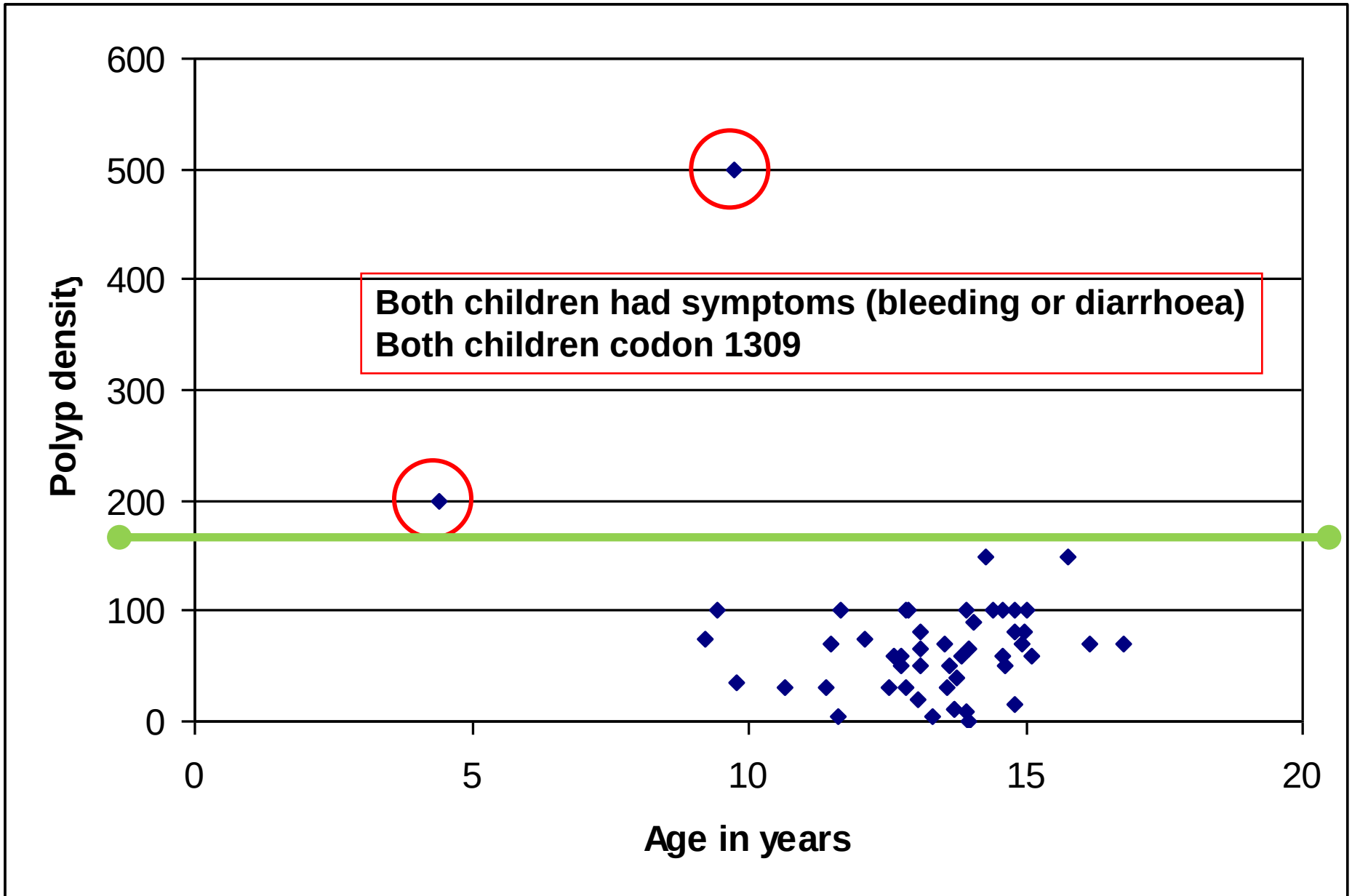




Which children had high adenoma burden?



Which children had high adenoma burden?



But when will you develop a cancer?

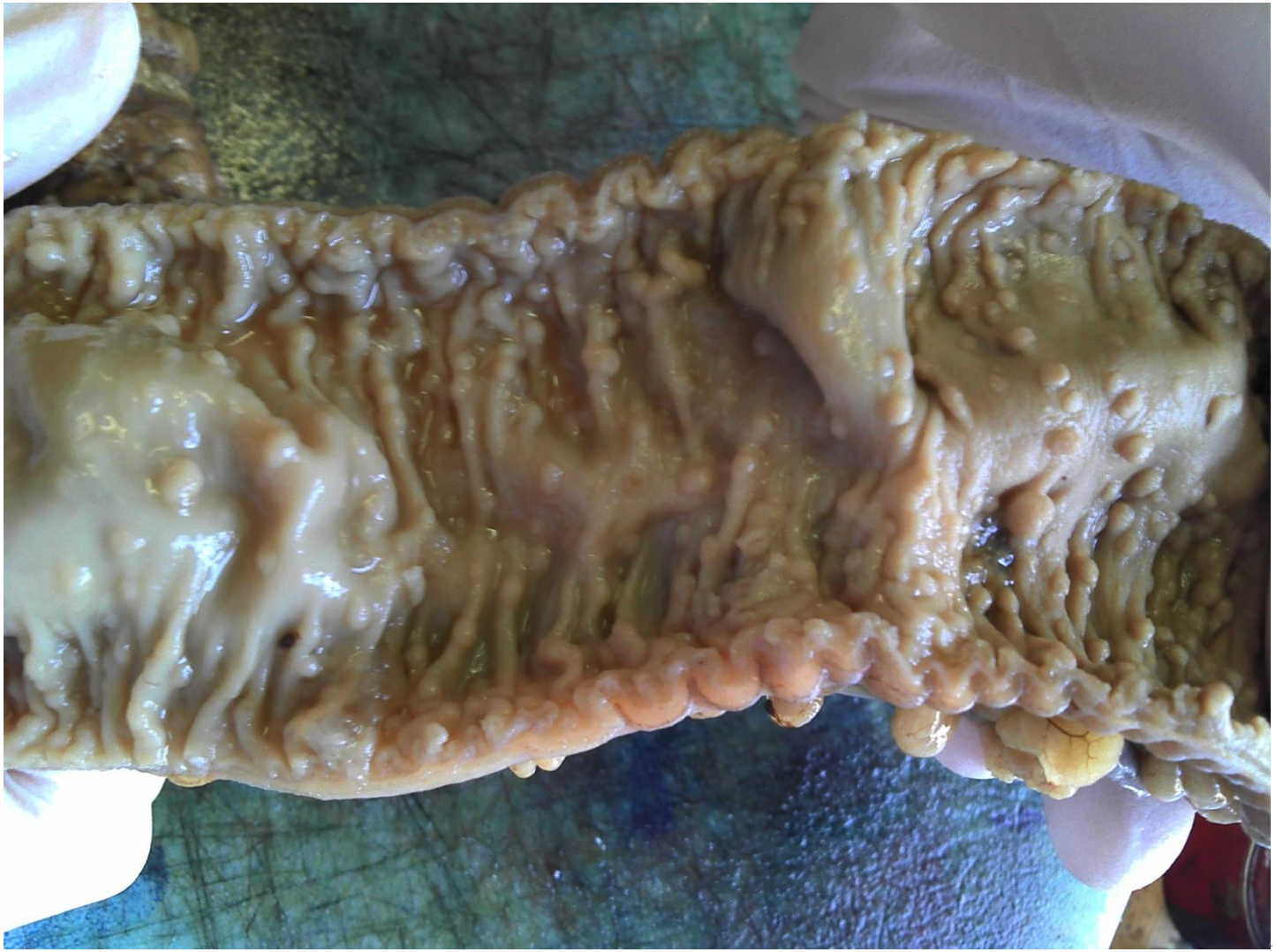
Table 3 Proportion of FAP patients with CRC diagnosed at $\leqslant$20 years of age*

Polyposis registry	Total number of CRCs	Number of CRCs (%) diagnosed		
		0–10 years	11–15 years	16–20 years
The Netherlands	106	0	1	1
Denmark	190	0	0	3
Germany	524	0	1	7
St Mark's	96	0	0	3
Finland	157	0	0	1
Total	1073	0	2 (0.2%)	15 (1.3%)

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

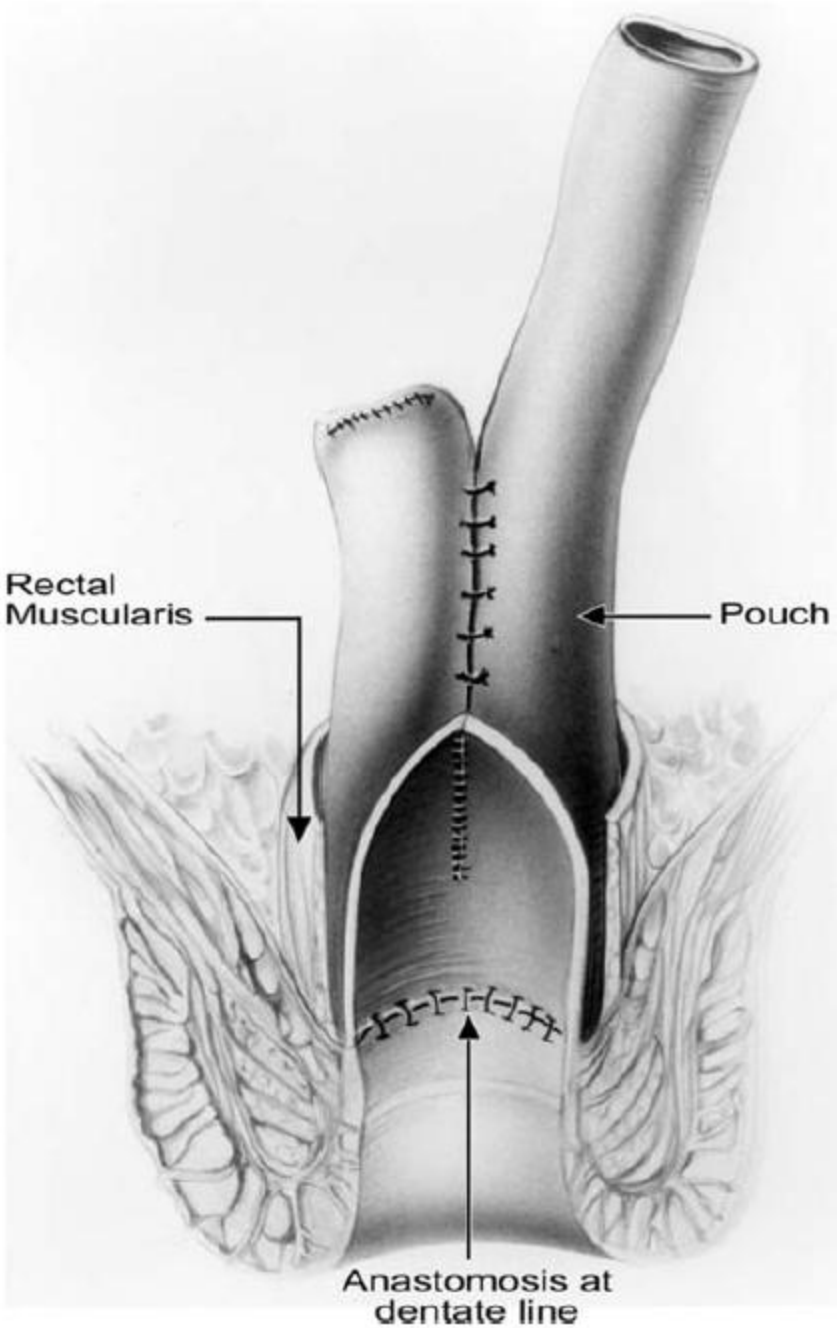


Why choose an ileo-rectal anastomosis

- 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

St MARK'S HOSPITAL


Rectal
Muscularis
Pouch
Anastomosis at
dentate line

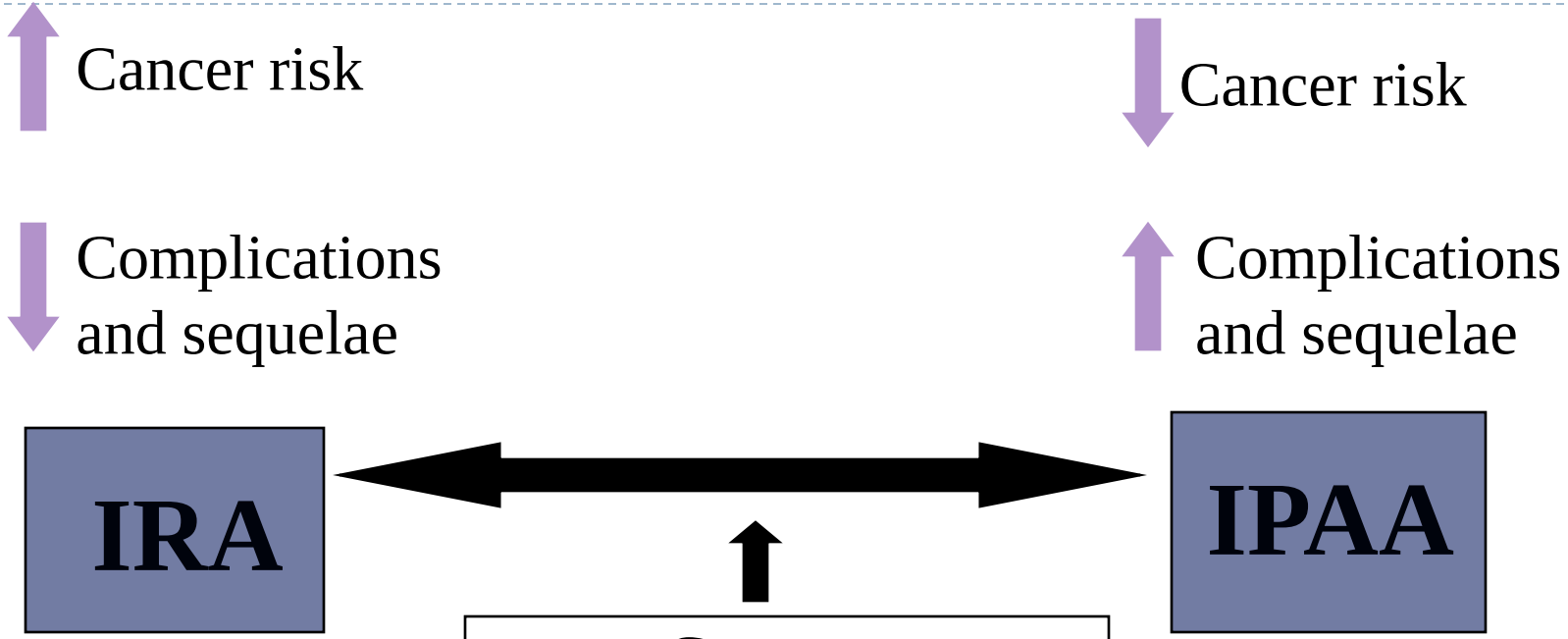
Why chose an ileo – pouch – anal - anastomosis

- 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

St MARK'S HOSPITAL

Colectomy in adolescents- IRA or IPAA?



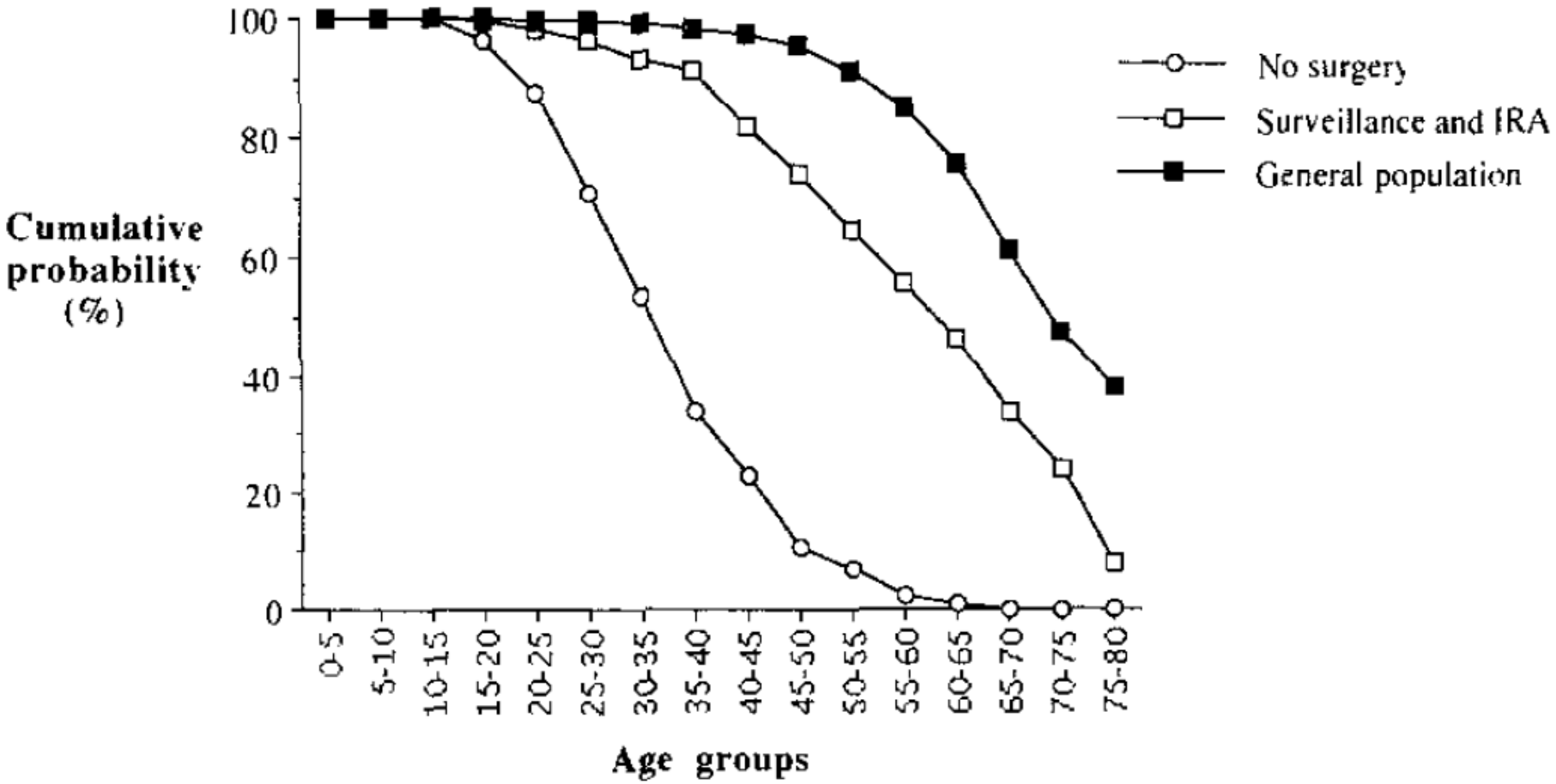
Genetics – implication for choice of surgery

Mutation	Rectum Preserved	Rectum Removed
157	7	0
540	2	0
1060	6	2
1068	15	1
1309	2	16
1328	0	3
1464	0	1*
1528	3	0
Total	35	23

* Patient choice, mild phenotype.

APC Genotype, Polyp Number, and Surgical Options in Familial Adenomatous Polyposis
The Cleveland Clinic Foundation, Cleveland, Ohio
Annals of Surgery. 227:57-62, 1998.

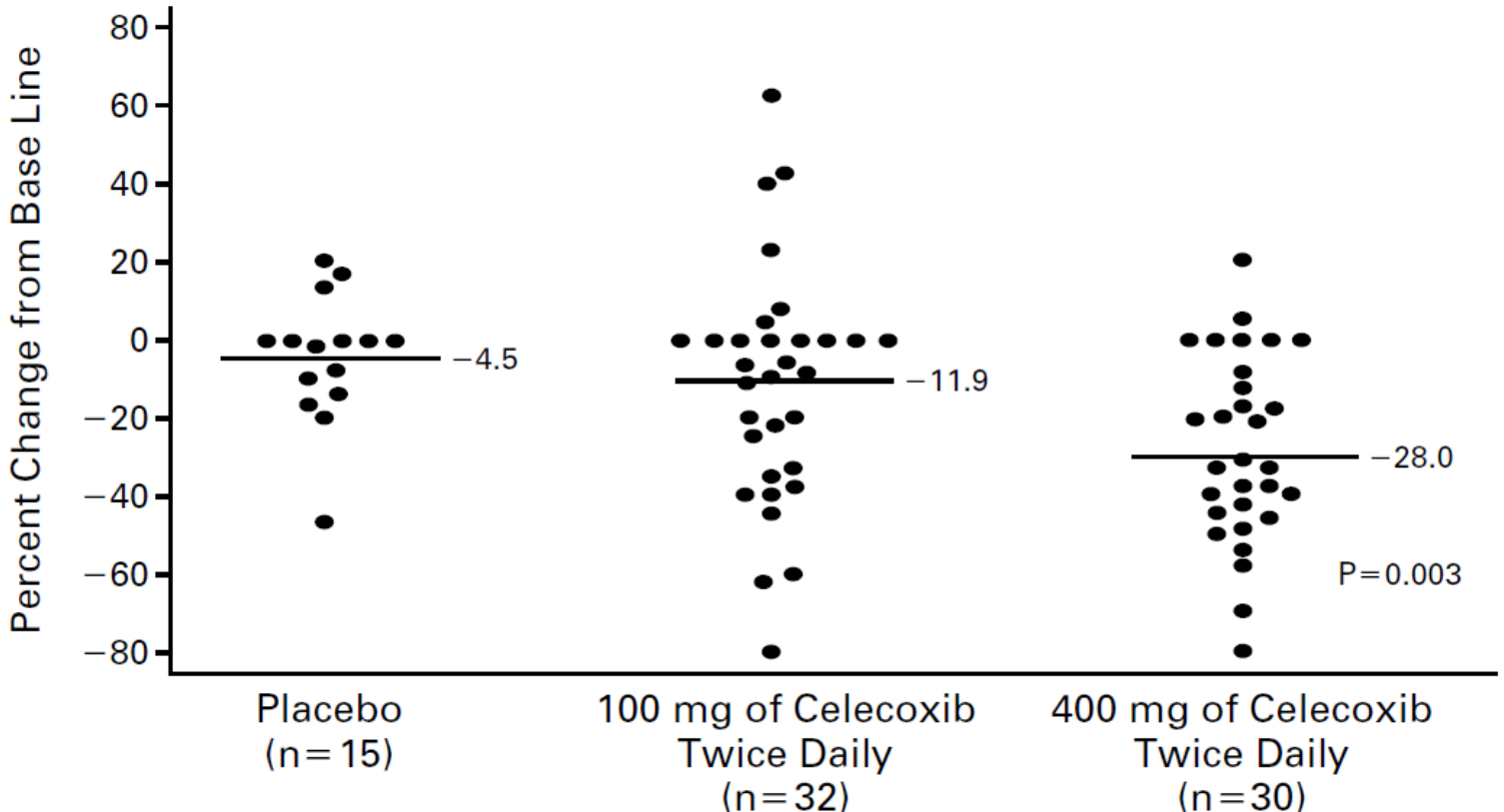
Life expectancy after surgery



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.



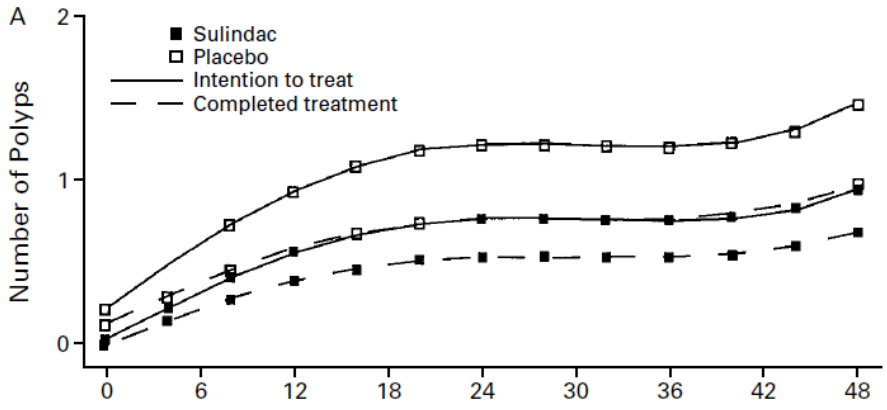
Adenoma prevention with sulindac

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. HYLIND, 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, JD[1], Gregory D. Ayers, MS[2], Ernie Hawk, MD, MPH[3], Ellen Richmond, RN, MSN[3], Craig Eagle, MD[4], Mabel Woloj, PhD[4], James Church, MD[5], Hennie Hasson, RN[6], Sherri Patterson, RN[7], Elizabeth Half, MD[8] and Carol A. Burke, MD[8]

Table 1. Celecoxib dose assignments by body weight and cohort

	Cohort 1, *n*=6 (2:1 drug: placebo)	Cohort 2, *n*=6 (2:1 drug: placebo)	Cohort 3, *n*=6 (2:1 drug: placebo)
Body weight	Celecoxib dose 4 mg/kg	Celecoxib dose 8 mg/kg	Celecoxib dose 16 mg/kg
25.0–37.5 kg	50 mg BID	100 mg BID	200 mg BID
37.6–50.0 kg	100 mg BID	150 mg BID	300 mg BID
>50.0 kg	100 mg BID	200 mg BID	400 mg BID

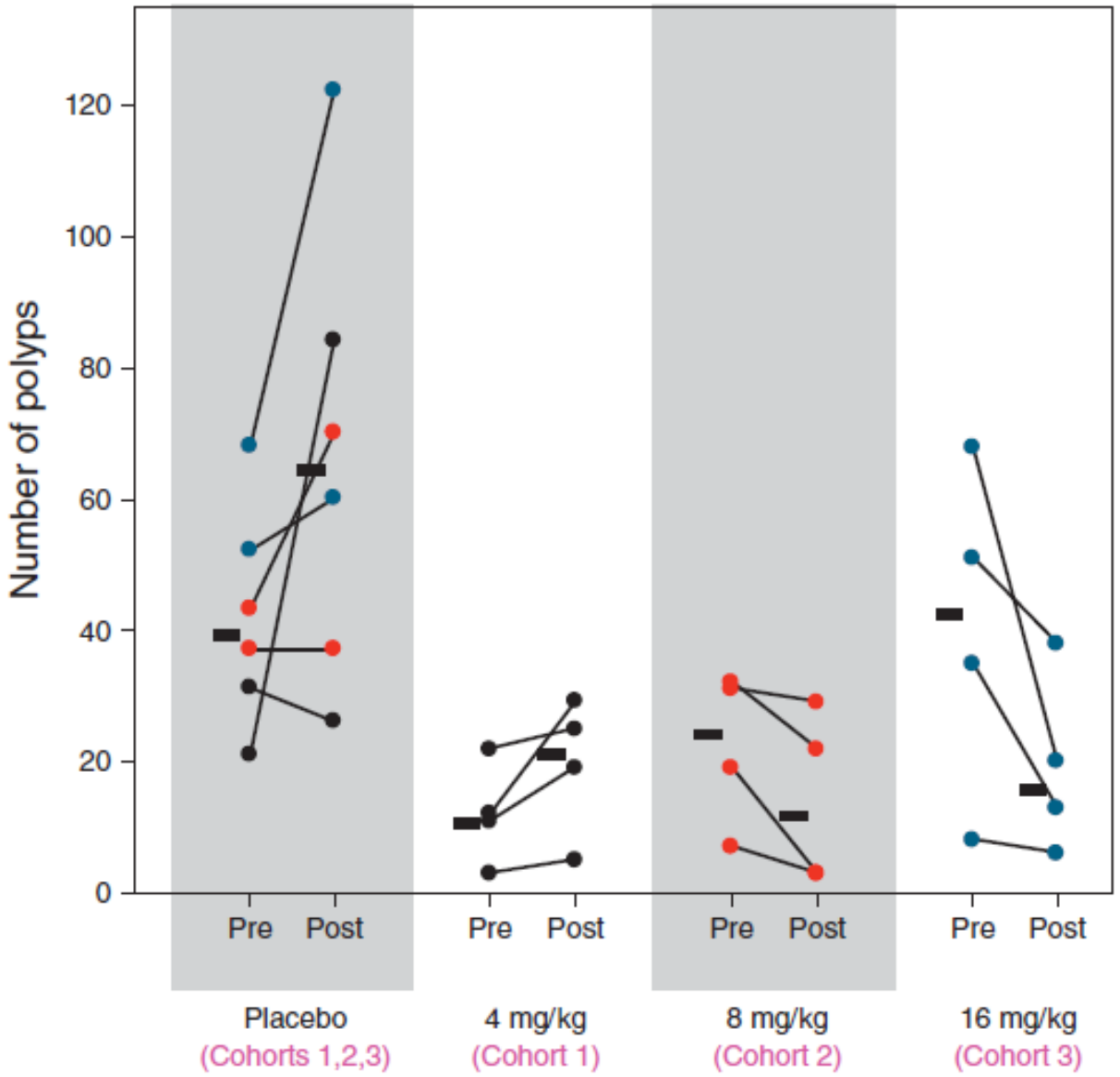
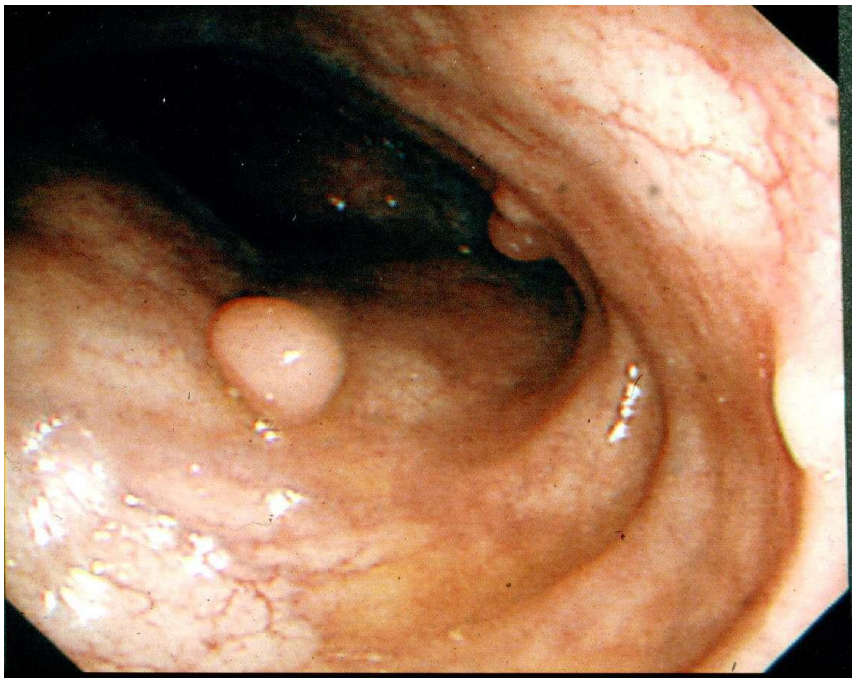


Figure 2. Celecoxib dose–response relationship among pediatric patients with familial adenomatous polyposis. The number of polyps at baseline

- 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.

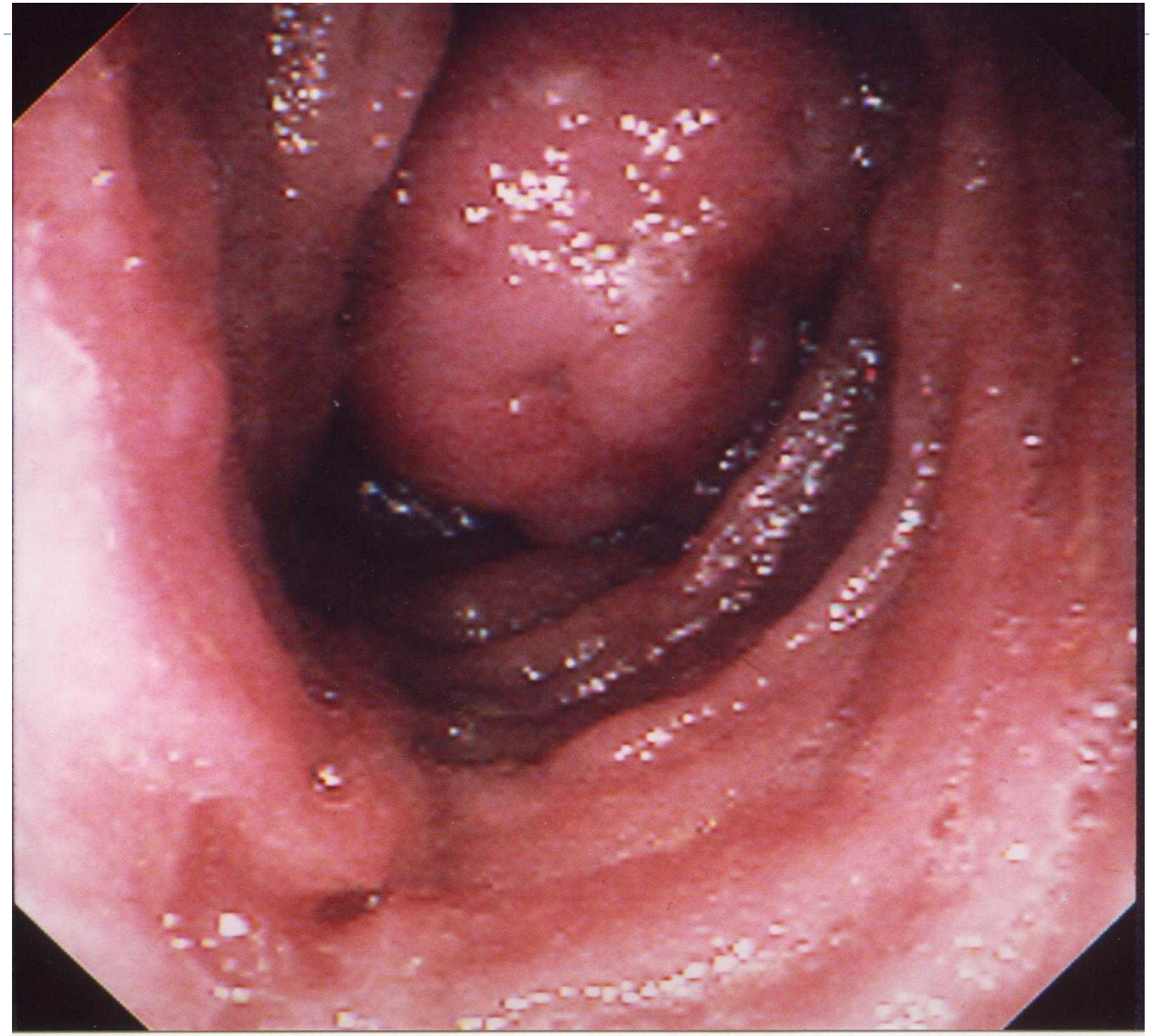


So what have we learnt together?

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**

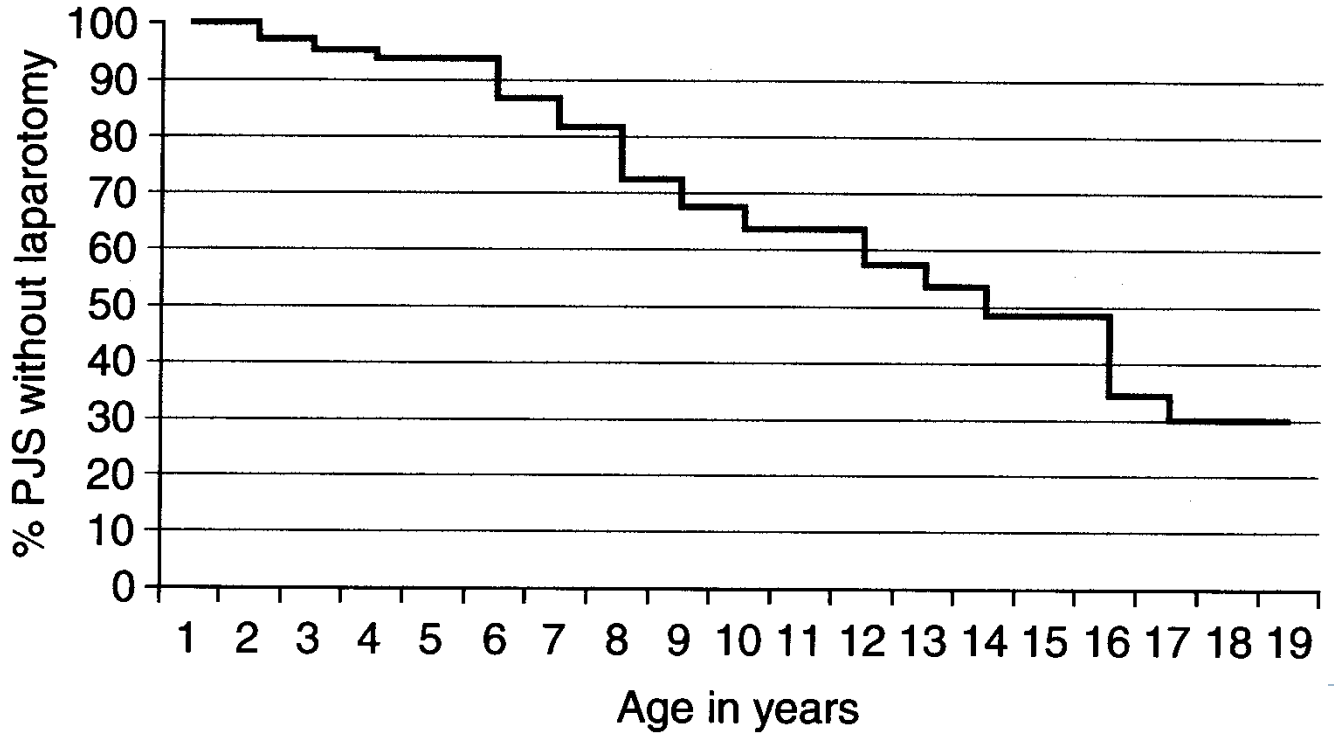


St MARK'S HOSPITAL

Complications of Childhood Peutz-Jeghers Syndrome: Implications for Pediatric Screening

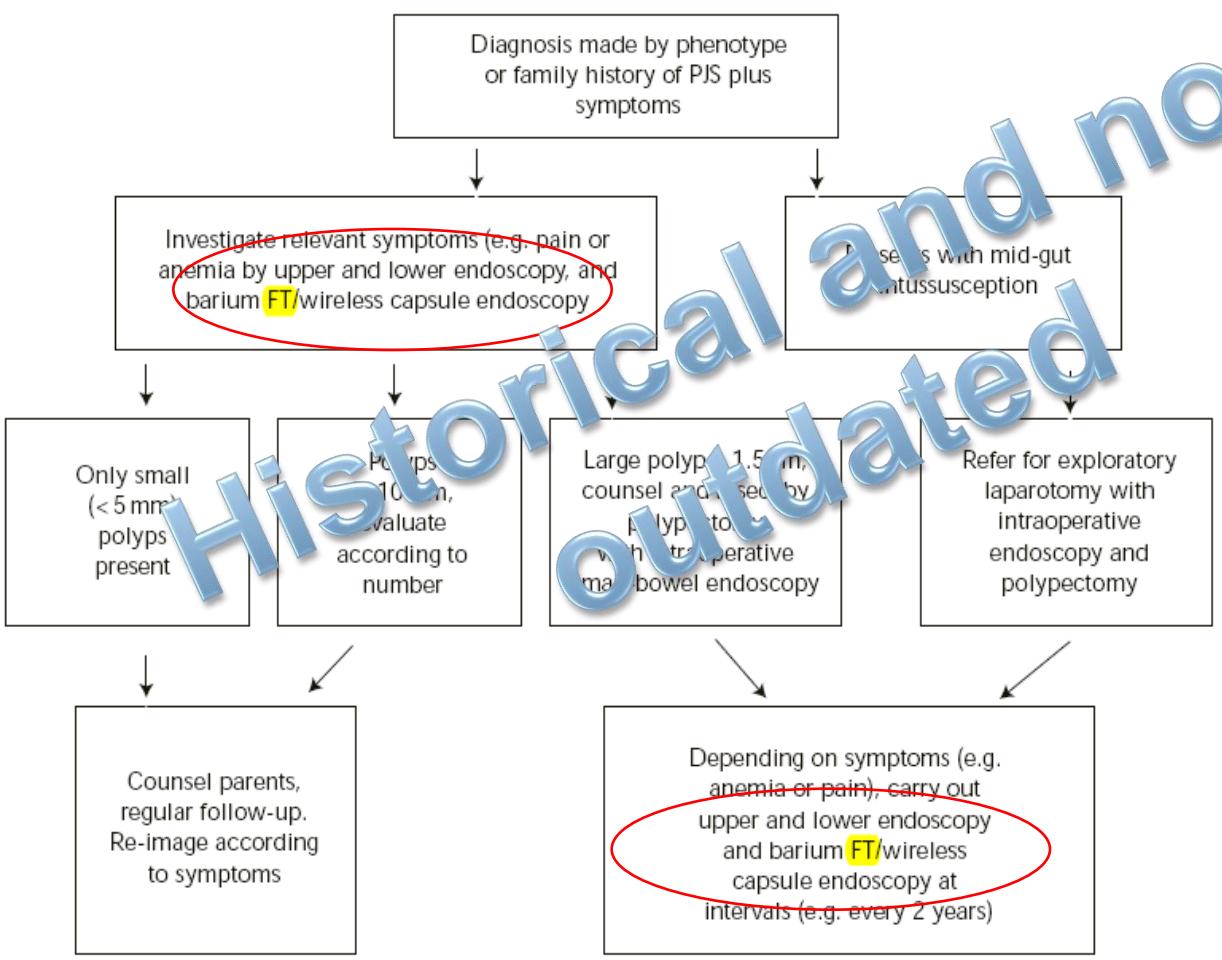
*R. Hinds, †C. Philp, †W. Hyer, and *J. M. Fell

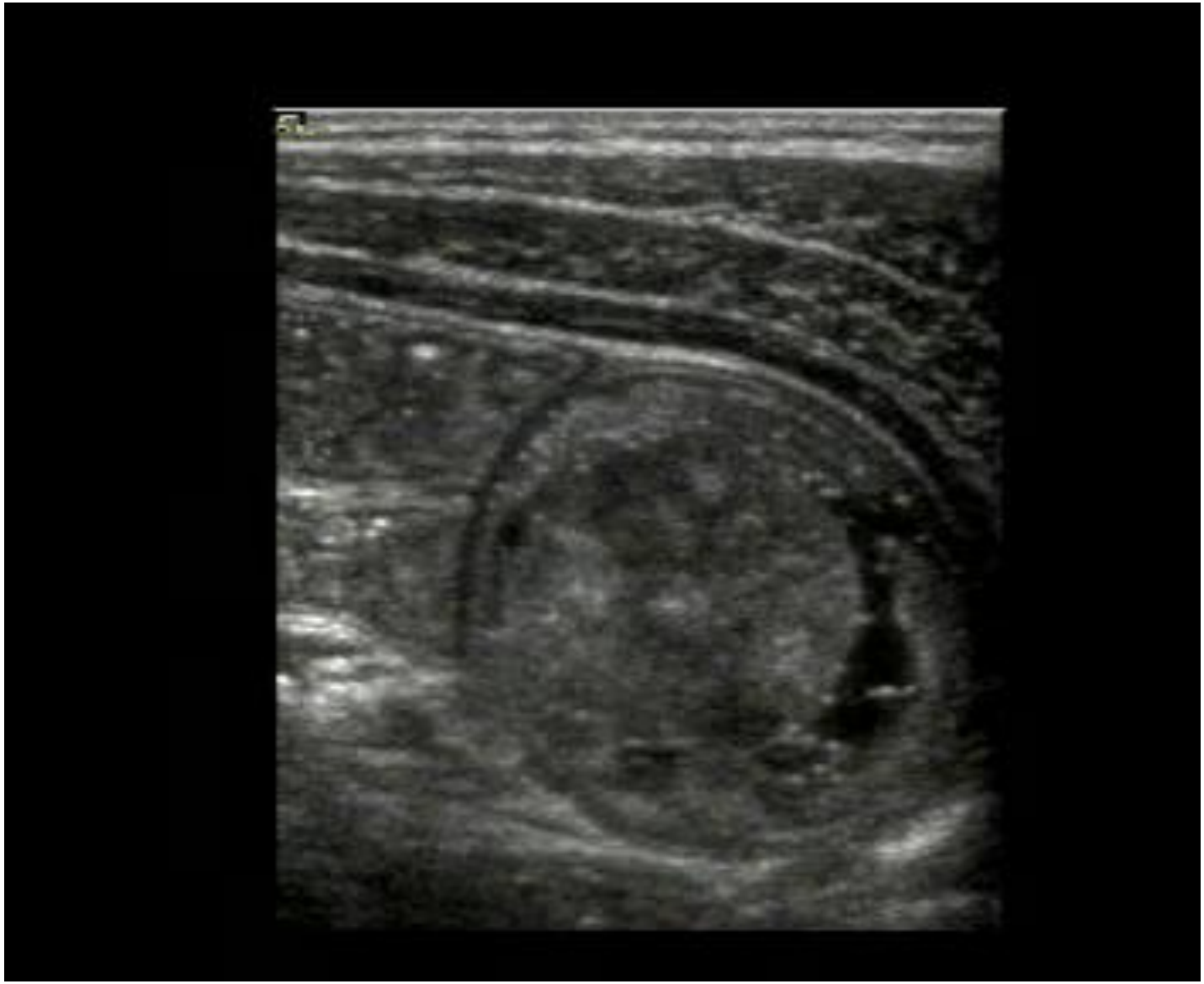
*Department of Paediatric Gastroenterology, Chelsea and Westminster Hospital, London; and the †The Polyposis Registry, St. Mark's Hospital, London, England



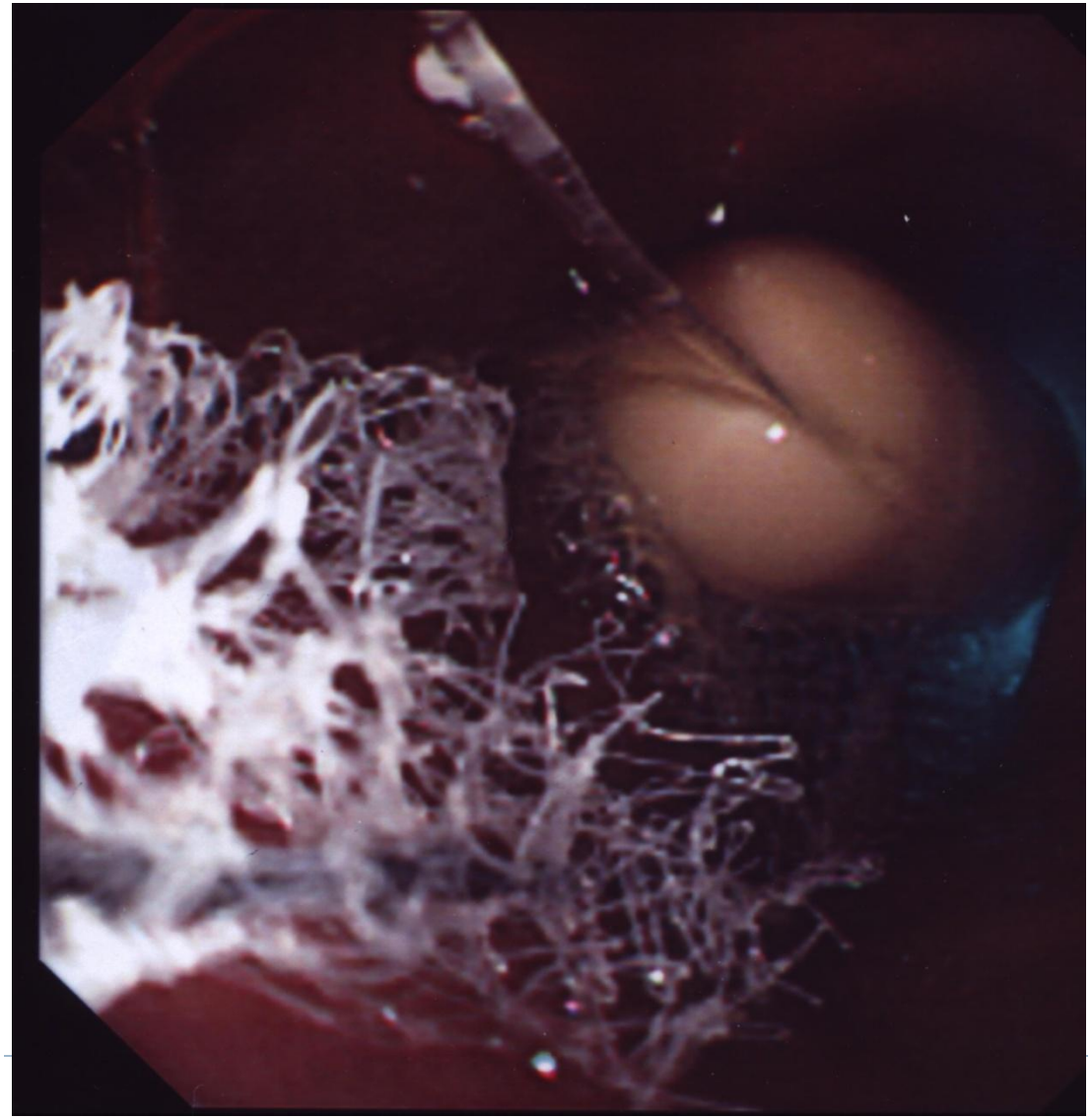
St MARK'S HOSPITAL

Imaging and protocols for PJS – time to change – perhaps the end of the barium contrast study





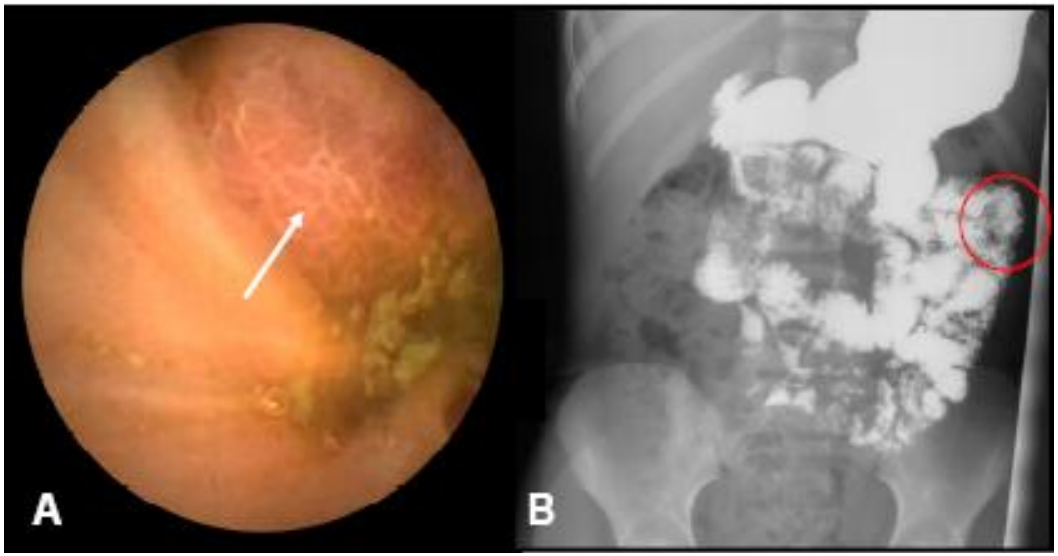
Capsule endoscopy



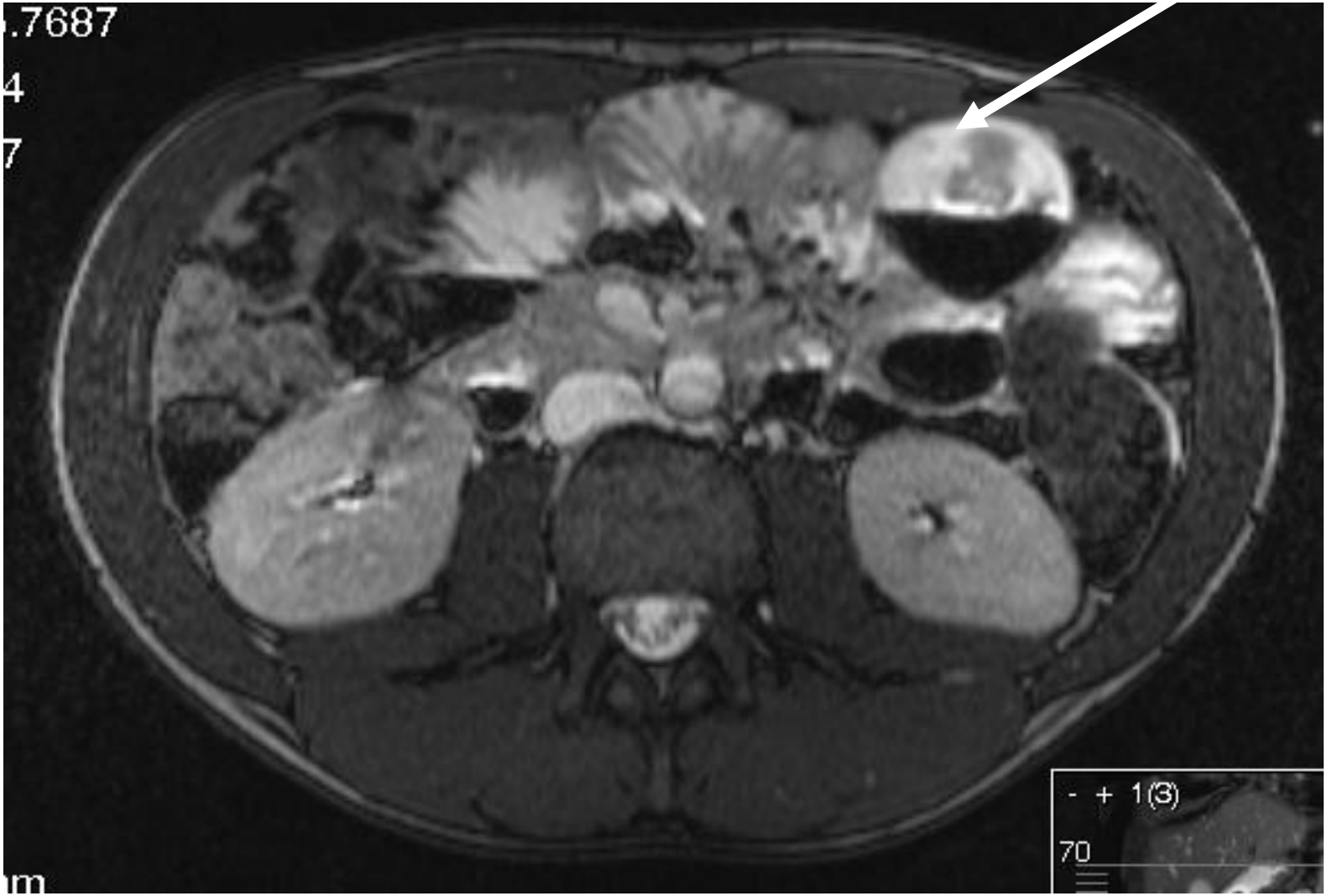
The end of the barium in PJS…..VCE is not perfect enough….

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.

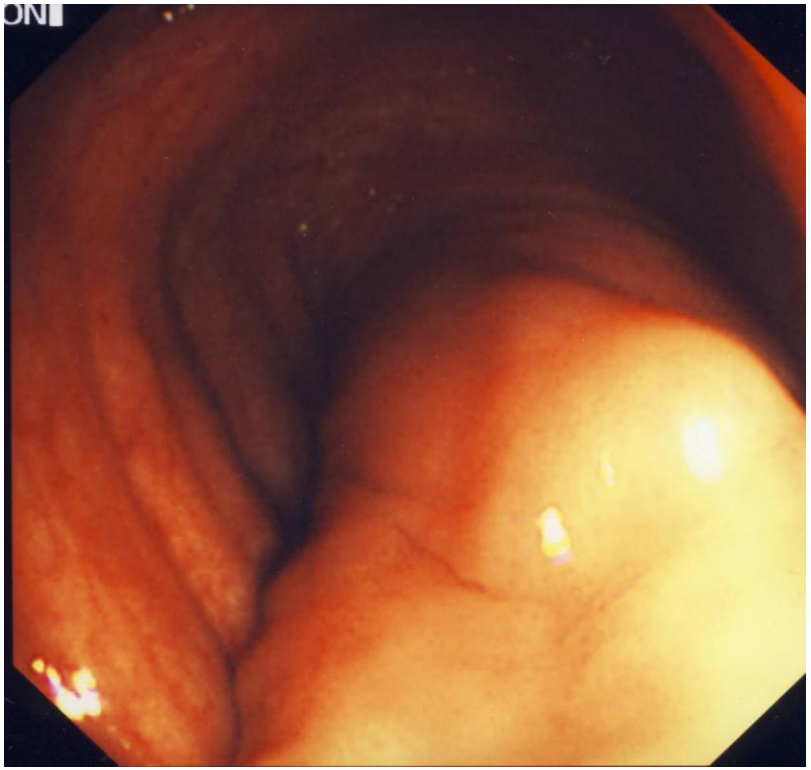


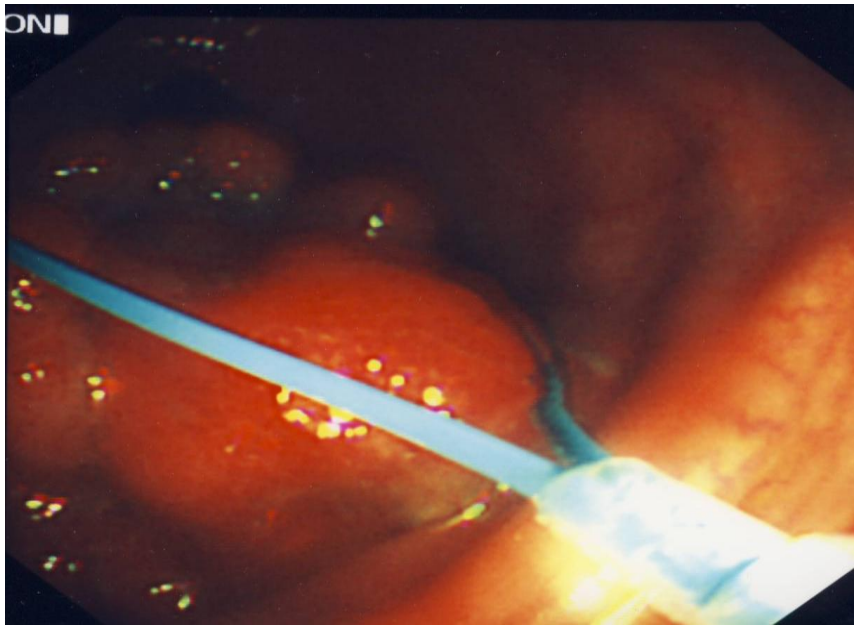
Postgate A, Hyer W, Phillips R, Brown G, Schofield G, Burling D, Gupta A, Marshall M, Bartram C, Taylor S, Latchford A, Bassett P, Fitzpatrick A, **Fraser C**

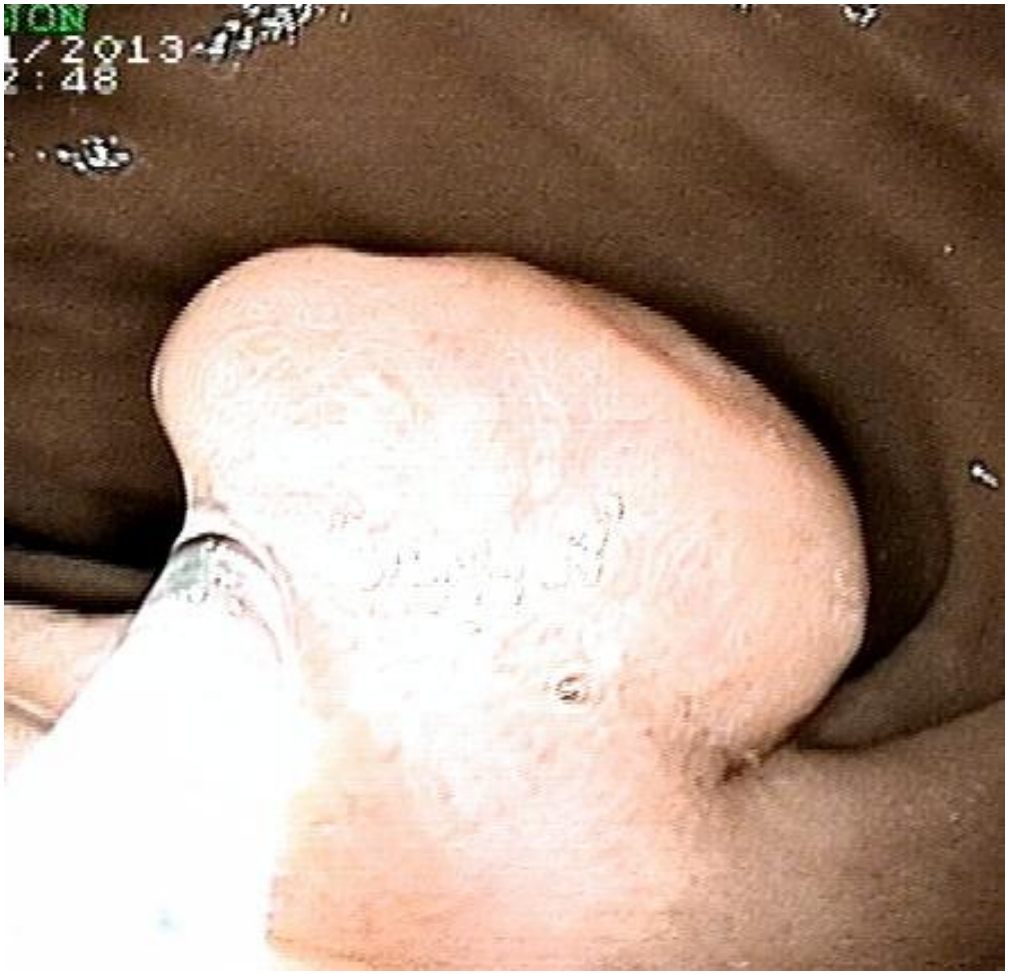


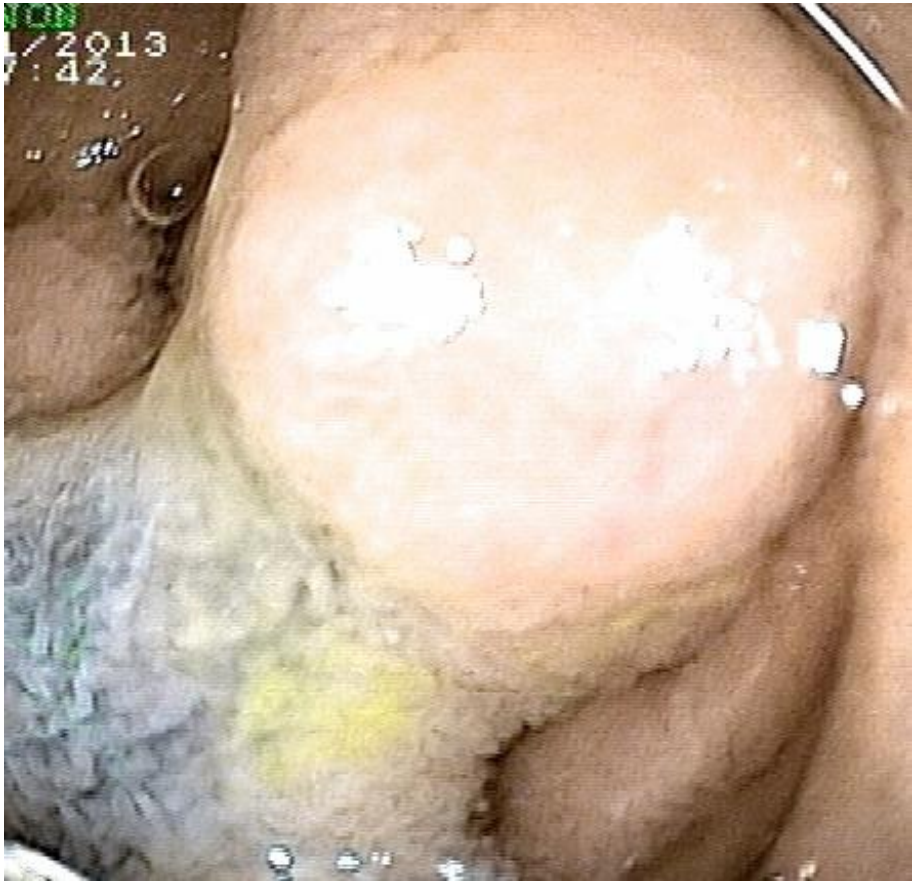
Close correlation between MRI and capsule endoscopy in adults (and children) with PJS. Gut 2009 Postgate A et al (n=9)

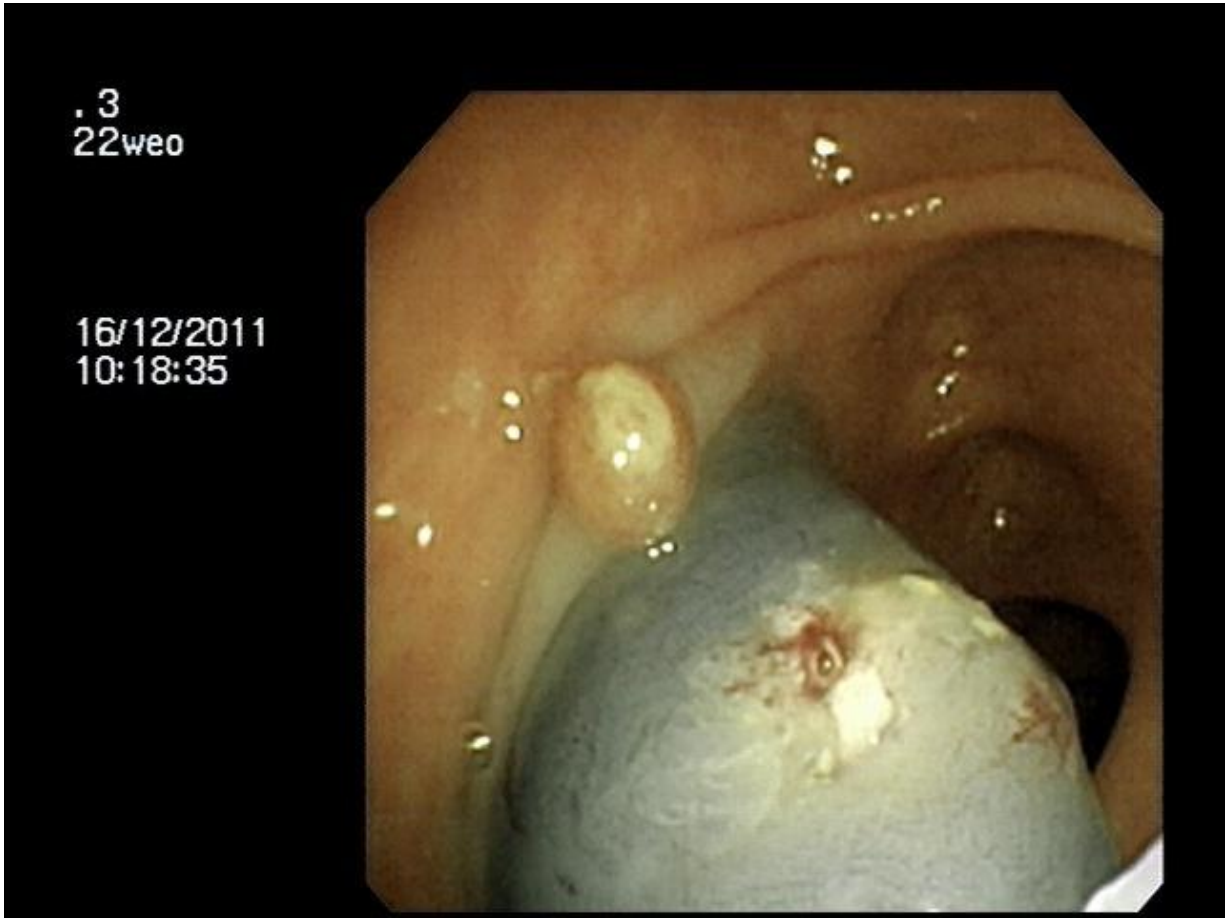
What polyp is too big in a child?



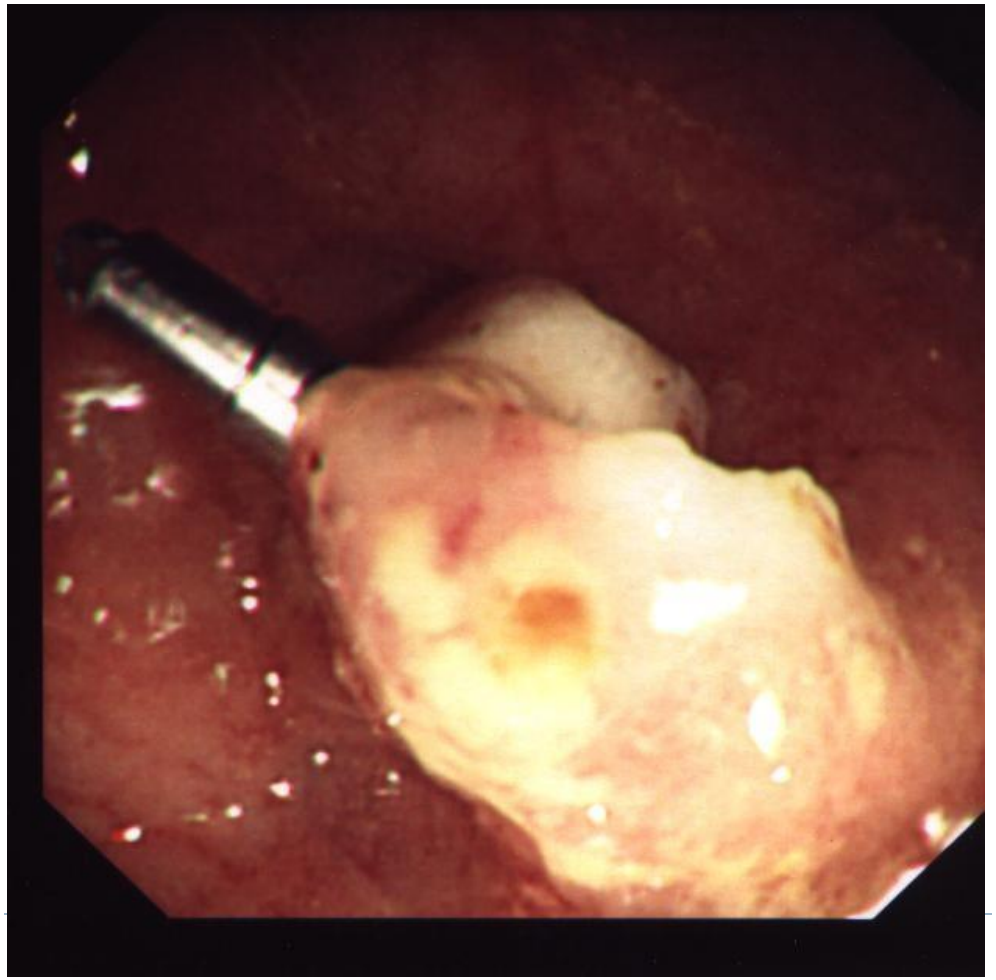



TON
1/2013
2:48

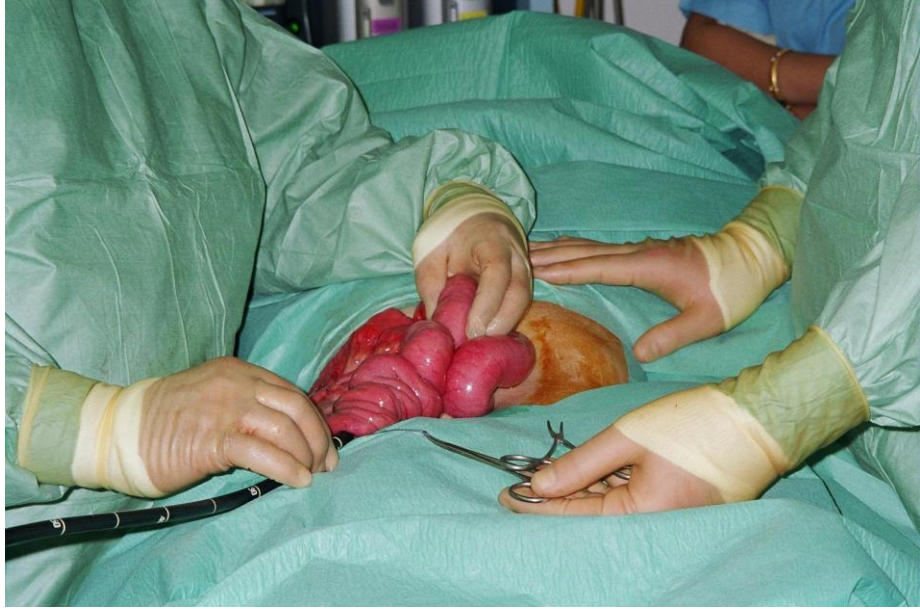

2013
:42.

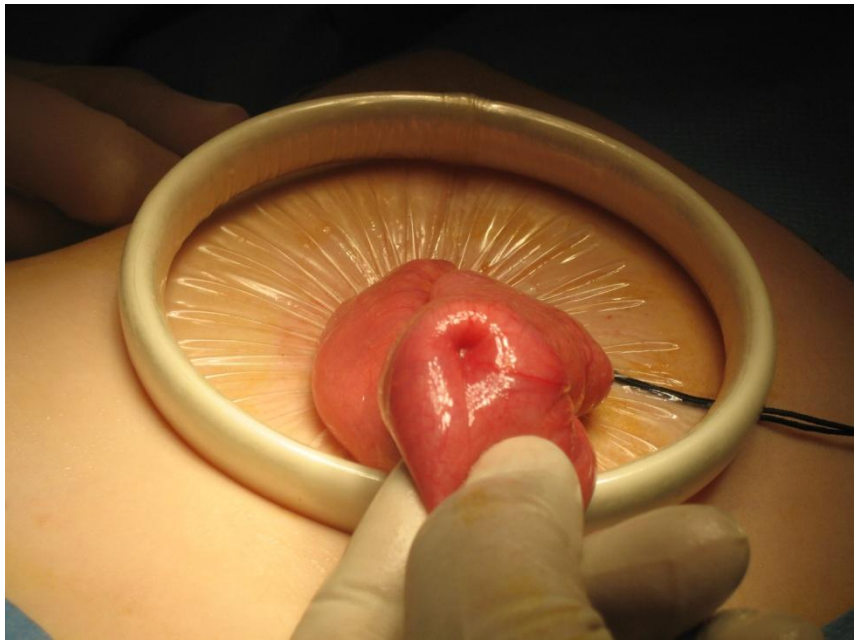

. 3
22weo
16/12/2011
10:18:35

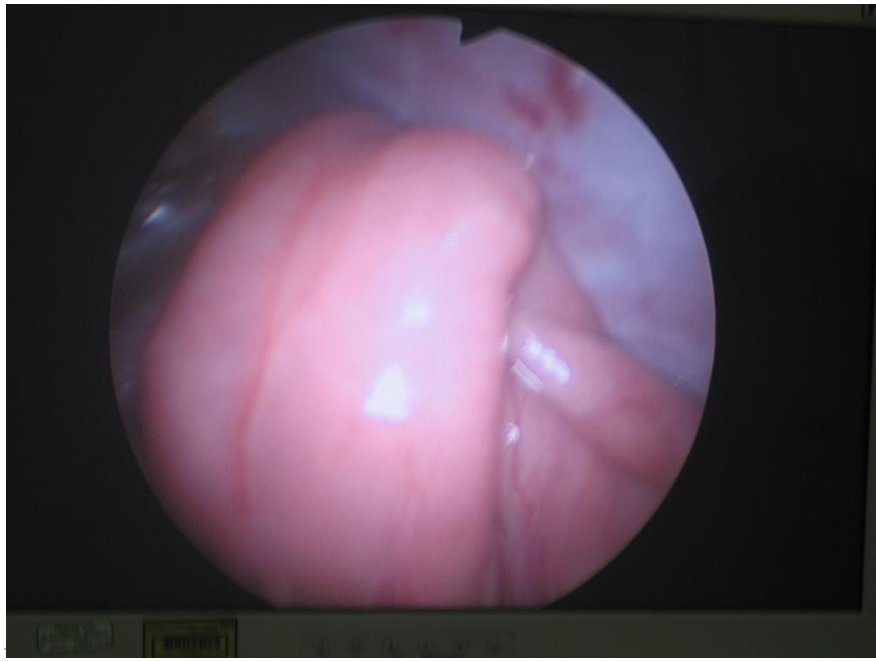
Preventing perforation at polypectomy



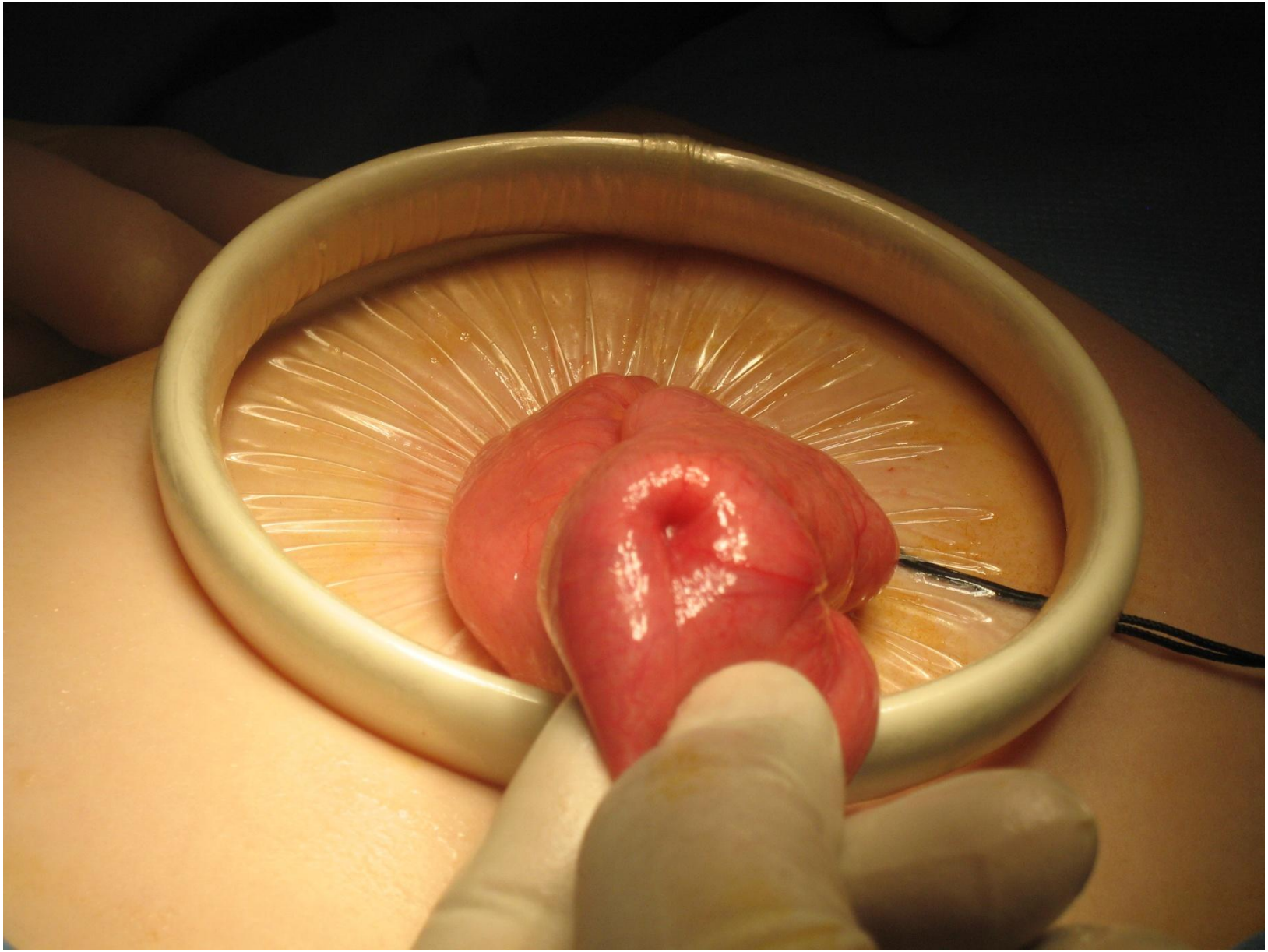
Surgery in PJS



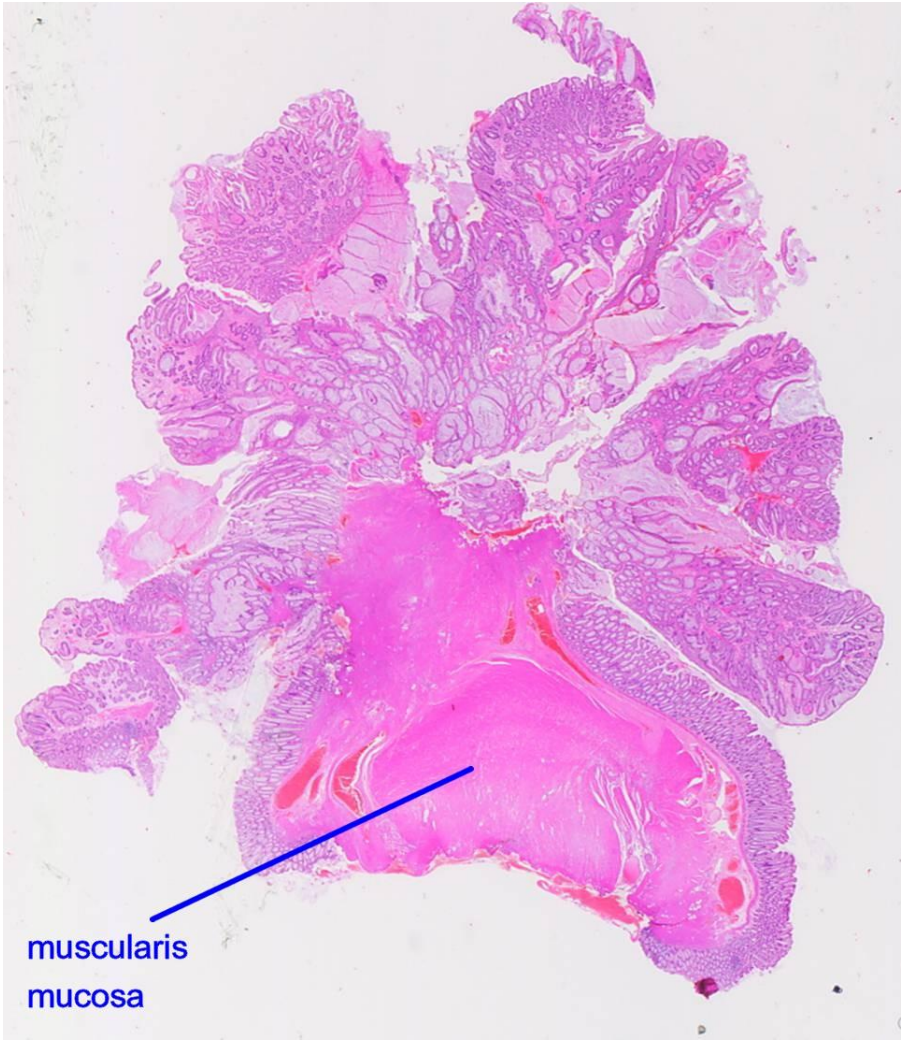


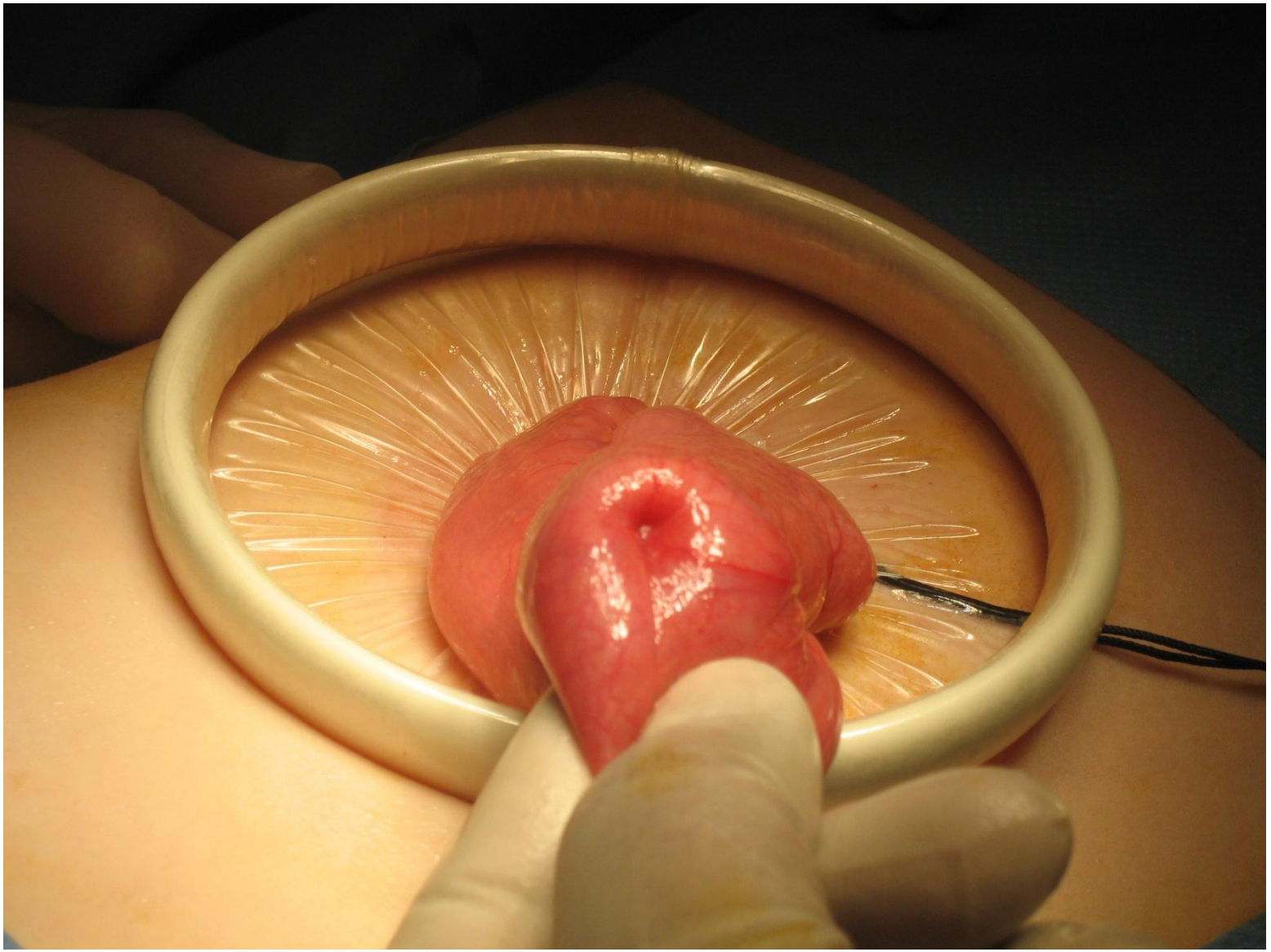


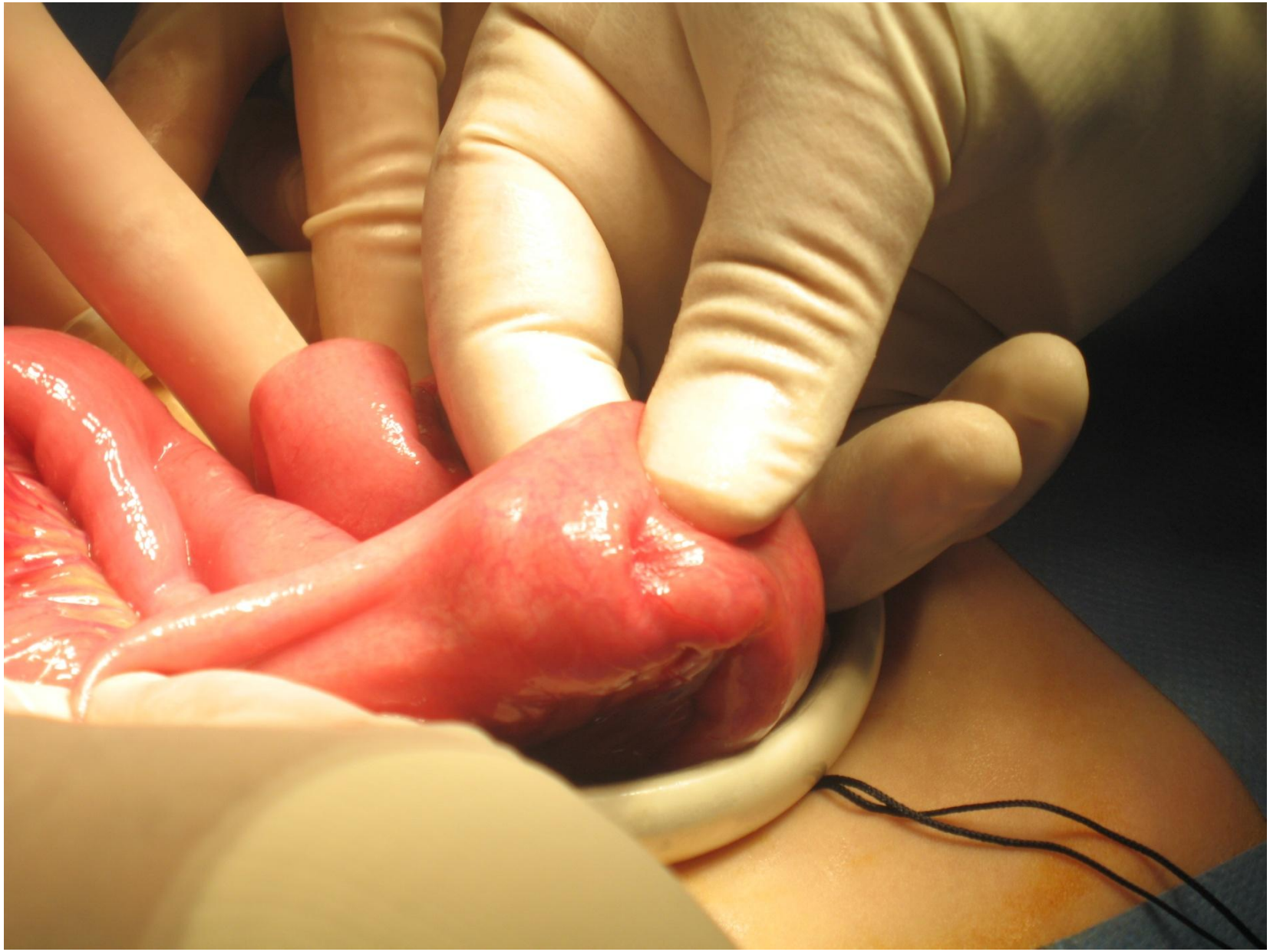
St MARK'S HOSPITAL



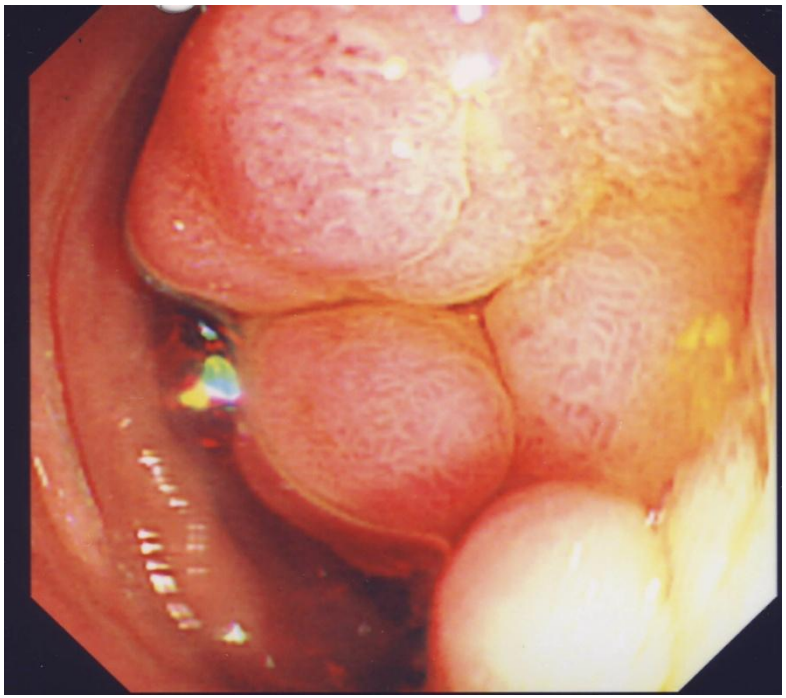
St MARK'S HOSPITAL

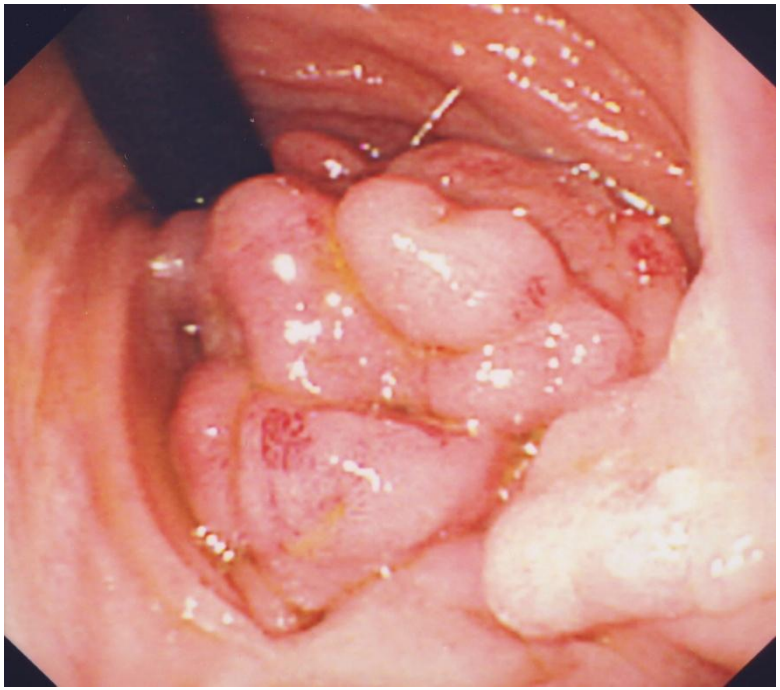

muscularis
mucosa





Realistic decisions about surgical/endoscopic choices





Double balloon enteroscopy 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

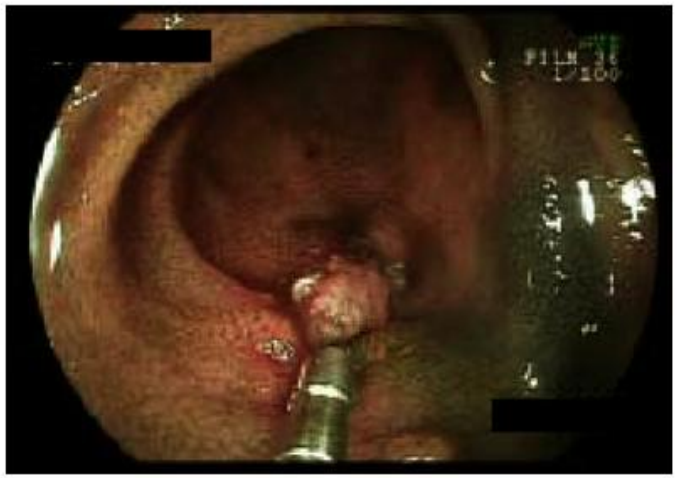


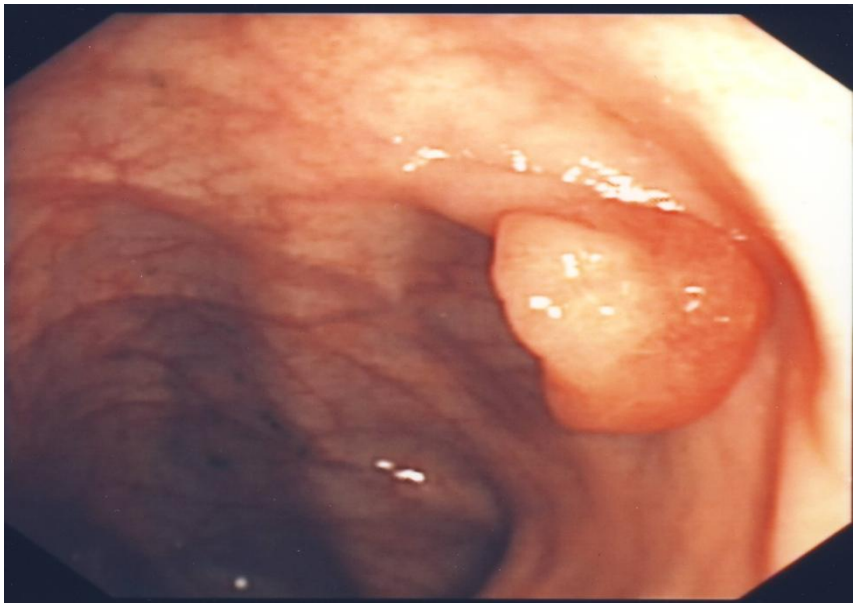
Fig. 5 DBE image showed that the polyp was resected, and the ulcer was clipped

- 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

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

Juvenile polyposis



Unwinding the Heterogeneous Nature of Hamartomatous Polyposis Syndromes

John M. Carethers, MD

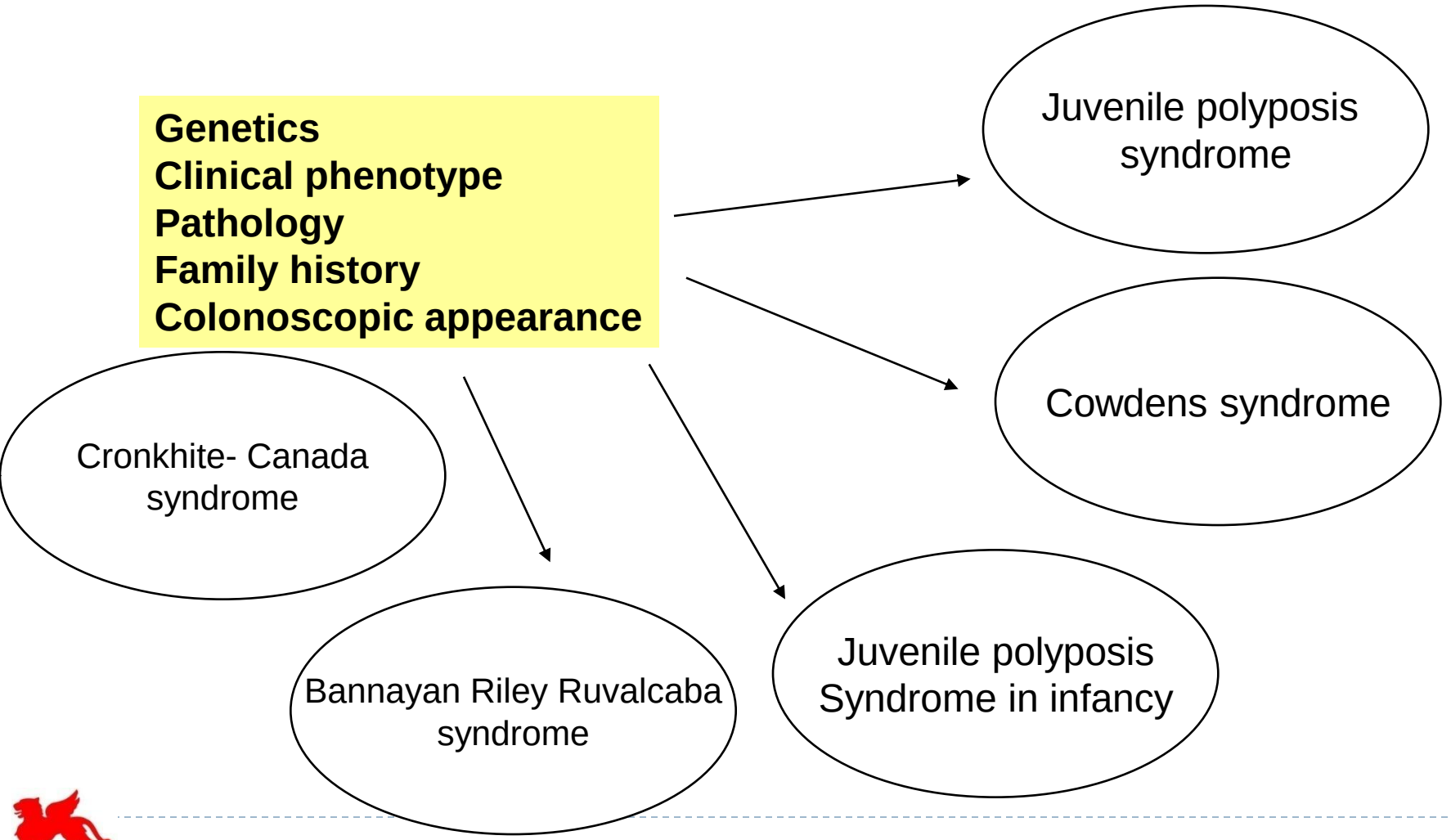
IN ANY CLASSIC "WHODUNIT" MYSTERY, THE GOAL OF THE investigator is to find and expose the guilty party. At the onset, there may be many suspects, some of whom may appear guilty. However, the shrewd investigator picks through those distractors to clearly eliminate them and focuses on specific details 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.

Author Affiliations: Department of Medicine and Rebecca and John Moores Comprehensive Cancer Center, University of California, San Diego; Veterans Administration Research Service, San Diego.
Corresponding Author: John M. Carethers, MD, GI Section, 111D, Veterans Administration San Diego Healthcare System, 3350 La Jolla Village Dr, San Diego, CA 92161 (jcarethers@ucsd.edu).

Issues for the severe infantile juvenile polyposis /Bannayan- Riley-Ruvalcaba

Unpicking the hamartomous syndromes – 21st century style



What genetics?

- LKB1
  - PJS
- PTEN
  - 85% of Cowden
  - 65% of Bannayan Riley Ruvalcaba syndrome
  - JPS
- SMAD 4
  - 20-50% JPS
- BMPR1A
  - 20-40% of JPS
- ENG
  - JPS, HHT

No cancer risk in childhood with JPS

Risk of colorectal cancer in juvenile polyposis

Lodewijk A A Brosens, Arnout van Hattem, Linda M Hylind, Christine Iacobuzio-Donahue, Katharine E Romans, Jennifer Axilbund, Marcia Cruz-Correa, Anne C Tersmette, G Johan A Offerhaus, Francis M Giardiello

Gut 2007;56:965–967. doi: 10.1136/gut.2006.116913

Age at diagnosis of colorectal cancer (years)	Sex	Race	Prior partial colectomy (age in years)	Death from colorectal cancer
30	F	W	No	No
32	F	W	Yes (28)	No
37	M	W	Yes (18)	Yes
41	M	W	No	Yes
48	F	W	No	No
52	M	W	Yes (19)	Yes
53	M	W	No	Yes
58	M	W	No	Yes

It is the anaemia and hypoalbuminaemia in the syndromic forms in infancy which create the clinical challenge

St MARK'S HOSPITAL

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

St MARK'S HOSPITAL