Hamartomatous Polyposes

31st European Congress of Pathology

Digestive Diseases-Rodger Haggitt Gastrointestinal Pathology Society:

Joint Session

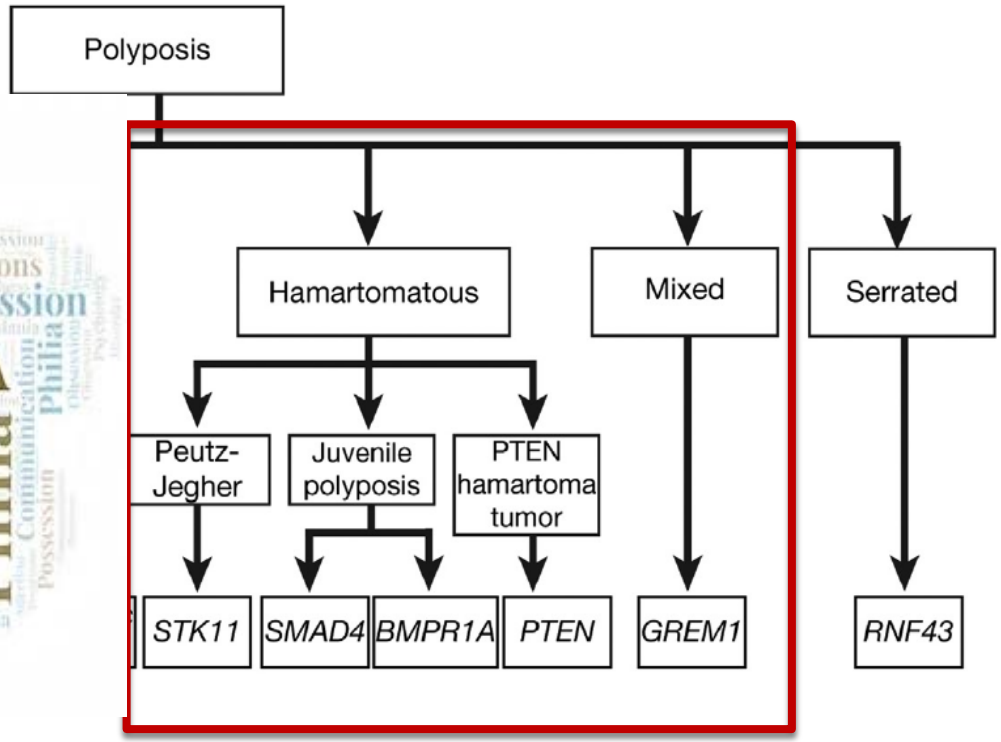
September 9th , 2019

Professor Kieran Sheahan

Pathology Dept. & Centre for Colorectal Disease

St Vincent's University Hospital

University College Dublin, Ireland



Recent Discoveries in the Genetics of Familial Colorectal Cancer and Polyposis

Laura Valle

Clinical Gastroenterology and Hepatology 2017;15:809–819

Overgrowth of cells & tissues that are native to the anatomic location (Greek = mistake/defect)

HAMARTOMATOUS POLYPOSES INTRODUCTION

1. RARE

2. OUR CENTRE HAS AN INTEREST IN FAMILIAL CRC , HOWEVER THERE ARE ONLY A SMALL NUMBER OF THESE FAMILIES IN THE CLINICS

3. SPAN THE PAEDIATRIC & ADULT RANGE

4. THESE POLYPS CAN POSE DIAGNOSTIC DIFFICULTY . INTER-OBSERVER REPRODUCIBILITY IS NOT PERFECT

5. THERE IS A DIFFERENTIAL DIAGNOSIS WITH OTHER SYNDROMIC POLYPS & WITH SPORADIC POLYPS

6. AN OVERLAP OF POLYPS OCCURS BETWEEN SYNDROMES (PTEN, JPS)

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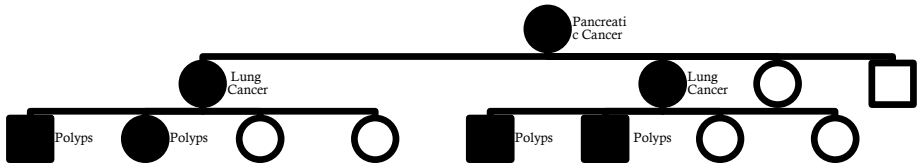
Clinical History

- 21 year old male
- Peutz-Jeghers syndrome (PJS) with confirmed whole deletion of STK11
- Multiple episodes of intussusception in the previous 4 years



- Polyposis, gastric, small intestinal & colorectal
- On surveillance
- Presented with small bowel obstruction (January 2018), resection
- Firm 5cm lesion felt proximally at duodenal-jejunal flexure, resected in May 2018

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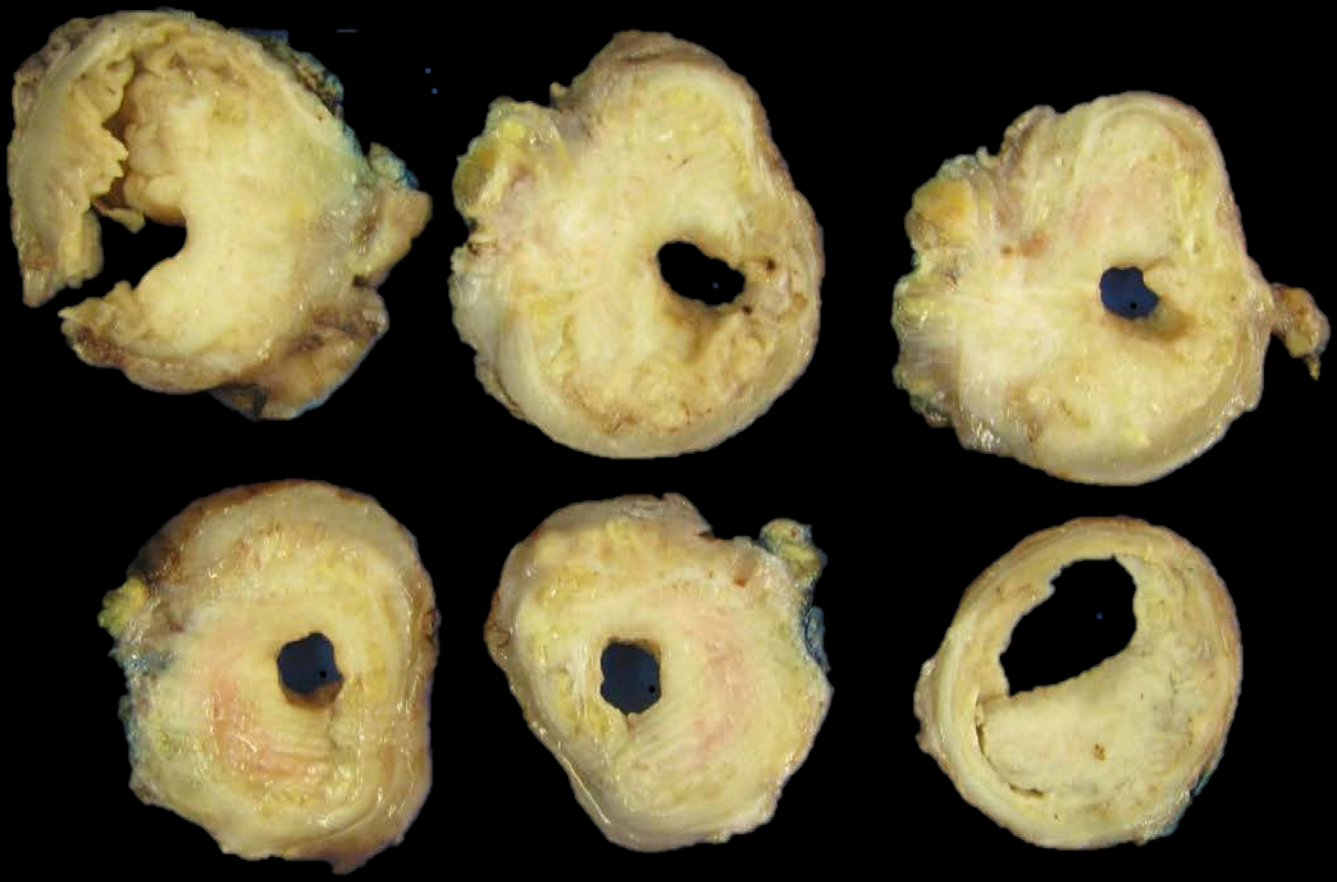
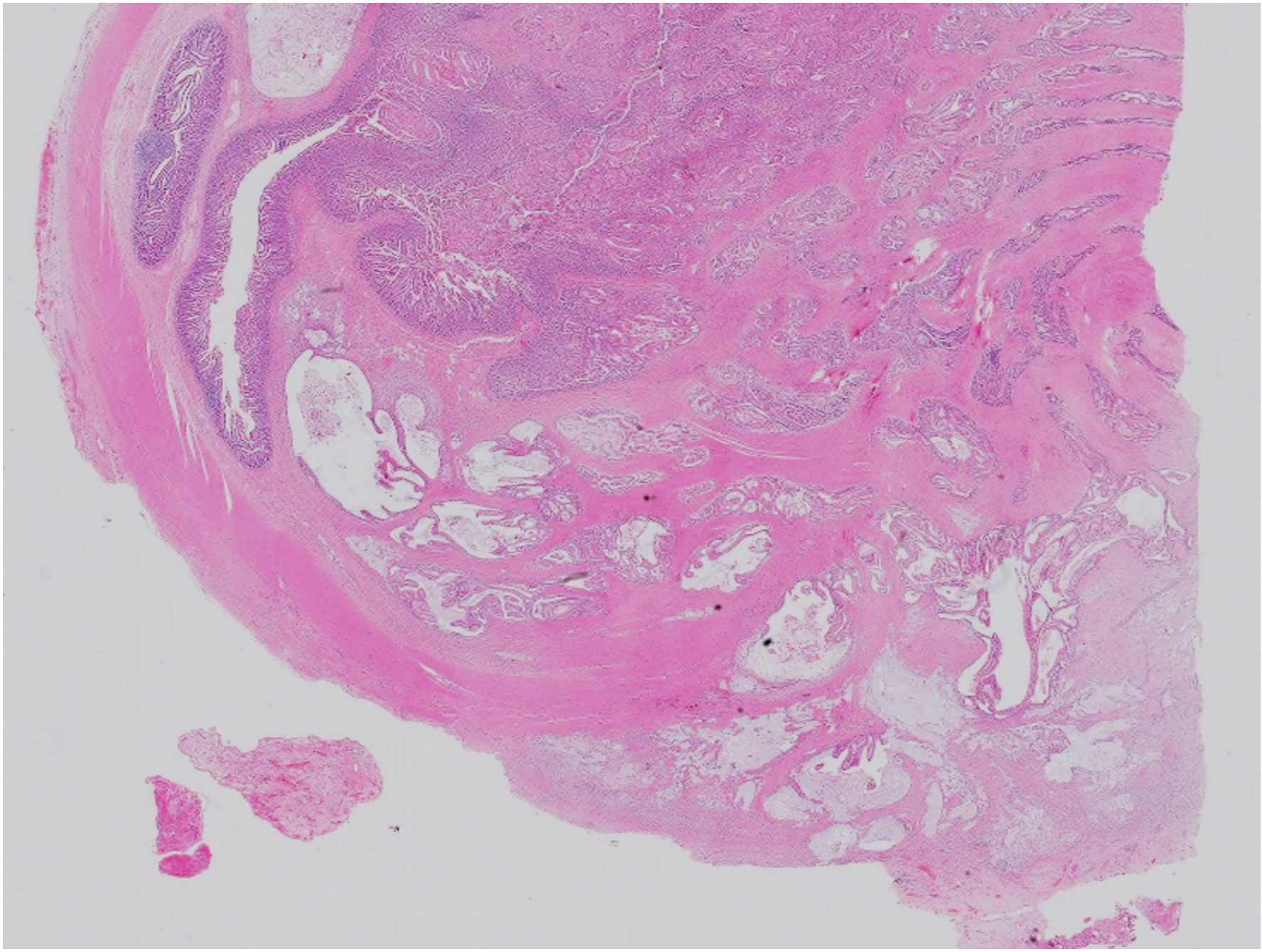
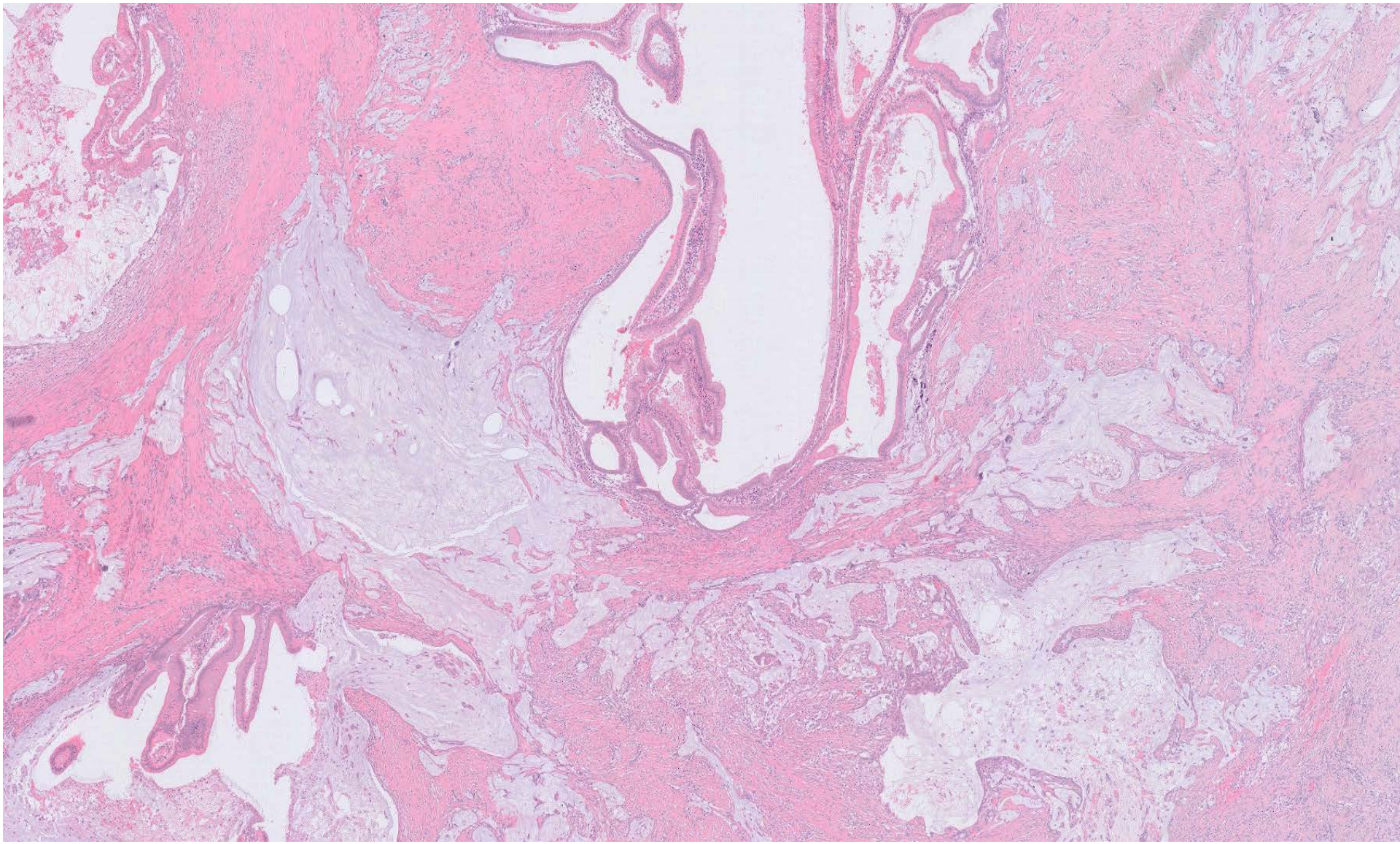
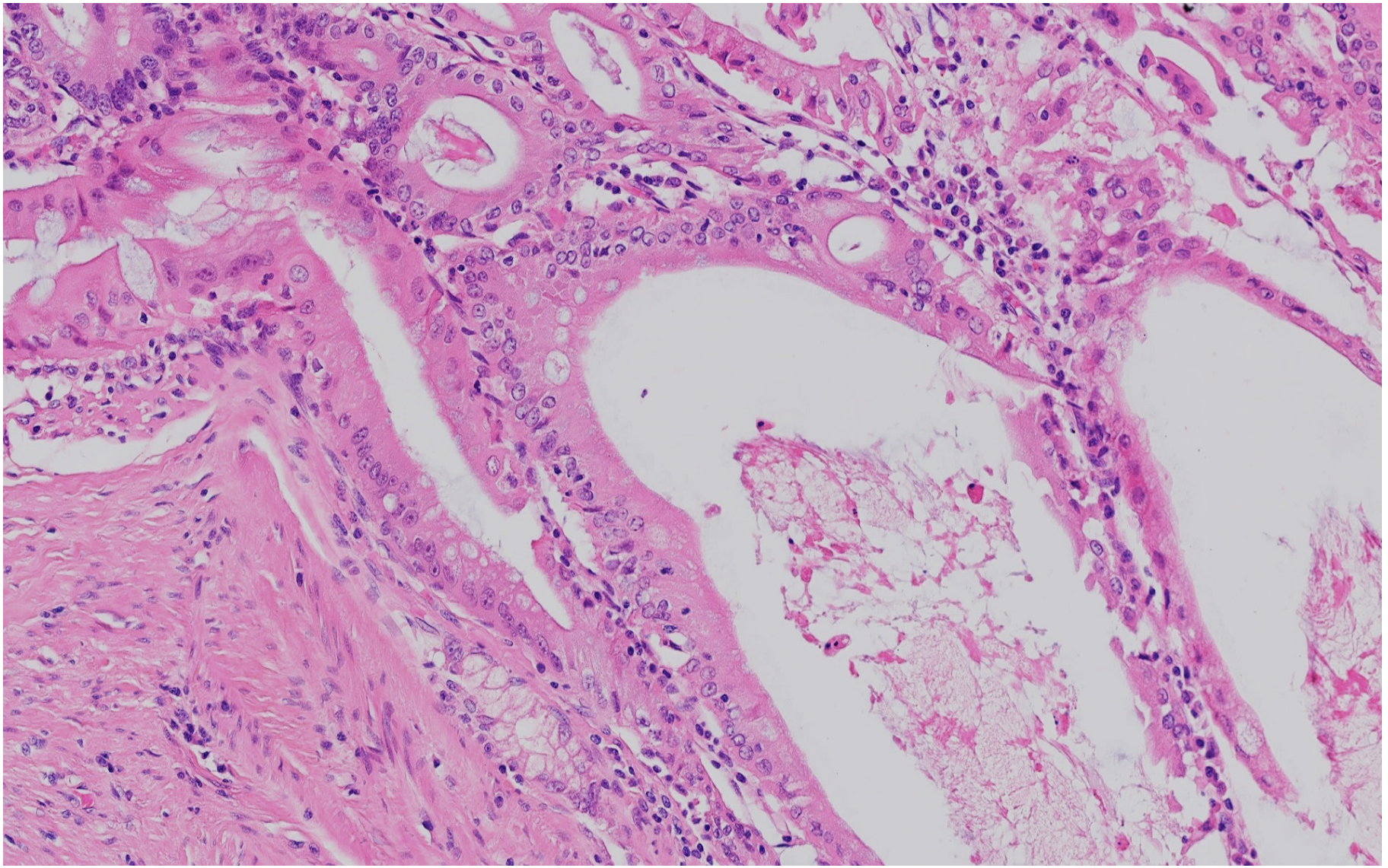
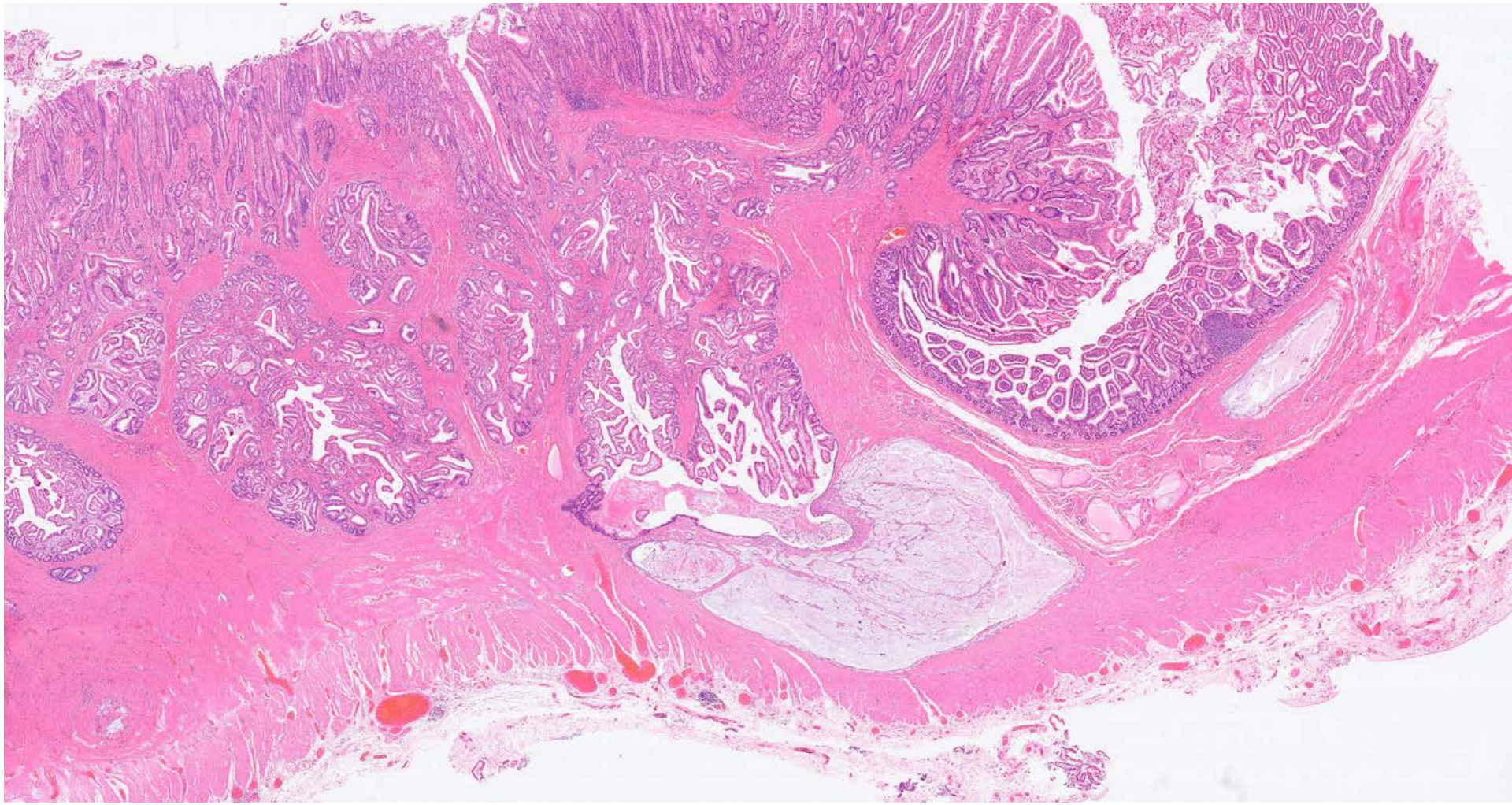








Previous resection
January 2018



What would you do next ?
? DIAGNOSIS

Differential Diagnosis

- Adenocarcinoma
- Epithelial Misplacement in a PJ Polyp

Investigations

- IHC
- Literature Review
- Second/expert opinion

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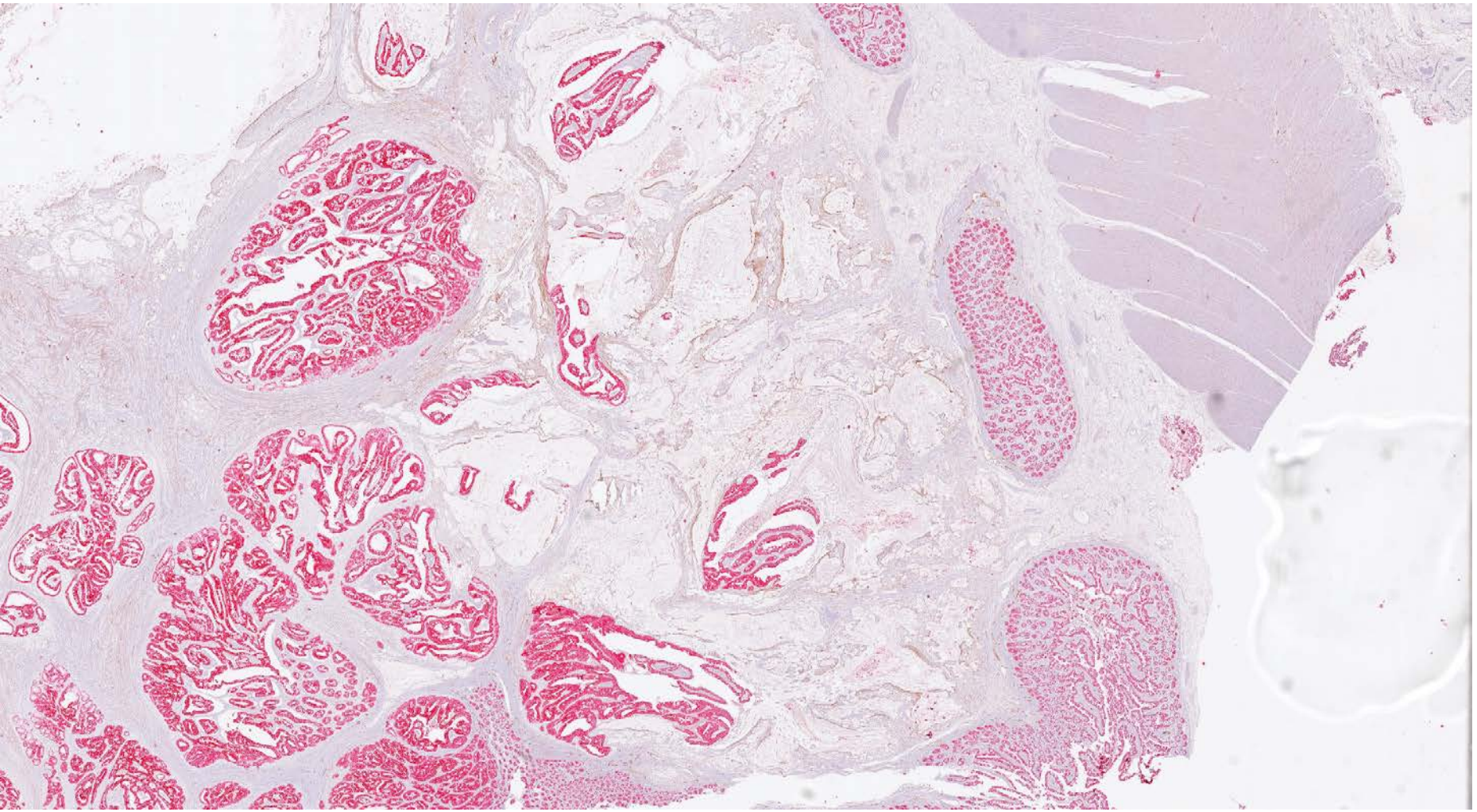
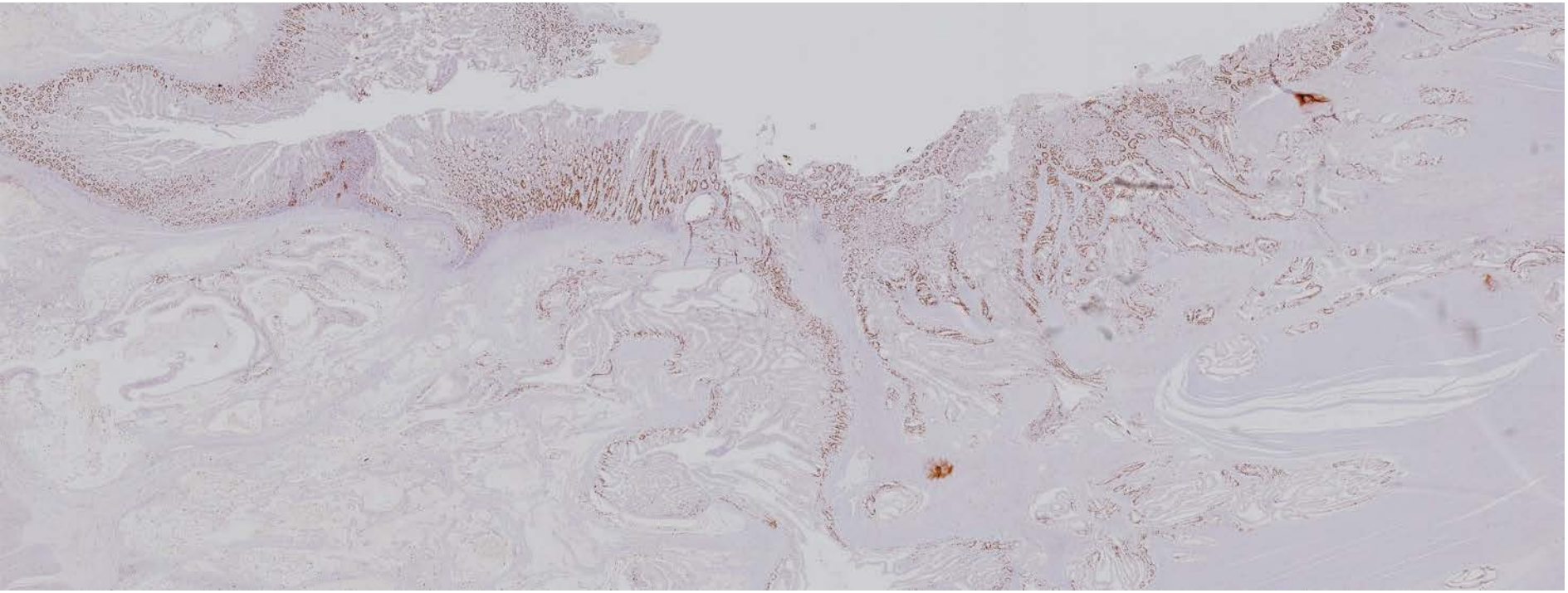
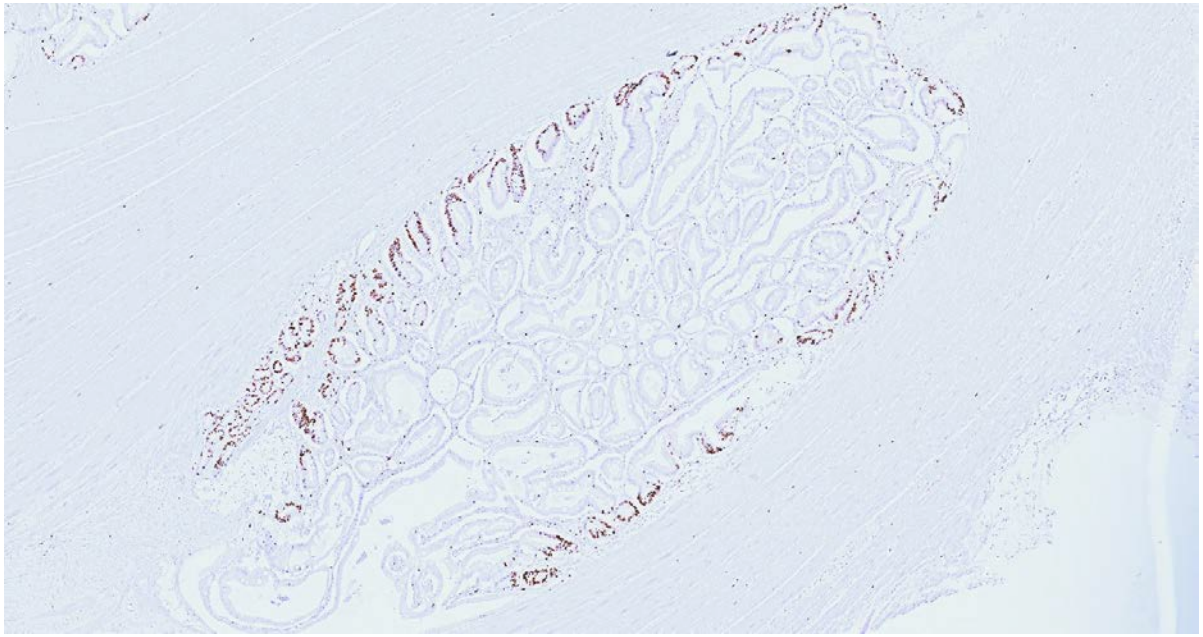
Dual pan cytokeratin/D2-40 IHC







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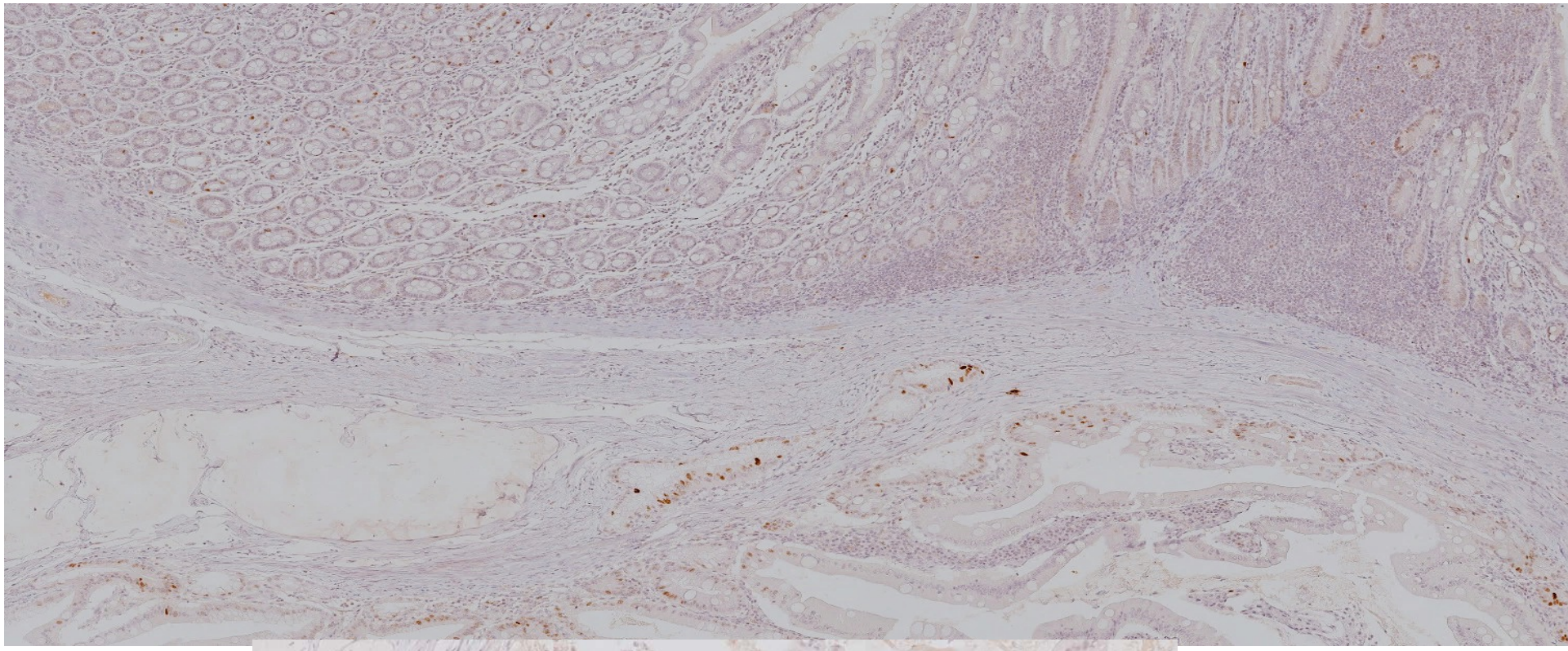

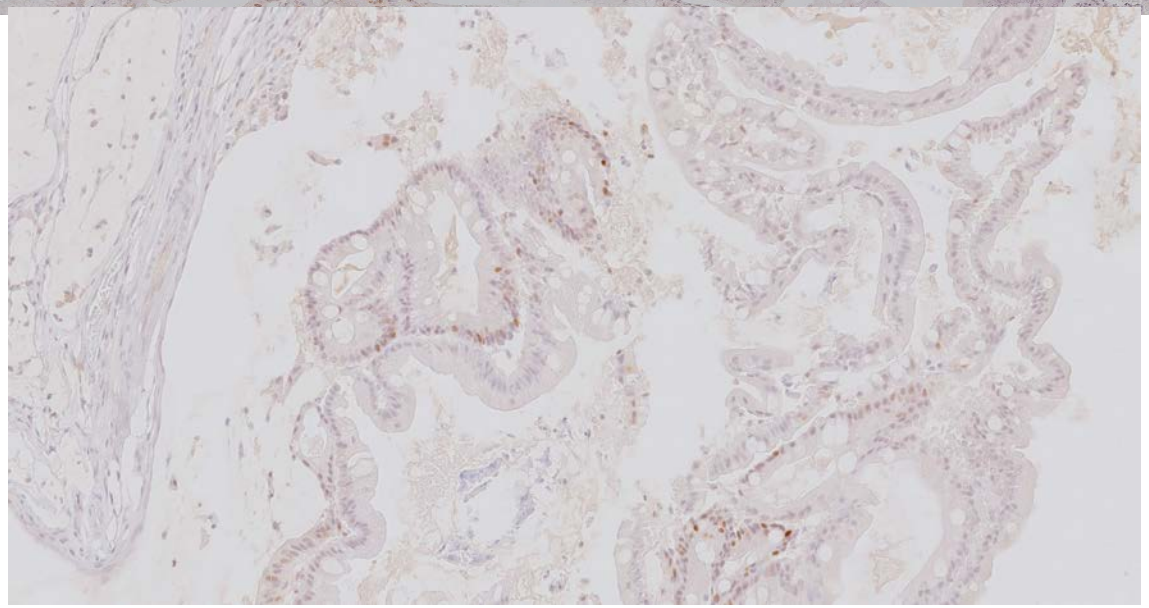

p53 = wild type pattern

The American Journal of Surgical Pathology *11(10): 743–749, 1987*

Epithelial Misplacement in Peutz-Jeghers Polyps

A Diagnostic Pitfall

N.A. Shepherd, M.B., B.S., M.R.C.Path, H.J.R. Bussey, B.Sc., Ph.D., and J.R. Jass, B.Sc., M.D., M.R.C.Path

TABLE 1. *Epithelial misplacement in all 40 Peutz-Jeghers patients*

Site	Polyps examined	Epithelial misplacement: No. polyps	SM[a] only	MP[b] only	Serosa
Stomach	88	0	0	0	0
Duodenum	38	1	0	1	0
Jejunum and ileum	202	29	11	8	10
Colon and rectum	163	0	0	0	0
Totals	491	30	11	9	10

[a] submucosa.
[b] muscularis propria.

Am J Surg Pathol, Vol. 11, No. 10, 1987

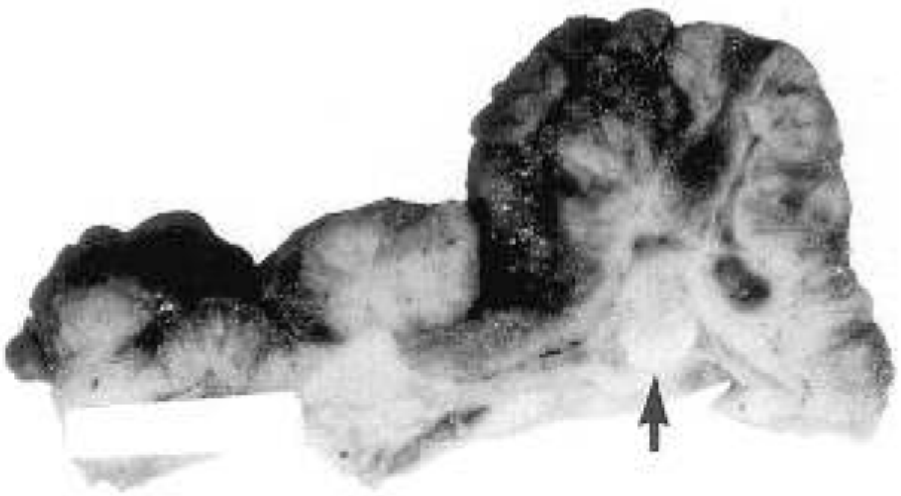

FIG. 1. Epithelial misplacement in a jejunal polyp, 11.2 cm in diameter, in a 17-year-old male patient with Peutz-Jeghers syndrome. There is a mucinous cyst in the serosa (arrow), with retraction of the intestinal wall into the base of the polyp.

Bottom line :

Misplacement only seen in small intestinal polyps with a prevalence rate of 10%

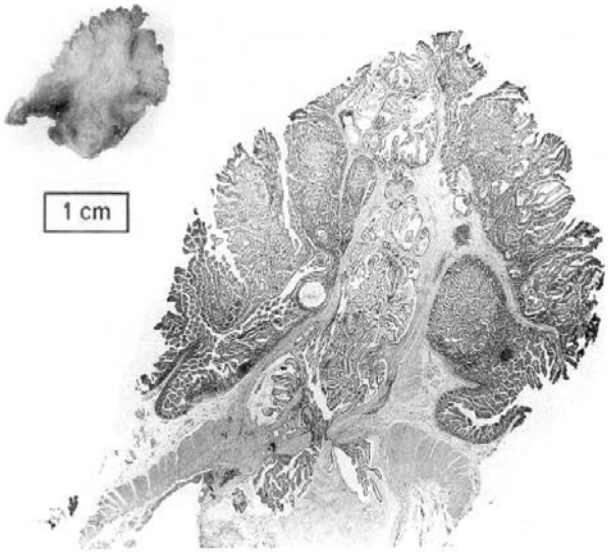

FIG. 2. A jejunal polyp from an 18-year-old female patient with Peutz-Jeghers syndrome. Epithelial misplacement is present in all layers of the bowel wall. A villous configuration is easily discerned. **Inset:** Macroscopic appearance of the polyp. It measures 1.6 cm in diameter.

Neil Shepherd

I do not think any pathologist could entirely rule out that this represents very well differentiated mucinous adenocarcinoma. In making this diagnosis one is making a dual diagnosis of epithelial misplacement & cancer which in this instance lacks logic.

ON THE BALANCE OF PROBABILITIES, I THINK THIS IS ALL EPITHELIAL MISPLACEMENT

Outcome

- Patient alive & well, September 2019 (16 months)

Whole exome sequencing is being performed to compare this lesion with another uncomplicated PJ polyp in the same patient. Analysis is 'ongoing'.

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Peutz-Jeghers Syndrome

Dr. Johannes Peutz, 1951

Dr. Harold M Jeghers

(Uit het R. K. Ziekenhuis, Westeinde, den Haag.)

OVER EEN ZEER MERKWAARDIGE, GECOMBINEERDE FAMILIAIRE POLYPOSIS VAN DE SLIJMVLIEZEN VAN DEN TRACTUS INTESTINALIS MET DIE VAN DE NEUSKEELHOLTE EN GEPAARD MET EIGENAARDIGE PIGMENTATIES VAN HUID- EN SLIJMVLIEZEN.

DOOR

J. L. A. PEUTZ,

1e geneesheer van het ziekenhuis.

Peutz, J. L. A. : Very remarkable case of familial polyposis of mucous membrane of intestinal tract & nasopharynx accompanied by peculiar pigmentations of skin and mucous membrane. (Dutch). Nederl. Maandschr. Geneesk. 1921 10: 134-146

GENERALIZED INTESTINAL POLYPOSIS AND MELANIN SPOTS OF THE ORAL MUCOSA, LIPS AND DIGITS*

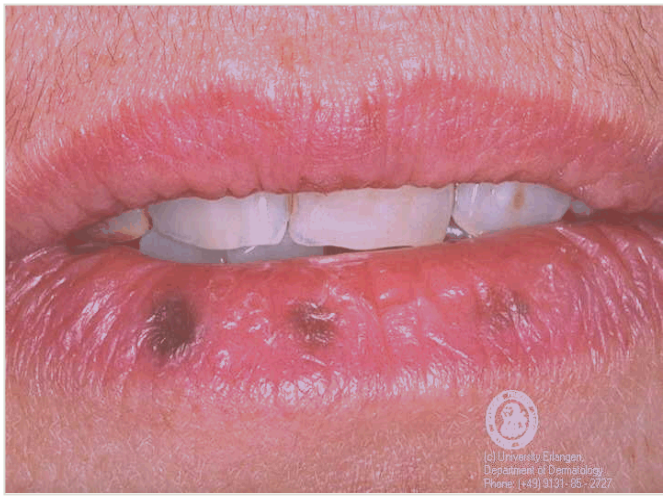
A Syndrome of Diagnostic Significance

Harold Jeghers, M.D.,† Victor A. McKusick, M.D.,‡ and Kermit H. Katz, M.D.§

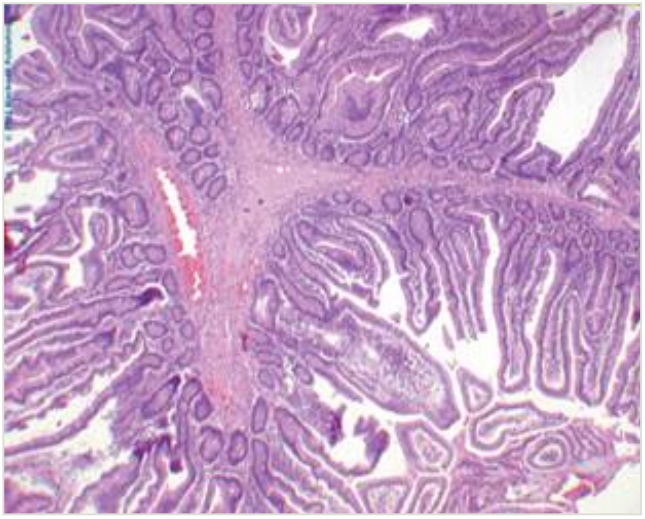
WASHINGTON, D. C., BALTIMORE, MARYLAND, AND BOSTON, MASSACHUSETTS

Jeghers H, McKusick VA,; Katz, KH : Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits. N Eng J Med. 1949 Dec 22;241(25):993

Peutz-Jeghers syndrome (PJS)



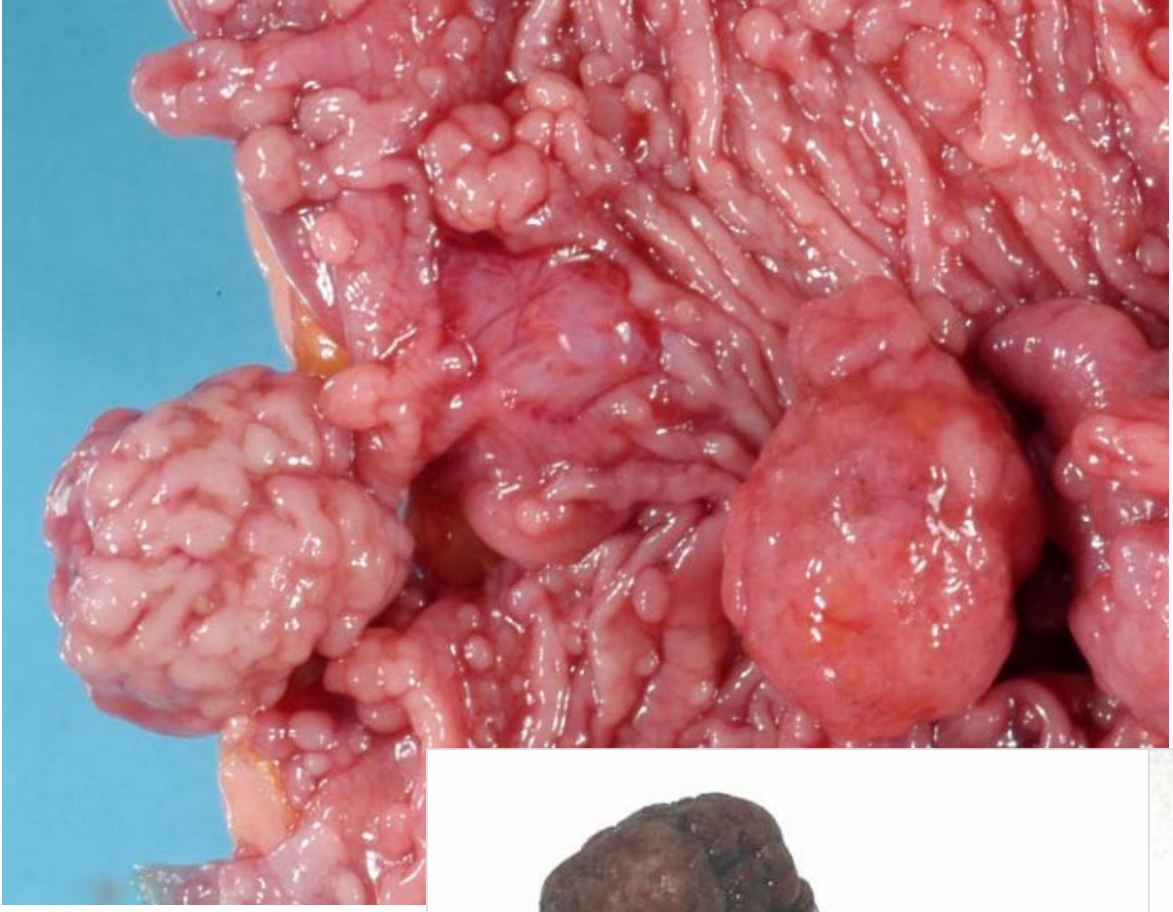
- Autosomal dominant inheritance (complete penetrance) 1: 80,000
- Polyps can occur throughout GI, but small intestine is main site of predilection
- Gene STK11/ LKB1 (p53-mediated apoptosis) encoding a serine/threonine kinase on chromosome 19p13.3 (cancer risk does not vary by type of mutation)
- 40% lifetime risk CRC after the age of 50.
- 95% risk of developing malignancy by age 65.
  - Carcinomas of pancreas (36%), stomach (29%), small intestine (13%),
  - Breast (54%), ovary (21%), endometrium (9%)
  - Lung cancer (15%).



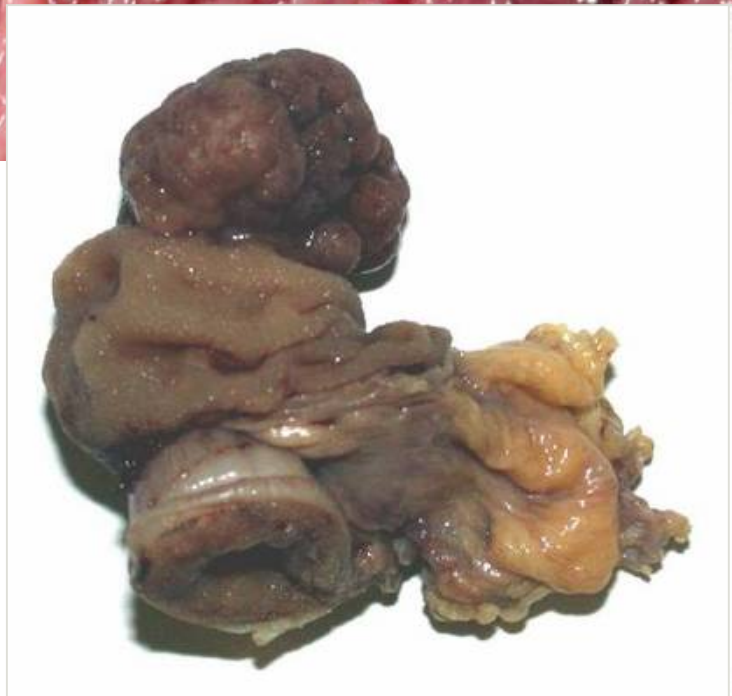
Clinical presentation

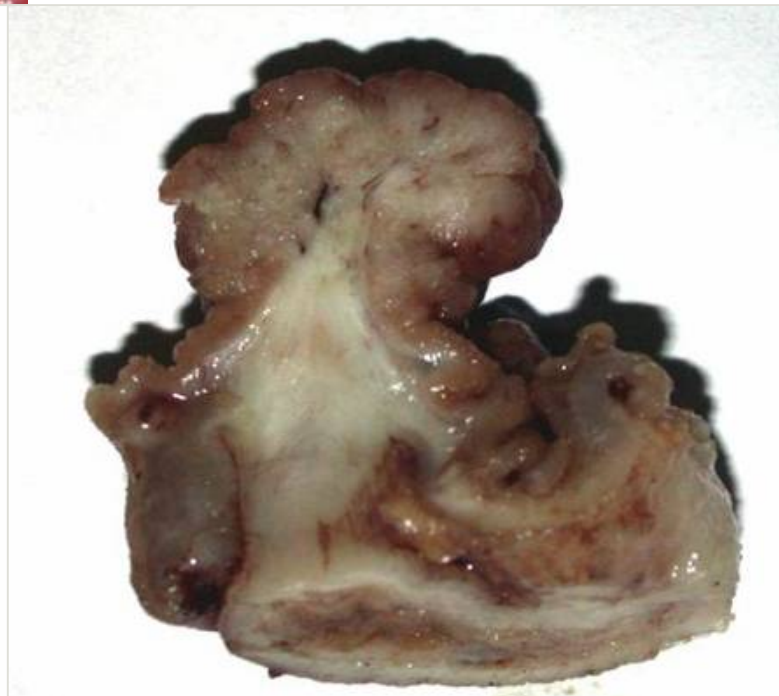
- Surgical emergency
- Childhood intussusception
- Obstruction
- Bleeding PR
- Volvulus

- Non-specific abdominal pain



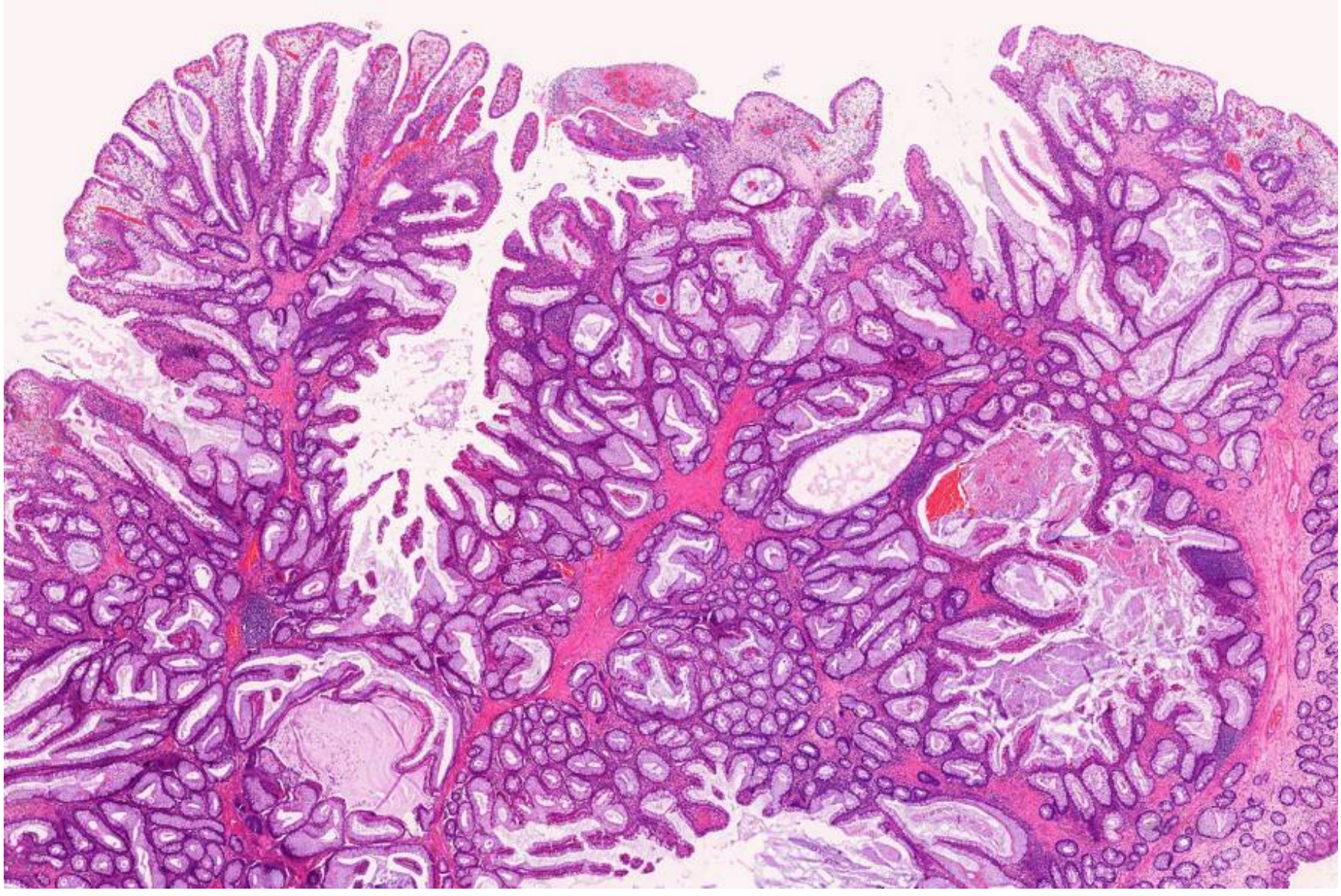
Peutz-Jeghers polyps





Peutz-Jeghers polyps

Frond-like pattern – arborization with smooth muscle
Cystic gland dilatation +/- into deep layers
Can show dysplasia but rare



DIAGNOSIS

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]

In a single individual, a clinical diagnosis of PJS may be made when any **ONE** of the following is present[16 17]:

1. Two or more histologically confirmed PJ polyps
2. Any number of PJ polyps detected in one individual who has a family history of PJS in close relative(s)
3. Characteristic mucocutaneous pigmentation in an individual who has a family history of PJS in close relative(s)
4. Any number of PJ polyps in an individual who also has characteristic mucocutaneous pigmentation.

Gut 2010;**59**:975–986. doi:10.1136/gut.2009.198499

DDX

- Juvenile Polyposis
- Hereditary Mixed Polyposis

Surveillance regimes are intensive
Main aim : reduce intussusception in childhood & remove polyp

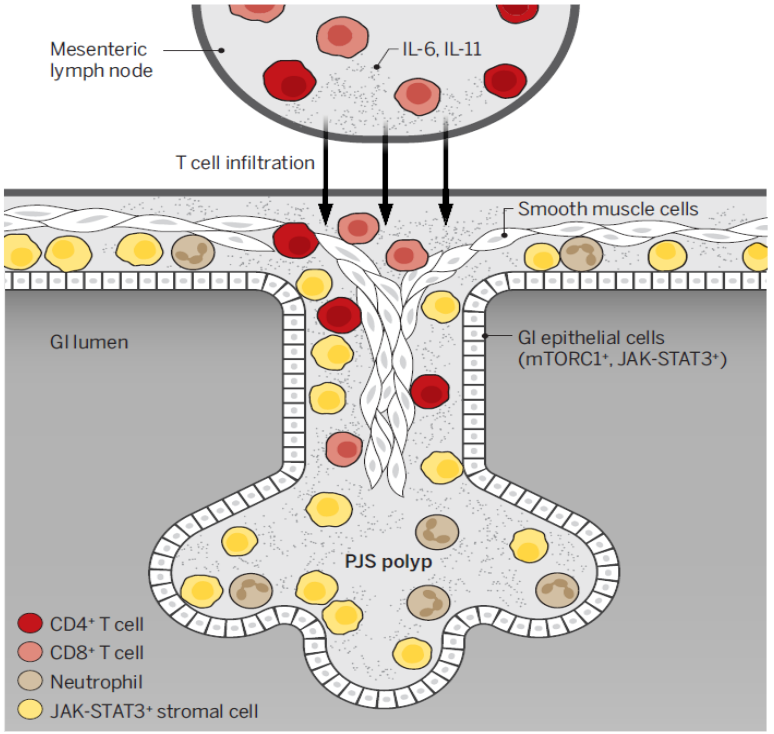
GUT INFLAMMATION

LKB1 deficiency in T cells promotes the development of gastrointestinal polyposis

M. C. Poffenberger[1,2], A. Metcalfe-Roach[1], E. Aguilar[1,2], J. Chen[1,2], B. E. Hsu[1,3], A. H. Wong[1,2], R. M. Johnson[1,4], B. Flynn[1,2], B. Samborska[1], E. H. Ma[1,2], S.-P. G L. Tonelli[1], L. Devorkin[6], P. Kim[6], A. Hall[1,7], S. Izreig[1,2], E. Loginicheva[8], N. Beauchemin[1,9], P. M. Siegel[1,3], M. N. Artyomov[8,10], J. J. Lum[6,11], G. Zogopoul J. Blagih[1,2], R. G. Jones[1,2,12]*

Deregulation of the tumor microenvironment in polyposis

Heterozygous loss of LKB1 expression in T cells or stromal cells is sufficient to induce proinflammatory cytokines, including IL-6 and IL-11, which recruit neutrophils and other inflammatory immune cells. This inflammatory microenvironment drives JAK-STAT3 signaling in stromal and epithelial cells, concurrent with epithelial mTORC1 activation, and is sufficient to induce polyp growth.



Potential for therapy

TUMORIGENESIS

Inflamed T cells and stroma drive gut tumors

Loss of a tumor suppressor in T cells and stromal cells drives gastrointestinal polyp growth

Pablo E. Hollstein *and* Reuben J. Shaw

an expanded stromal compartment, and

Juvenile Polyposis

- A familial cancer syndrome with autosomal dominant trait
- The average onset is 18 years.
- Approximately half of cases arise in patients with no family history
  (de novo)
- Germline mutations involve the TGF-β signal transduction pathway
  - SMAD-4 gene on 18q21.1 (40%)
  - BMPR1A on 10q22.3 (40%)

Juvenile Polyposis

- Affects 1:100,000
- 5 - 200 colorectal polyps
- Congenital anomalies in 15% (macrocephaly & dystonia)
- Significant risk of CRC
  - From around 20y and increases in the 4th decade of life
  - Lifetime risk of CRC is up to 68% by age 60
  - Gastric cancer 15–21%
  - Small intestinal carcinoma 10%
- Two groups
  - JPS (pure)
  - JPS + other features
    - Hereditary haemorrhagic telangiectasia (HHT) or congenital conditions

Juvenile Polyposis

Diagnostic criteria:

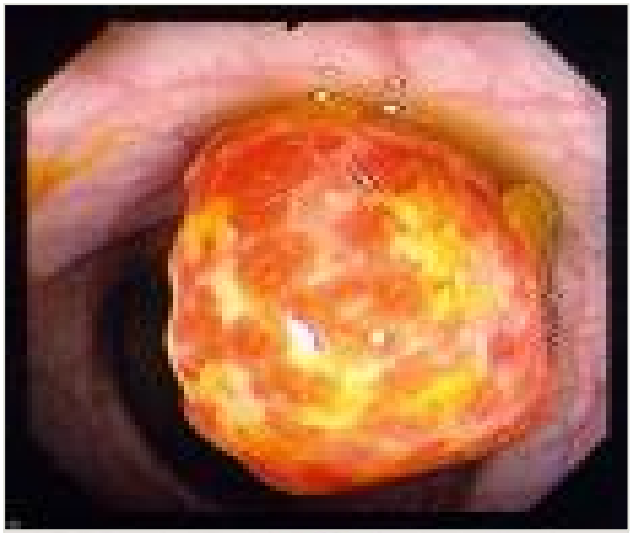
3-5 juvenile polyps in colorectum

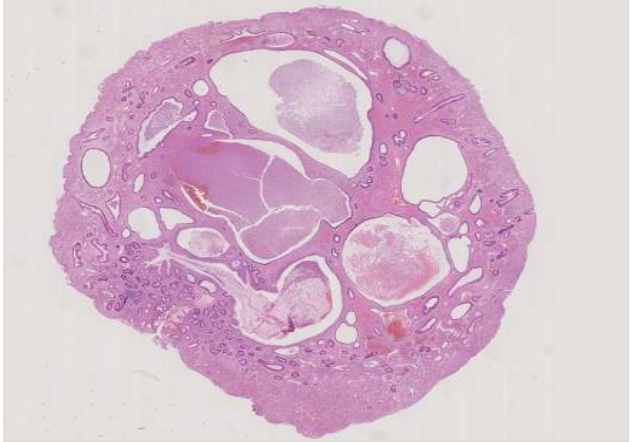
or

juvenile polyps throughout GI tract

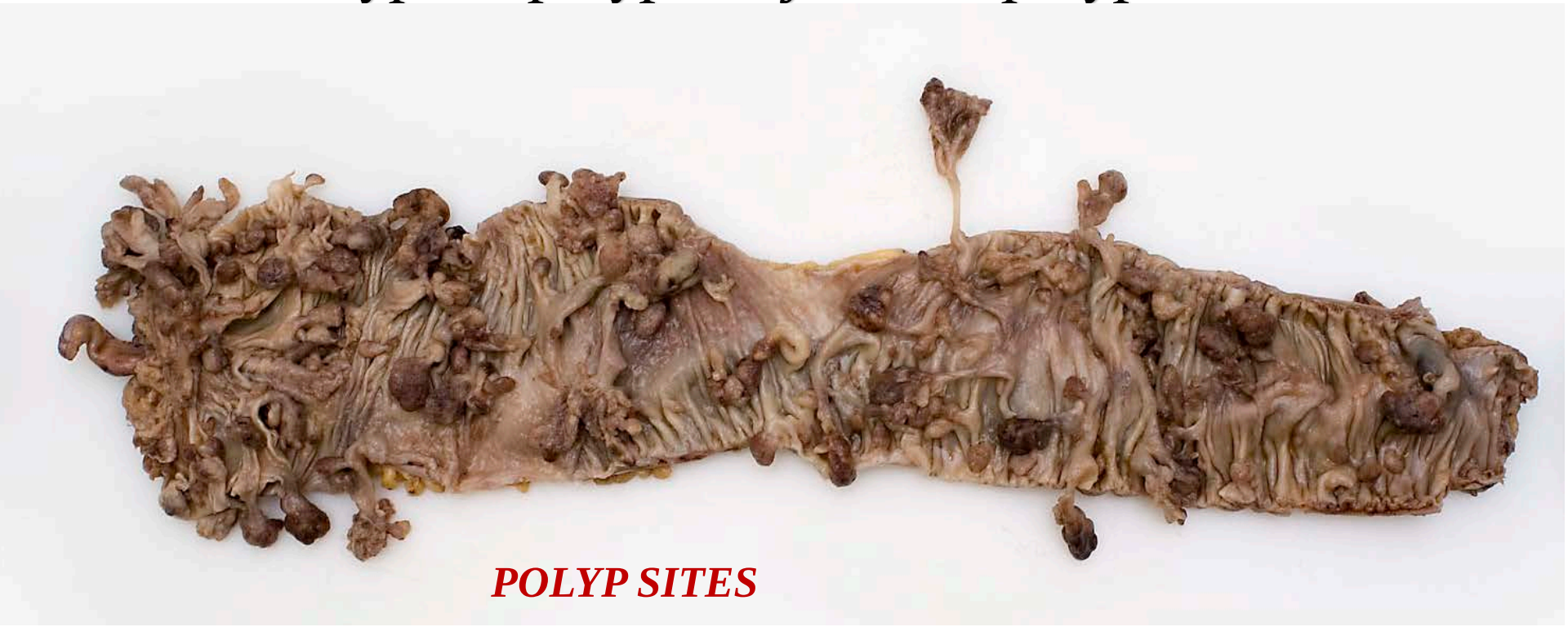
or

juvenile polyp(s) + family history





Typical polyps of juvenile polyposis



POLYP SITES

GASTRIC ONLY = 36%

GASTRIC & INTESTINE = 27%

COLORECTUM ONLY 36%

CANCERS FOLLOW POLYP DISTRIBUTION

Juvenile Polyposis Genetics (mutation found in 50%)

- *SMAD4* : 40% of families
  - recurrent ‘hotspot’ mutation, 1372–1375delACAG, accounts for about half of *SMAD4* cases
  - 20% of individuals with a *SMAD4* mutation develop JPS/Hereditary Haemorrhagic Telangiectasia (HHT)

- *BMPR1A* : 40% of families

- NO EXTRAINTESTINAL CANCER RISK

Frayling, IM. Juvenile Polyposis Syndrome, in Oxford Desk Reference: Clinical Genetics. Firth, HV and Hurst, J, eds. (2014) OUP.

Juvenile Polyposis

CLINICAL PRESENTATION

INFANTS

GI BLEEDNG,

INTUSSUSCEPTION,

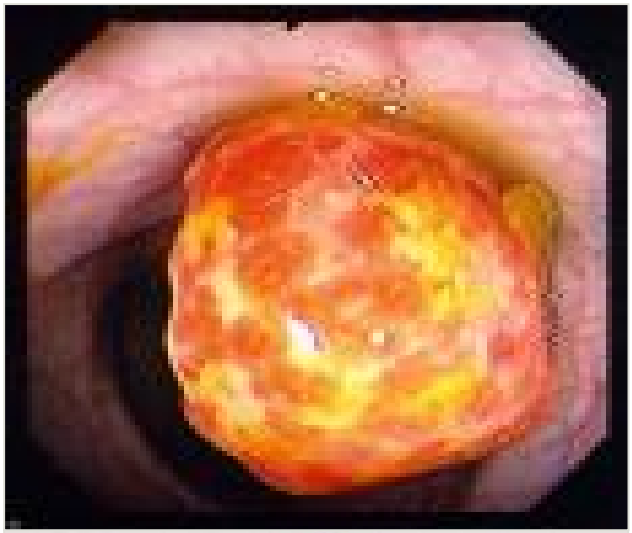
RECTAL PROLAPSE,

PROTEIN-LOSING ENTEROPATHY,

15% CONGENITAL BIRTH DEFECT

ADULTS

GI BLEEDNG,



ENDOSCOPY: SMOOTH, SPHERICAL,

'RED HEAD' ON A STALK 5-50mm

PATHOLOGY: MUCIN-FILLED CYSTIC DILATATION OF EPITHELIAL TUBULES IN AN INFLAMED LAMINA PROPRIA. ABSENCE OF SMOOTH MUSCLE PROLIFERATION

Juvenile Polyposis
DIFFERENTIAL DIAGNOSIS

- OTHER INFLAMMATORY POLYPS
  - IBD-ASSOCIATED

- PROLAPSE-ASSOCIATED POLYP
  - INFLAMMATORY CAP POLYP
  - INFLAMMATORY CLOACOGENIC POLYP
  - SOLITARY RECTAL ULCER SYNDROME
  - DIVERTICULAR-ASSOCIATED POLYPS

- CRONKITE-CANADA SYNDROME

- INFLAMMATORY MYOGLANDULAR POLYP (AJSP 1992;16; 772).

Juvenile Polyposis

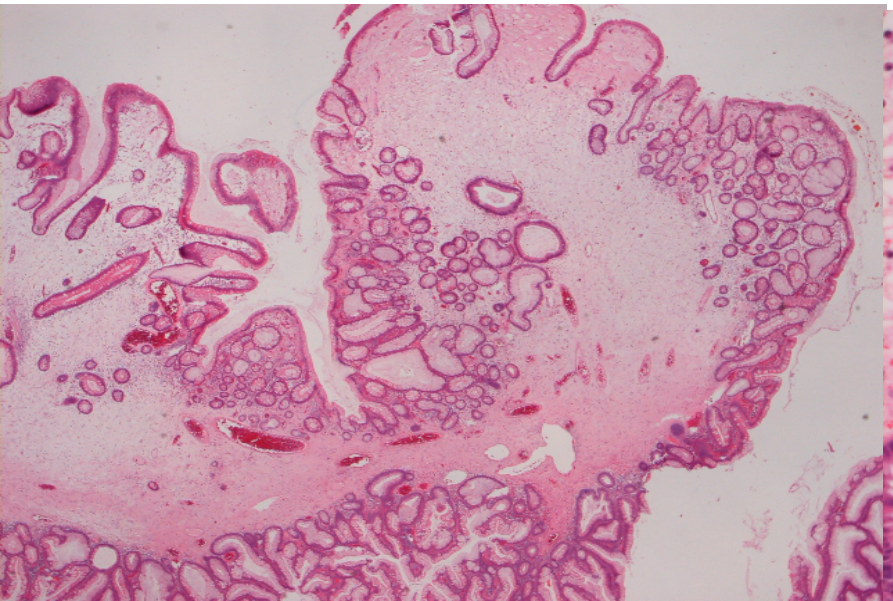
SINGLE VS MULTIPLE CONUNDRUM

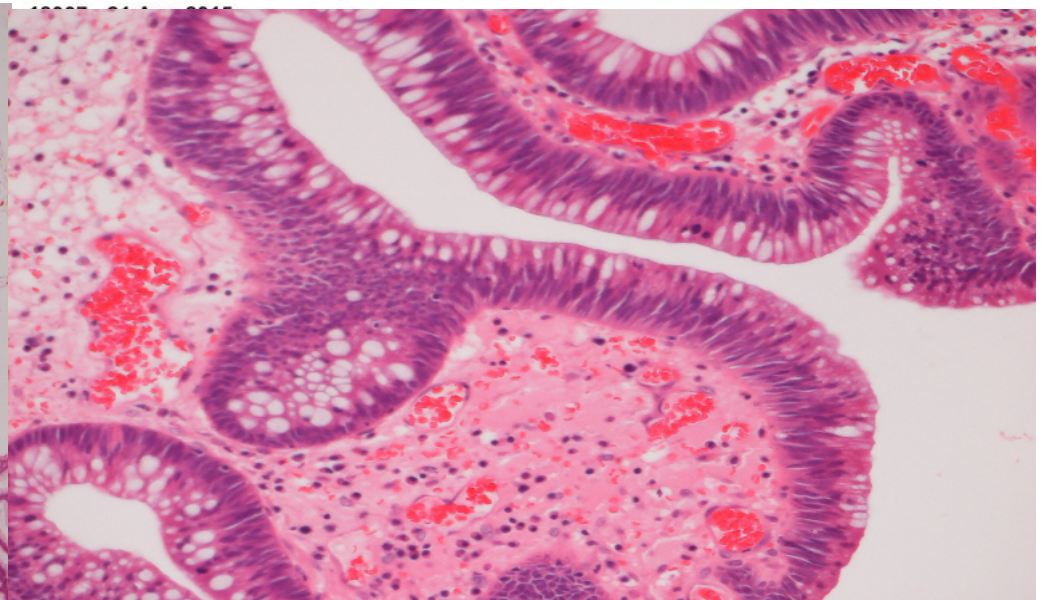
- Relatively common (1% children/adolescents)
- ISOLATED – NO MALIGNANT POTENTIAL
- Almost exclusively distal colon & rectum
- Small bowel Juvenile Polyp = likely Syndrome
- *MORE FROND-LIKE, LESS STROMA, FEWER DILATED GLANDS, & MORE PROLIFERATION THAN SYNROMIC POLYPS (not reproducible)*

Clinical History & Pathology

- 67 year old male (now)
- Multiple colorectal polyps over a 26 year period with a total of 19 adenomas & 5 juvenile polyps

Working diagnosis = Attenuated FAP until juvenile polyp appeared





Hereditary mixed polyposis syndrome due to a *BMPR1A* mutation

Mixed Juvenile & adenomatous polyposis

J. M. O'Riordan*, D. O'Donoghue*, A. Green†, D. Keegan*, L. A. Hawkes‡, S. J. Payne‡, K. Sheahan* and D. C. Winter*

*The Centre for Colorectal Disease, St Vincents' University Hospital, Elm Park, Dublin, Ireland, †The National Centre for Medical Genetics, Our Lady's Childrens Hospital, Crumlin, Dublin, Ireland and ‡The North West Thames Regional Genetics Service, Northwick Park Hospital, Harrow, UK

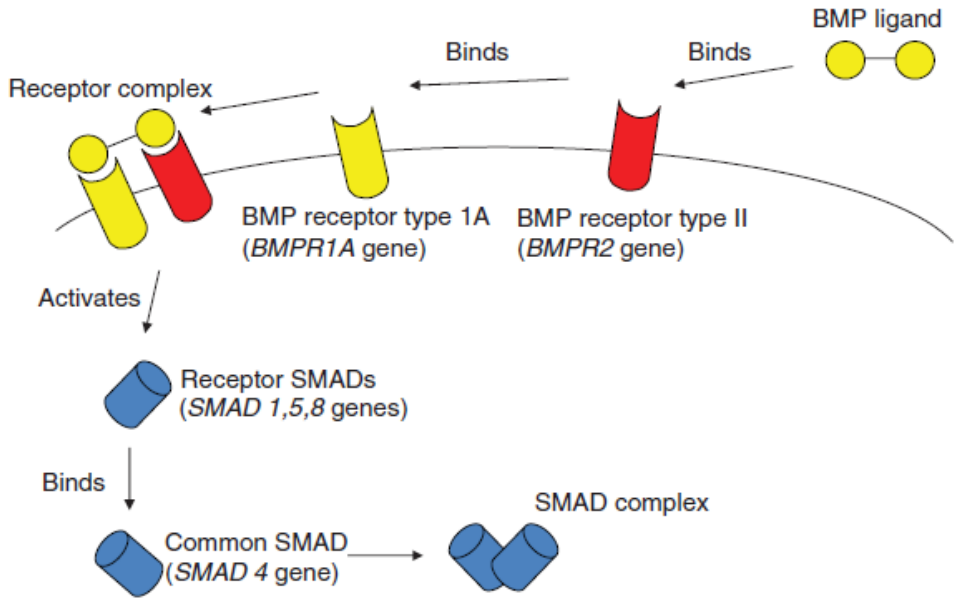


Figure 1 Diagram showing the important elements of the BMP signalling pathway which is closely related to the TGF-β pathway, an important pathway in the inhibition of cell growth. Both pathways share a common signalling element, SMAD4. Germline mutations of *SMAD4* and *BMPR1A* genes have been associated with JPS and HMPS.

Colorectal Disease, **12**, 570–573

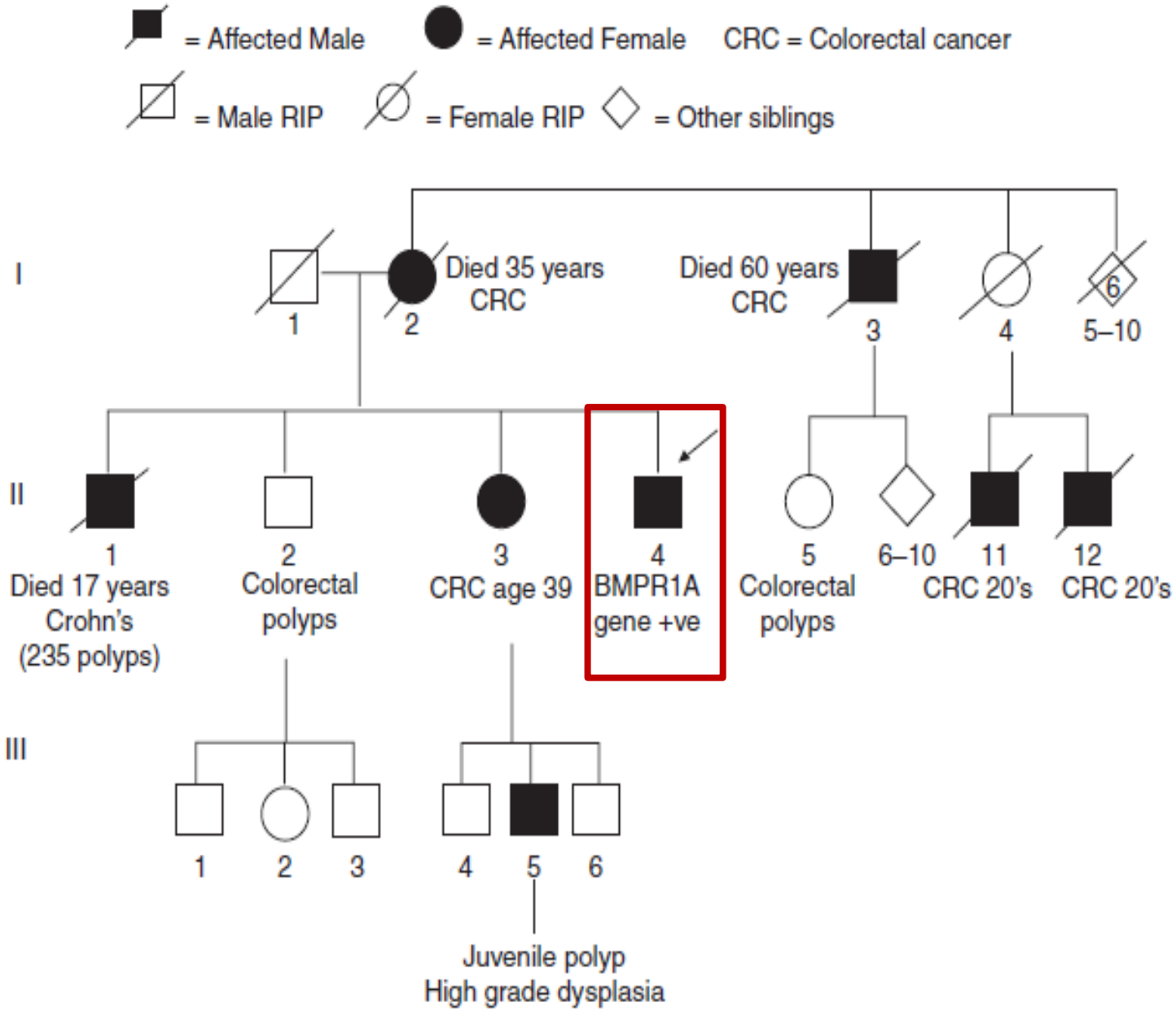
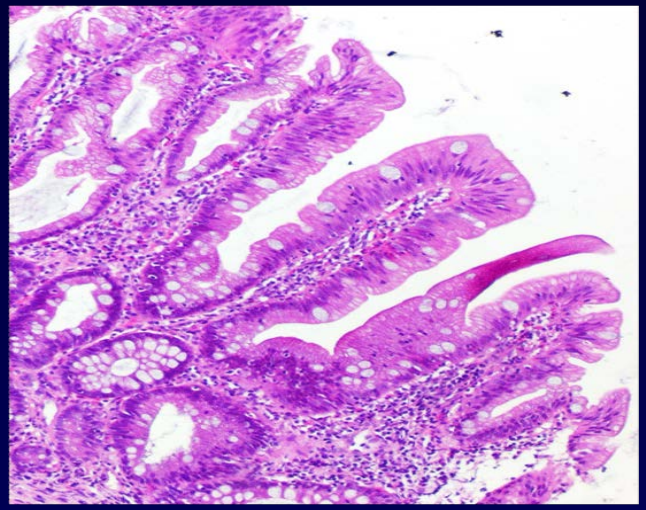


Figure 2 Family pedigree and relationship of *BMPR1A* gene mutation.

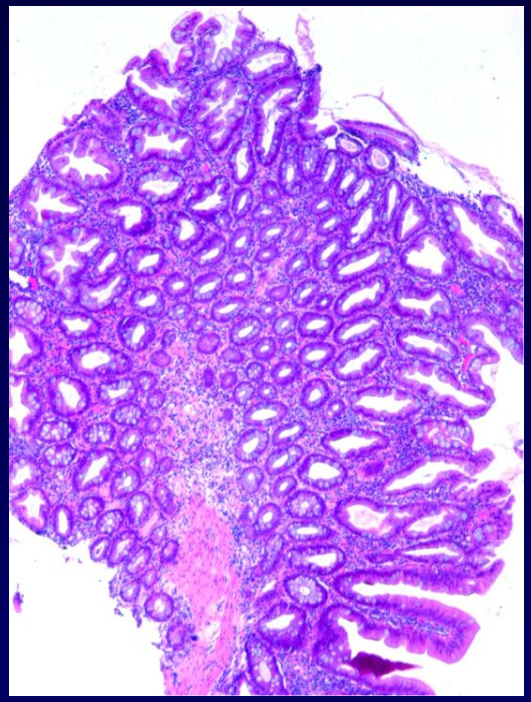
Hereditary Mixed Polyposis Syndrome: HMPS
WATCH THIS SPACE

Adenoma with serrated features

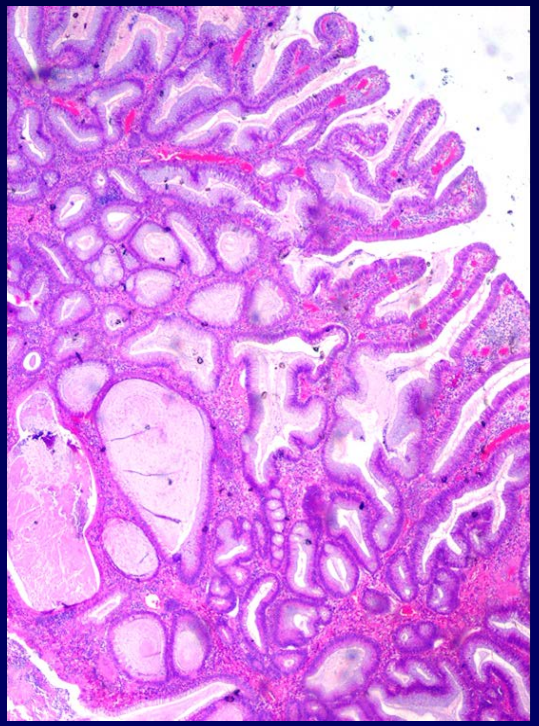


Courtesy: Dr Ian Frayling & Prof. Ian Tomlinson

Mixed hyperplastic – adenomatous polyp



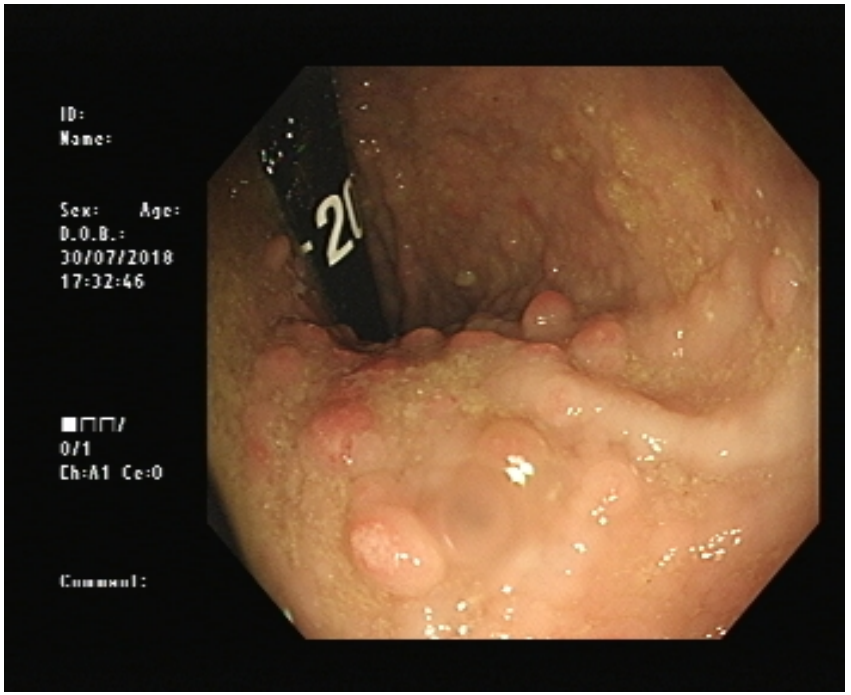
Mixed juvenile-hyperplastic-adenoma

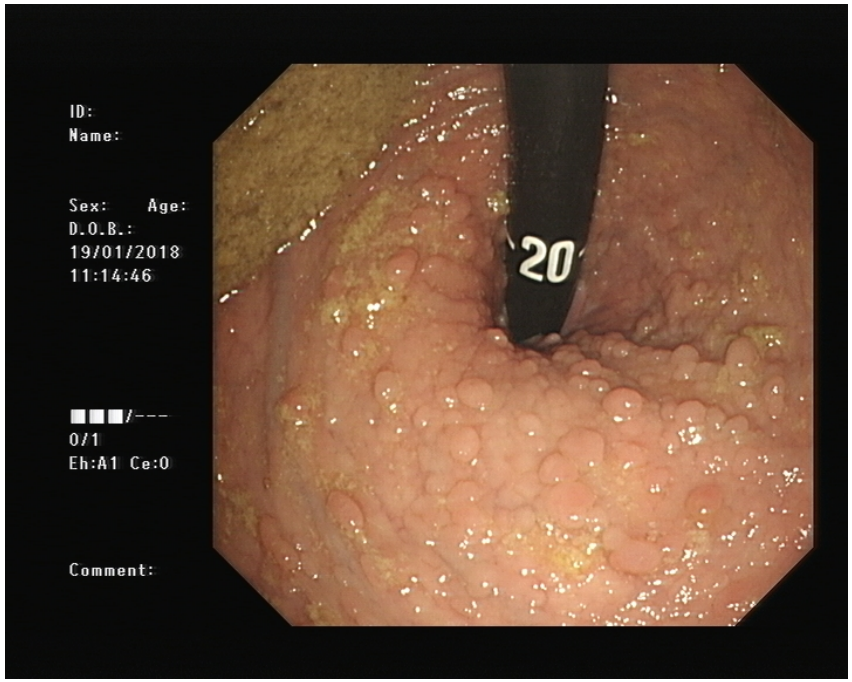


Tomlinson, Ian, et al. "Multiple common susceptibility variants near BMP pathway loci GREM1,BMP4, and BMP2 explain part of the missing heritability of colorectal cancer." PLoS genetics 7.6 (2011): e1002105.
McKenna, Danielle B., et al. "Identification of a novel GREM1 duplication in a patient with multiple colon polyps." Familial cancer 18.1 (2019): 63-66.

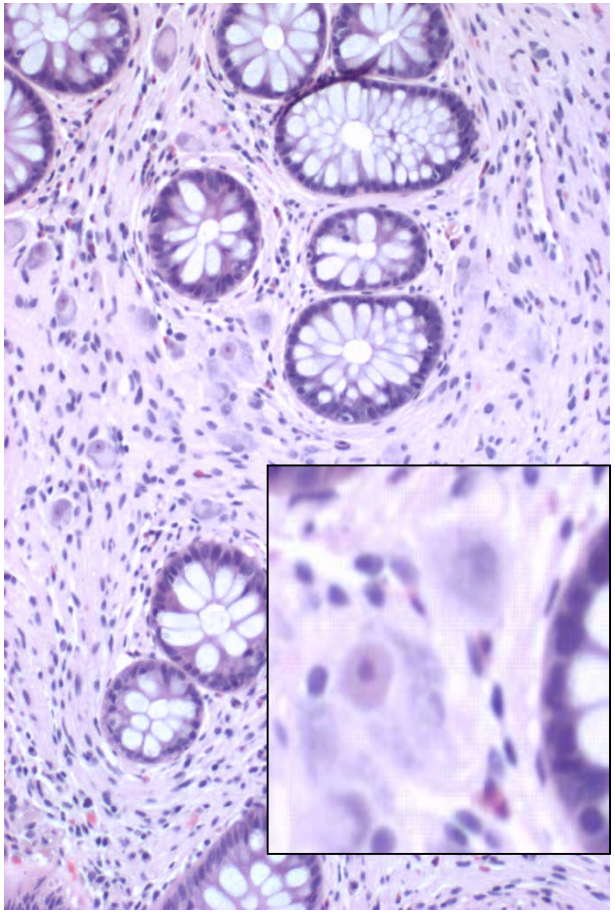
Clinical History

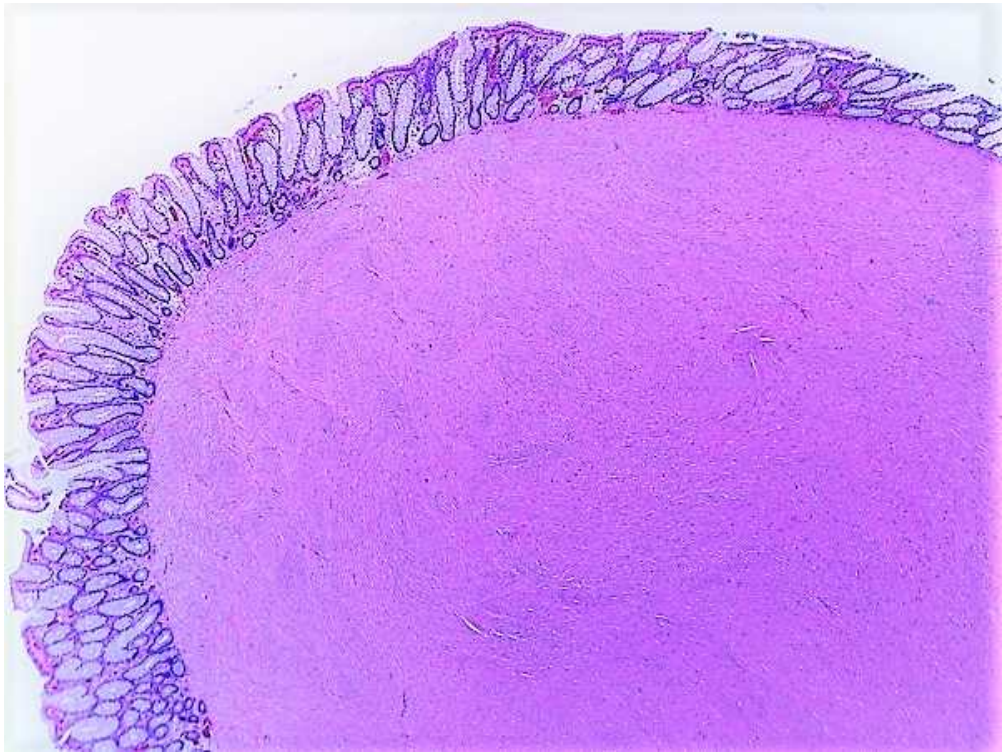
- 38 year old female
- Episodes of rectal bleeding
- Polyposis, colorectal (15 -20 polyps, 0.5 – 1cm)





PATHOLOGY





Mucosal ganglioneuroma and leiomyoma x2

Clinical History

- 38 year old female
- Episodes of rectal bleeding
- Polyposis, colorectal (15 -20 polyps, 0.5 – 1cm)
- **3 biopsied (leiomyoma x2, ganglioneuroma x1)**
- **Surveillance endoscopy (1 year) 3 polyps biopsied (mucosal prolapse polyp, ganglioneuroma x2)**
- **Pathology report conclusion =** R/O Cowden syndrome

- PTEN mutation found
- 1 year later, breast carcinoma
- 2 years later, follicular thyroid carcinoma
- 9 years later prophylactic hysterectomy (age 47)
- Regular surveillance for GI malignancy (age 48)

St. Vincent's University Hospital

UCD DUBLIN

Centre for COLORECTAL DISEASE

PTEN (PHOSPATASE & TENSIN HOMOLOG) HAMARTOMA TUMOUR SYNDROME (PHTS)

- Autosomal dominant (1/200,000 *underestimate)*

  Incorporates /replaces
  Cowden syndrome (CS)
  Bannayan-Riley-Ruvalcaba (BRR) syndrome,
  Adult Lhermitte-Duclos syndrome
  Autism spectrum disorders associated with macrocephaly

- Majority of clinical data is on CS (only 35% with clinical criteria have PTEN mutation)

cancers

MDPI

Review

PTEN Hamartoma Tumor Syndrome: A Clinical Overview

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Received: 9 May 2019; Accepted: 14 June 2019; Published: 18 June 2019

check for updates

Consensus diagnostic criteria for CS were initially established in 1996 by an international research consortium. This was prior to identification of the CS gene and the criteria were based upon early clinical experience and compilations of cases published in the literature, with their inherent ascertainment biases [14]. The single largest patient series in any of these reports comprised 21 patients [15]. It was not until 2013 that an evidence-based review led to a significant revision of the diagnostic criteria (summarized in Table 1), which were then adopted by the U.S. National Comprehensive Cancer Network [16,17].

Table 1. Revised *PTEN* hamartoma tumor syndrome (PHTS) diagnostic criteria.

Revised *PTEN* Hamartoma Tumor Syndrome (PHTS) Clinical Diagnostic Criteria [16,17]
Operational Diagnosis in an Individual (either of the following):
(1) Three or more major criteria, but one must include macrocephaly, Lhermitte–Duclos disease, or gastrointestinal hamartomas; OR
(2) Two major and three minor criteria;
Operational Diagnosis in a Family where One Individual Meets Revised PHTS Clinical Diagnostic Criteria or Has a *PTEN* Mutation:
(1) Any two major criteria with or without minor criteria; OR
(2) One major and two minor criteria; OR
(3) Three minor criteria
Major Criteria
Breast cancer
Endometrial cancer (epithelial)
Thyroid cancer (follicular)
Gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps) (≥3)
Lhermitte–Duclos disease (LDD), adult
Macrocephaly (≥97 percentile)
Macular pigmentation of the glans penis
Multiple mucocutaneous lesions (any of the following):
Multiple trichilemmomas (≥3), at least one biopsy proven
Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)
Mucocutaneous neuromas (≥3)
Oral papillomas (particularly on tongue and gingiva), multiple (≥3) OR biopsy-proven OR dermatologist-diagnosed
Minor Criteria
Autism spectrum disorder
Colon cancer
Esophageal glycogenic acanthosis (≥3)
Lipomas (≥3)
Mental retardation (i.e., Intelligence Quotient (IQ) ≤ 75)
Renal cell carcinoma
Testicular lipomatosis
Thyroid cancer (papillary or follicular variant of papillary)
Thyroid structural lesions (e.g., adenoma, multinodular goiter)
Vascular anomalies (including multiple intracranial developmental venous anomalies)

CLINICAL SYNDROME

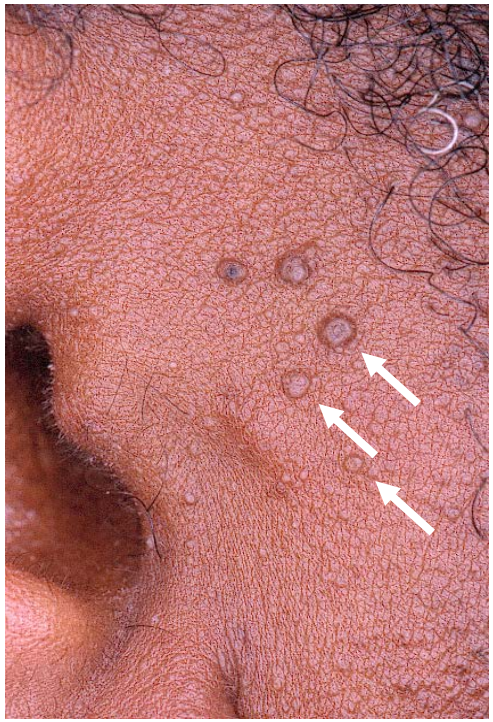
- Multiple hamartomas of skin (trichilemmomas), GIT & soft tissues (angiomas, fibromas, lipomas)
- Benign thyroid disease
- Macrocephaly
- Dysplastic gangliocytoma of cerebellum
- Learning difficulties

- GI polyps: characteristic

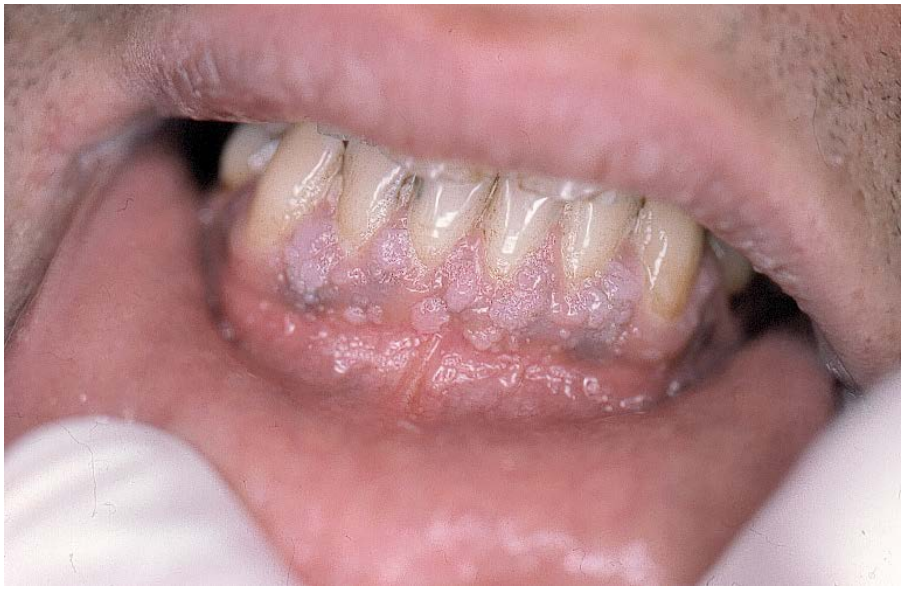
- Cancer risk high for breast, follicular thyroid , endometrium, renal carcinomas

- The risk for colorectal cancer is ‘only’ 9% but occurs at a younger age.
    - Colonoscopy 2-yearly from 40 years

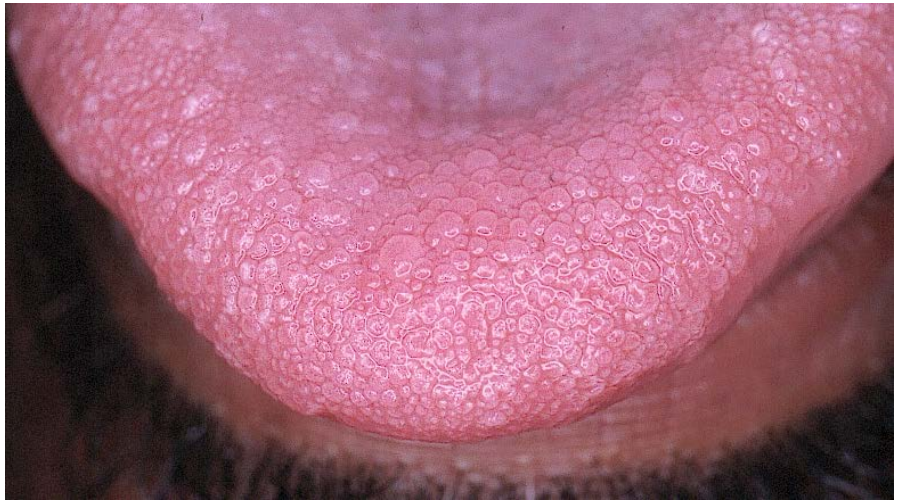
Tan M-H et al. “Lifetime Cancer Risks in Individuals with Germline PTEN Mutations” Clin Cancer Res. 2012 18(2): 400–407.



Trichilemmomas



Papillomatosis of the gums

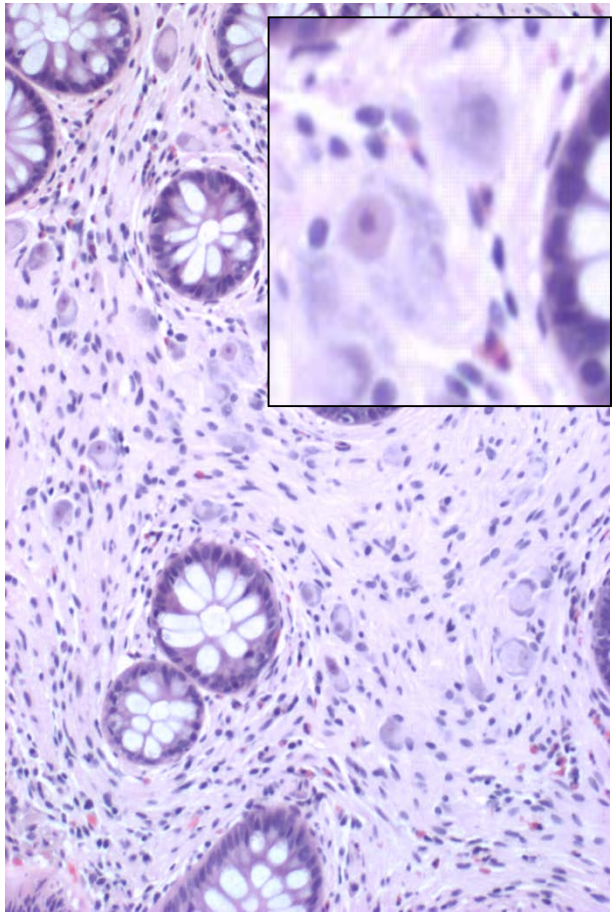


Lingual papillomatosis

Courtesy: Prof. Frédéric Caux, Hôpital Avicenne, Bobigny

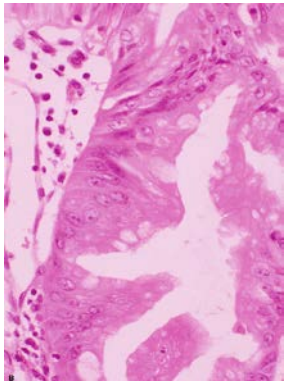
PTEN/ Cowden Syndrome

- Large bowel Ganglioneuroma (characteristic)



Additional Polyps in PTEN

- Leiomyoma
- Juvenile polyp
- Hyperplastic polyp
- Adenoma
- Lymphoid polyps



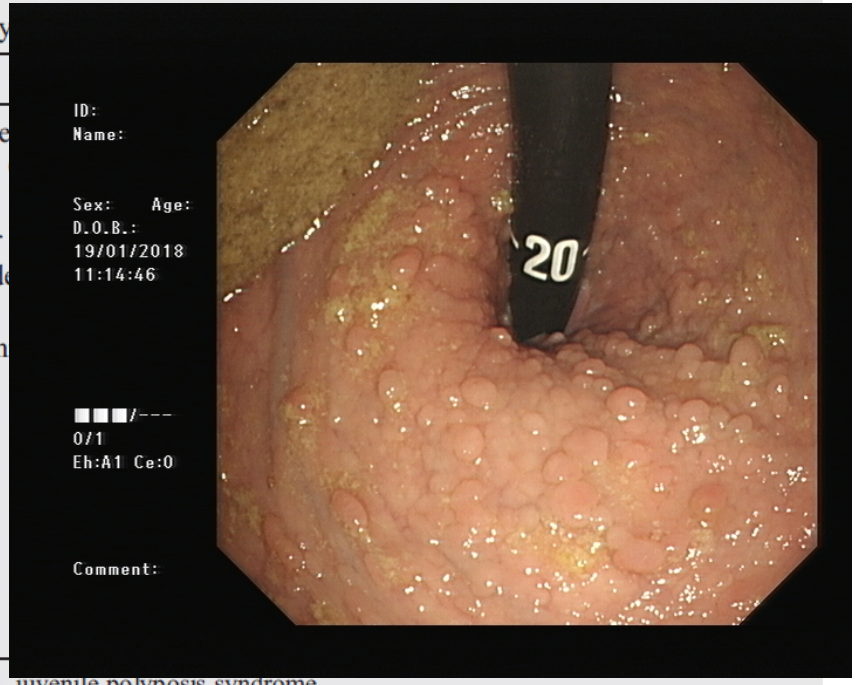
PTEN Syndrome GI POLYPS

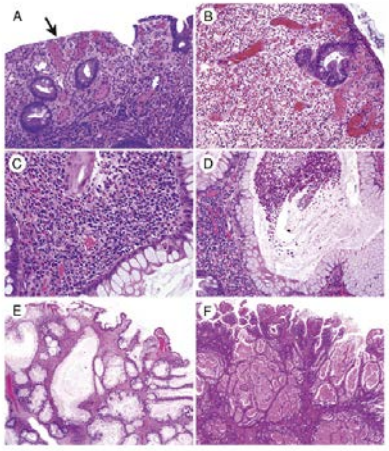
SPECIFIC FEATURES

Table 3 Characteristic features of specific hamartomatous polyp ty

	CS	PJS
Location	Usually colon	Small or large
Mean size	Small (mean, 0.4 cm)	Small (mean,
Architecture	Sessile	Exophytic
Erosion	Almost never	Almost never
Lamina propria	Expanded, fibrotic	Expanded, ed and fibrotic
Inflammation	Mild chronic	Marked chron
Cystic glands	Least occurrence	Common
Thick mucin	No	Common
Smooth muscle proliferation	Mild	Highest level
Lymphoid follicles	Common	No
Ganglion cells	Rare	No
Nerve fibers	Rare	No
Mucosal fat	Rare	No

Abbreviations: CS, Cowden syndrome; PJS, Peutz-Jeghers syndrome; JuvPS, juvenile polyposis syndrome.





n = 375 polyps

CS = 15 pts
PJP = 13 pts
JPS = 12 pts

Sporadic = 32 pts

Human Pathology (2016) 49, 39–48

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Morphologic characterization of hamartomatous gastrointestinal polyps in Cowden syndrome, Peutz-Jeghers syndrome, and juvenile polyposis syndrome☆,☆☆

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PTEN (PHOSPATASE & TENSIN HOMOLOG) HAMARTOMA TUMOUR SYNDROME (PHTS) & IMMUNE DYSREGULATION

1. Increased susceptibility to infection
2. Increased frequency of auto-immune disease
3. Increased cancer risk: may be partly due to an immune tolerant tumour microenvironment

Translational Oncology
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Volume 12 Number 2 February 2019 pp. 361–367 361

PTEN Hamartoma Tumor Syndrome and Immune Dysregulation[1,2,3]

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TAKE HOME MESSAGES

- **POLYPECTOMY** (vs BIOPSY) ADVISED FOR DEFINITE DIAGNOSIS
- **PJP**: BEWARE EPITHELIAL MISPLACEMENT
- **PJP & PTEN HAMARTOMA SYNDROME:** HIGH RISK OF EXTRAINTESTINAL CANCER
- **JUVENILE POLYPOSIS** : MAIN RISK IS GI CANCERS. REMEMBER HHT
- **CORRELATE POLYP HISTOLOGY** WITH CLINICAL & ENDOSCOPIC FINDINGS AT ALL TIMES

TAKE HOME MESSAGES

- **EMBRACE THE ROLE OF THE PATHOLOGIST IN THE DIAGNOSIS OF HEREDITARY CANCER**

- **GERMLINE TESTING IS BECOMING MORE SENSITIVE & SPECIFIC FOR PRECISE SYNDROMIC DIAGNOSIS**

- **CLINICAL CRITERIA REMAIN VALID IN MANY CASES**

- **NEW THERAPEUTIC OPTIONS MAY APPEAR IN THE FUTURE**

Frayling, IM, & Arends, MJ. (2015). How can histopathologists help clinical genetics in the investigation of suspected hereditary gastrointestinal cancer? **Diagnostic Histopathology 21(4)**:137-146..

How to Screen for Hereditary Cancers in General Pathology Practice

Brandon S. Sheffield, MD; Veronica Hirsch-Reinshagen, MD; Kasmintan A. Schrader, MBBS, PhD, FRCPC

(Arch Pathol Lab Med. 2016;140:899–909;

ACKNOWLEDGEMENT

- Centre for Colorectal Disease, SVUH, Dublin
- Medical & Lab staff, SVUH
- Dr Ian Frayling, Cardiff
- Prof Neil Shepherd, Cheltenham, UK

Peutz-Jeghers Syndrome

Site	Risk ratio (95% CI)	Frequency (%)	Mean age (y)	Age range (y)
Oesophagus	57 (2.5-557)	0.5	67	-
Stomach	213 (96-368)	29	30	10-61
Small bowel	520 (220-1306)	13	42	21-84
Colon	84 (47-137)	39	46	27-71
Pancreas	132 (44-261)	36	41	16-60
Lung	17 (5.4-39)	15	-	-
Testis	4.5 (0.12-25)	9	8.6	3-20
Breast	15.2 (7.6-27)	54	37	9-48
Uterus	16 (1.9-56)	9	-	-
Ovary	27 (7.3-68)	21	28	4-57
Cervix	1.5 (0.31-4.4)	10	34	23-54

Frayling, IM. Peutz-Jeghers Syndrome, in Oxford Desk Reference: Clinical Genetics. Firth, HV and Hurst, J, eds. (2014) OUP.
Adapted from: Giardiello FM, Brensinger JD, et al. Very high risk of cancer in familial Peutz–Jeghers syndrome. Gastroenterology 2000: 119 (6): 1447–53.