



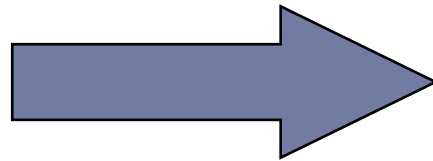
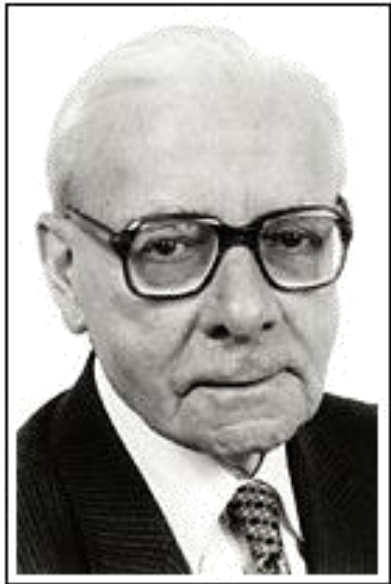
Dr Warren Hyer  
Consultant Paediatric Gastroenterologist  
St Mark's Hospital, UK

Familial Adenomatous Polyposis.

Genetics, colonoscopy screening  
and surgery.

# From surgeons to paediatric gastroenterologists

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# Objectives

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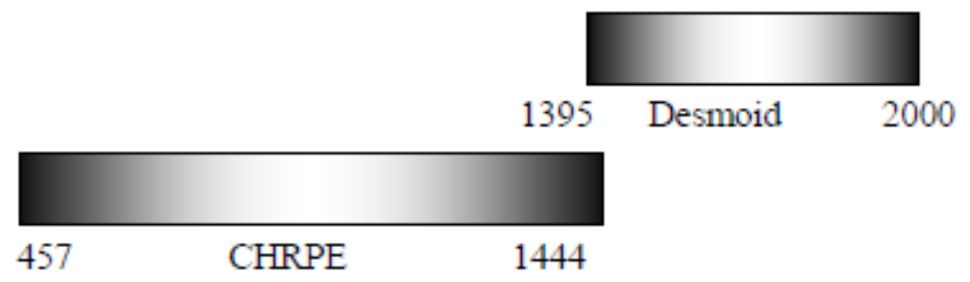
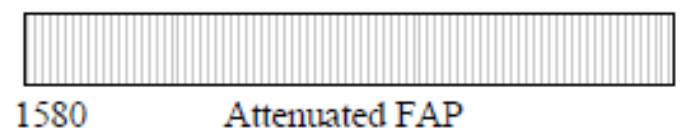
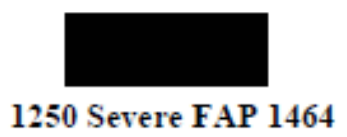
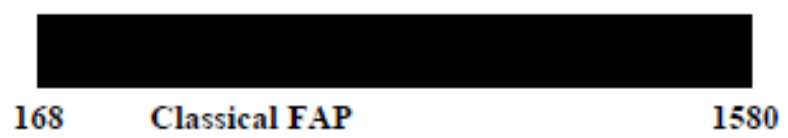
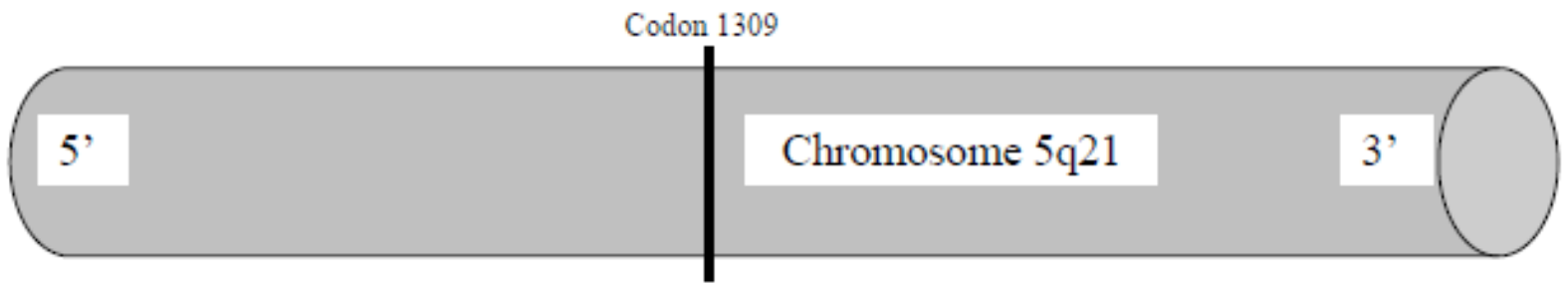
- ▶ To examine the genetic basis for FAP and the nature of the APC gene
- ▶ How and when should adolescents undergo colonoscopic surveillance
- ▶ What are the surgical choices for patients with FAP and which procedure should we recommend for our patients.

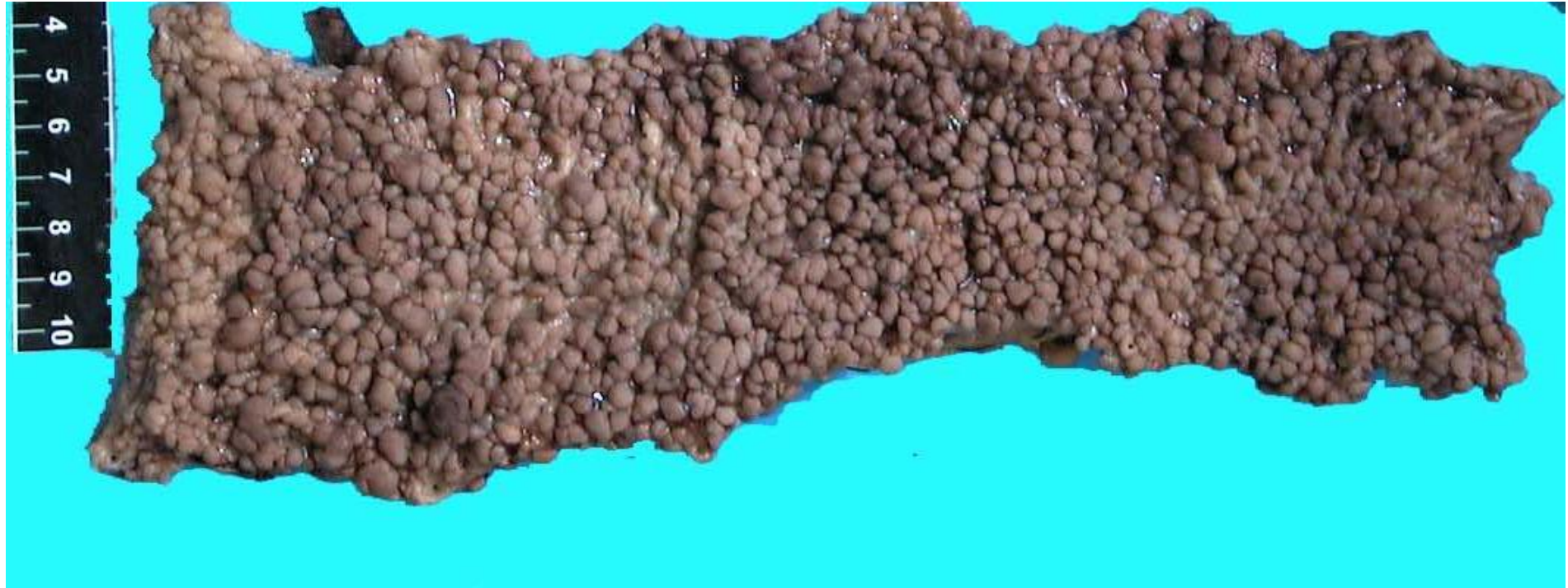
# Clinical scenario

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- ▶ 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

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- ▶ 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.

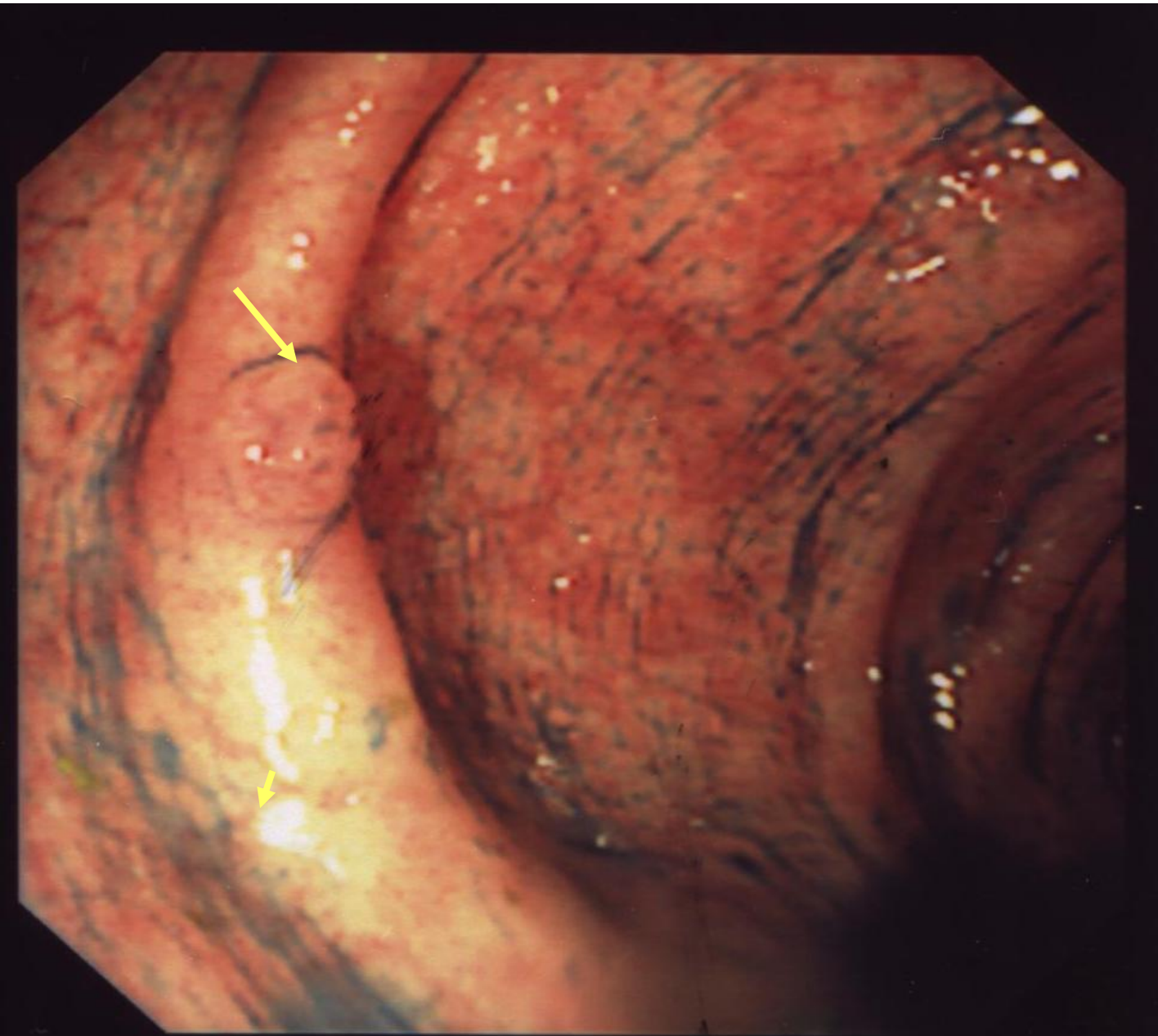
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# Dysmorphic syndromes and FAP

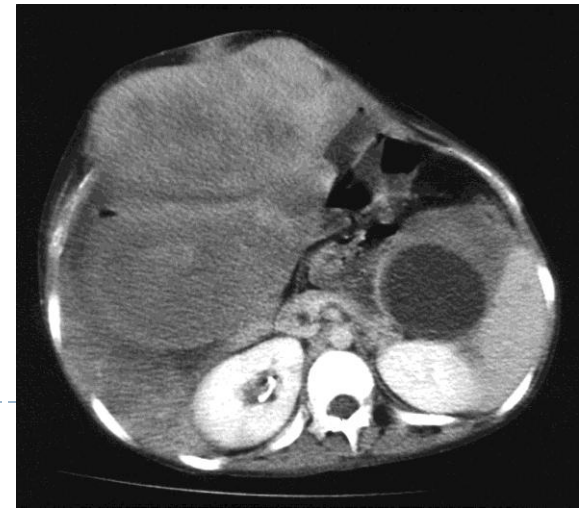
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# Desmoid disease- codon >1400

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# Hepatoblastoma and FAP.

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## **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

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# Modifier genes

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## 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

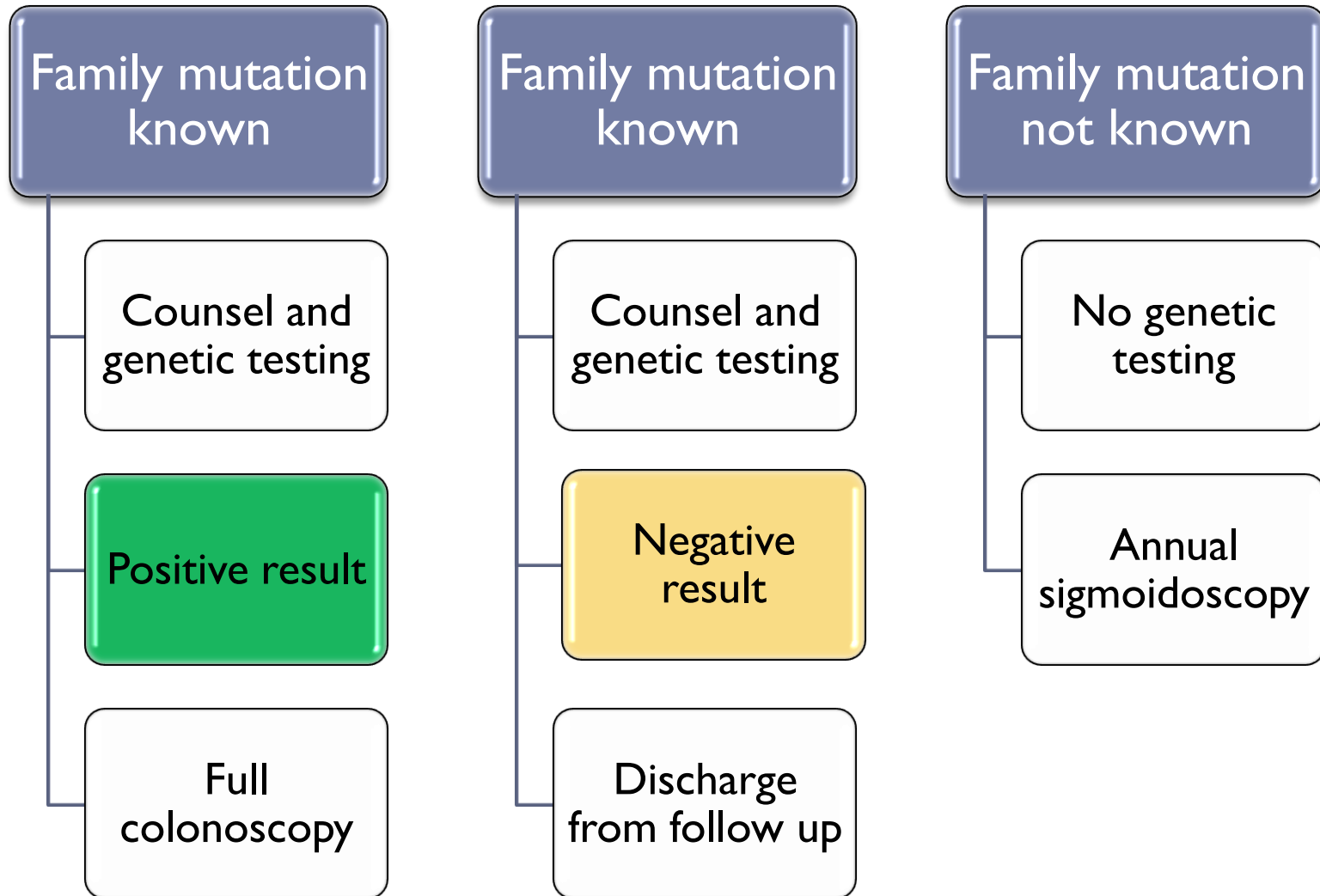
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*Gut* 2002;51:420–423

## Genotype – phenotype correlation

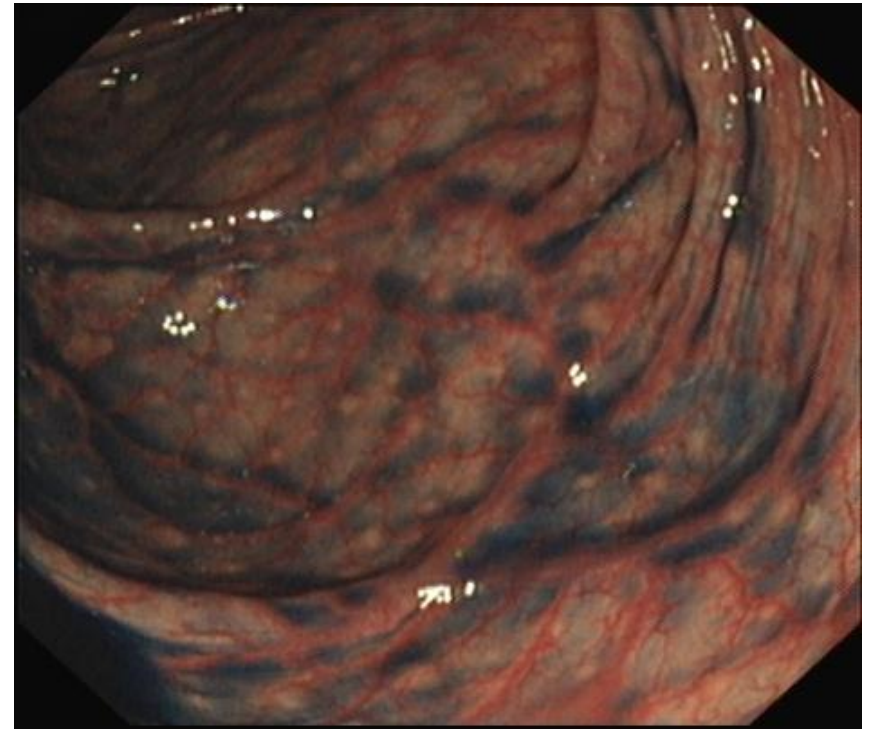
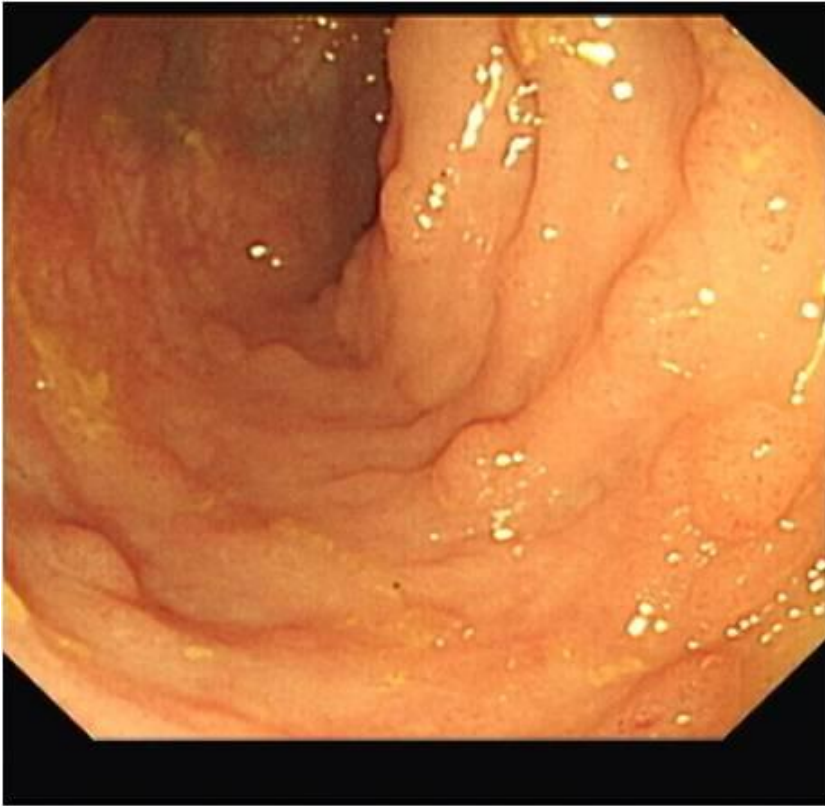
Does the location of the gene mutation impact on clinical care?

# Undergoing genetic testing



# What to do at colonoscopy

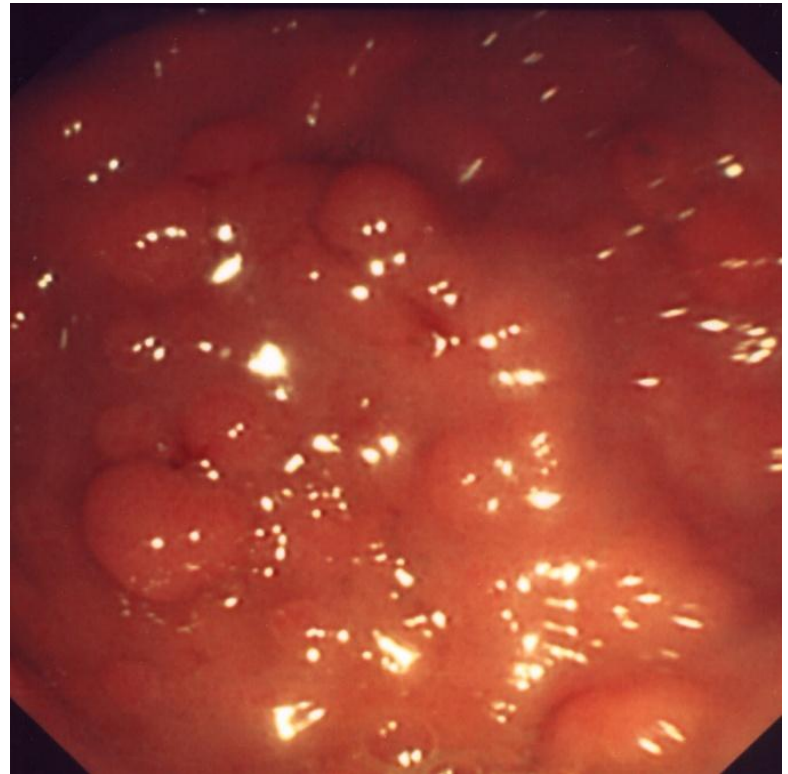
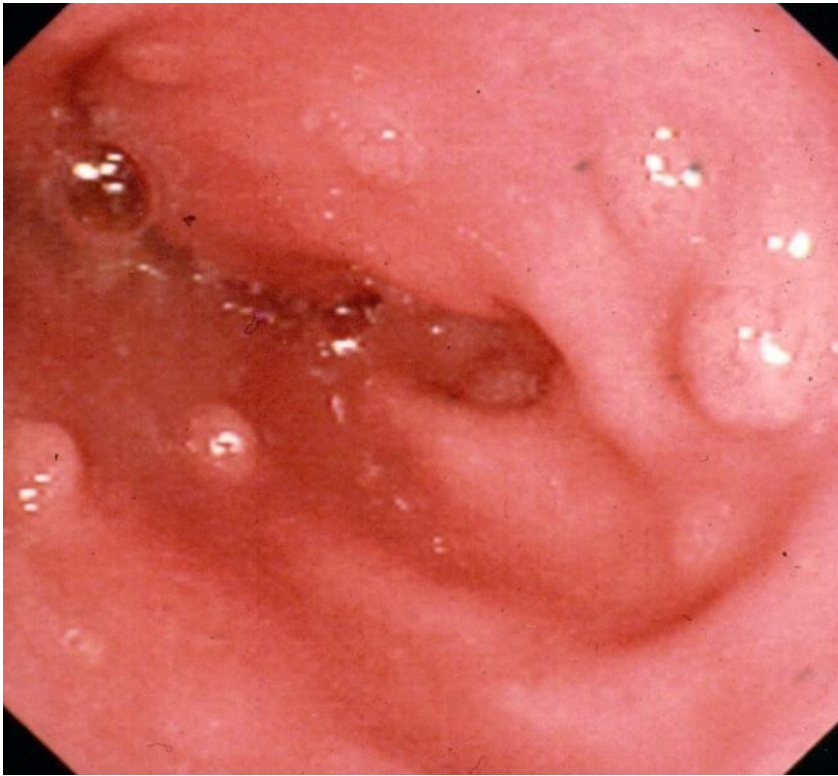
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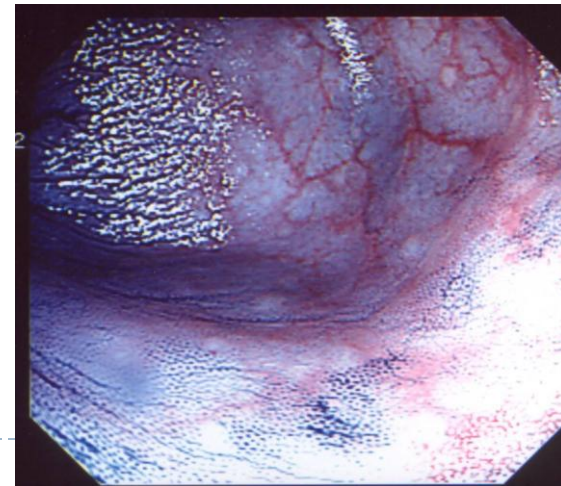
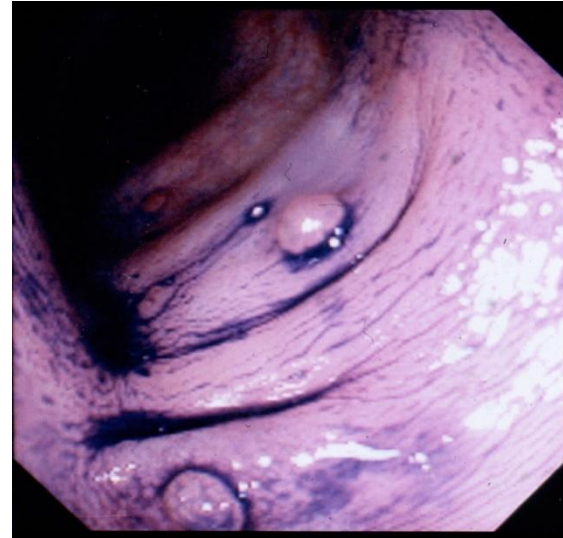
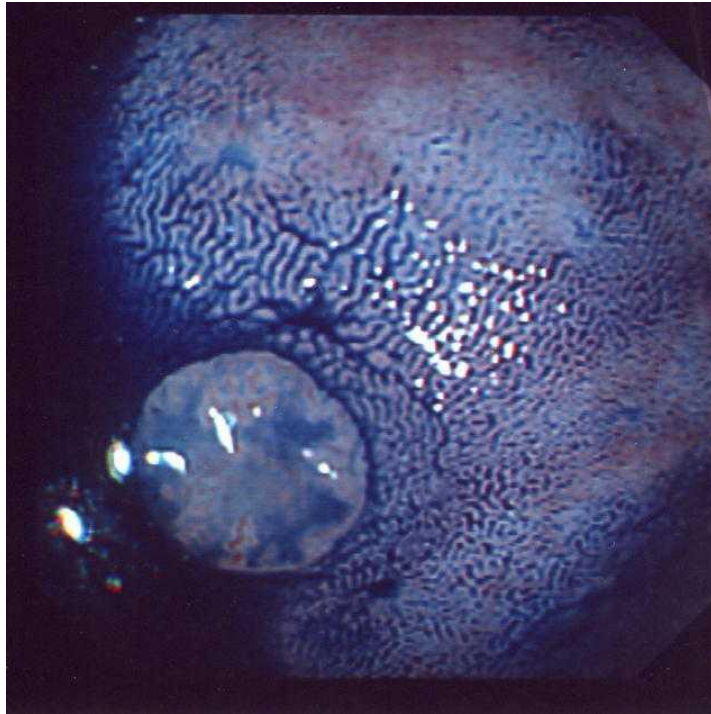
# Assess adenoma burden in the rectum

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# Dye spray in FAP – identifying dysplasia & adenomas

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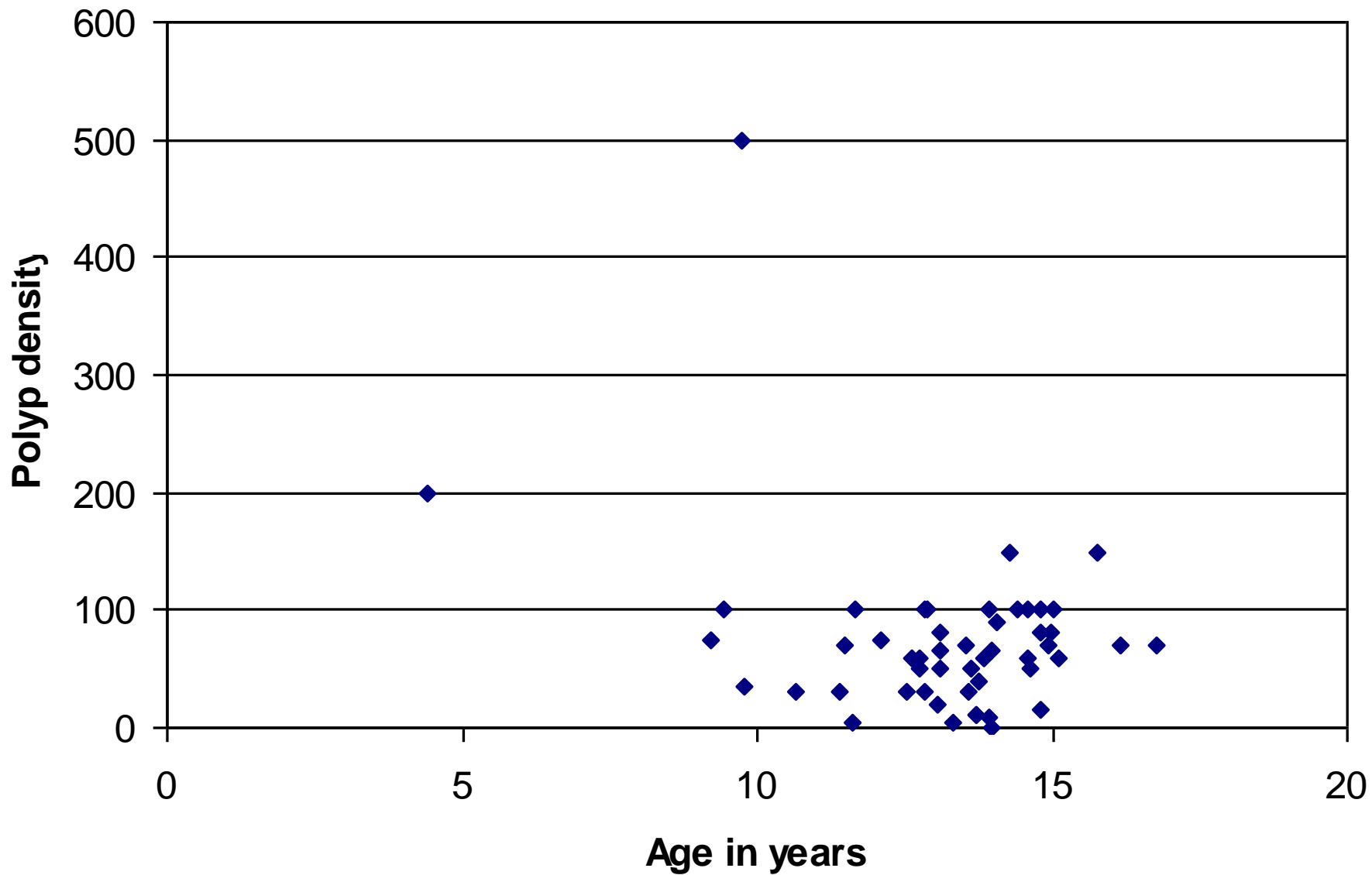


# We underestimate polyp burden

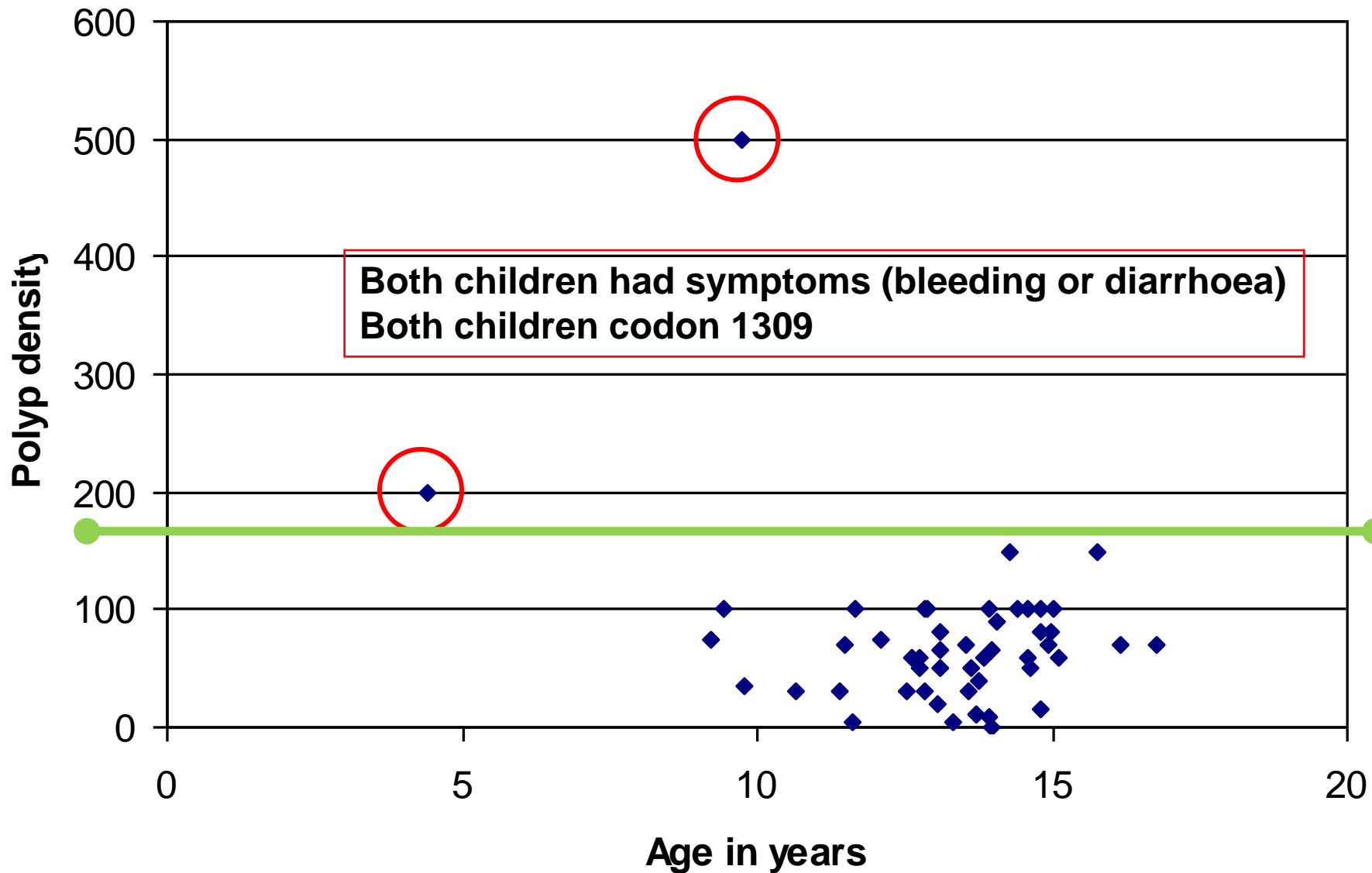
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## Which children had high adenoma burden?



# Which children had high adenoma burden?



# Number of malignancies / degree of dysplasia

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123 children ultimately diagnosed with FAP

**No malignancies identified  $\leq$  16 years**

Histopathology available from 112 colectomy specimens (median age 17 years, range 10-31)

4 children had severe dysplasia

108 mild - moderate dysplasia

**All with significant GI symptoms in adolescence**

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# But when will you develop a cancer?

**Table 3** Proportion of FAP patients with CRC diagnosed at  $\leq 20$  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

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- ▶ 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

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# Why choose an ileo-rectal anastomosis

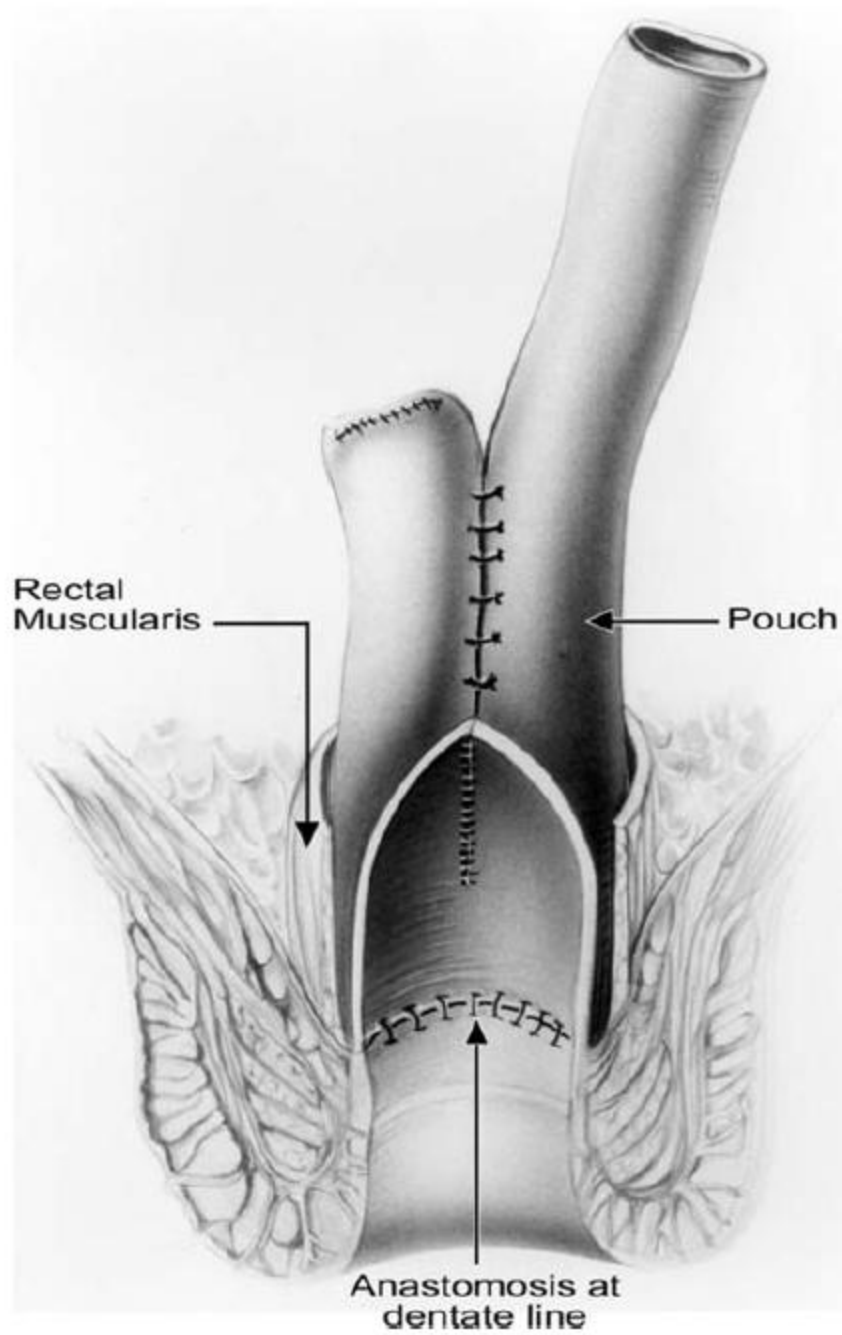
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- ▶ Straightforward and amenable to minimally invasive surgery.
- ▶ Preferable for the more mild phenotype
- ▶ Short hospital stay
- ▶ Excellent continence
- ▶ At risk of subsequent rectal stump polyposis and a lifetime 5% risk of CRC in the rectal stump.
- ▶ At 20 years, 12% risk of CRC
- ▶ 6 monthly rectal stump surveillance
- ▶ Might require conversion to IPAA later

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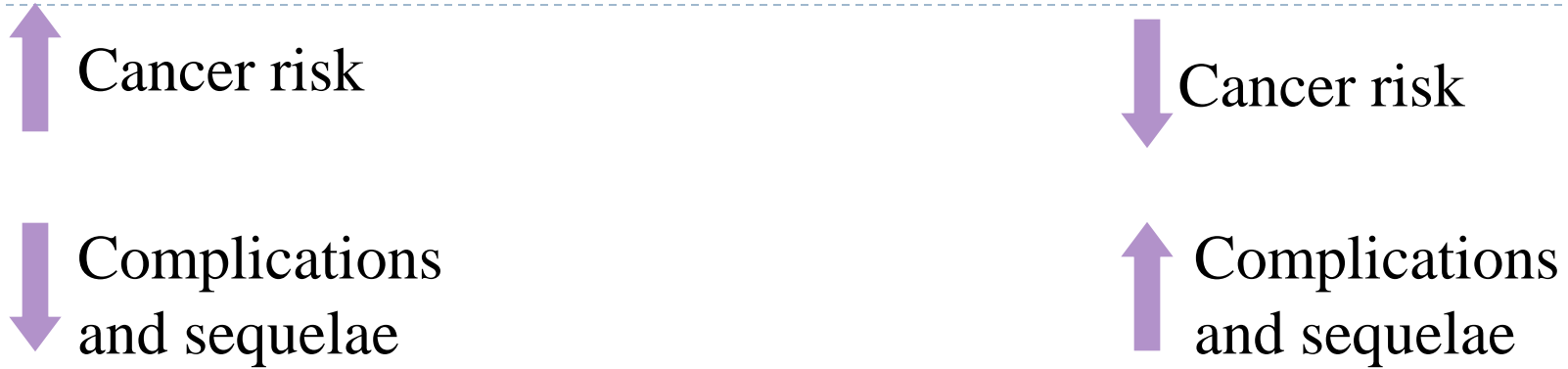


# Why chose an ileo – pouch – anal - anastomosis

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- ▶ 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?



**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 >3cms

# Genetics – implication for choice of surgery

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<b>Mutation</b>	<b>Rectum Preserved</b>	<b>Rectum Removed</b>
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.

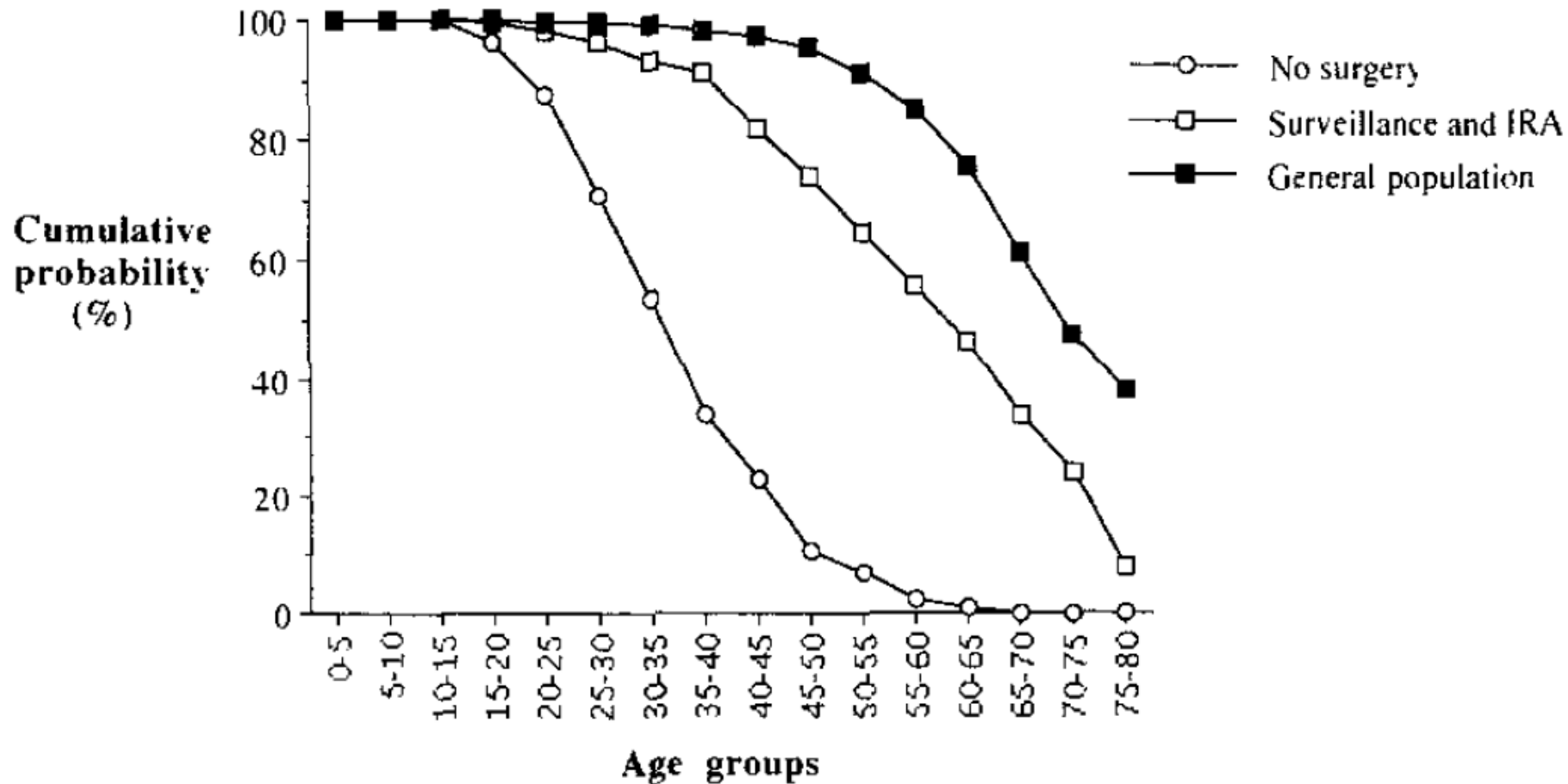
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APC Genotype, Polyp Number, and Surgical Options in Familial Adenomatous Polyposis

The Cleveland Clinic Foundation, Cleveland, Ohio

Annals of Surgery. 227:57-62, 1998.

# Life expectancy after surgery

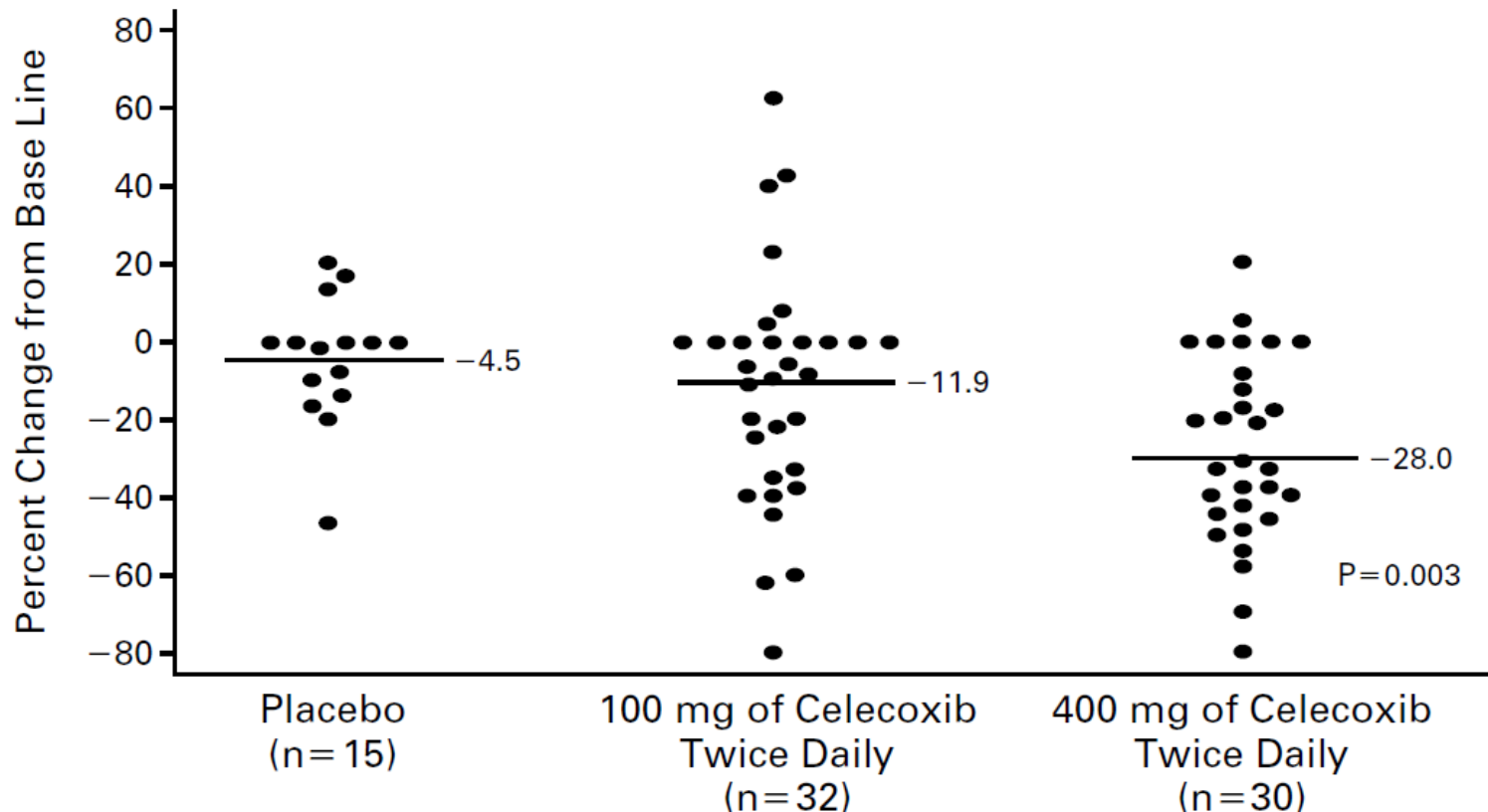




Will the timing of surgery be delayed with use of NSAID?

## 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.



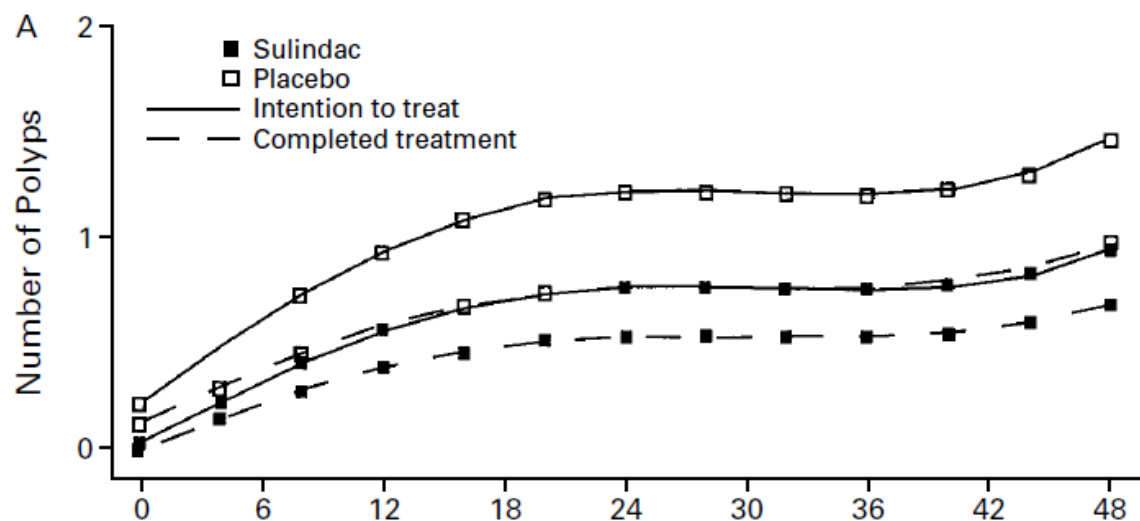
# Adenoma prevention with sulindac

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**

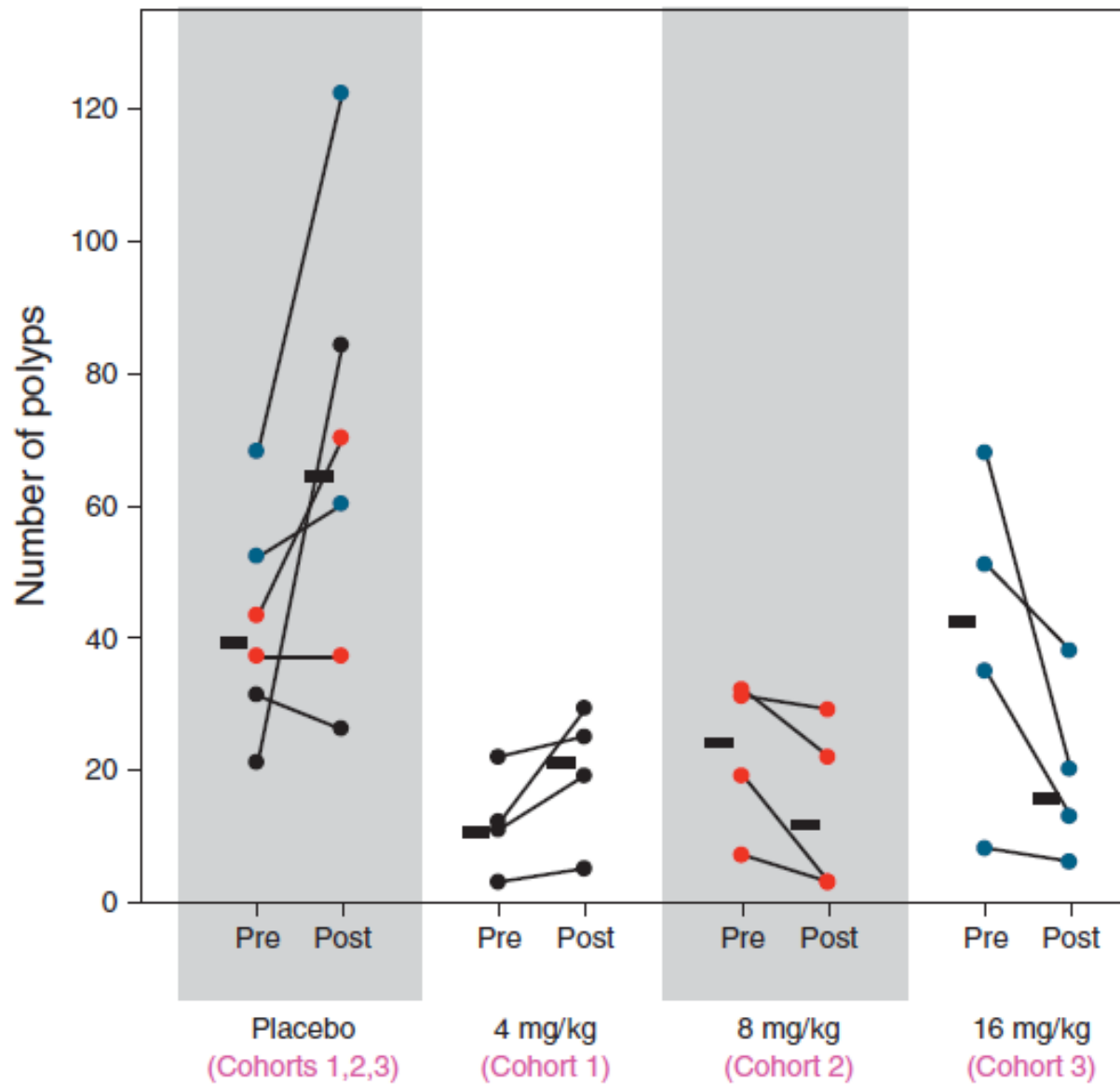


# The Safety and Efficacy of Celecoxib in Children With Familial Adenomatous Polyposis

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

**Table 1.** Celecoxib dose assignments by body weight and cohort

	Cohort 1, <i>n</i> =6 (2:1 drug: placebo)	Cohort 2, <i>n</i> =6 (2:1 drug: placebo)	Cohort 3, <i>n</i> =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

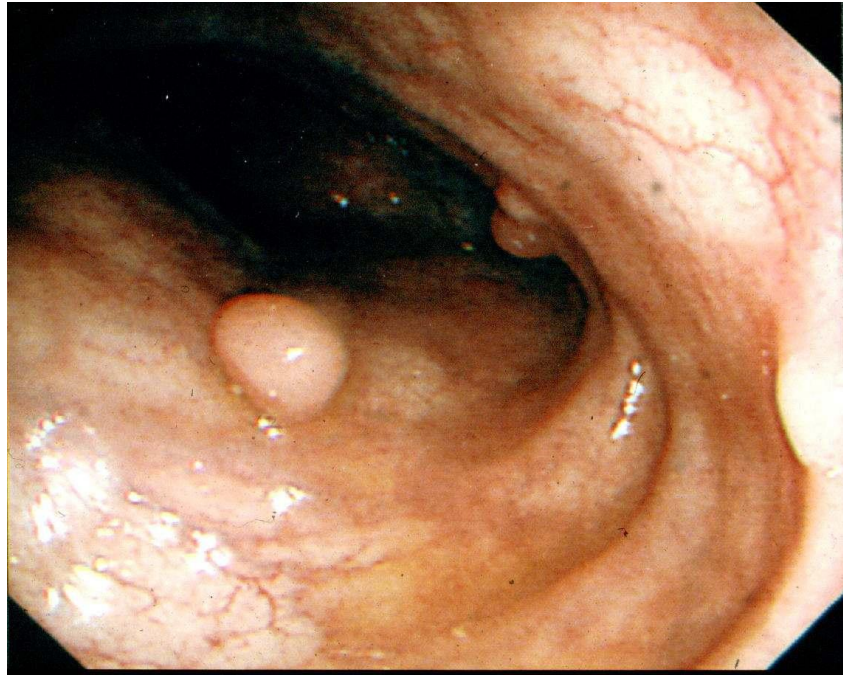


**Figure 2.** Celecoxib dose–response relationship among pediatric patients with familial adenomatous polyposis. The number of polyps at baseline

# Surgical choices for colectomy

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- ▶ 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.

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- ▶ 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**



# Current guidelines

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*Gut* 2008;**57**:704–713.

## Guidelines

### Guidelines for the clinical management of familial adenomatous polyposis (FAP)

H F A Vasen,<sup>1</sup> G Möslin,<sup>2</sup> A Alonso,<sup>3</sup> S Aretz,<sup>4</sup> I Bernstein,<sup>5</sup> L Bertario,<sup>6</sup> I Blanco,<sup>7</sup> S Bülow,<sup>8</sup> J Burn,<sup>9</sup> G Capella,<sup>10</sup> C Colas,<sup>11</sup> C Engel,<sup>12</sup> I Frayling,<sup>13</sup> W Friedl,<sup>4</sup> F J Hes,<sup>14</sup> S Hodgson,<sup>15</sup> H Järvinen,<sup>16</sup> J-P Mecklin,<sup>17</sup> P Møller,<sup>18</sup> T Myrhøi,<sup>5</sup> F M Nagengast,<sup>19</sup> Y Parc,<sup>20</sup> R Phillips,<sup>21</sup> S K Clark,<sup>21</sup> M Ponz de Leon,<sup>22</sup> L Renkonen-Sinisalo,<sup>16</sup>

# Conclusion to screening in FAP

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  - ▶ Surveillance of rectum
  - ▶ Not suitable if  $>20$  rectal adenomas,  $>1000$  colonic adenomas, or rectal polyp  $>3$ cms.

# Thank you

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## UK Polyposis team

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

## WCPGHAN invitation

