Gastric polyposis syndromes including NETs

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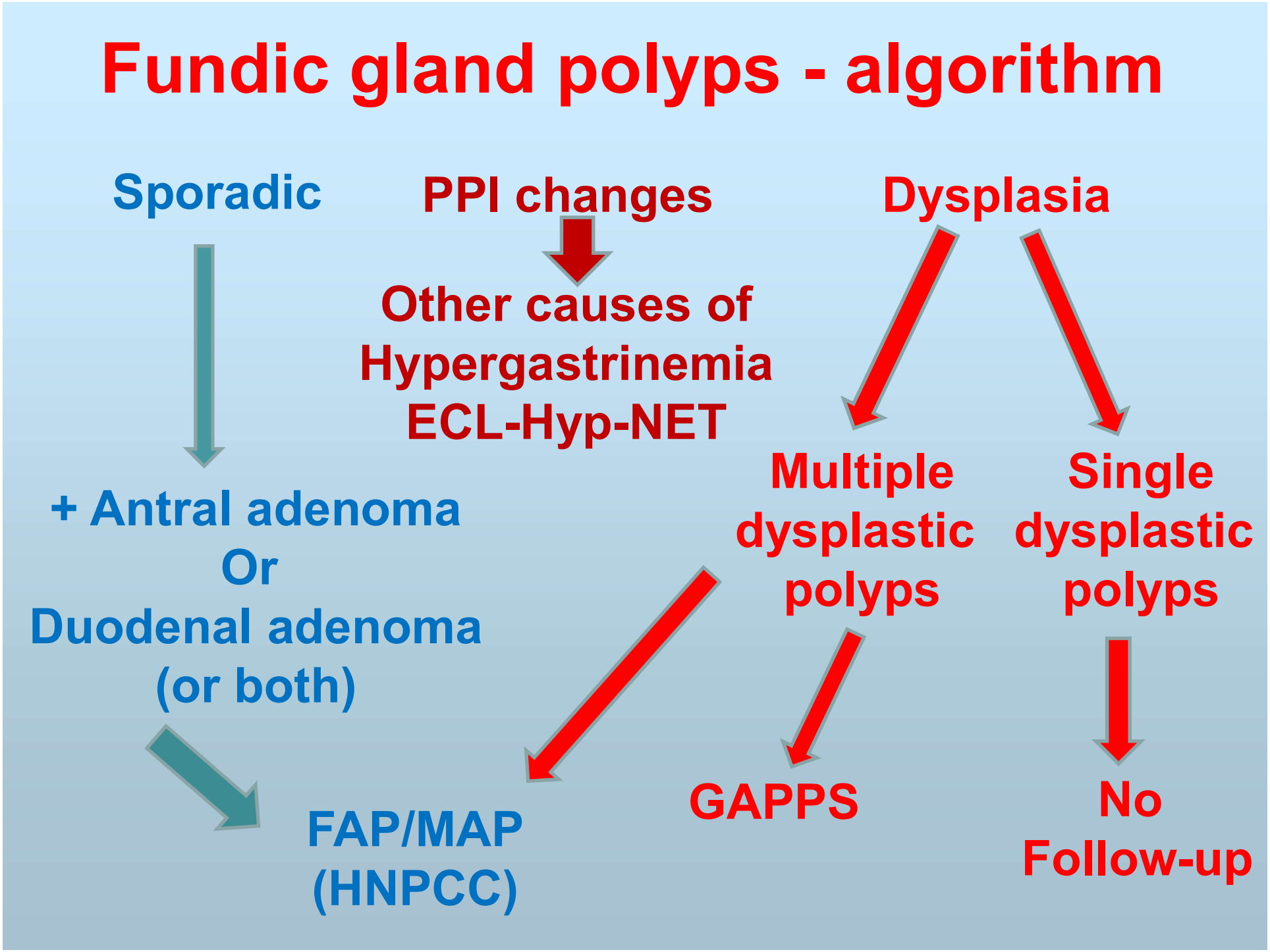
Gastric polyps & syndromes

- Non-neoplastic polyps and syndromes
  - Dysplasia can occur in all non-neoplastic polyps
    - Fundic gland polyps, (FAP, GAPPS)
    - Hyperplastic/Inflammatory (JPS)
    - Hypertrophic gastropathies
      - Cronkhite- Canada, Ménétrier's
- Adenomas/dysplasias
  - In native gastric mucosa (Lynch)
    - Foveolar, pyloric, oxyntic
  - In metaplastic mucosa
- NETs (Atrophic/Autoimmune gastritis, ZES)

Fundic gland polyps - algorithm



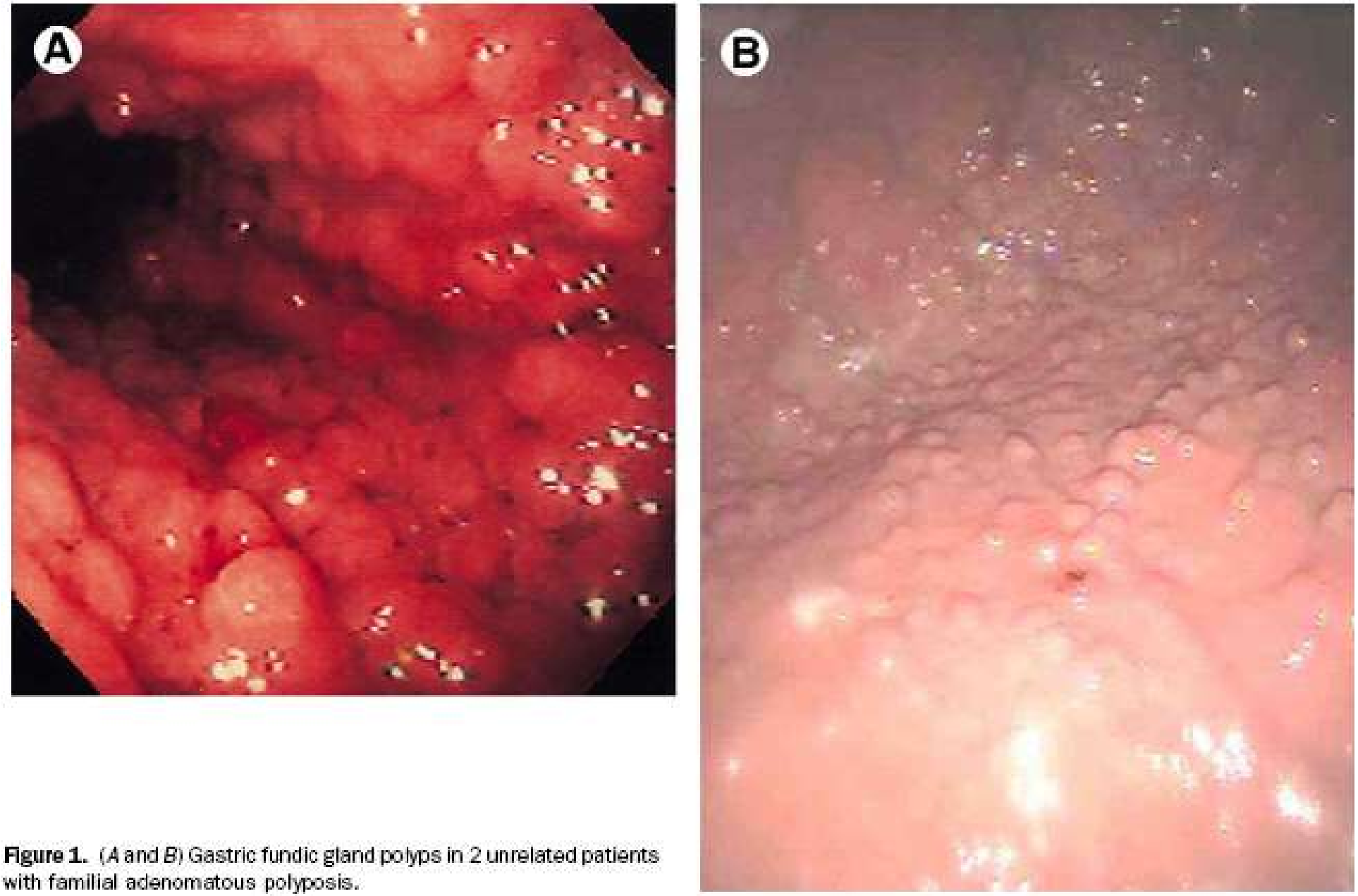
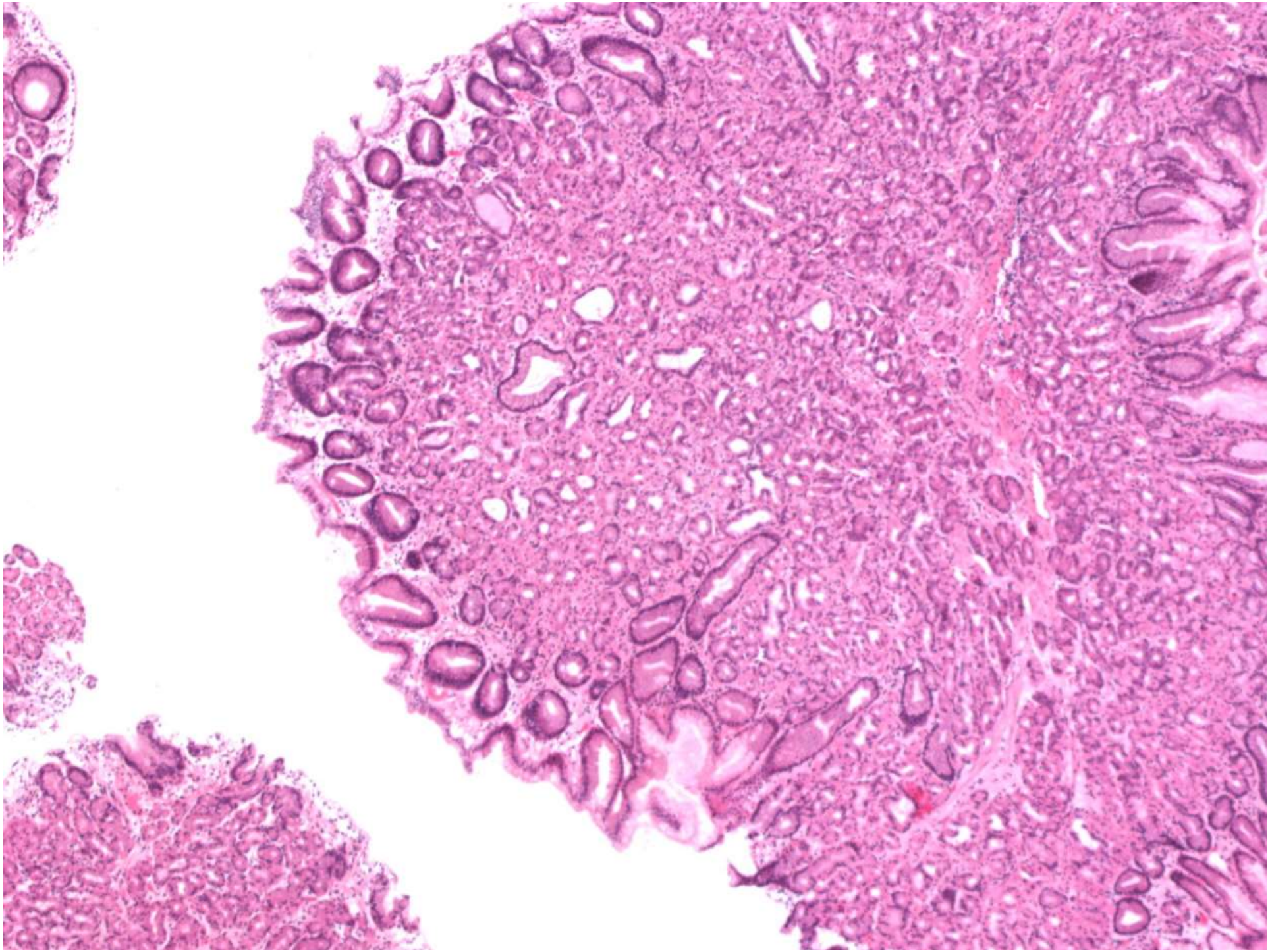
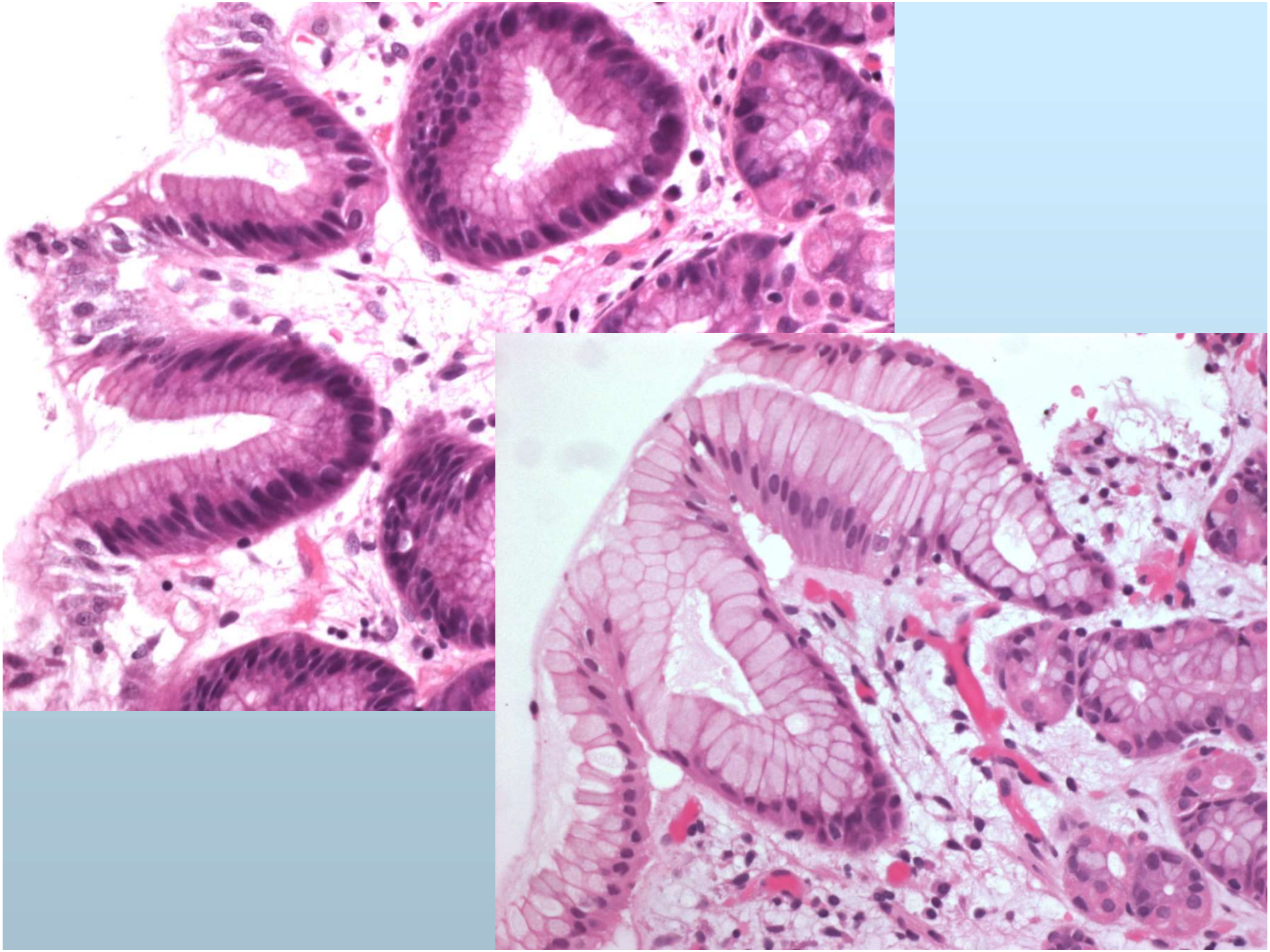


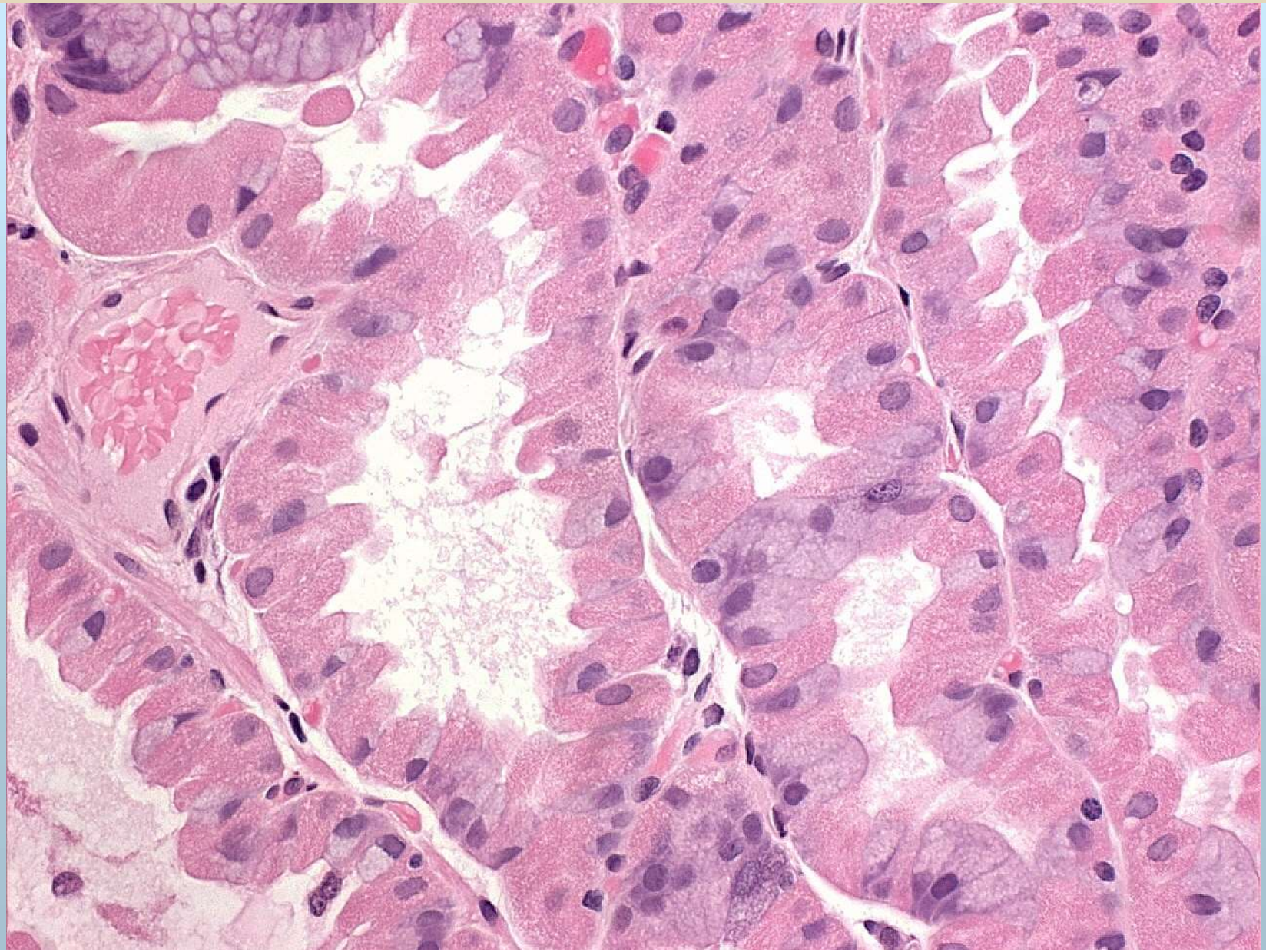
Figure 1. (*A* and *B*) Gastric fundic gland polyps in 2 unrelated patients with familial adenomatous polyposis.

Burt R Gastroenterology 2003;125:1462–1469

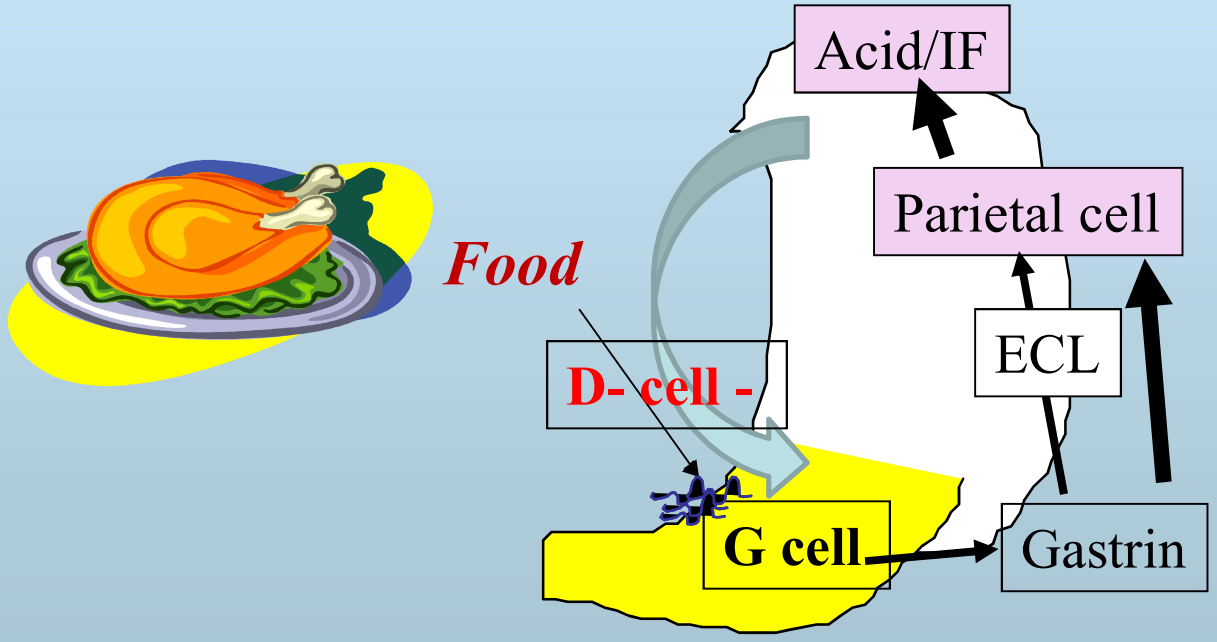




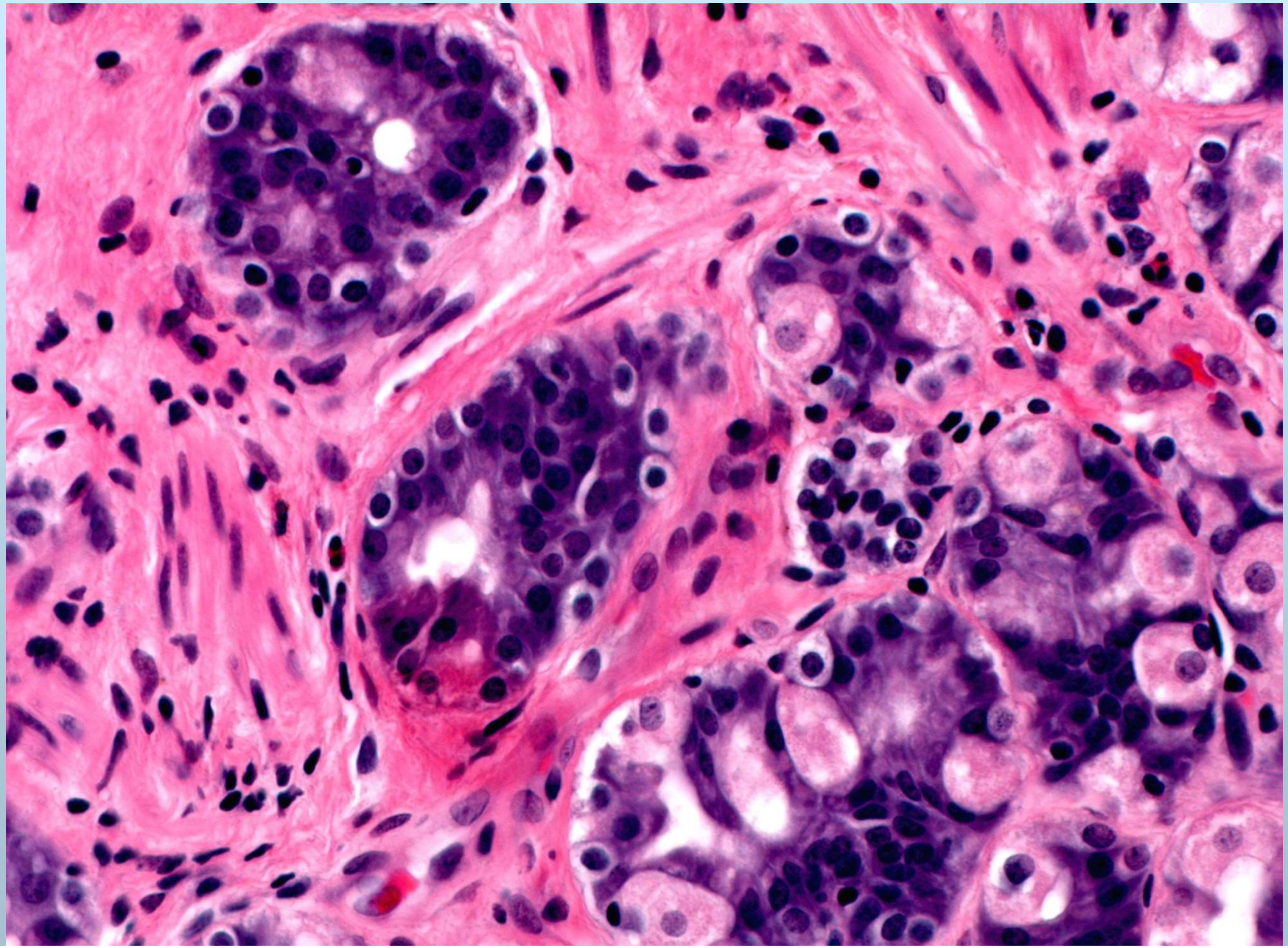
FGPs –PPIs - hypergastrinemia

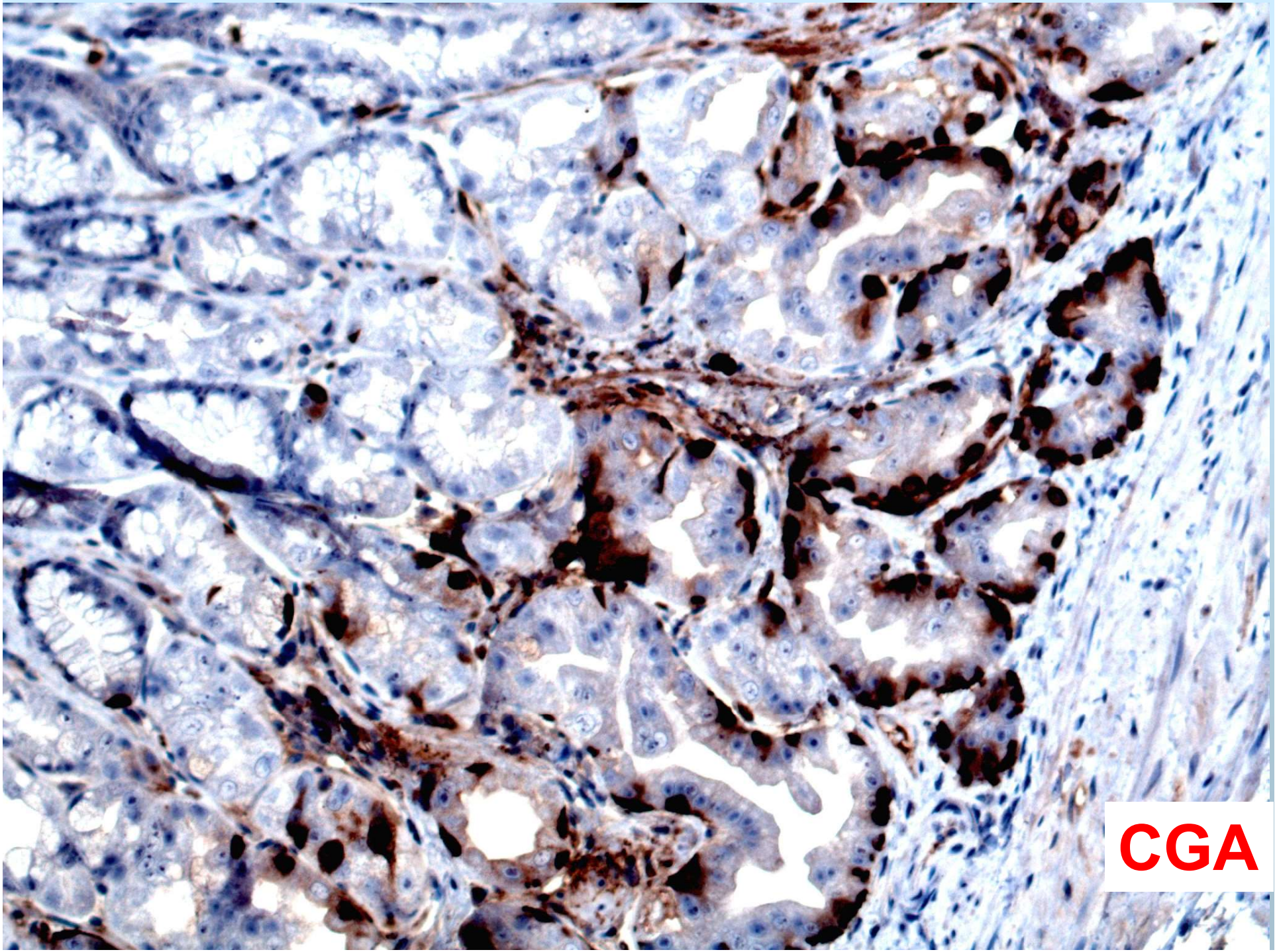


Acid Secretion Pathophysiology



Body – long term PPIs




CGA

AP&T Alimentary Pharmacology and Therapeutics

Gastric carcinoids after long-term use of a proton pump inhibitor

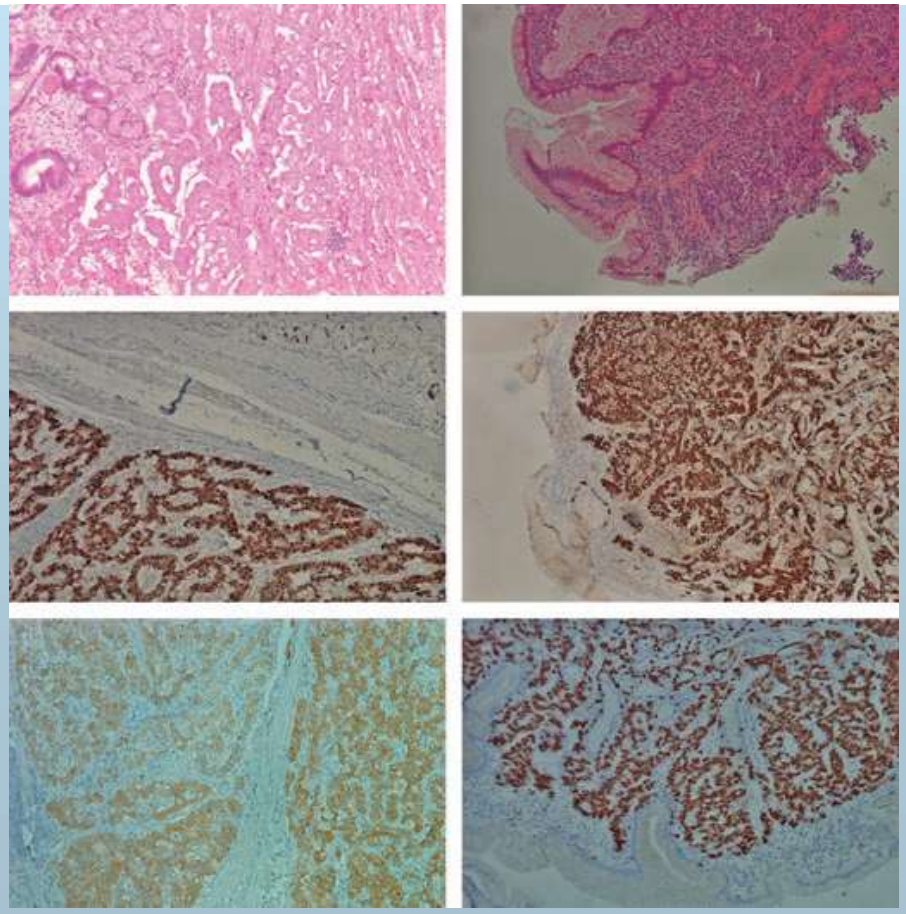
C. S. Jianu*,†, R. Fossmark*,†, T. Viset‡, G. Qvigstad*,†, Ø. Sørdal†, R. Mårvik§ & H. L. Waldum*,†

Aliment Pharmacol Ther 2012; 36: 644–649

PPIs 12-13y
ECL hyperplasia
regressed in 2y
Following
cessation
of PPIs

CGA

VMAT2



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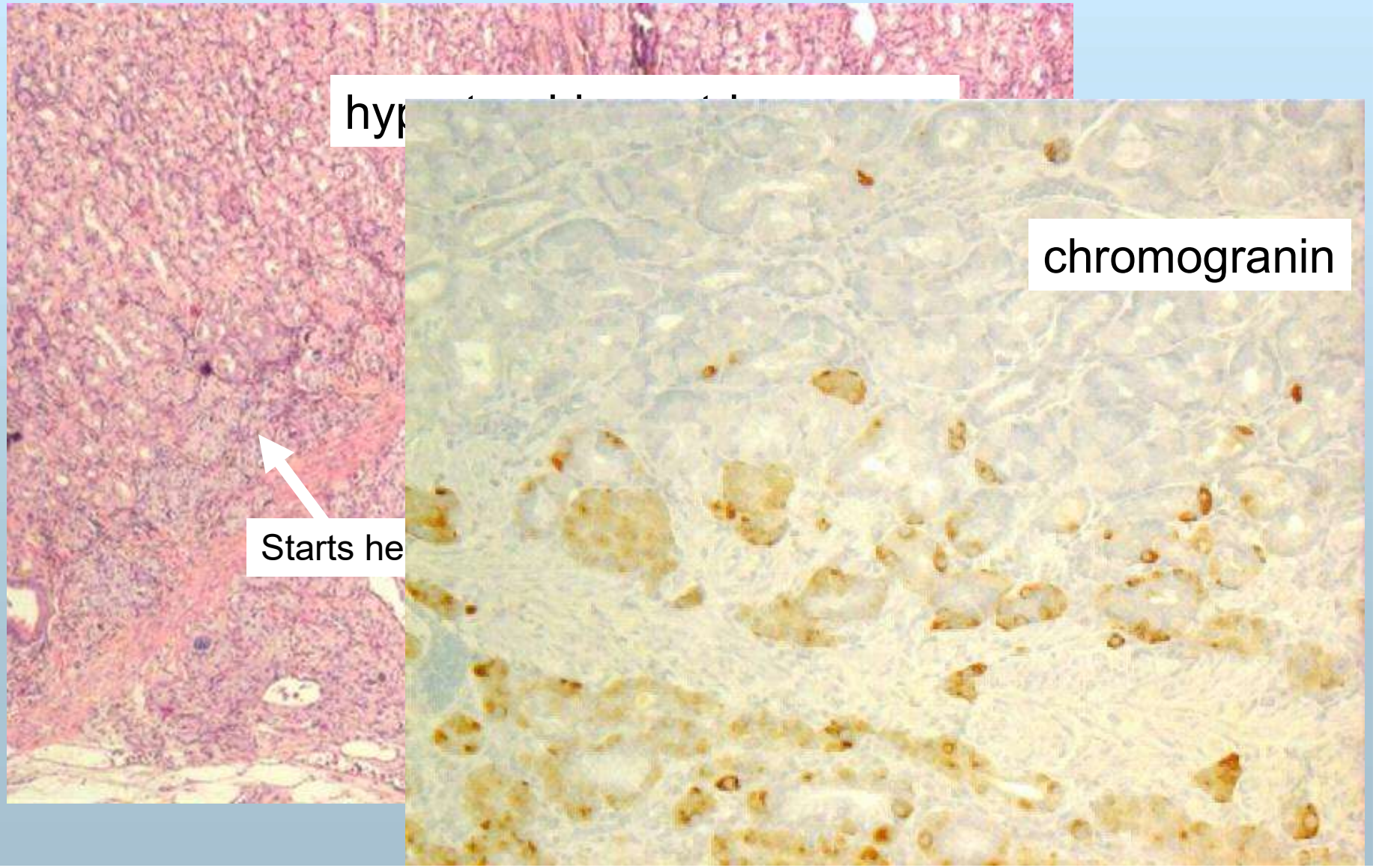
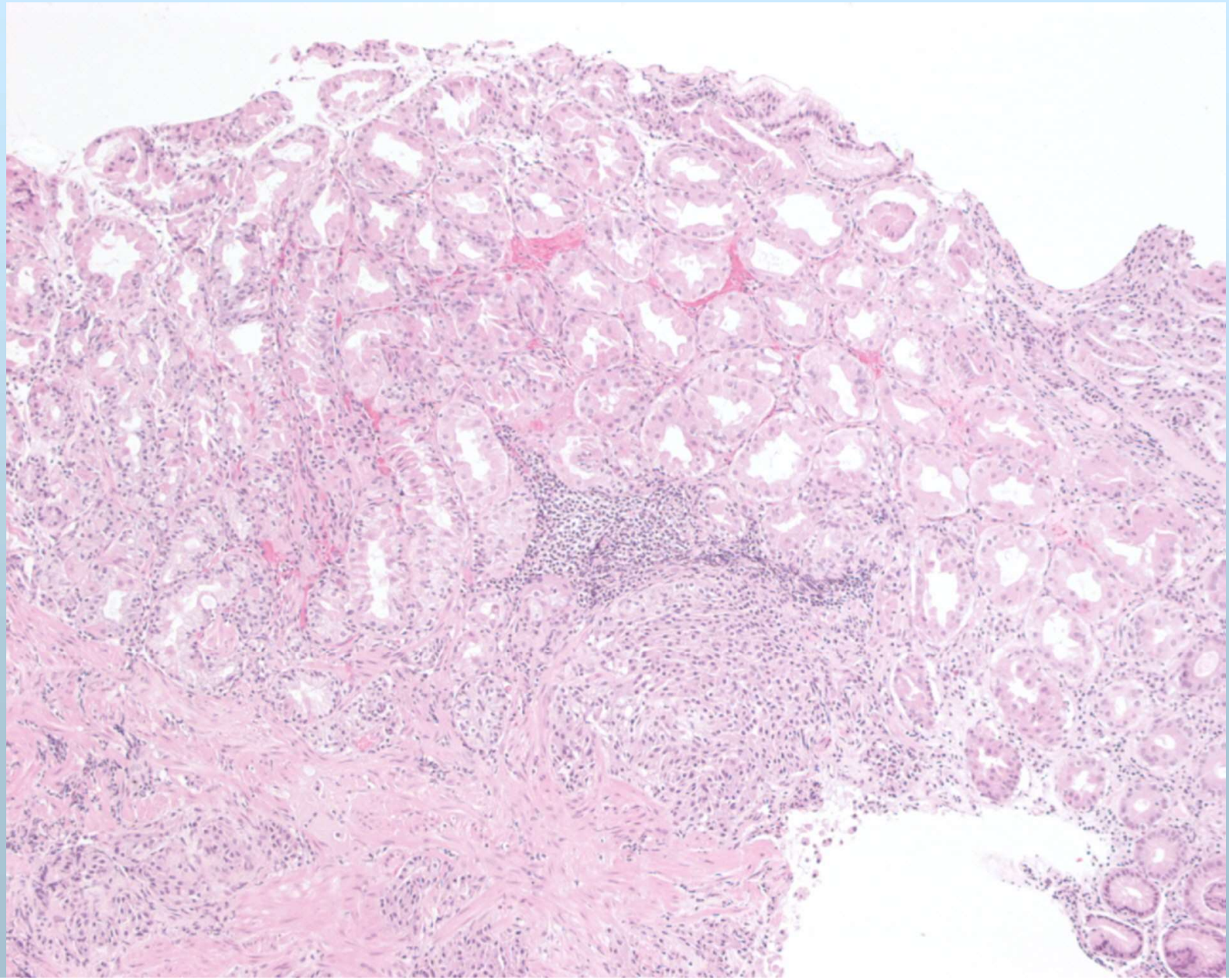
VMAT2

Gastric NET in MEN1 (Zollinger Ellison)



ZES and NET (oxyntic mucosa)



GASTRIC NETs (clinical)

Type 1 (c.80%)- Chronic atrophic/autoimmune gastritis

Elevated serum gastrin - high gastric pH
Iron deficiency and / or pernicious anemia
Tumors invariably multiple – can mimic FGPs.
Indolent - Large tumors - 5% to 7.5% metastatic rate
Background mucosa – atrophic + ECLH +/- IM

Type 2 (c.10 %) - Gastrinomas and MEN1

Indolent – c .10% metastatic rate
Background mucosa – parietal cell hypertrophy +ECLH

Type 3, Sporadic (c.10 %) – antral or oxyntic

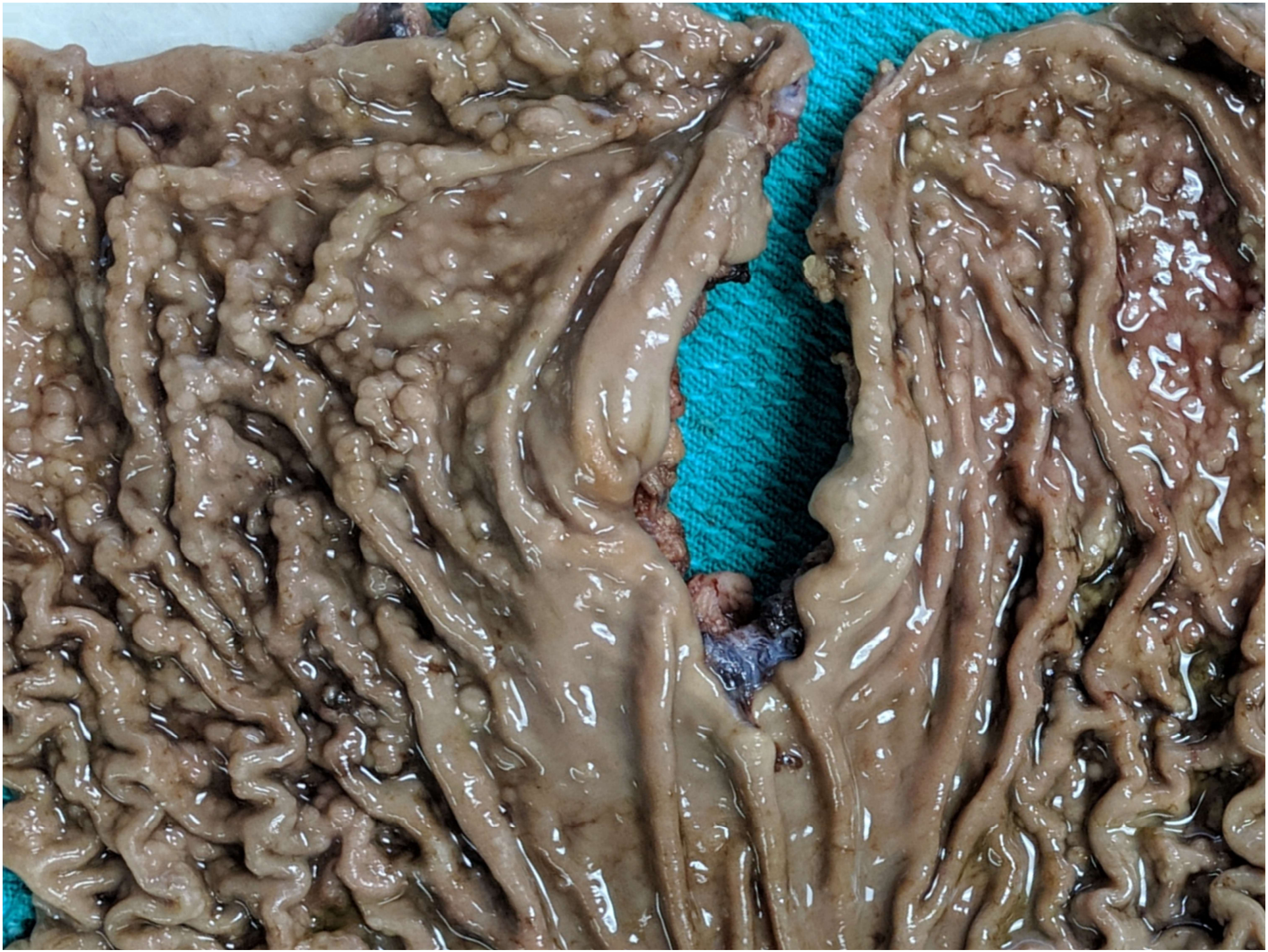
50% + metastatic rate with a correspondingly higher mortality than the other 2 types
Background mucosa – normal, Hp, PPI if on PPIs

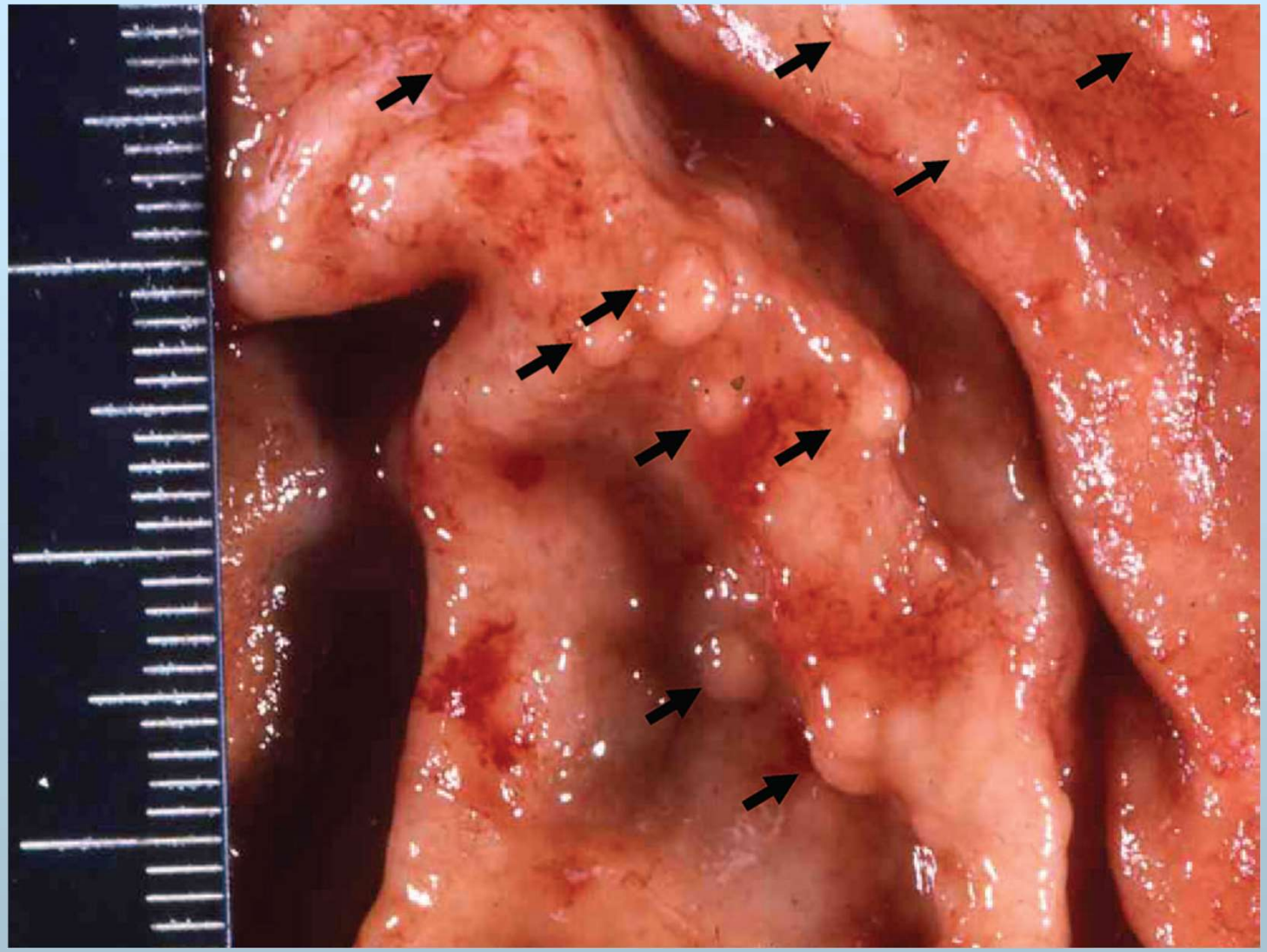
GASTRIC NETs -Type 2 (ZES type)

Typically gastrinomas and MEN1
Usually already on PPIs (so ECLH missed)

Longterm PPIs

Rarely patients unable to produce protons - gastric pH 7 – no acid related symptoms (Abraham SC et al Am J Surg Pathol 2005)
But morphology indistinguishable from ZES

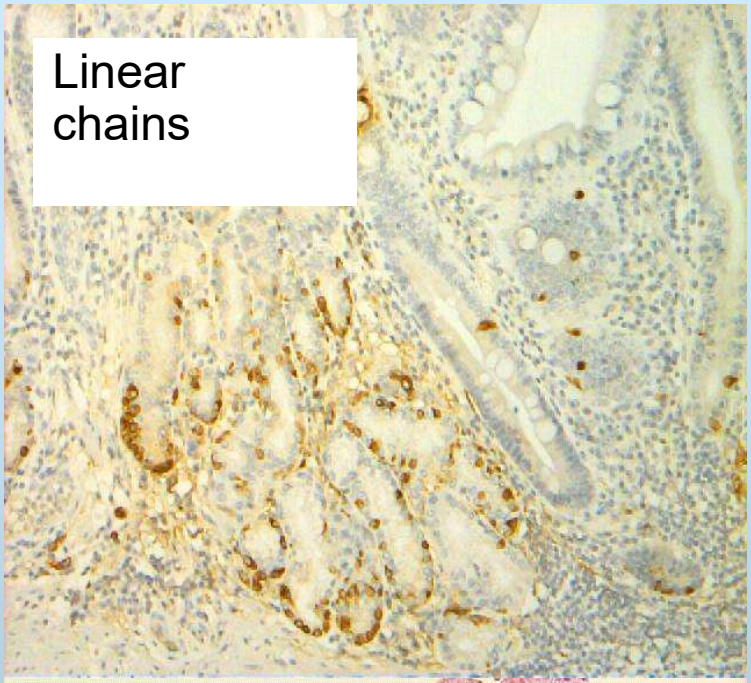


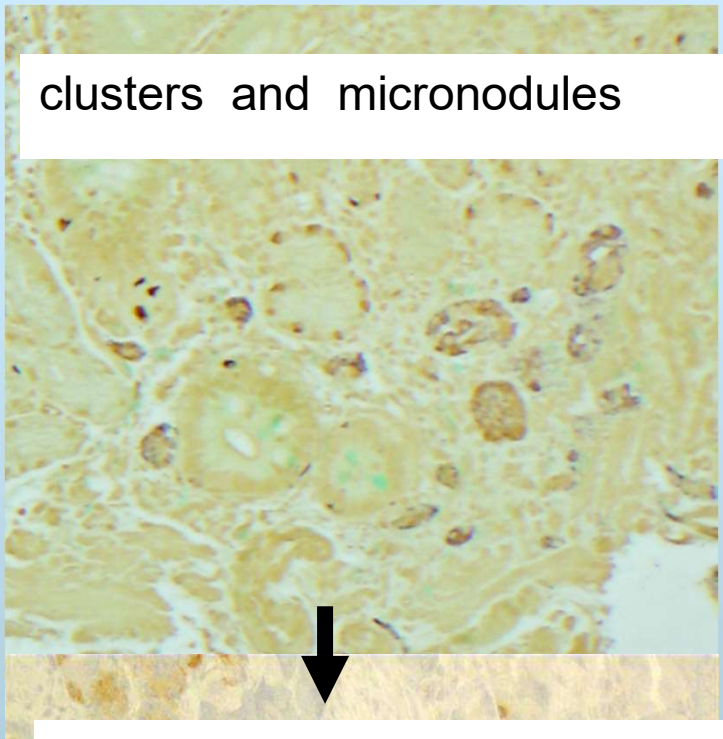


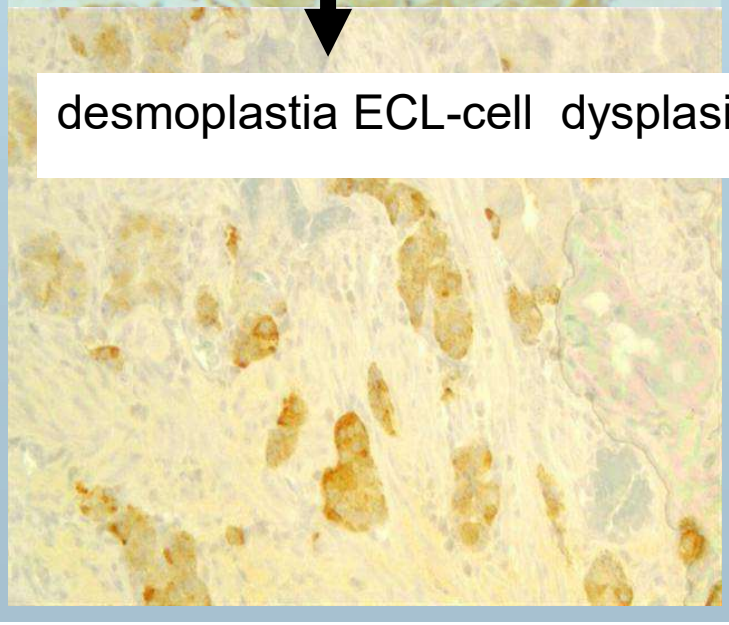
Type 1. Atrophic /AutoImmune Gastritis (loss of oxyntic mucosa)

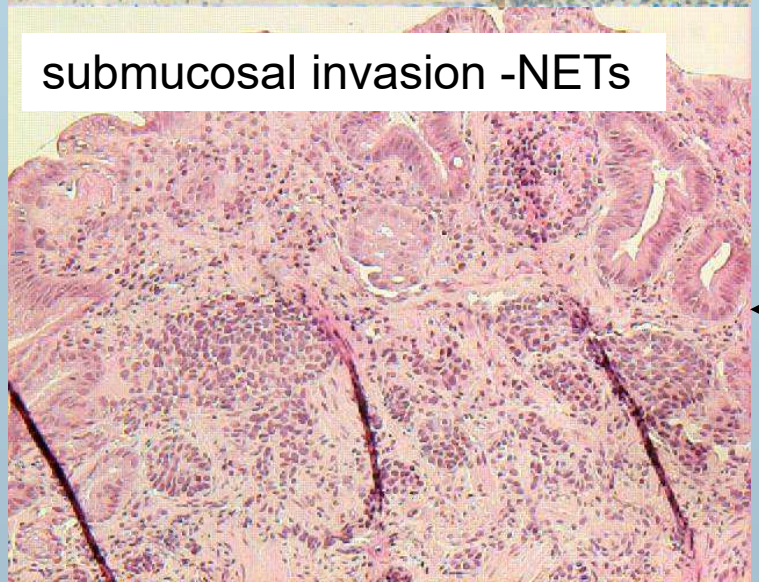
- Parietal cell loss (low acid) induces hypergastrinemia which induces ECL hyperplasia (Do serology – IF, PC Abs, B12)
- Endocrine cells form linear hyperplasia
- Eventually form clusters and micronodules /microcarcinoids (DON'T sign out as NETs)
- Later develop early desmoplastic stromal reaction (ECL dysplasia)
- Enlarge and invade submucosa (NETs)
- Long term risk is IM-dysplasia –Ca
  - Eradicate Hp if still present.

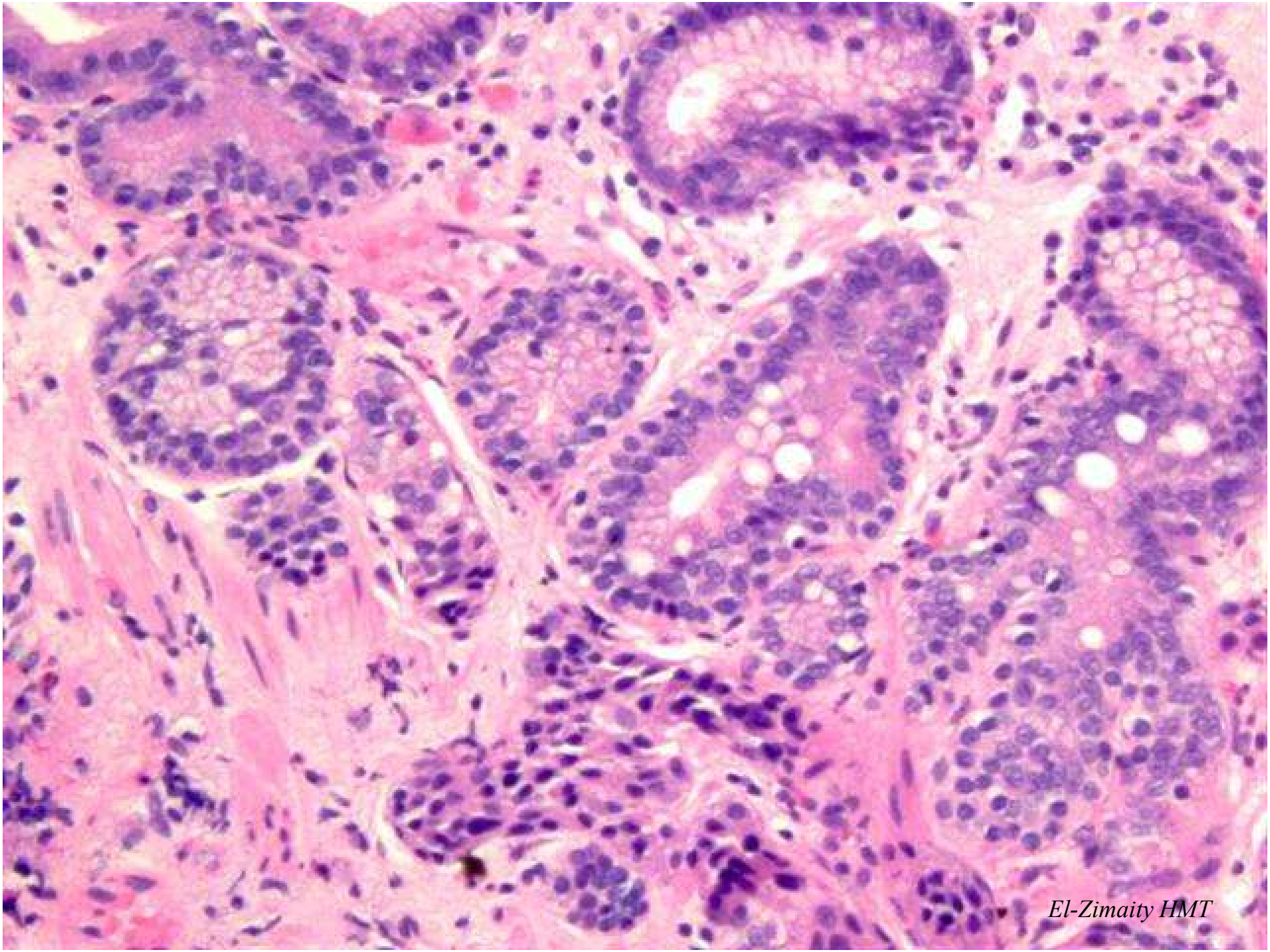
ECL- Proliferation



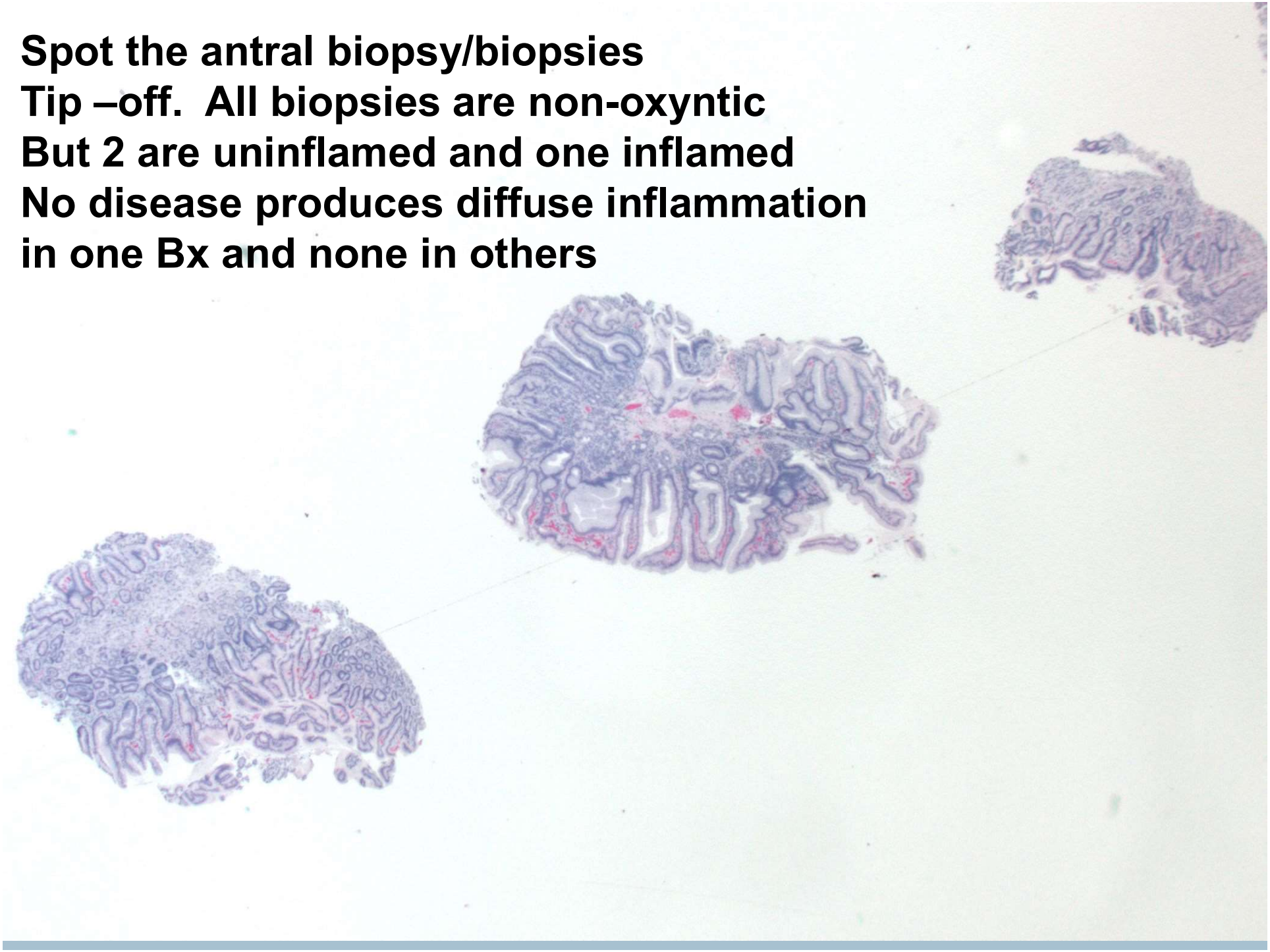


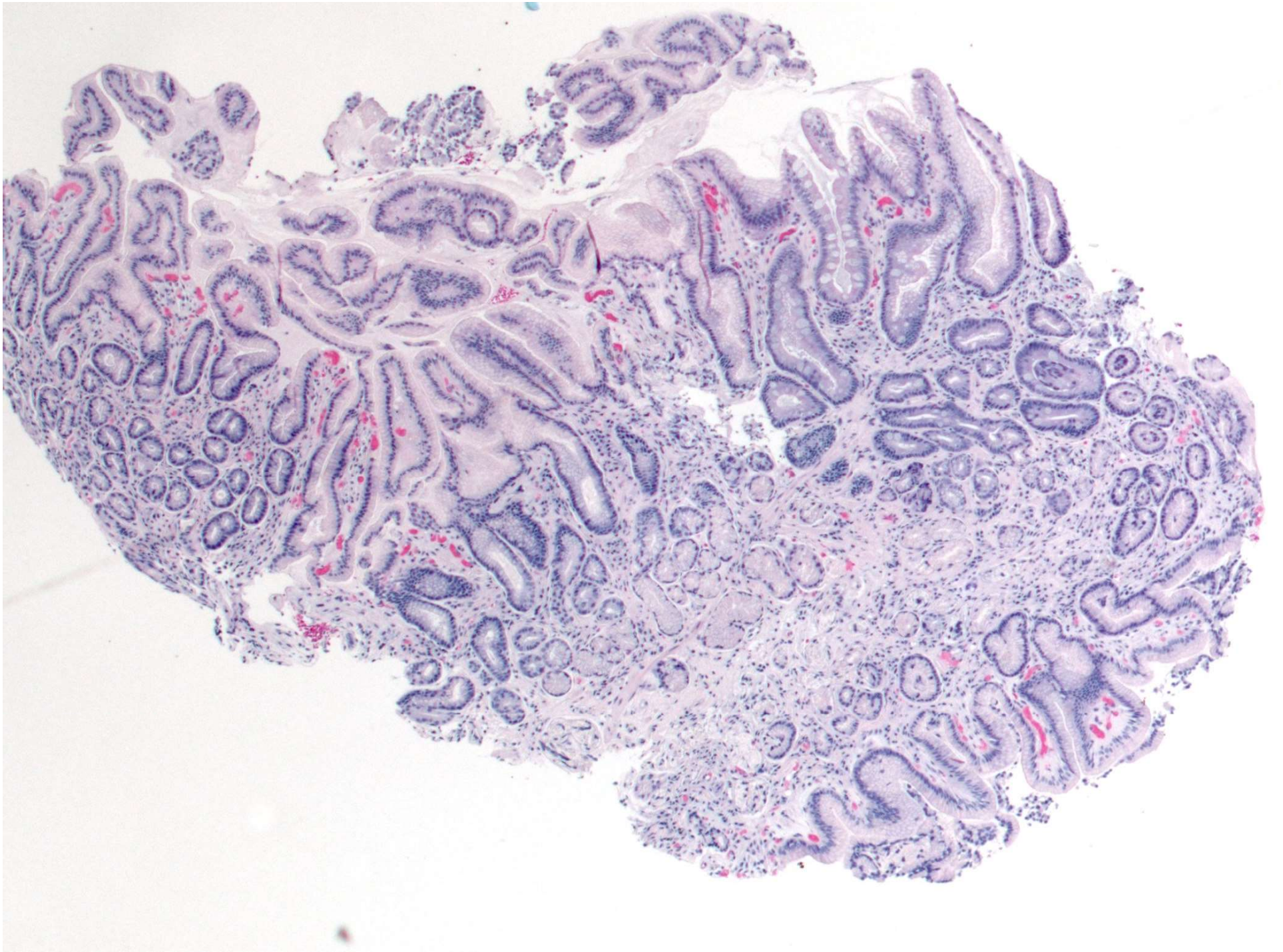


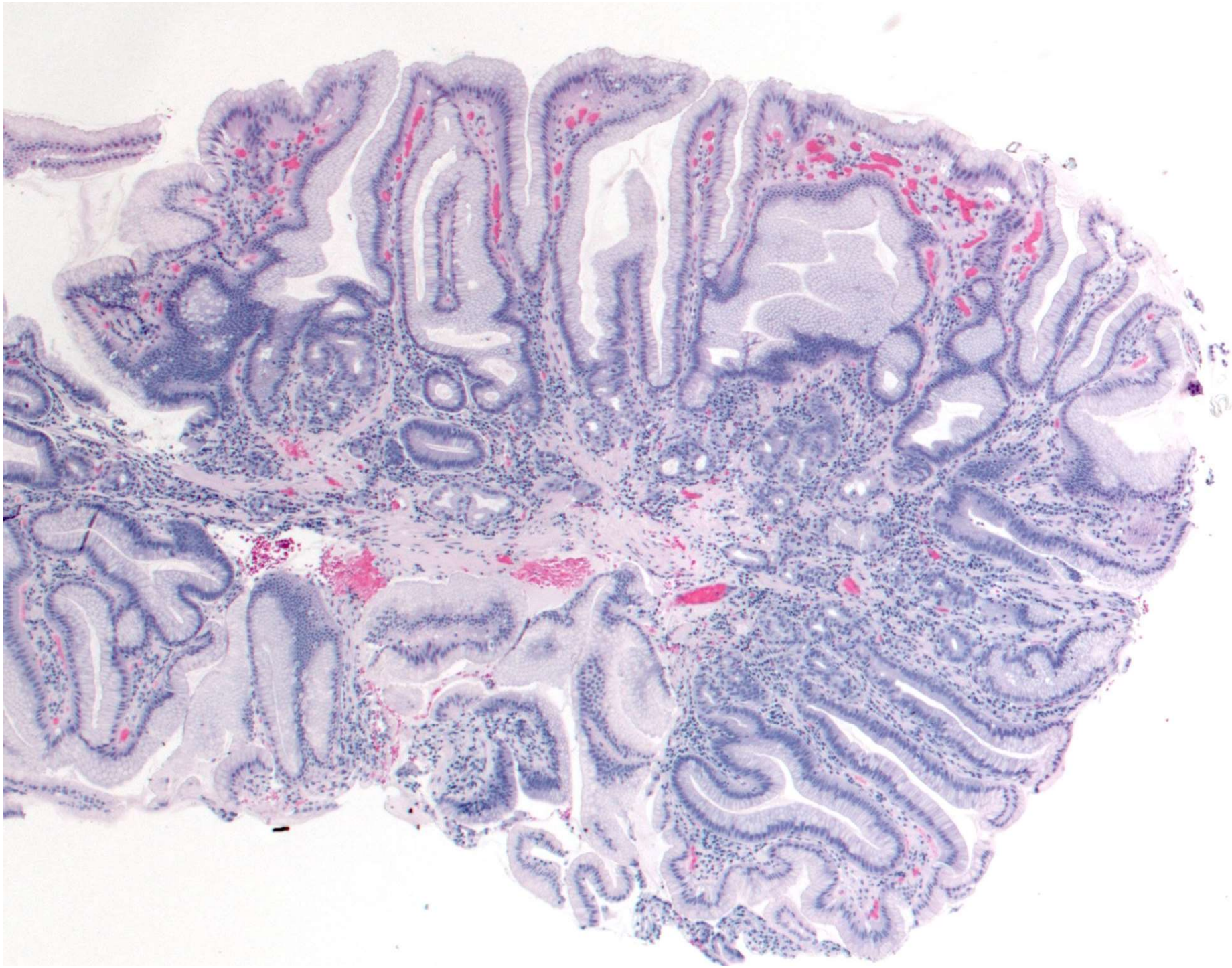


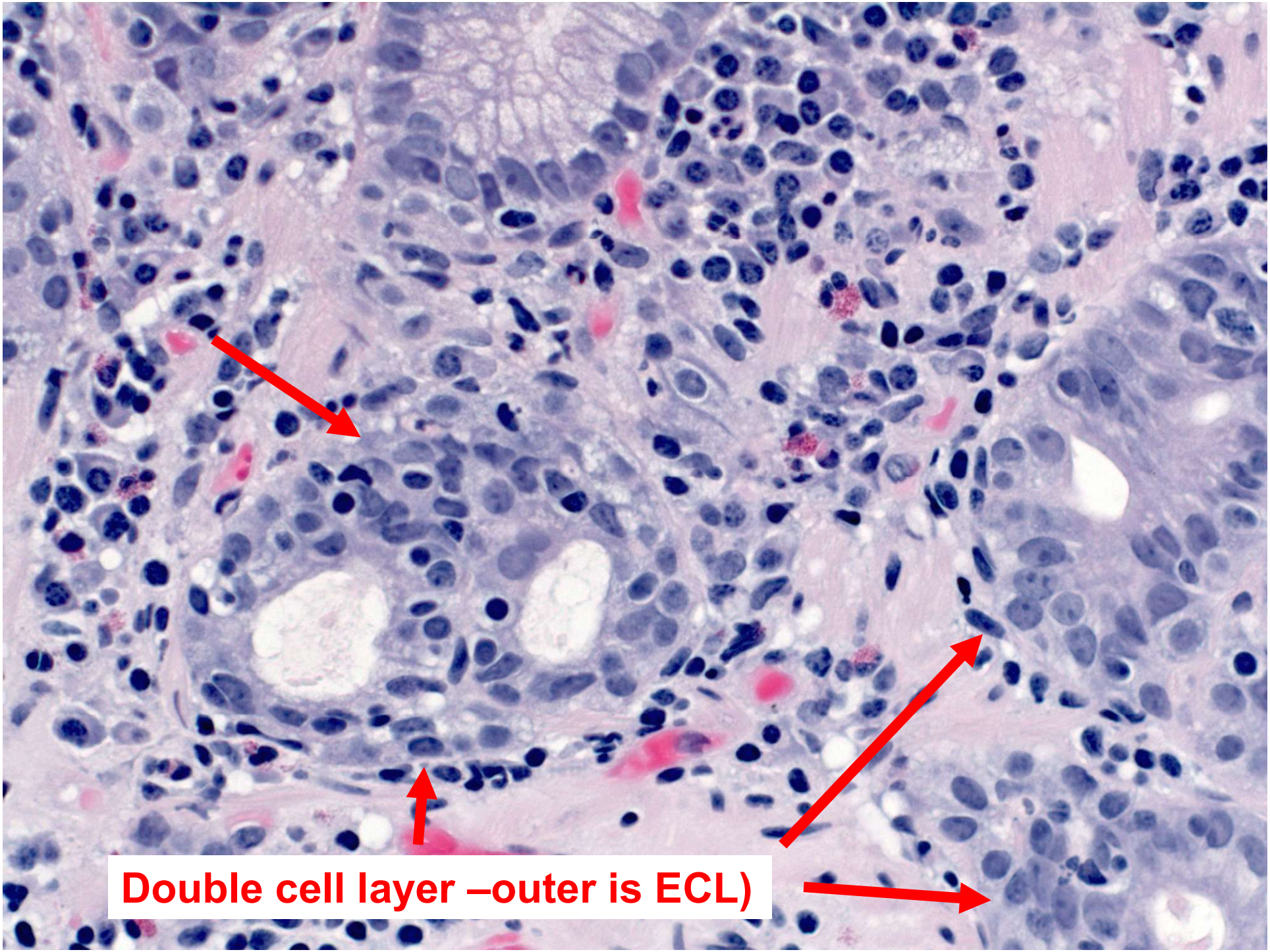

El-Zimaity HMT

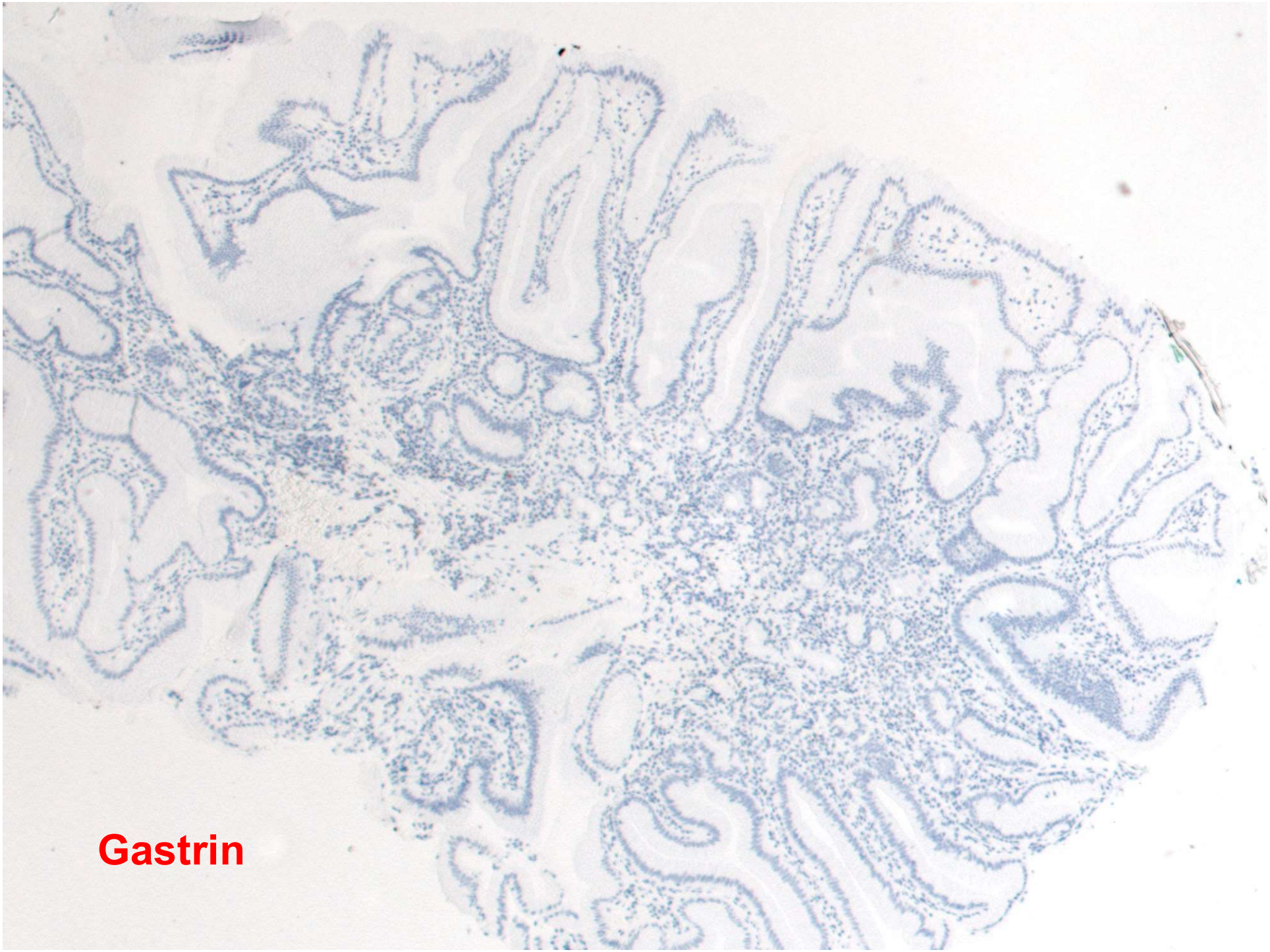
Spot the antral biopsy/biopsies
Tip –off. All biopsies are non-oxyntic
But 2 are uninflamed and one inflamed
No disease produces diffuse inflammation in one Bx and none in others

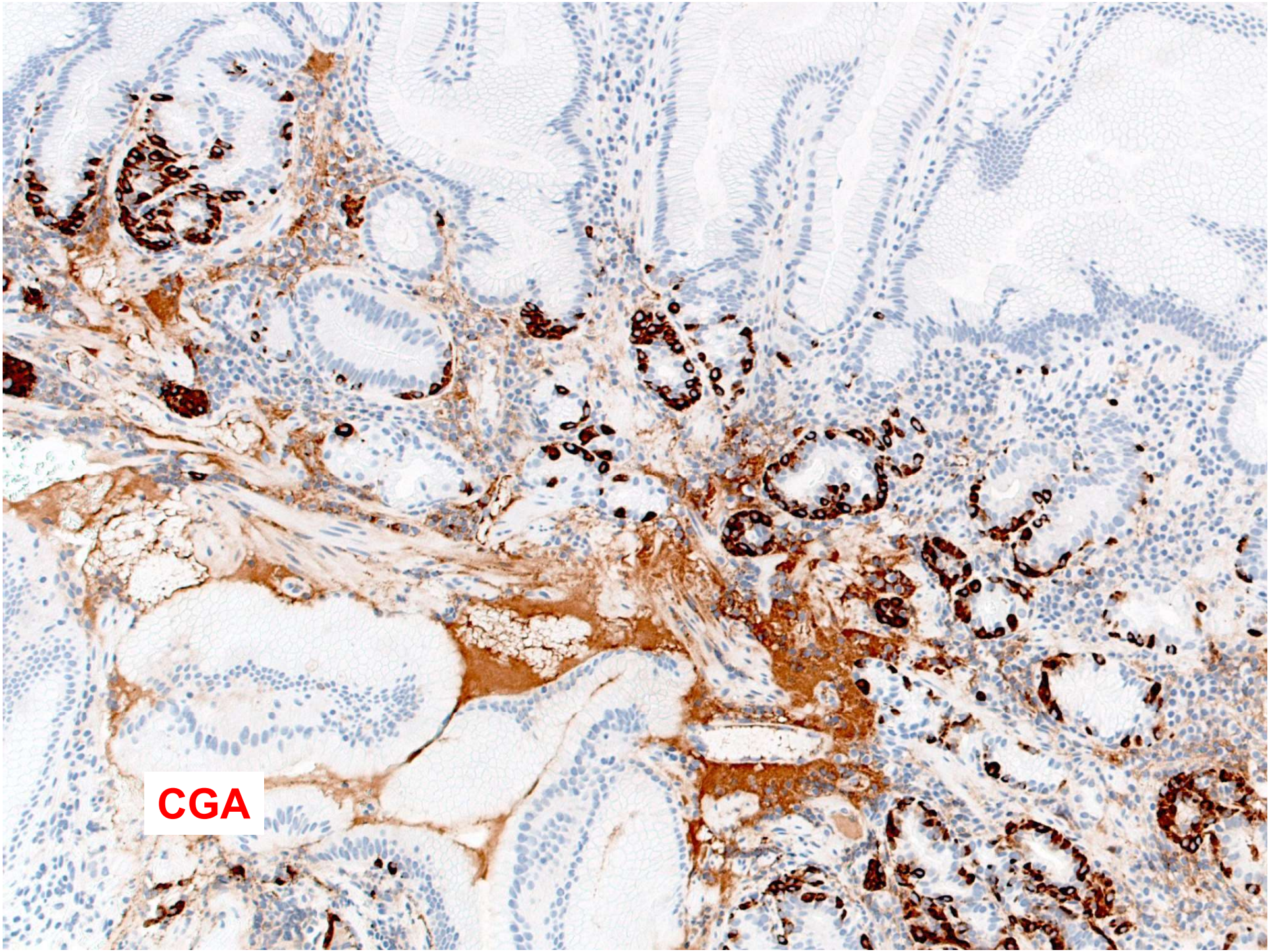







Double cell layer –outer is ECL)


Gastrin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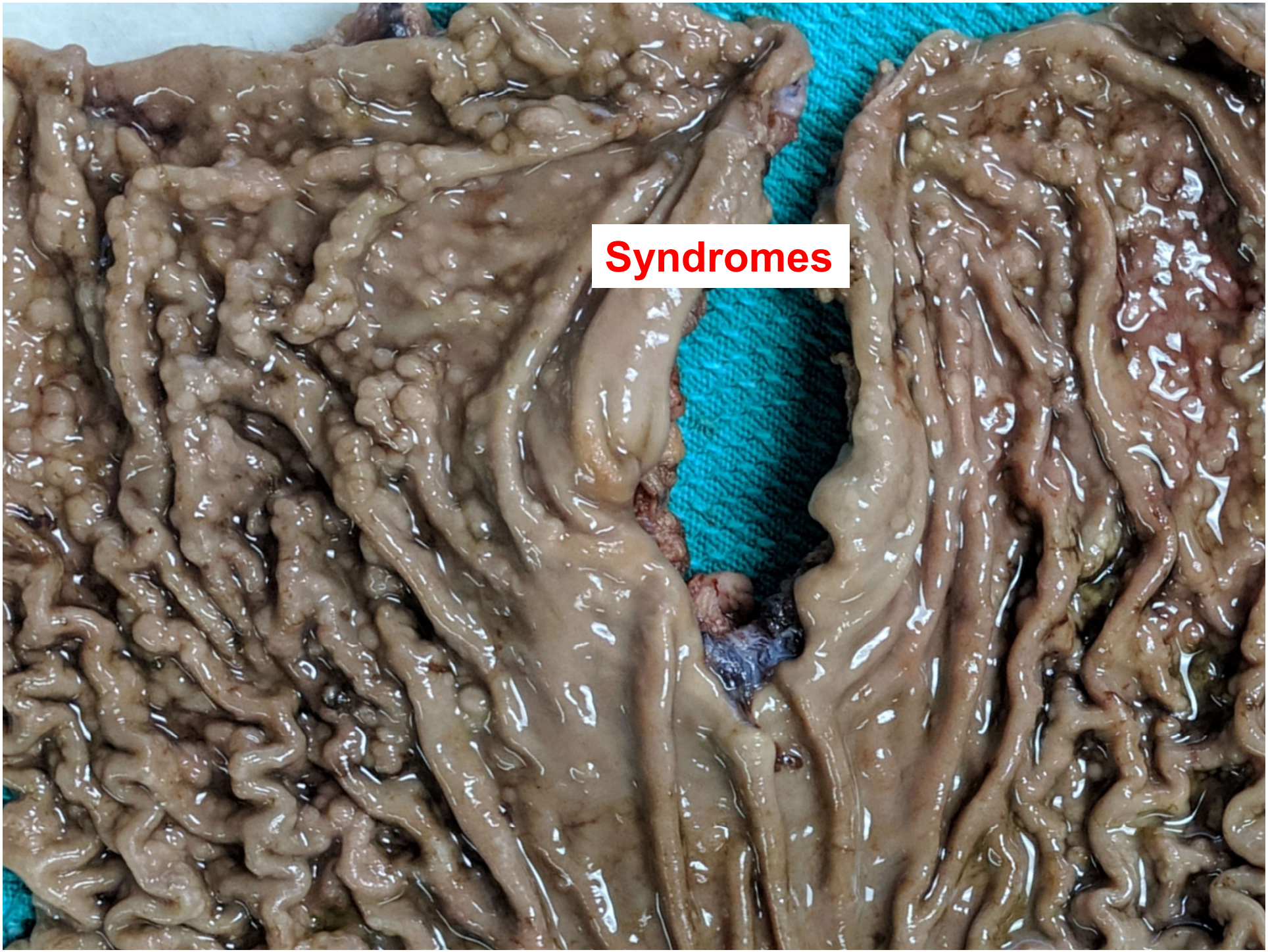

Syndromes

Stomach in FAP

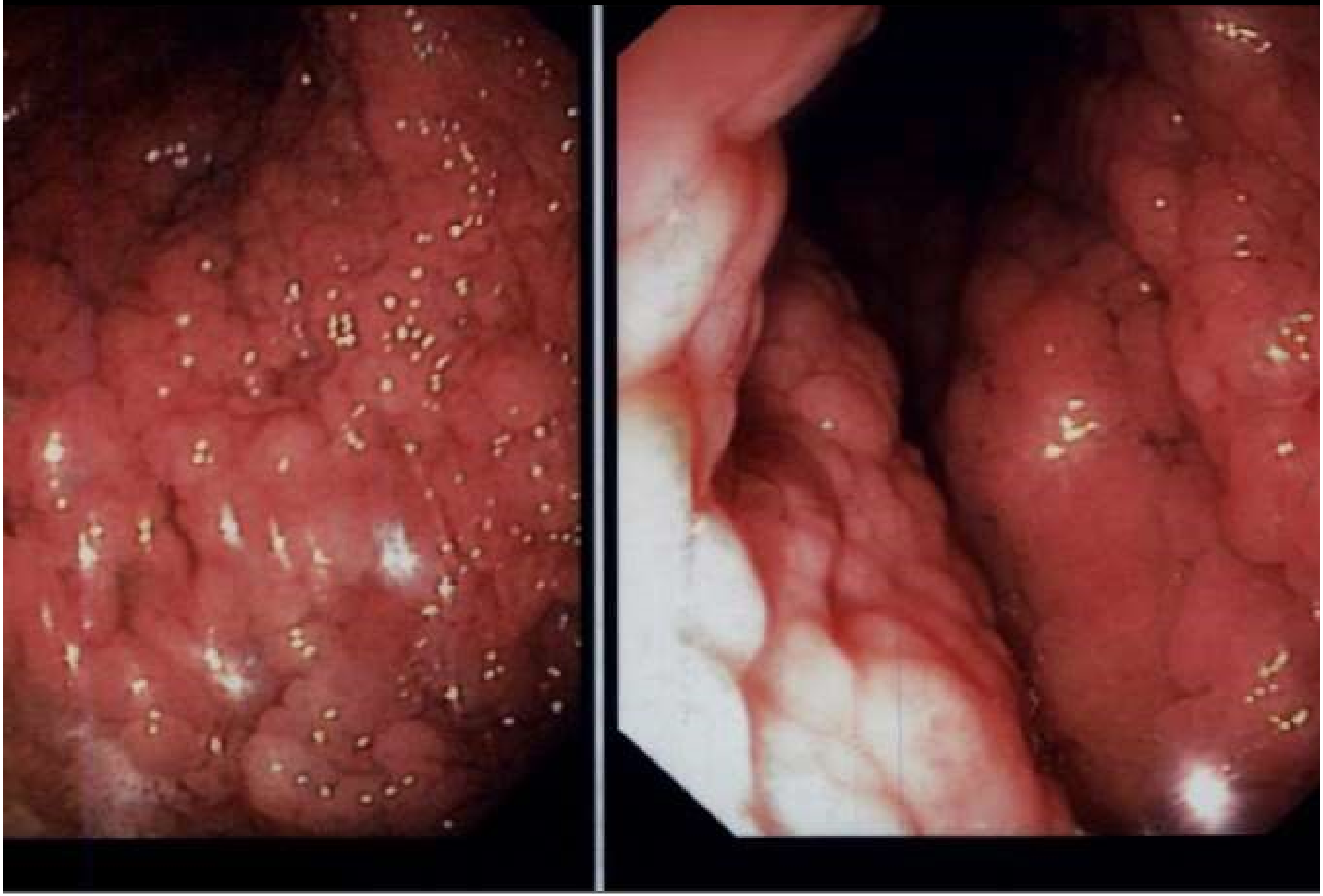
- Fundic gland polyps/polyposis
- Dysplasia in 25-45%
  - IFD/LGD (HGD and Ca rare)
- If known FAP/AFAP only biopsy if "suspicious"
  - Large, ulcerated

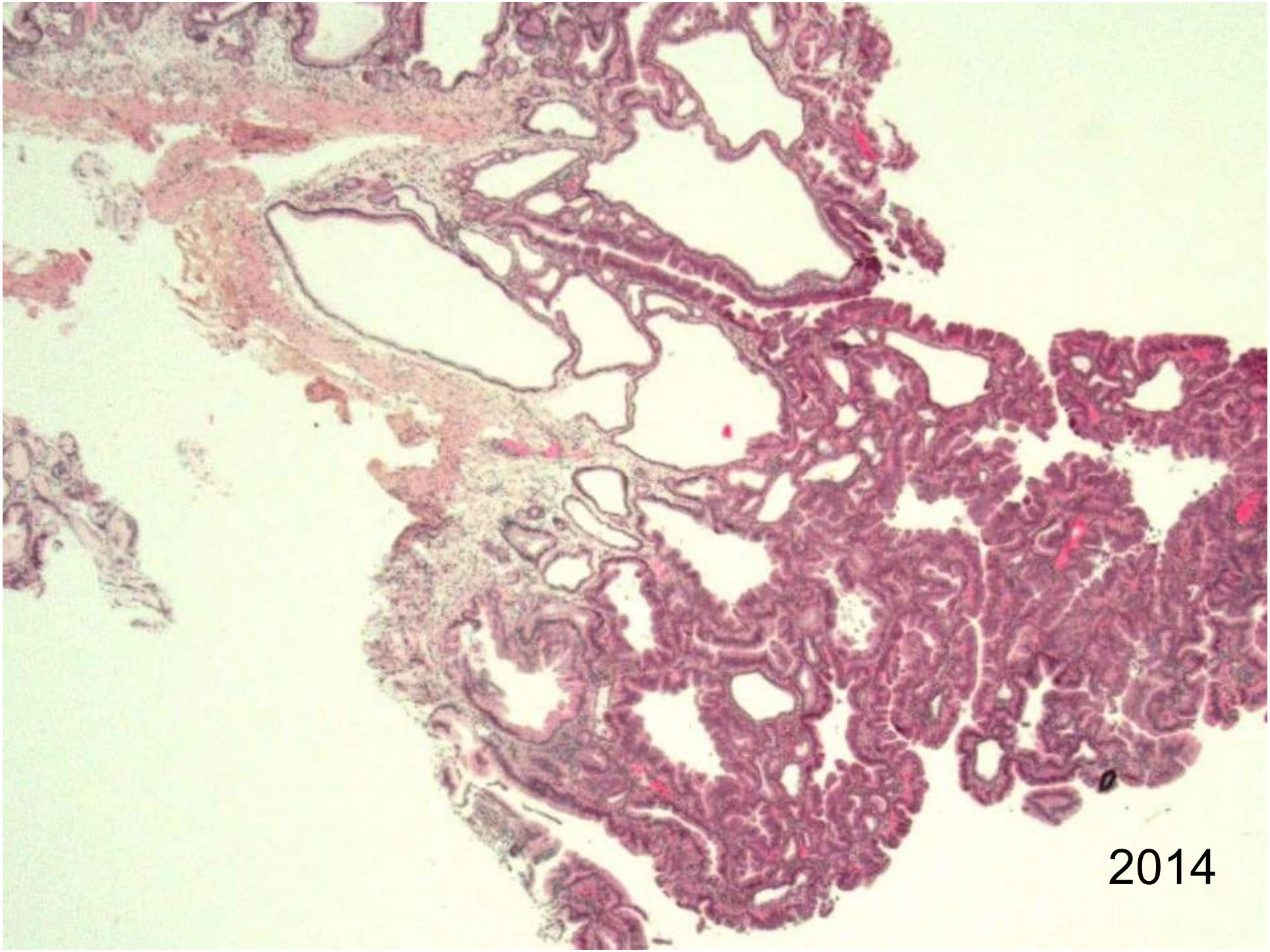
- Multiple dysplastic FGPs – NO known FAP
  - Presence of antral or duodenal/ampullary adenomas should alert to possible presence of underlying FAP or GAPPS.

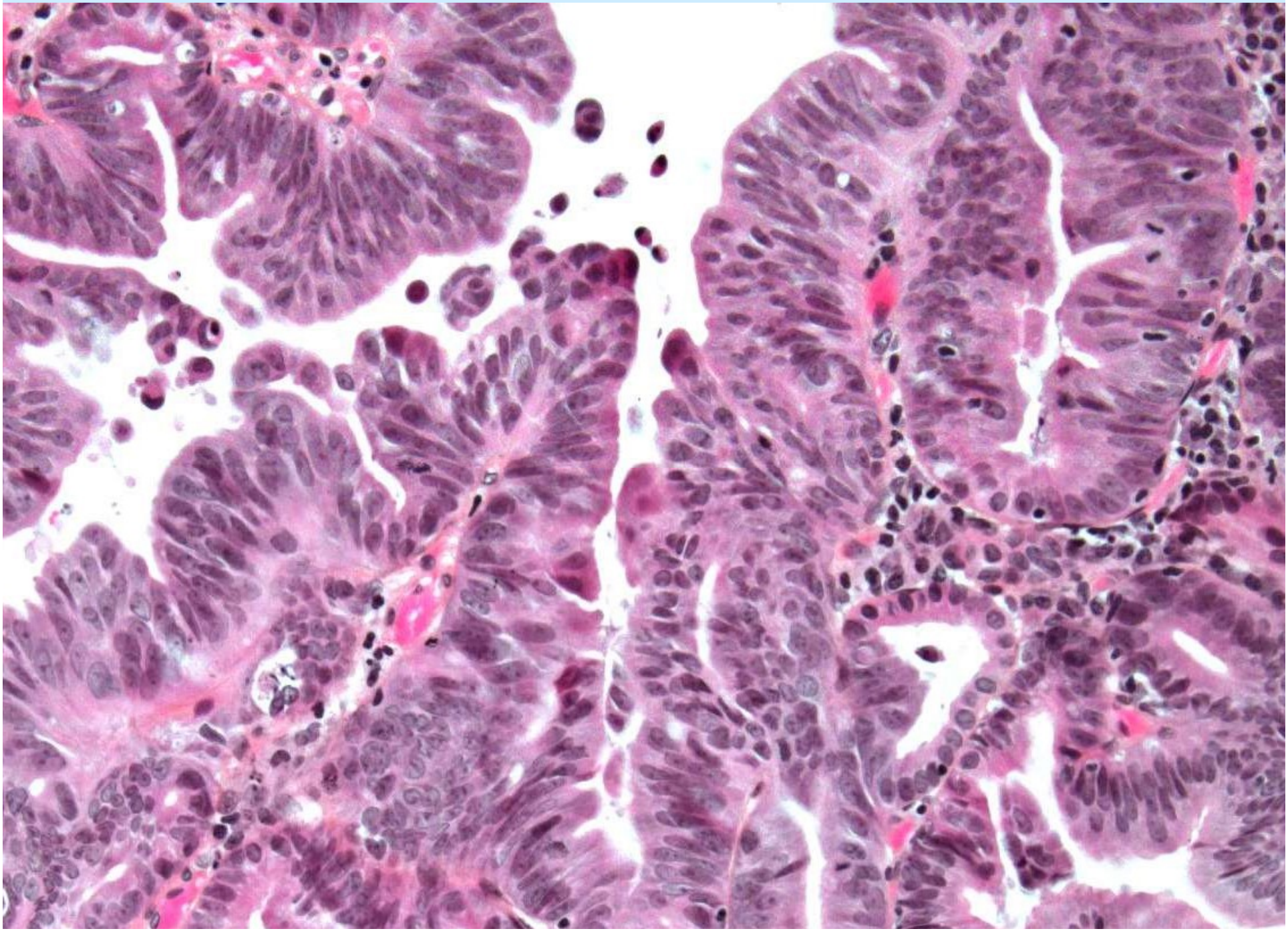
Case Hx

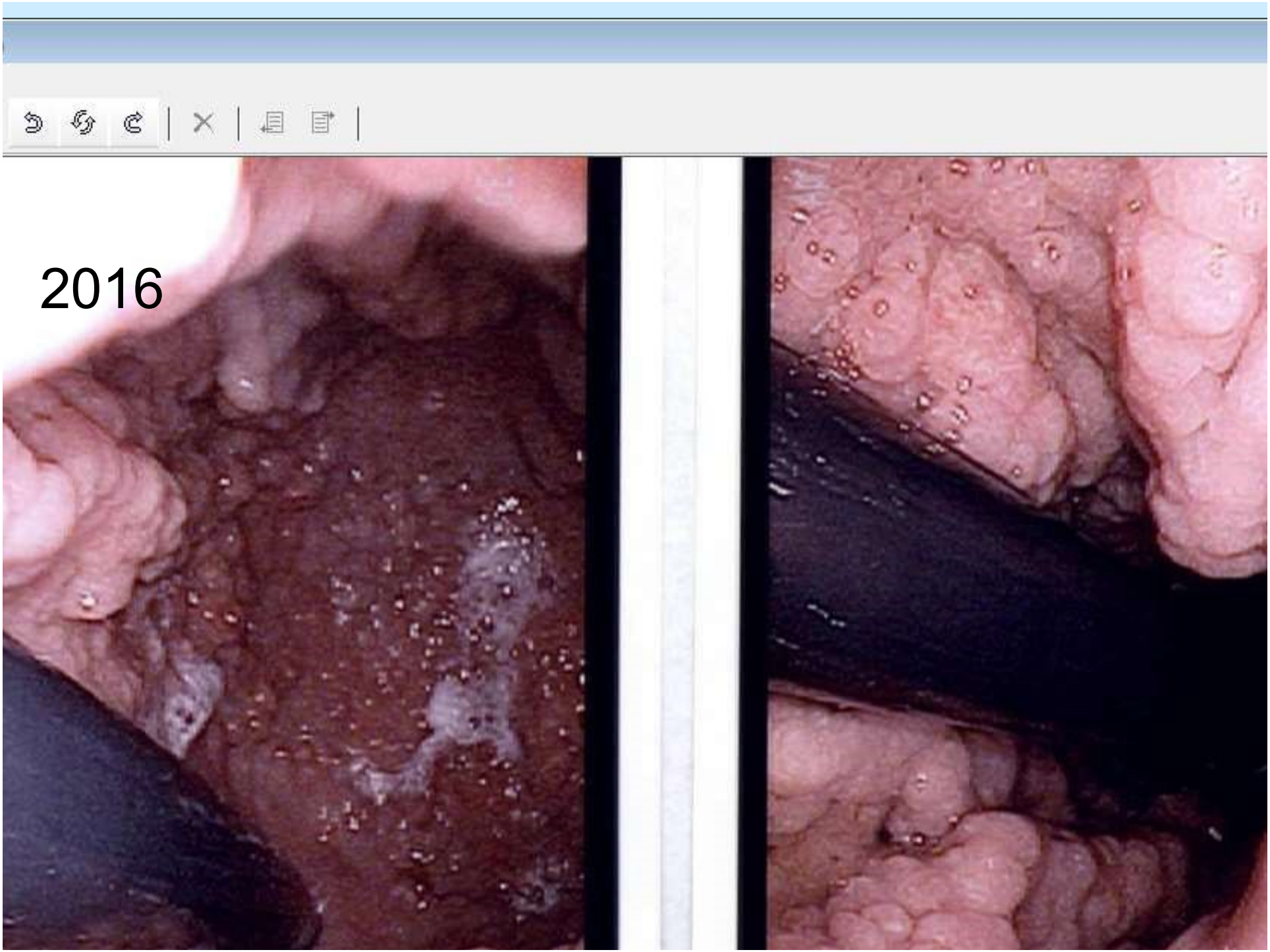
- 71 y/o female with 20 yrs of acid reflux
- Omeprazole since 1998
- First UGI endoscopy in 2000 showed diffuse FGP involving 80% of the body and fundus and normal antrum
- Followed up every few years

Courtesy Dr Paul Manley Kingston, ON



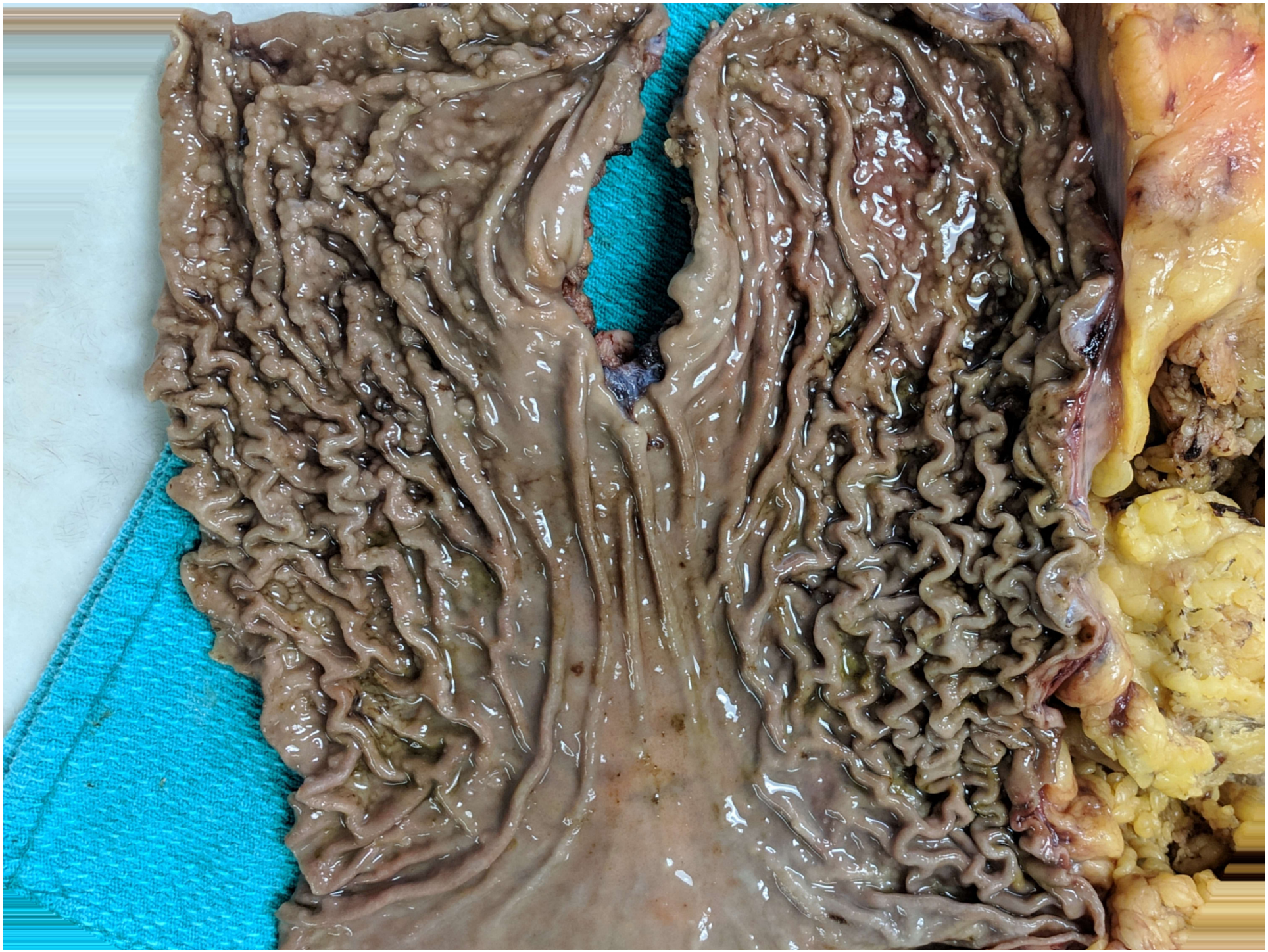

2014

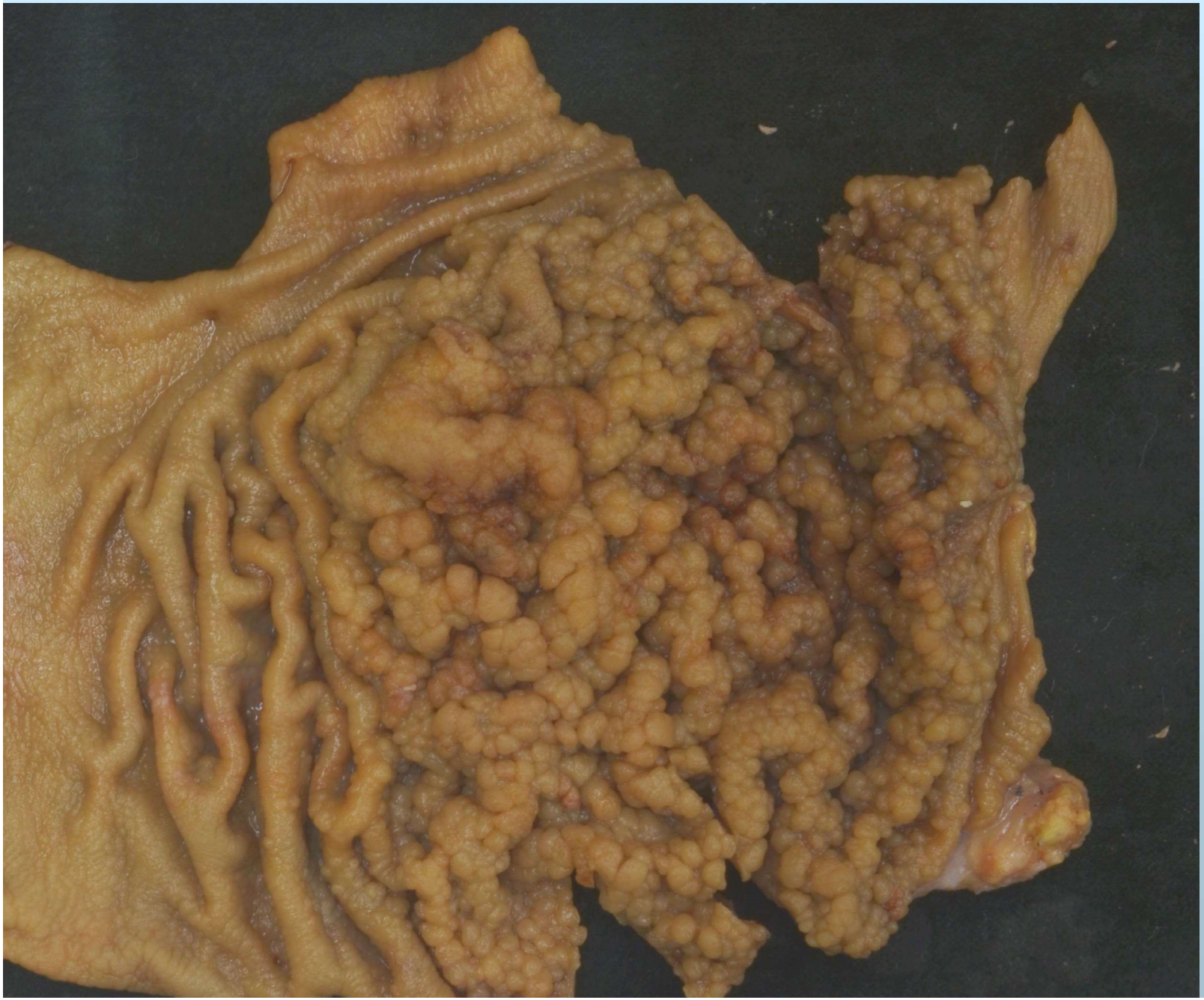


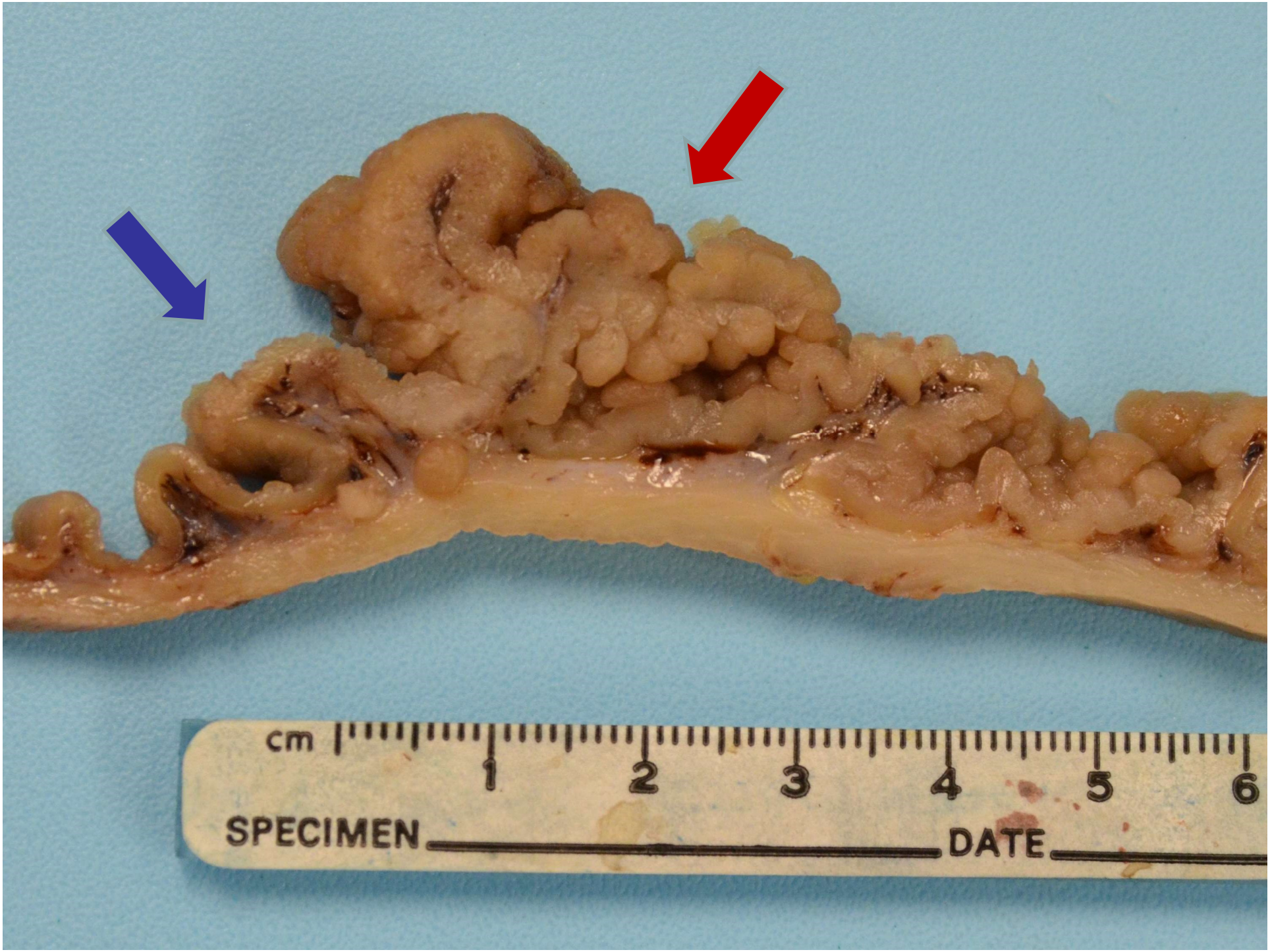

2016

Gastric Adenocarcinoma with Proximal Polyposis (GAPPS) was suggested in 2014 and she was tested for it in 2016

- Found to have a pathogenic mutation in the APC 1b promoter diagnostic of GAPPS
- 2 children tested and found to be carriers of the mutation and have gastric polyps



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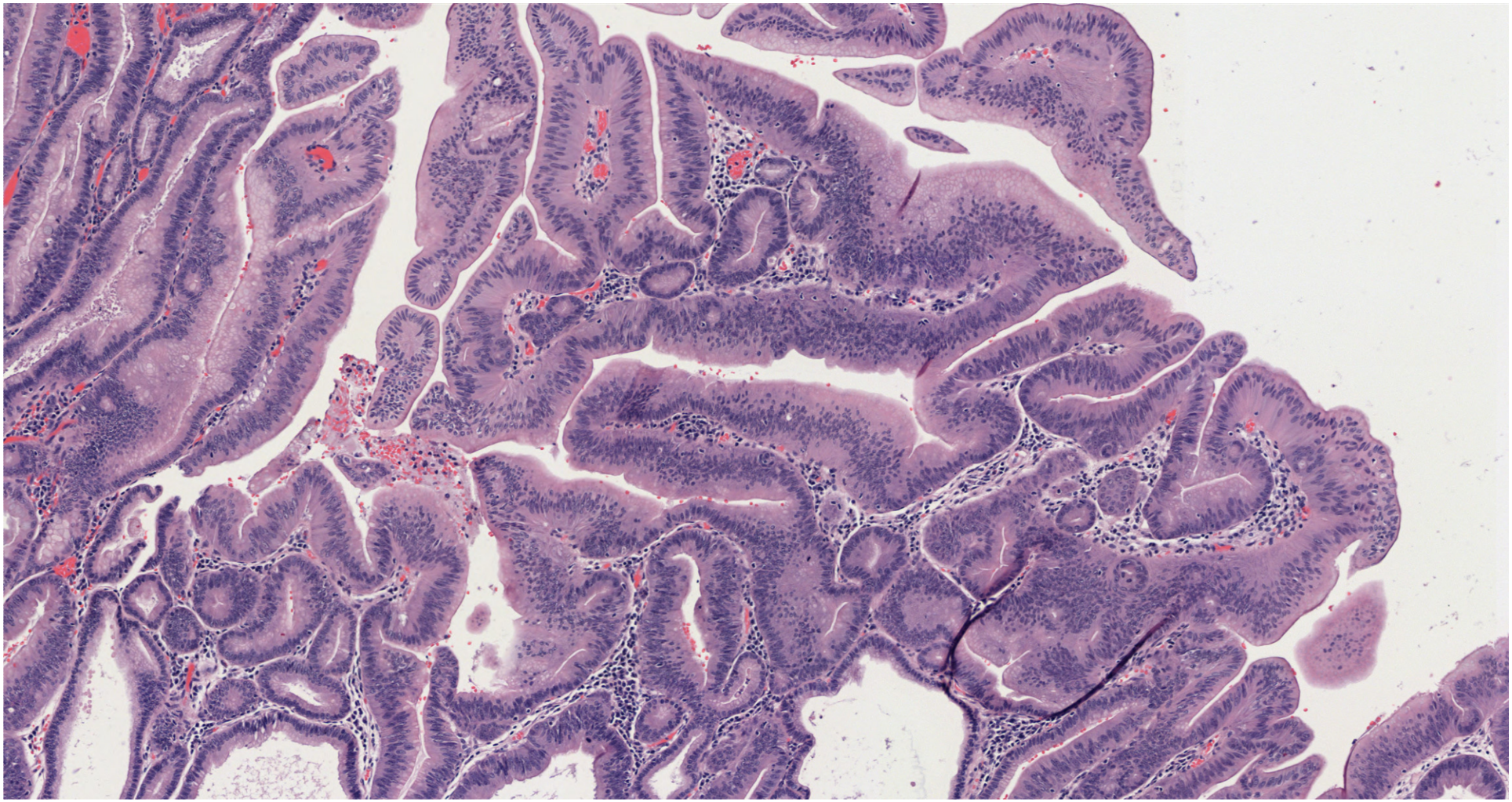
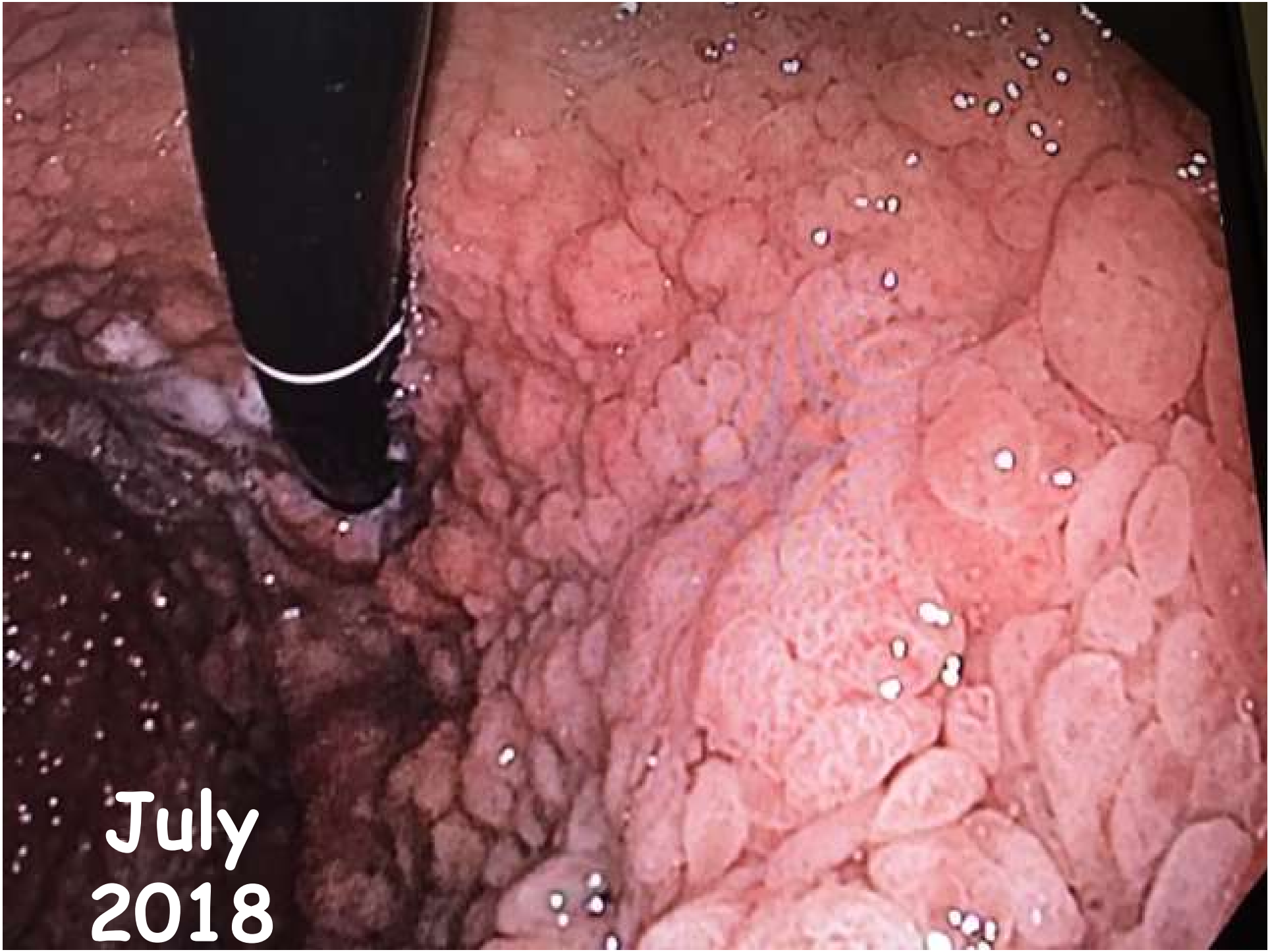
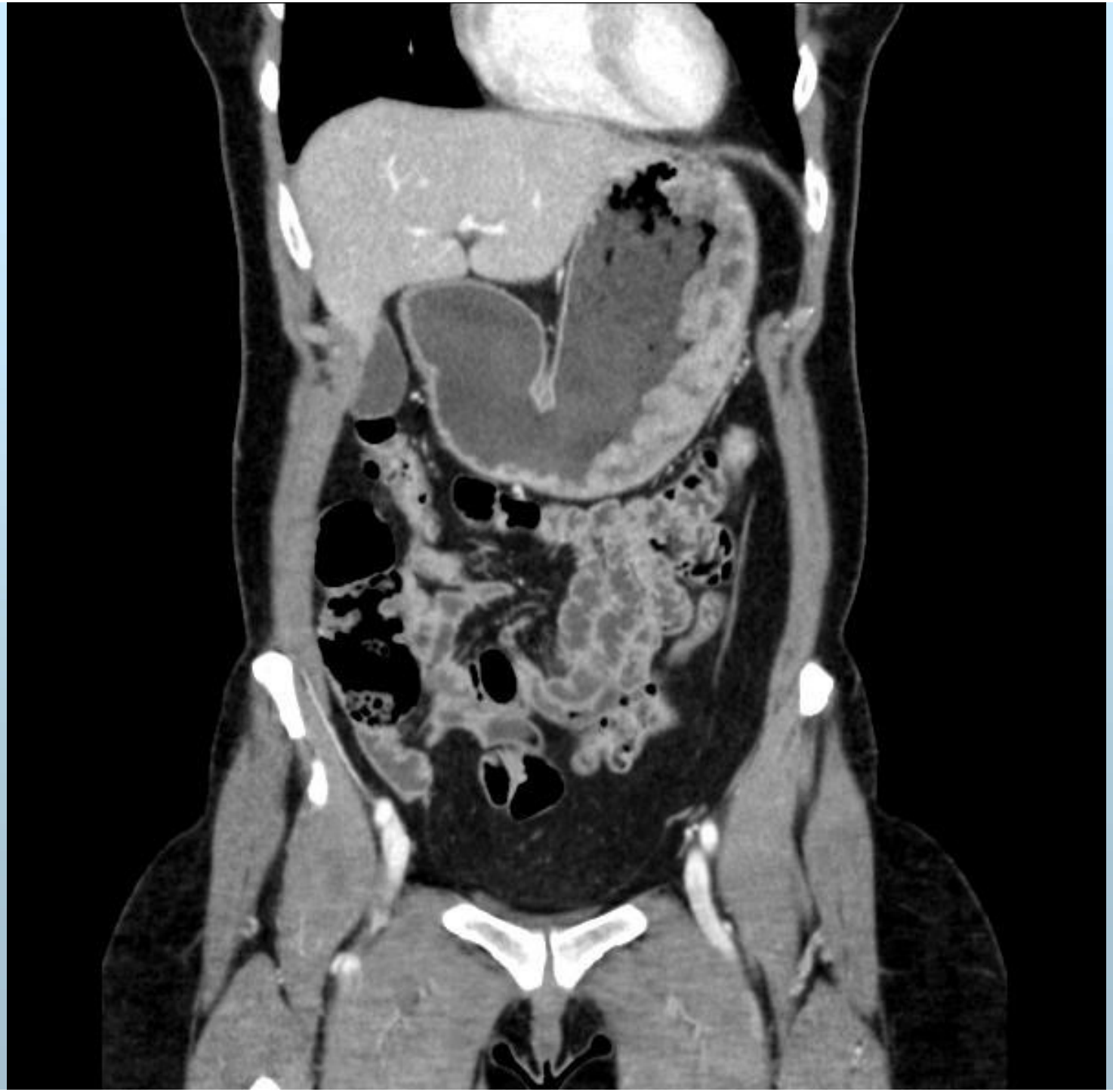
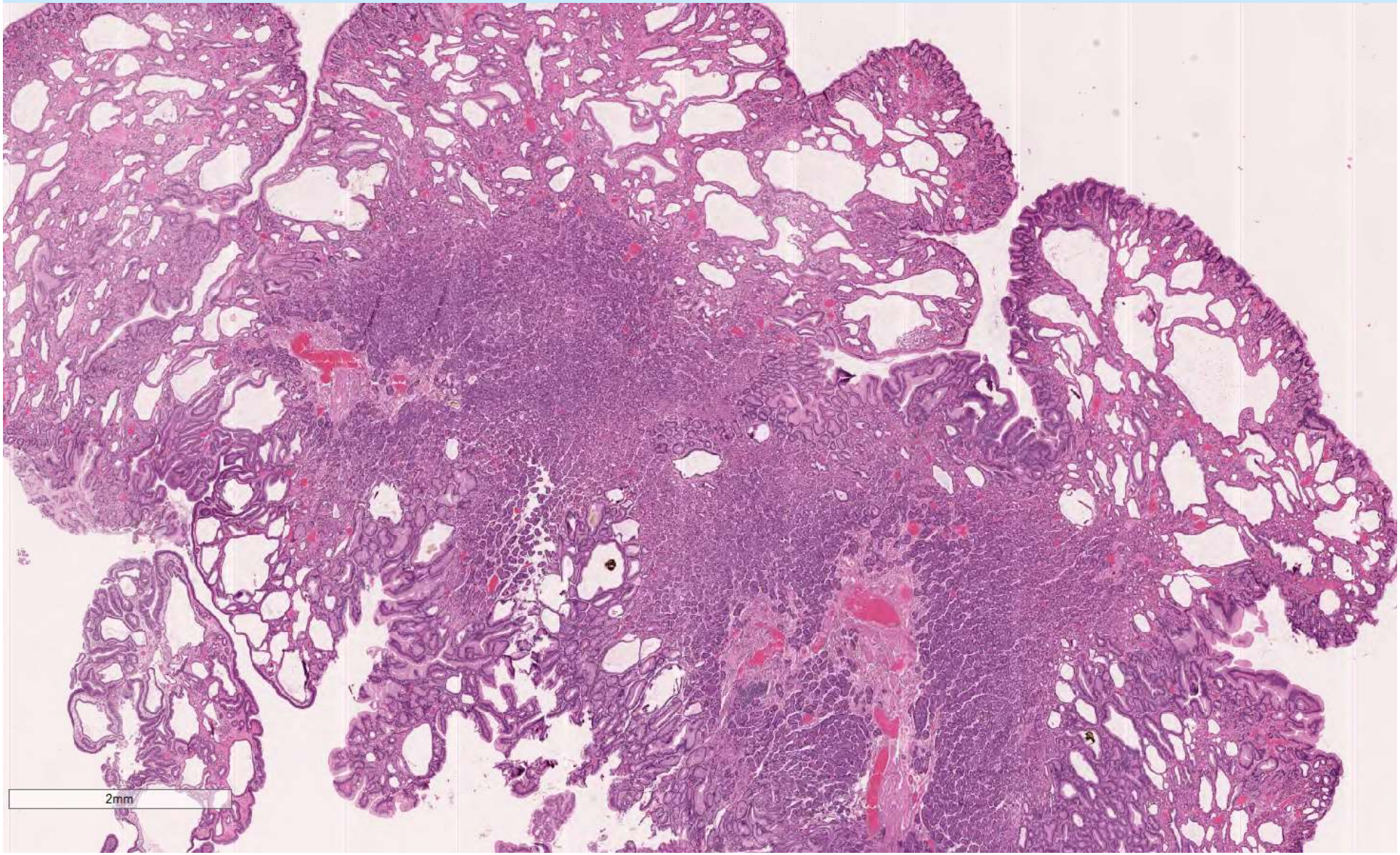


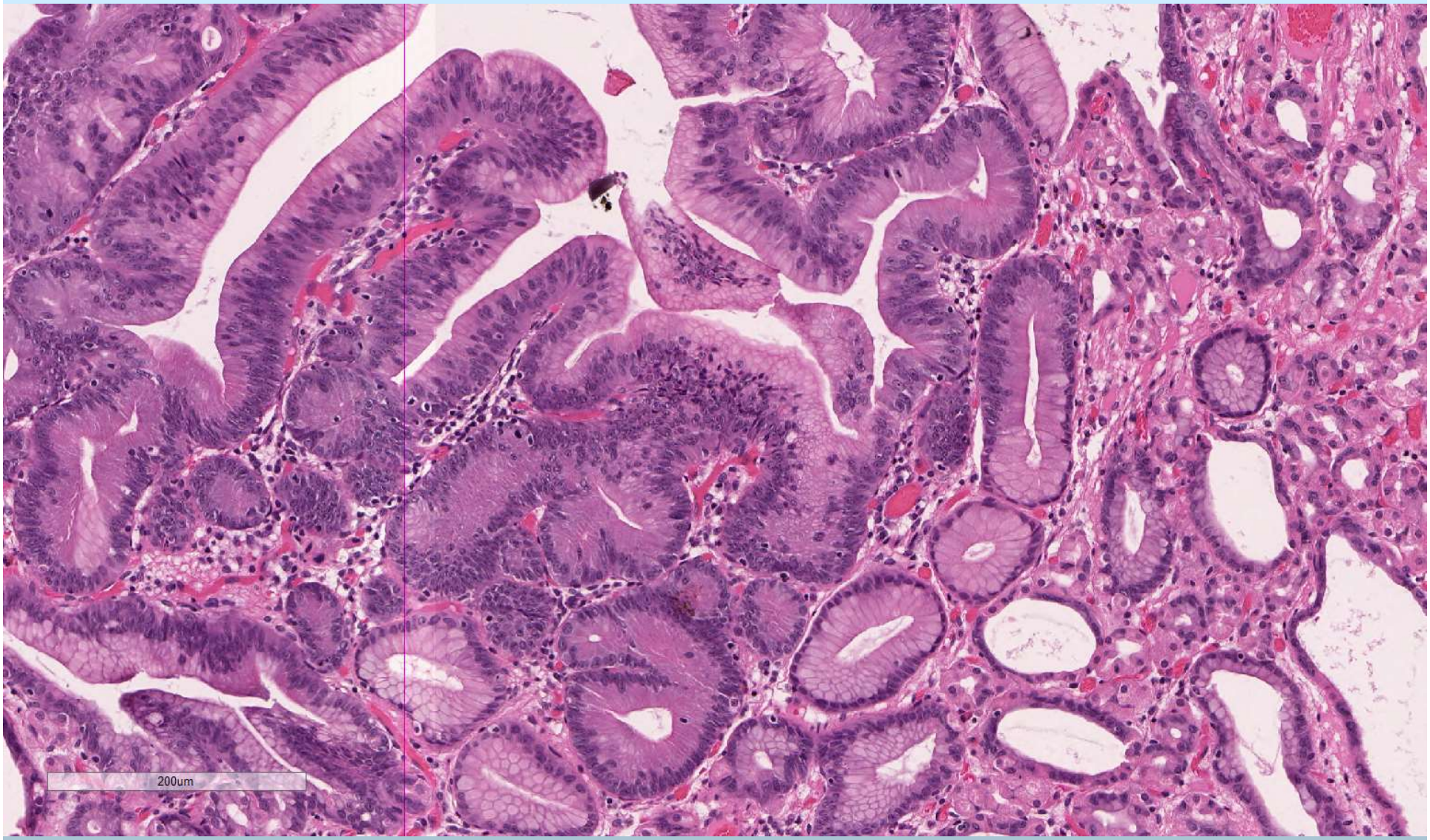
- A 53 y.o. woman with a history of multiple gastric polyps, undergoing endoscopic surveillance (unrelated)


July
2018



Biopsy (2018)

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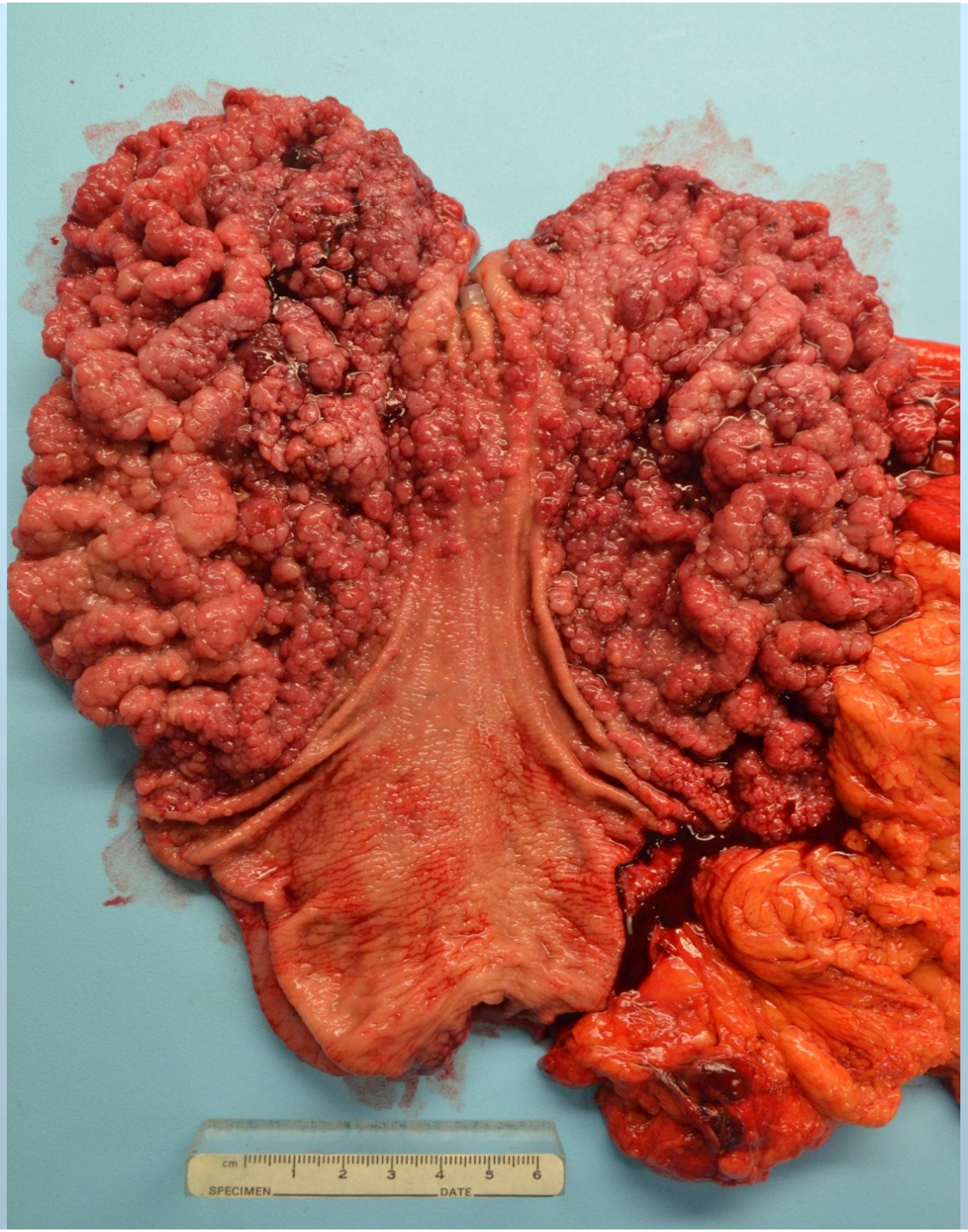
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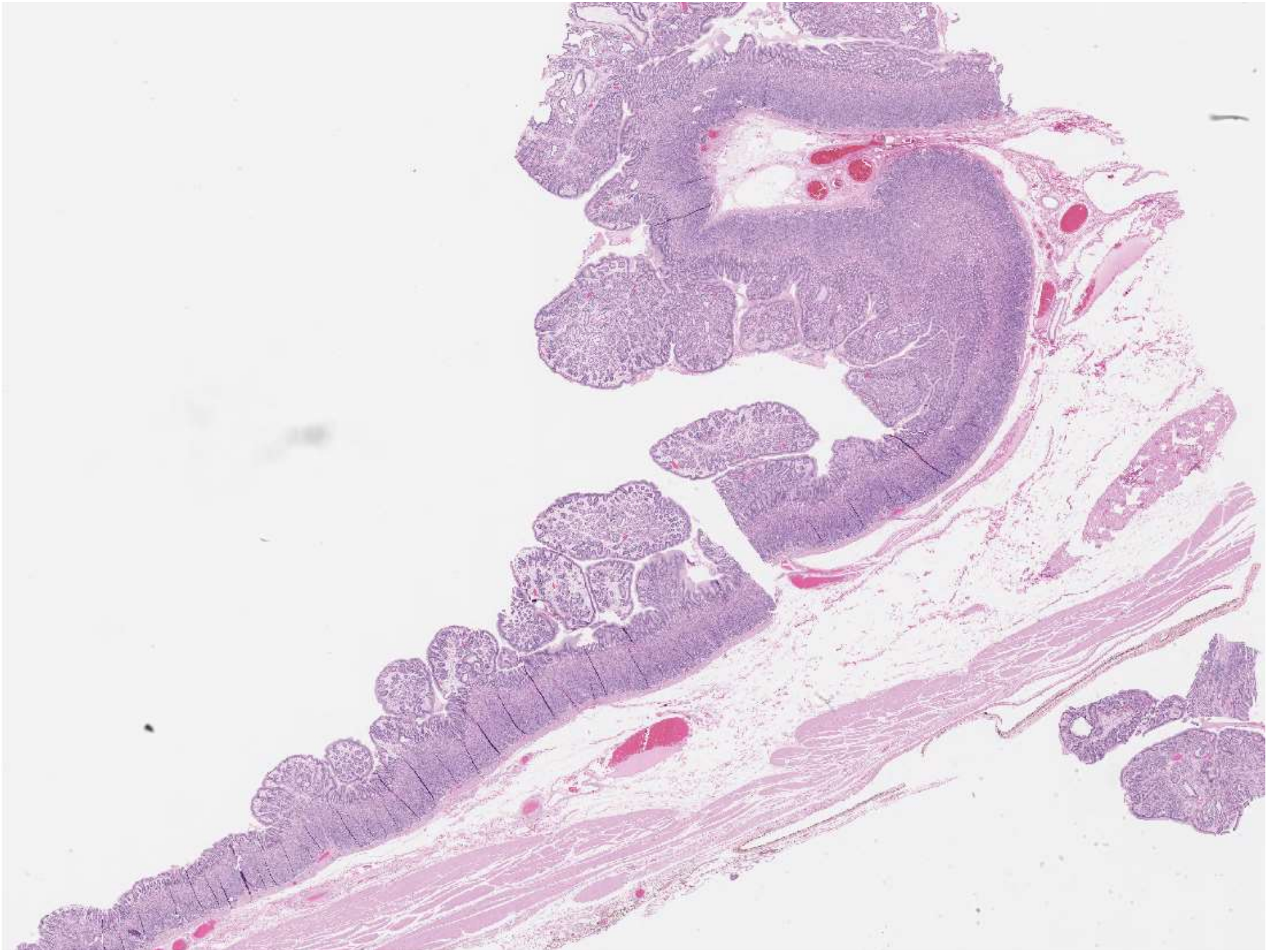

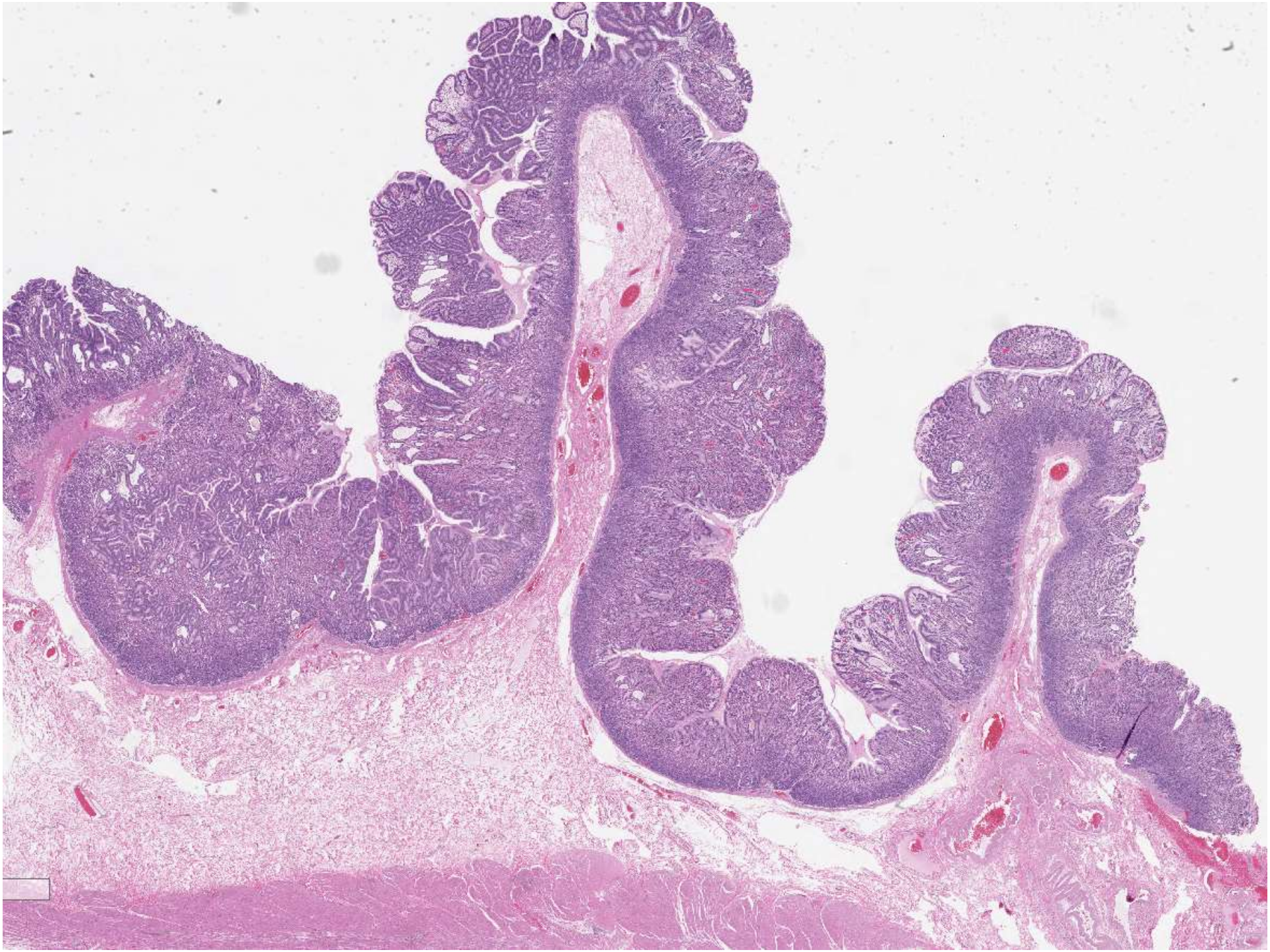

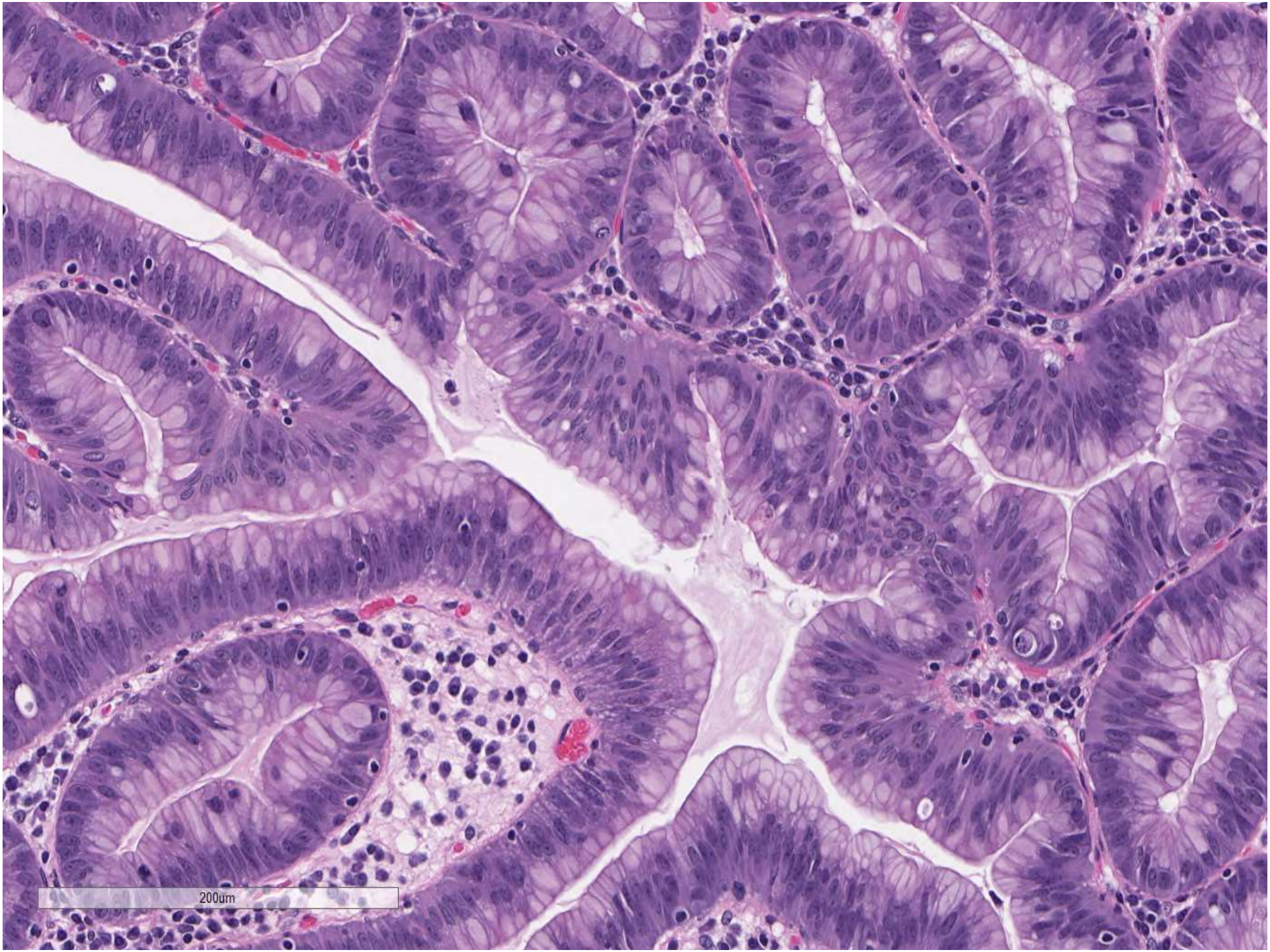
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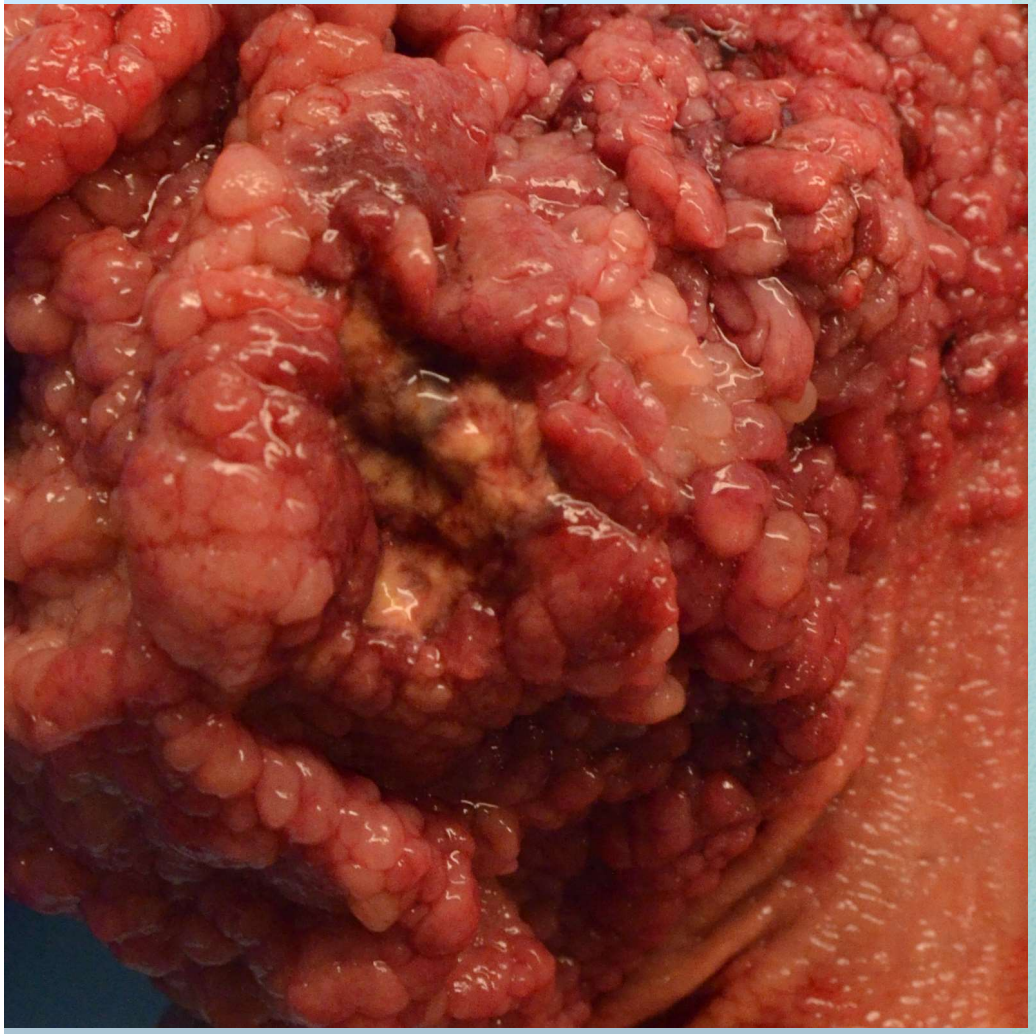

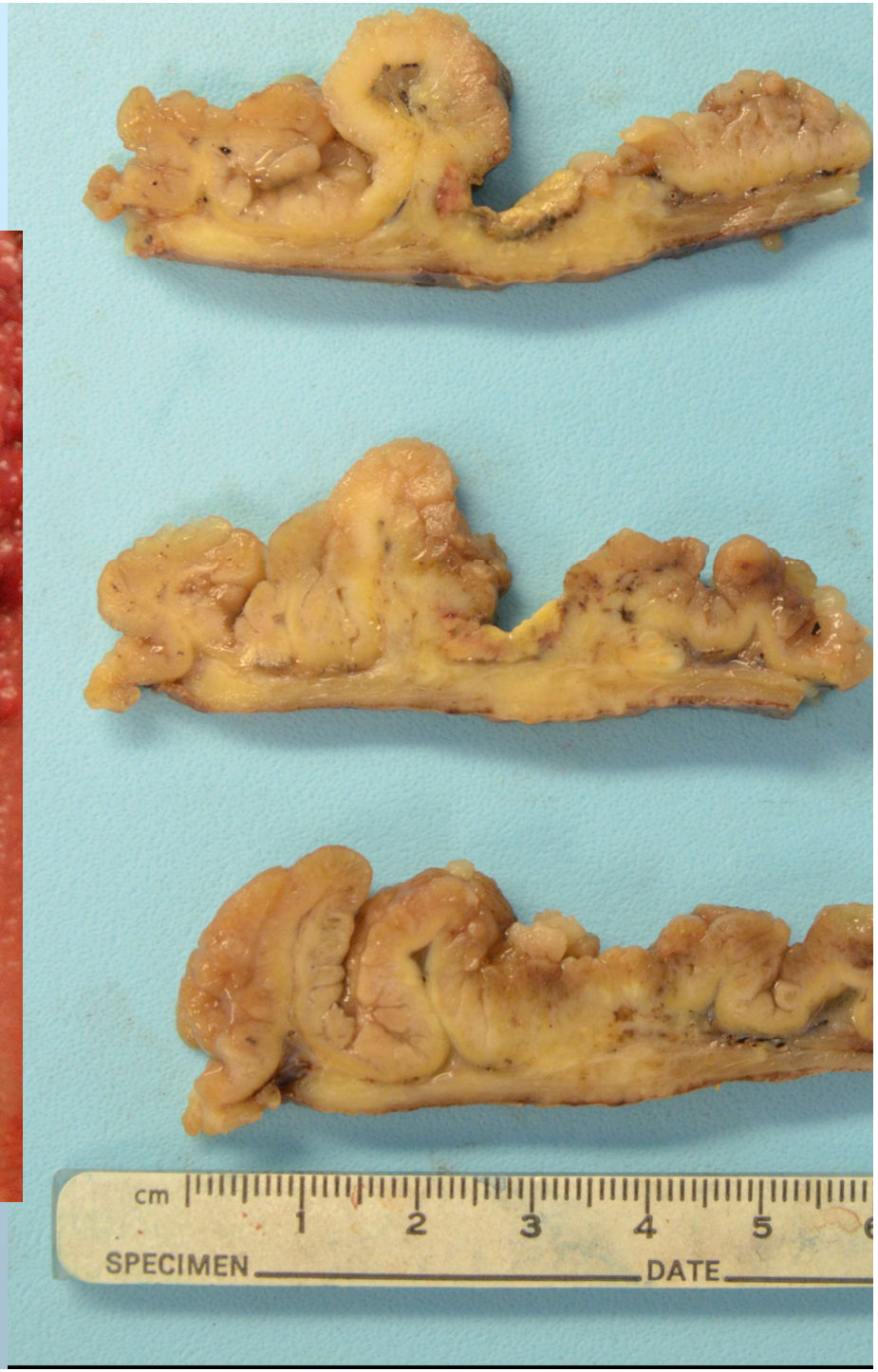
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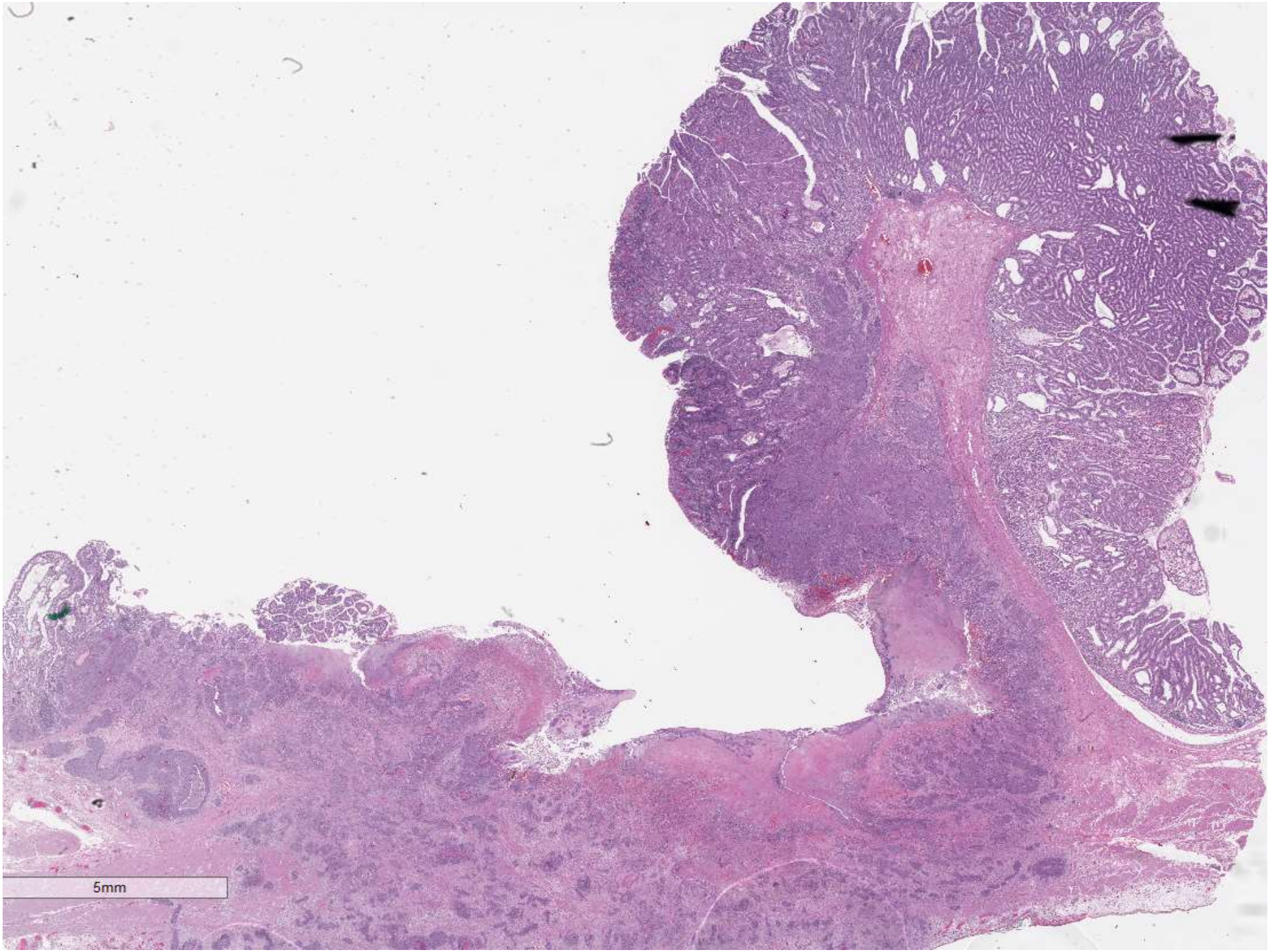
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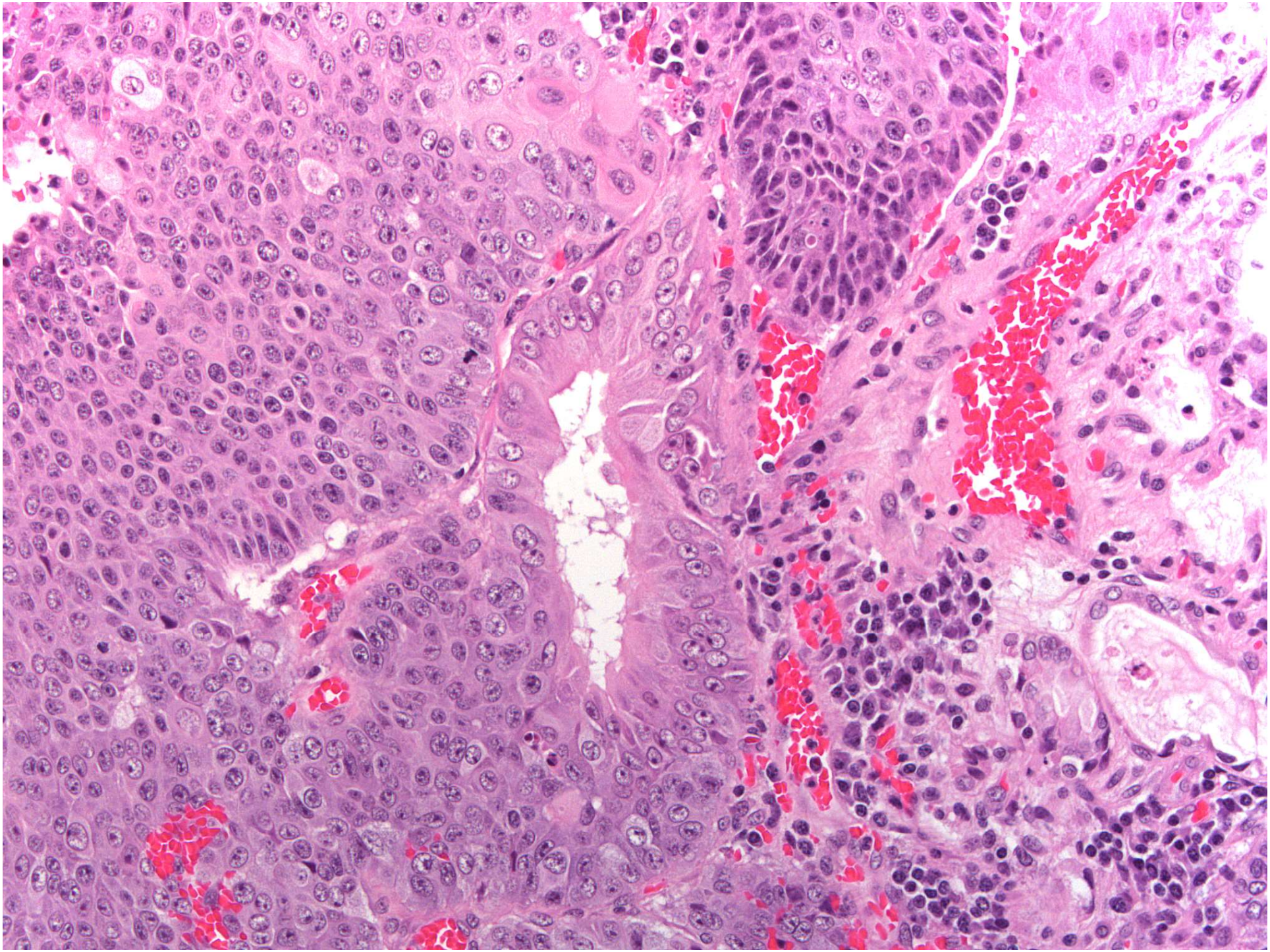

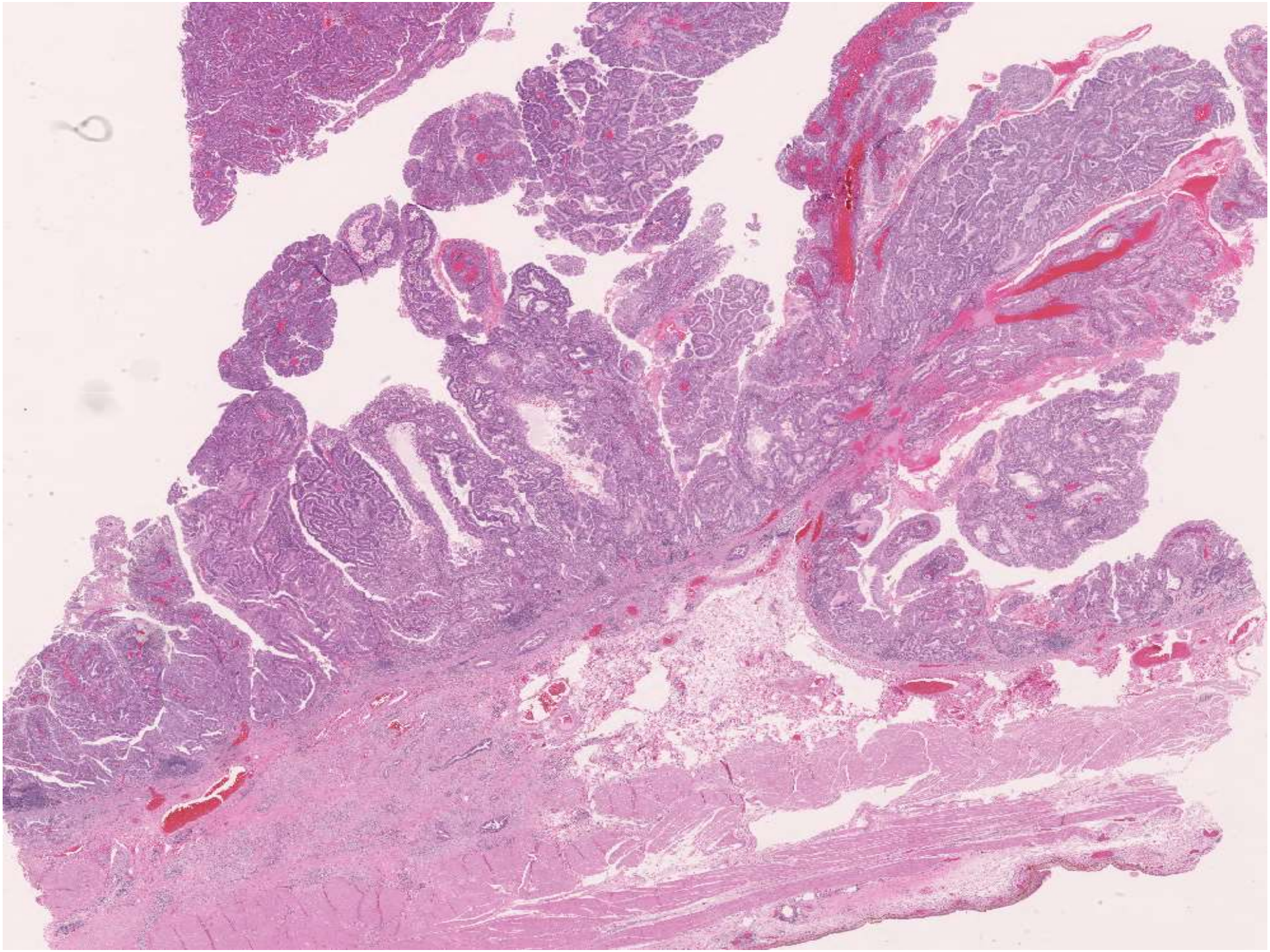

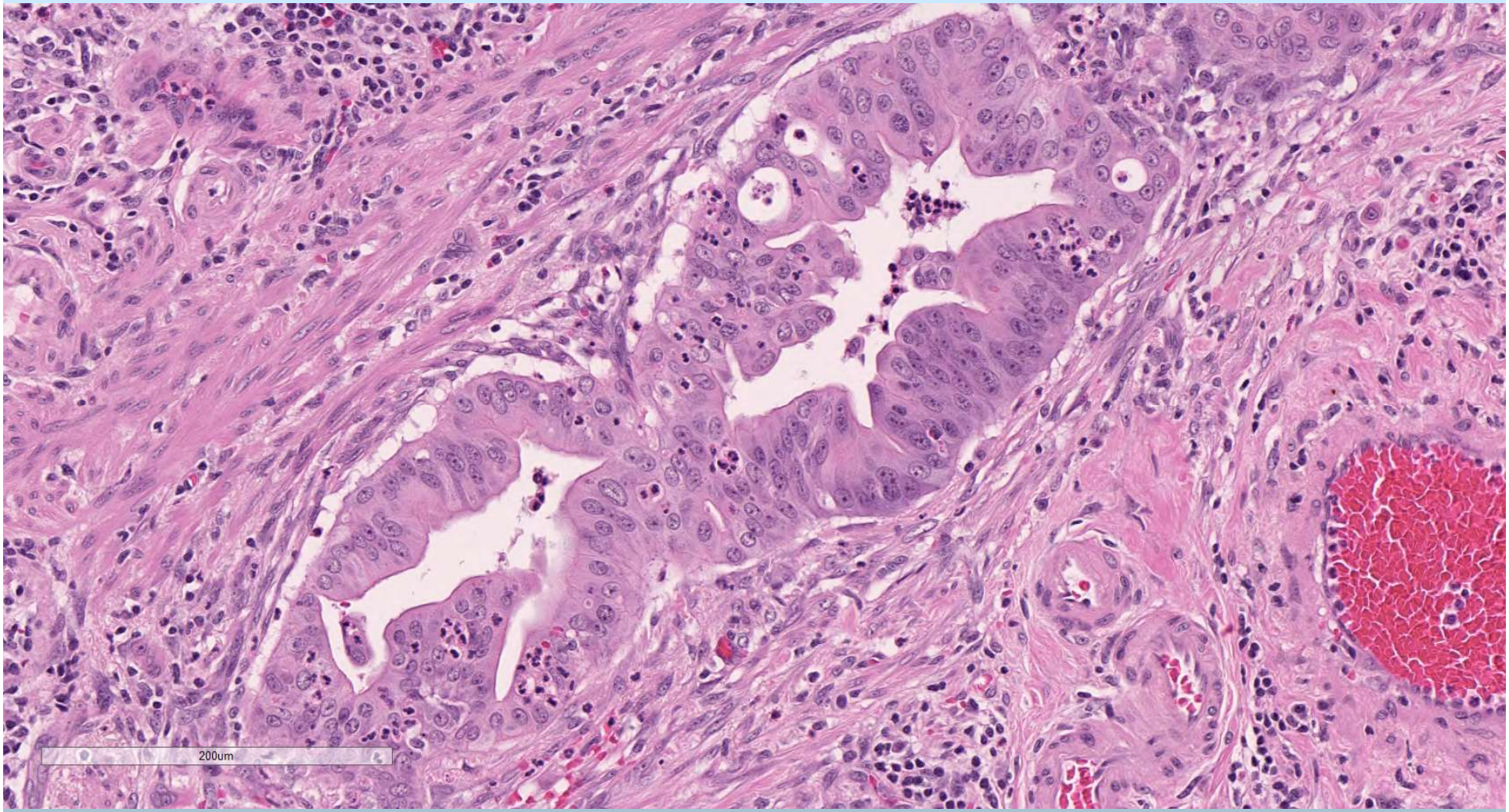
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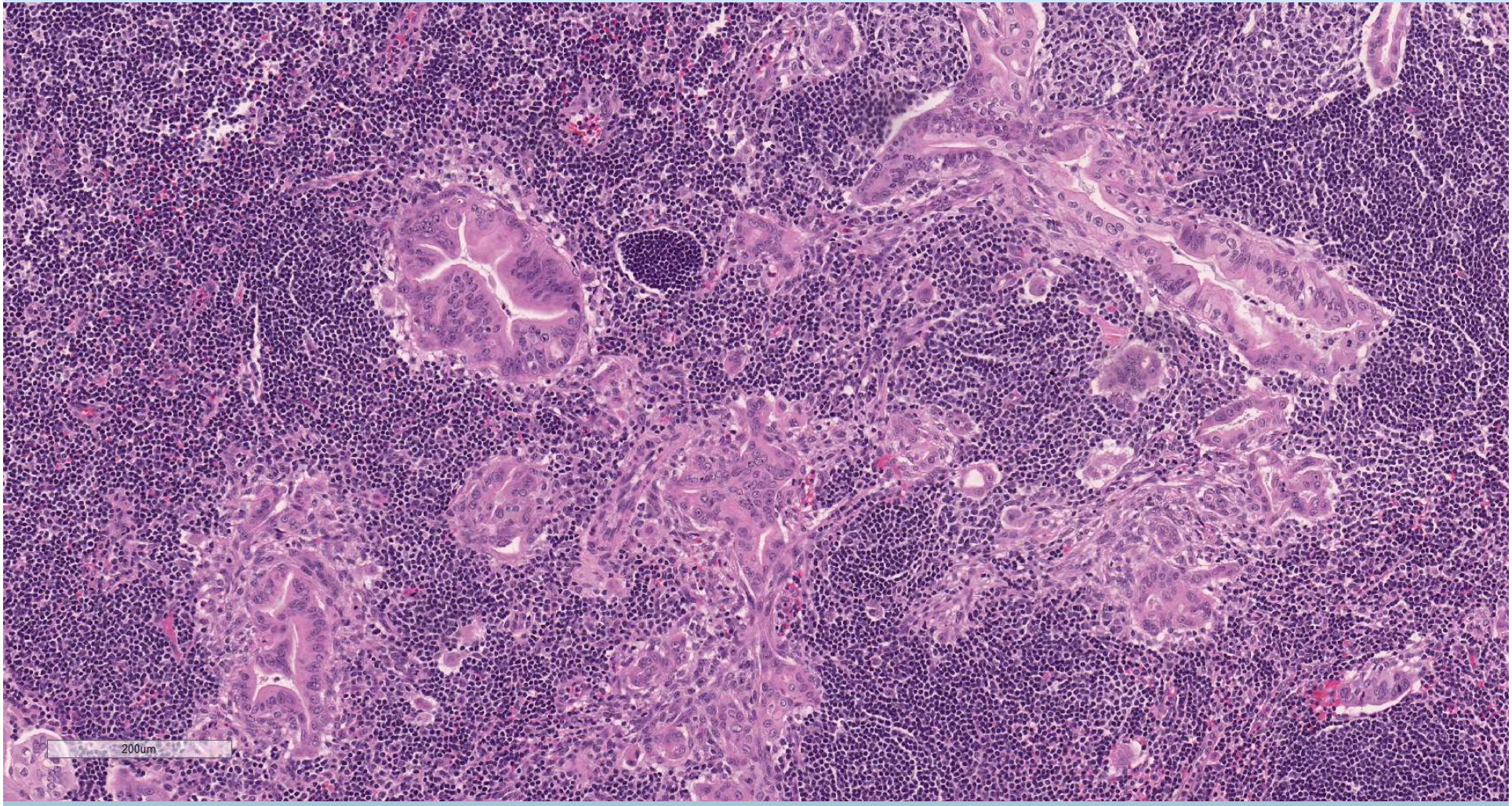
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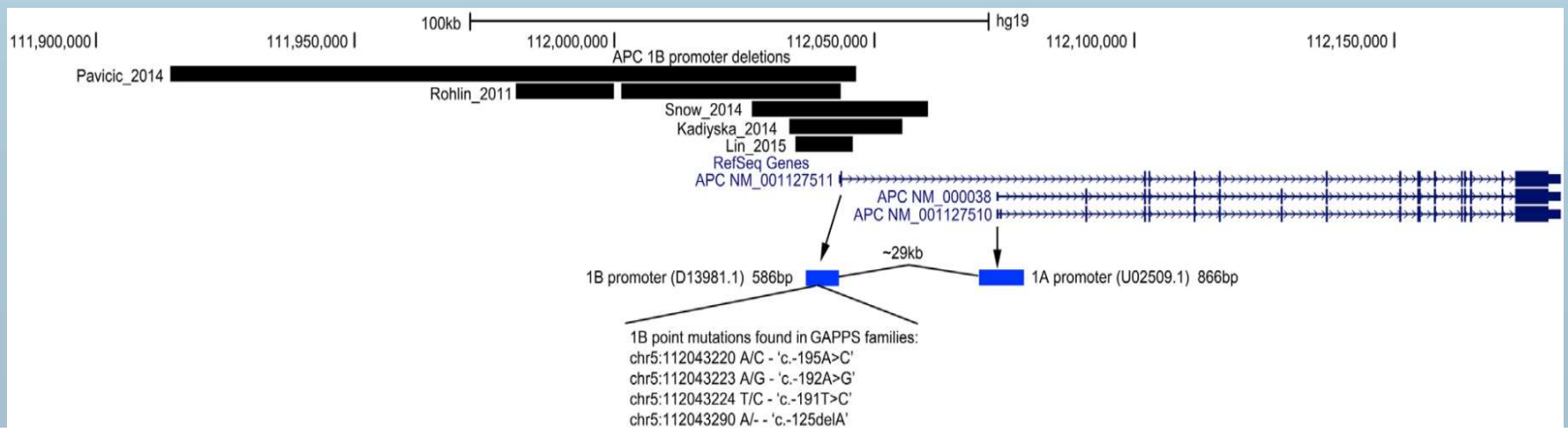
Gastric adenocarcinoma and proximal polyposis syndrome (GAPPS)

- First described in 2012:
  - Australian and North American kindred
- Autosomal dominant pattern with incomplete penetrance
- Typical gastric phenotype may be evident from 10 years
- Earliest gastric cancer at 23 years

Diagnosis of GAPPS

- Identification of the point mutation in the promoter 1β of the APC gene (e.g.c.-191T>C, c.-192A>G, and c.-195A>C):
  - all positioned within the Ying Yang 1 (YY1) binding motif, hence reducing the APC transcriptional activity.



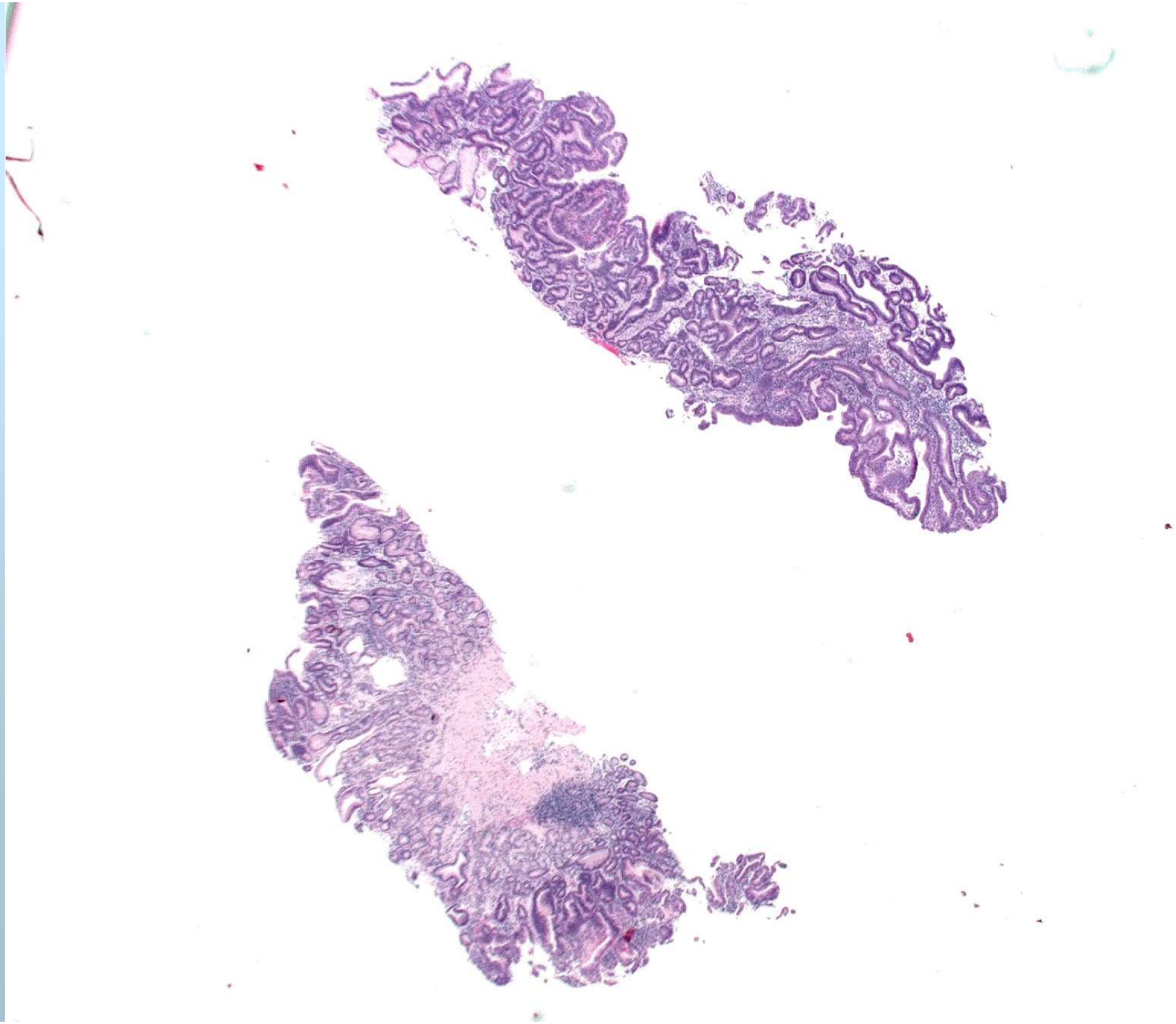
Management

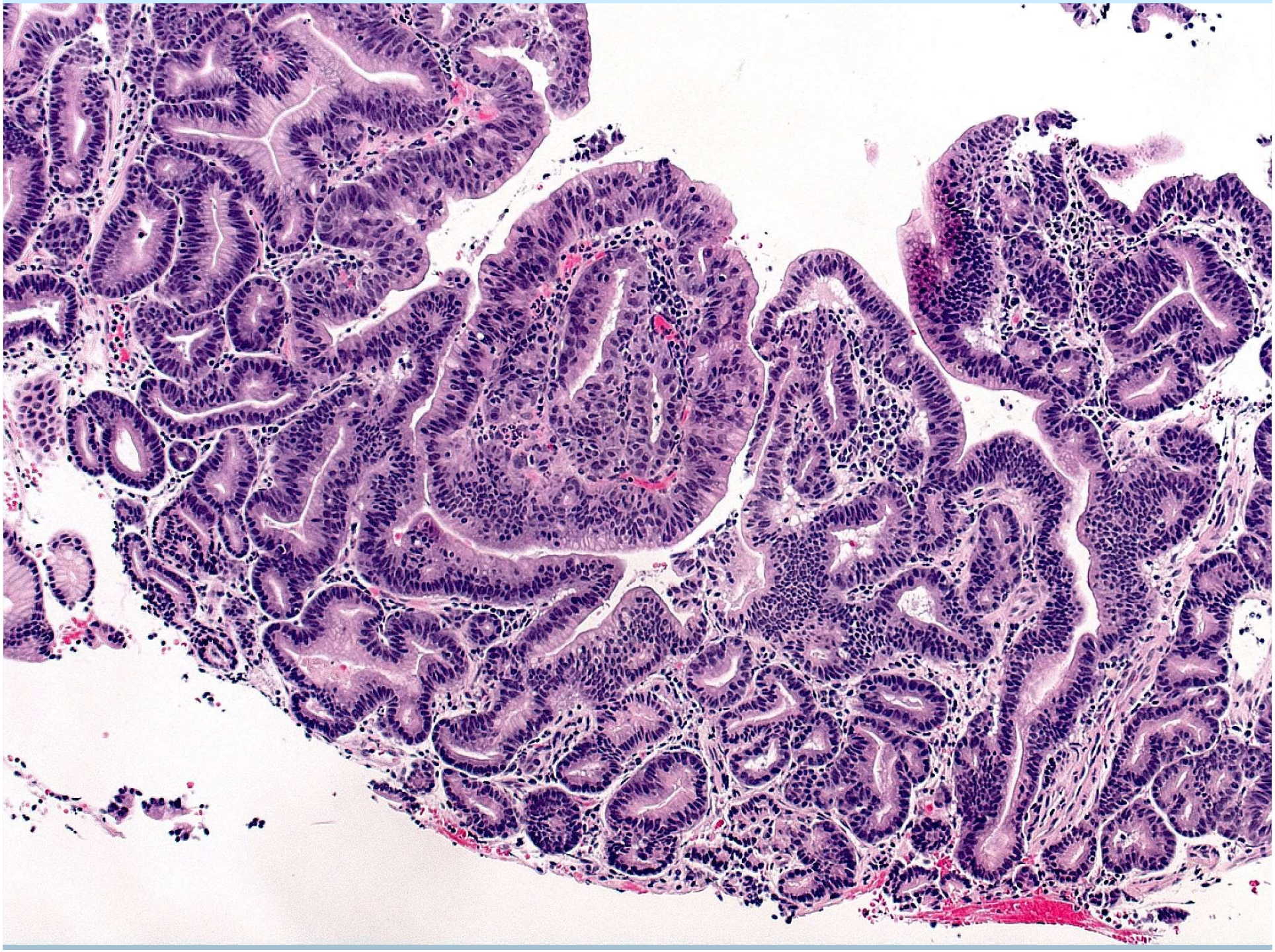
- Upper endoscopic surveillance (difficult to detect early carcinomas in the field of polyposis)
- Prophylactic gastrectomy (+/- large polyp, +/- dysplasia)
- Therapeutic gastrectomy (biopsy proven carcinoma)
- ?? Colonoscopic surveillance

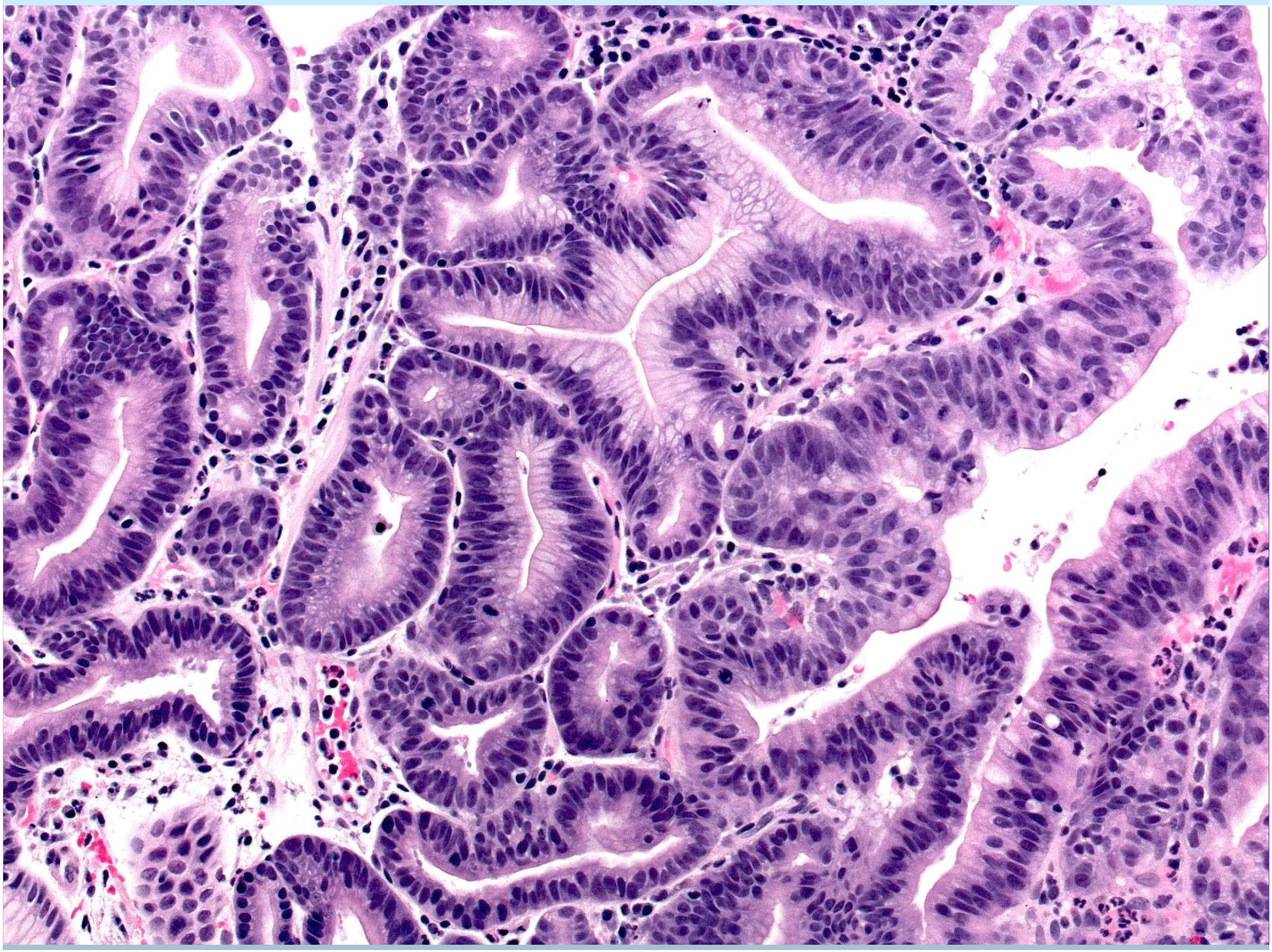
Stomach and Lynch syndrome

F42 Family history of gastric Ca
Endoscopy - Gastric polyp found

Please present @ Gastro-Esophageal Tumor Boards







Gastric adenoma with LGD and focal HGD

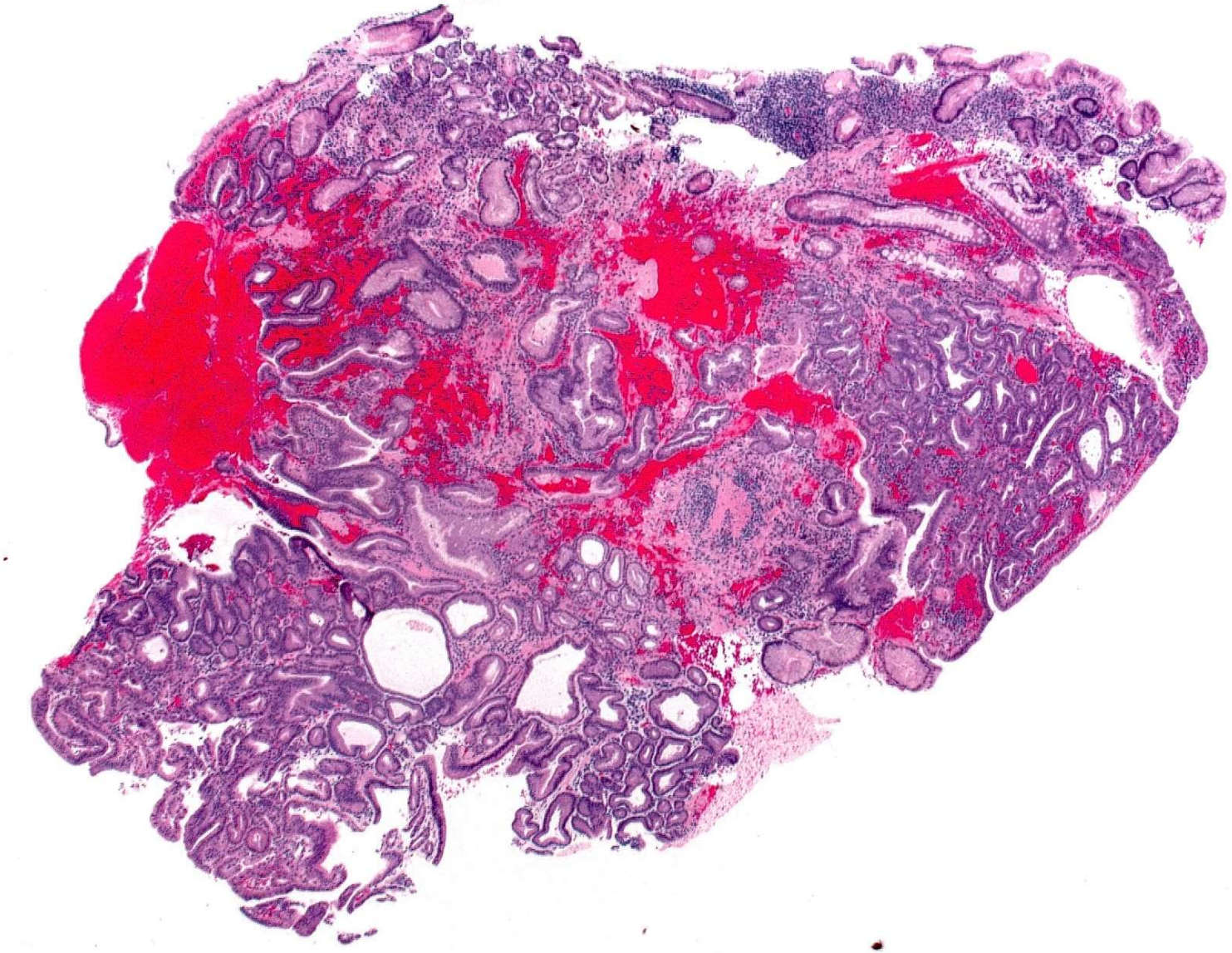
Day before Tumor Board

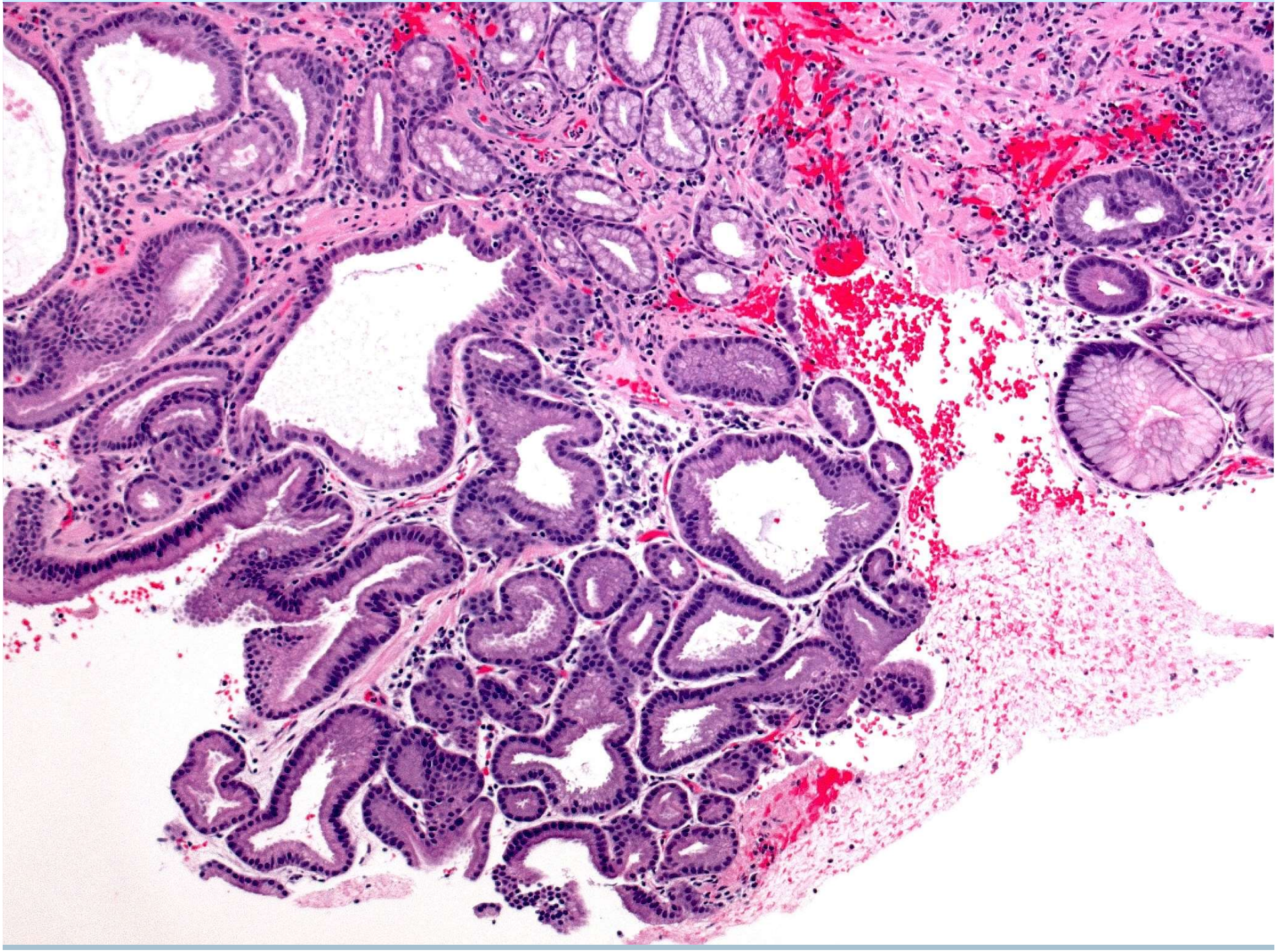
Scoped her again yesterday
You should be getting the slides soon

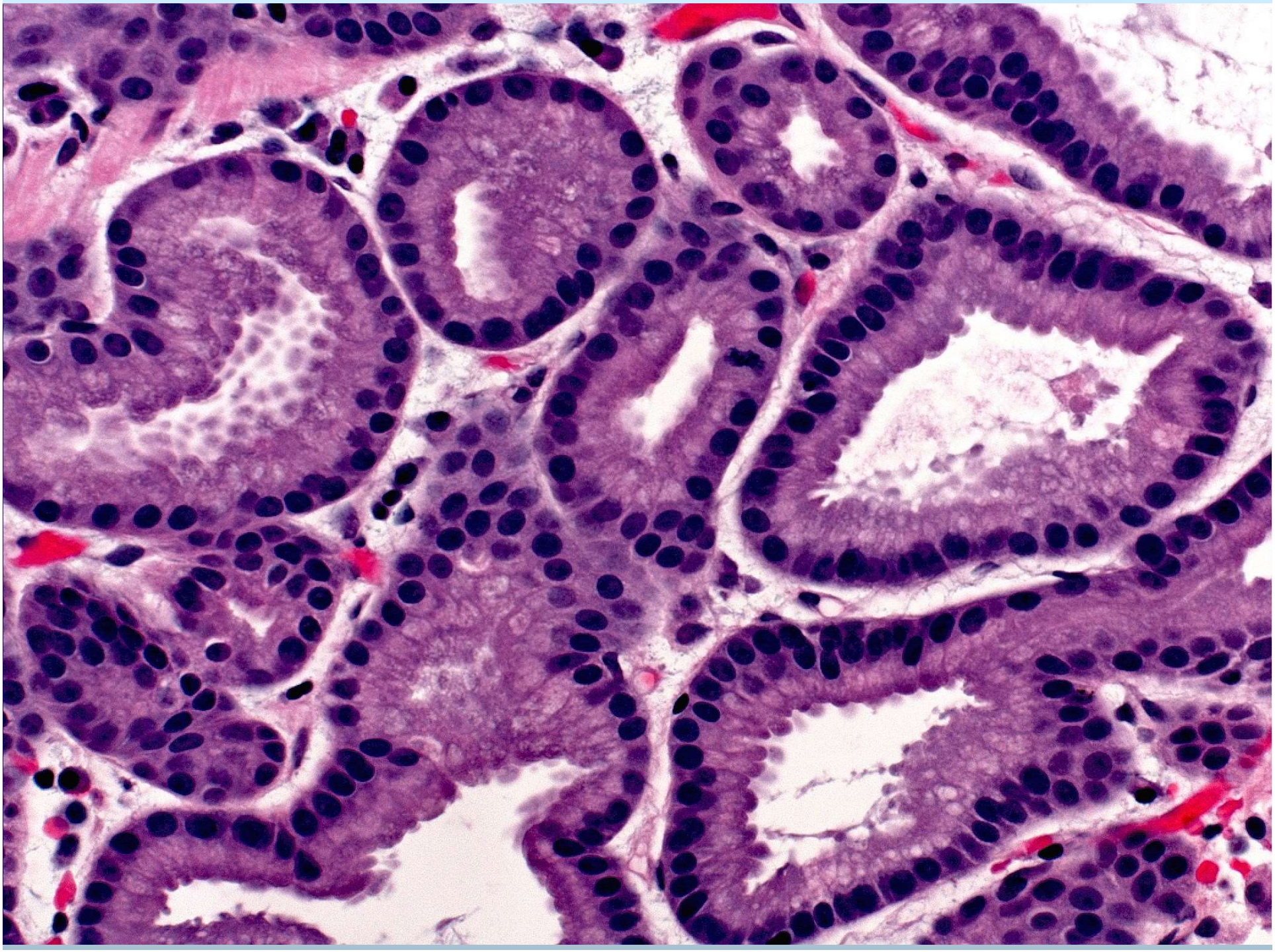
Oh – She also said she has a history of Endometrial carcinoma 10 years ago when she was 32, and was told she had Lynch syndrome.

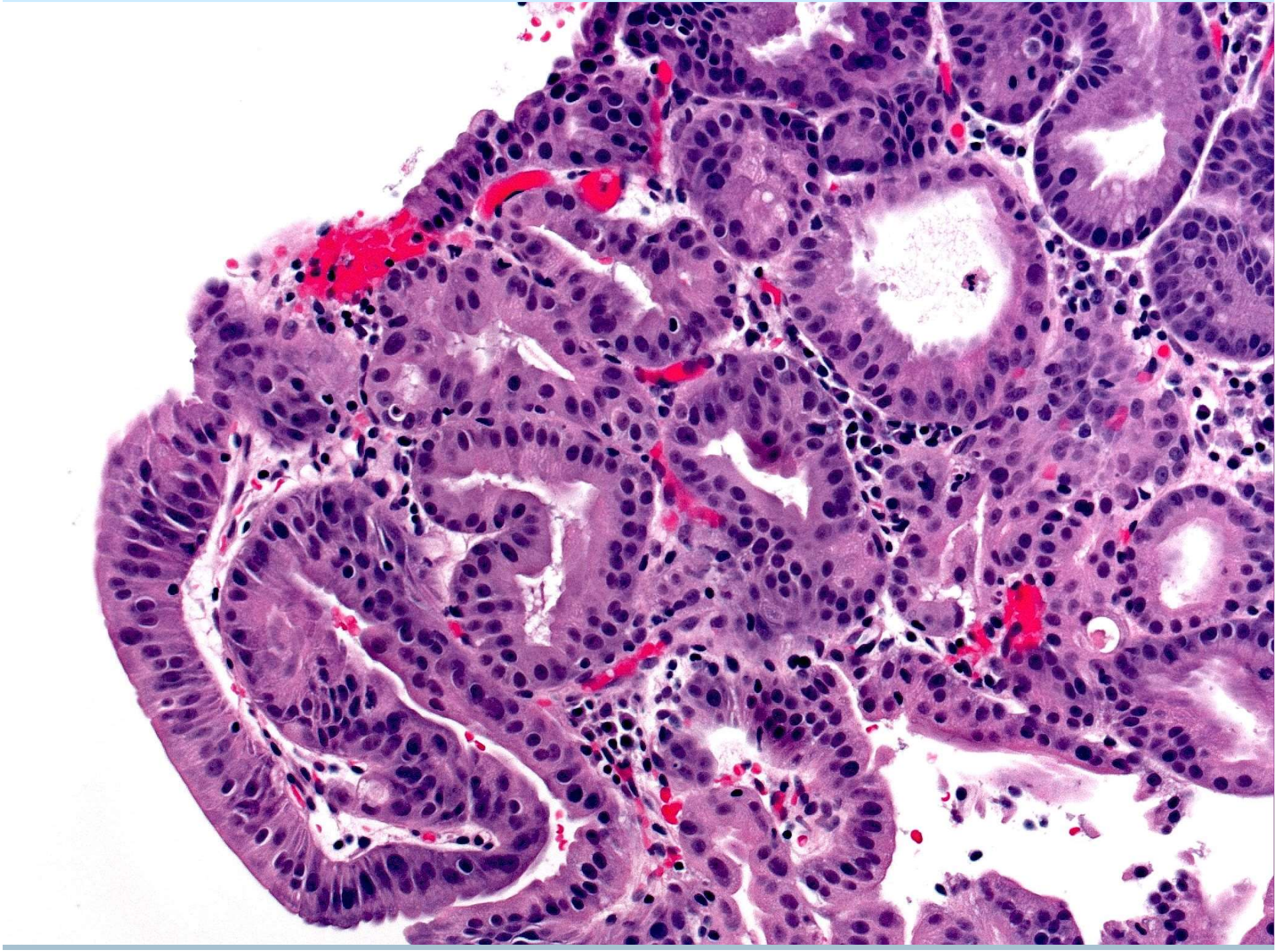
Had a colonoscopy then which was normal but nothing since

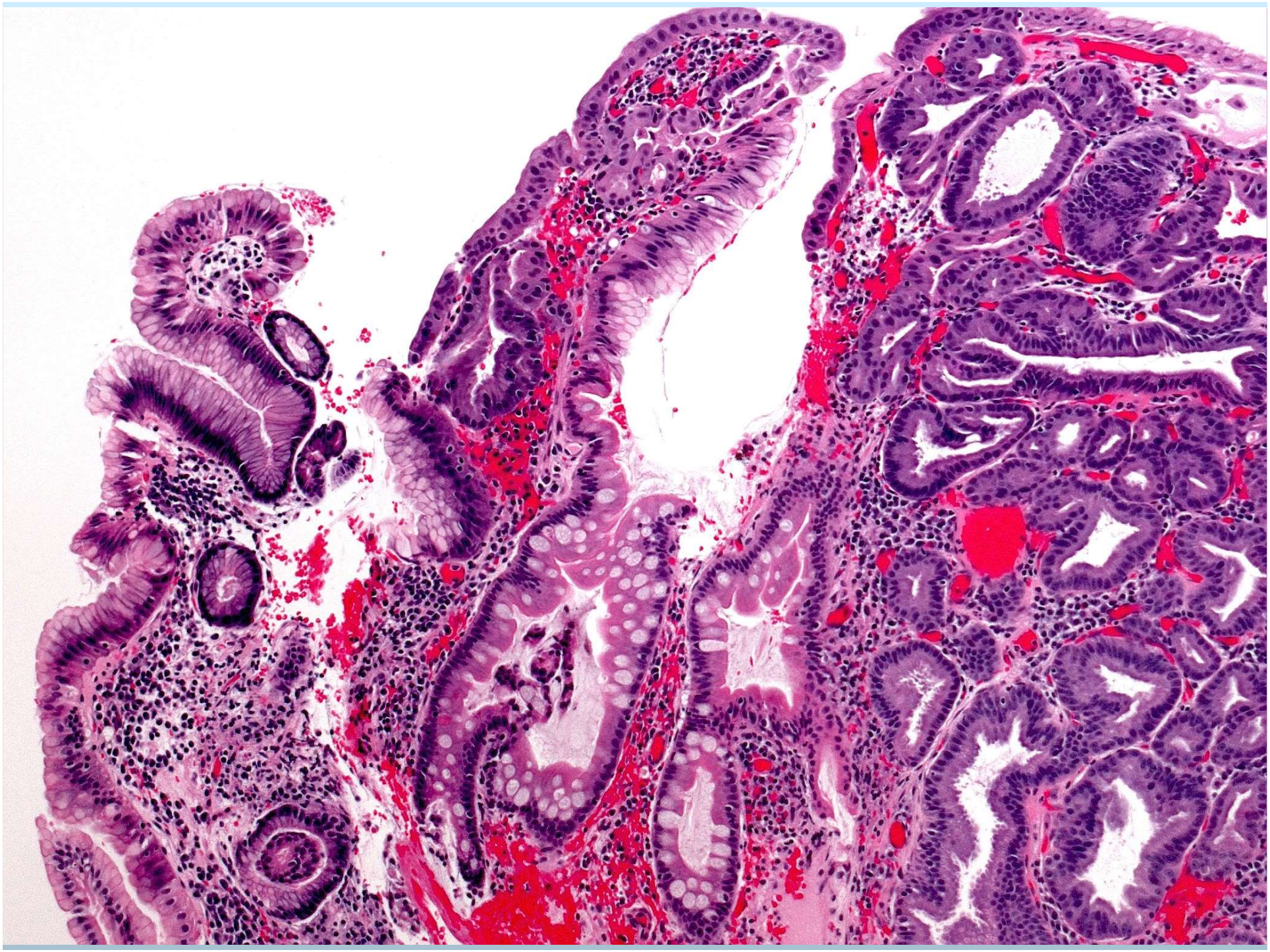
Polyp cardia





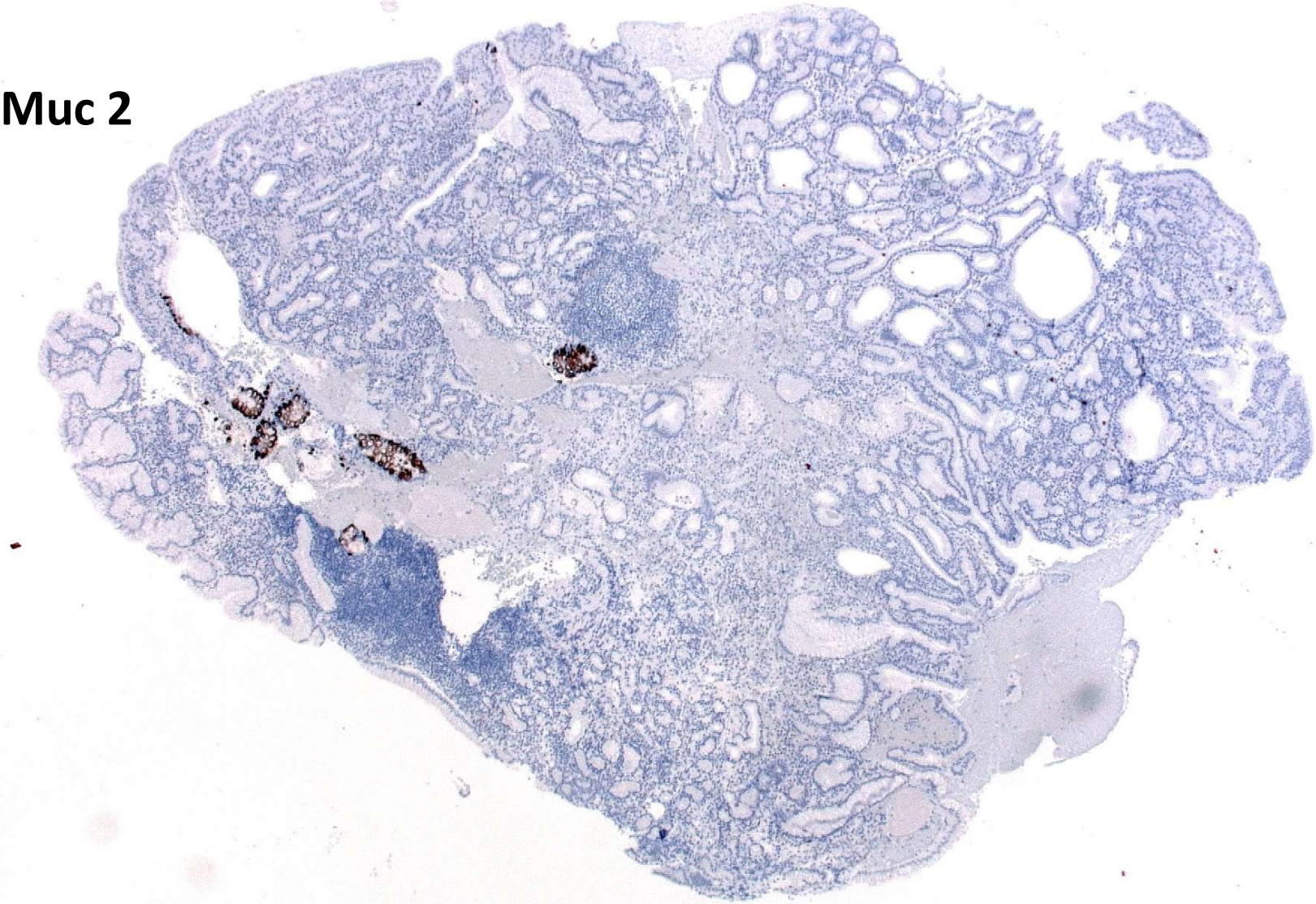




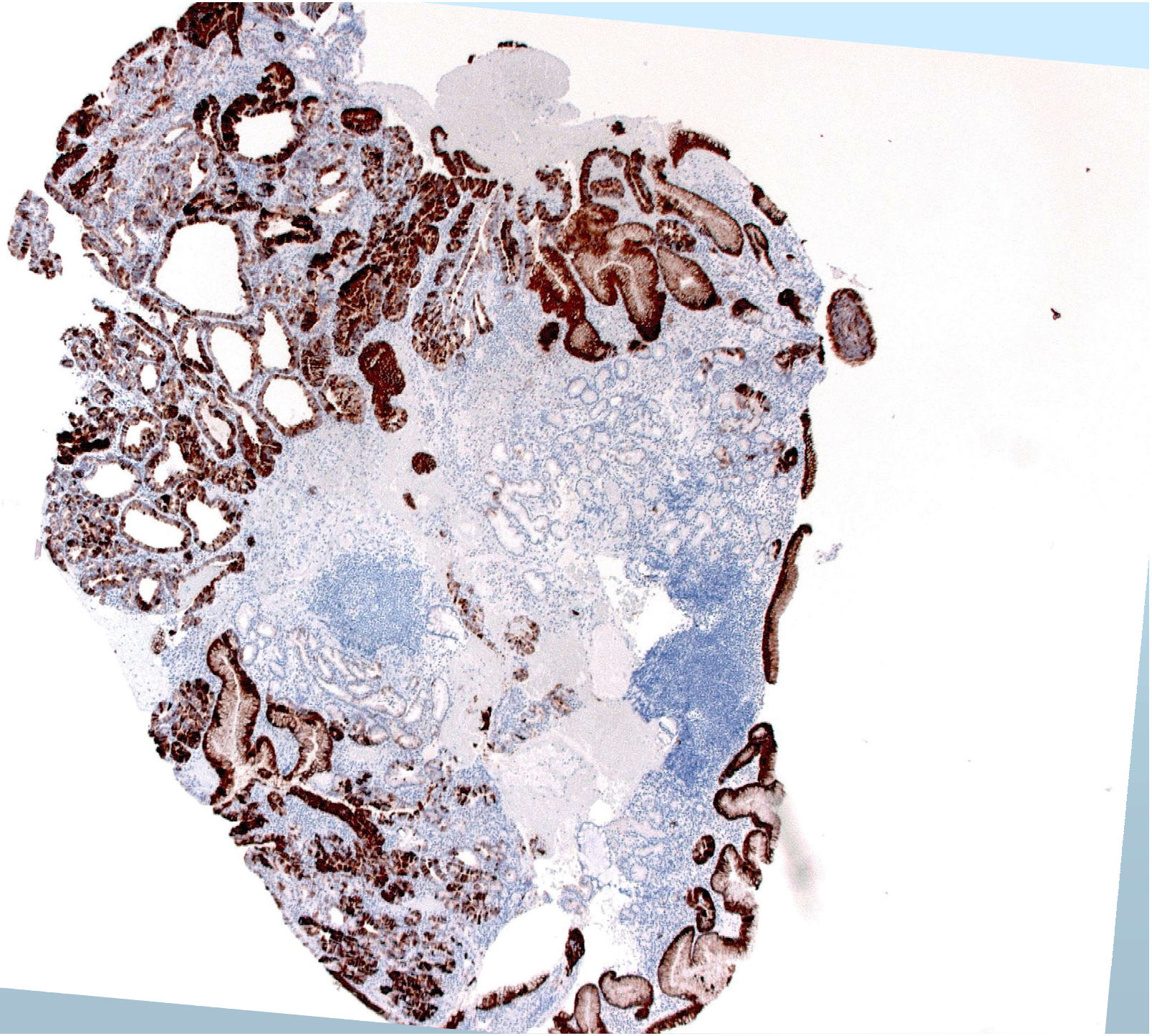


Pyloric gland adenoma
Background intestinal metaplasia

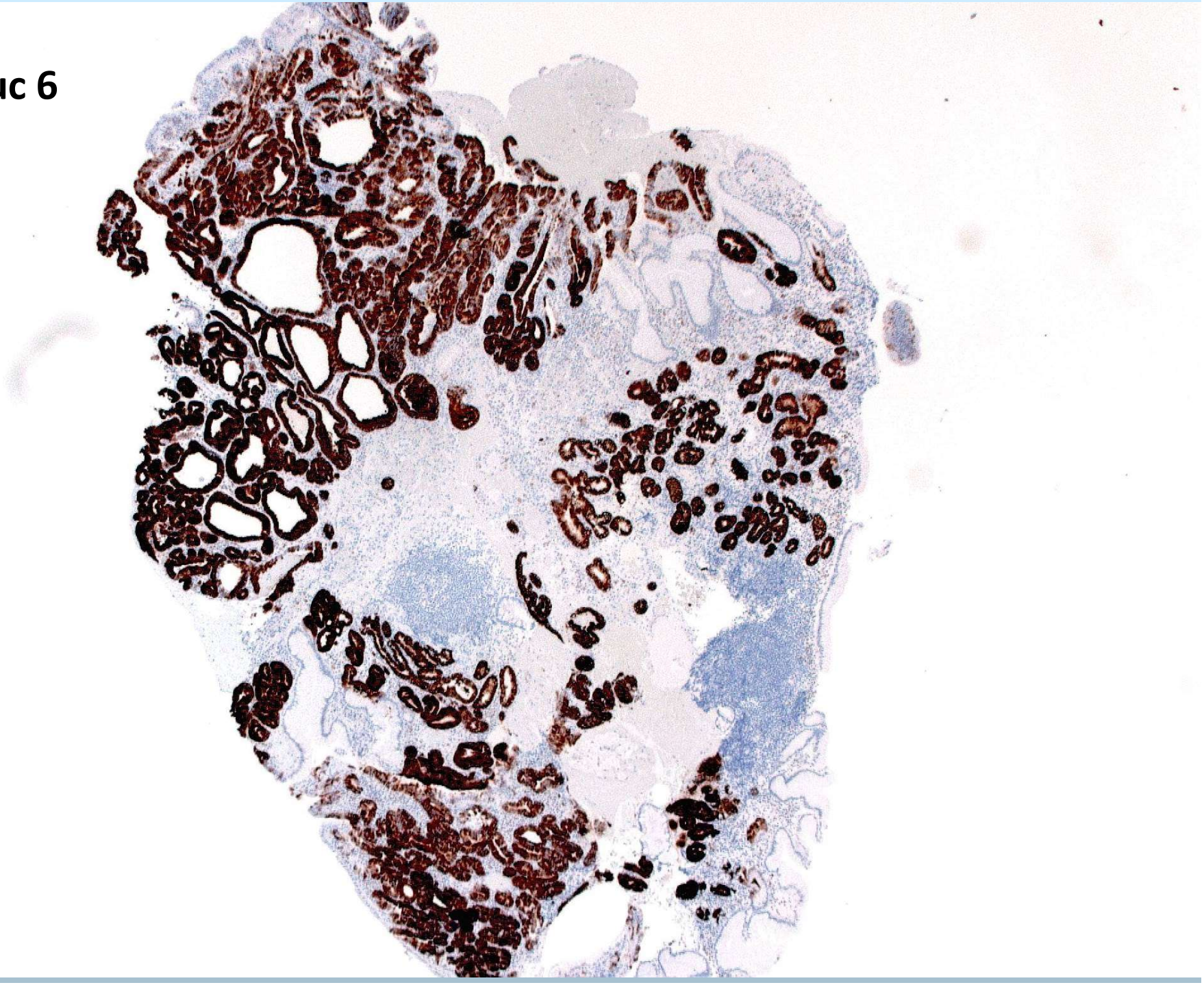
Muc 2



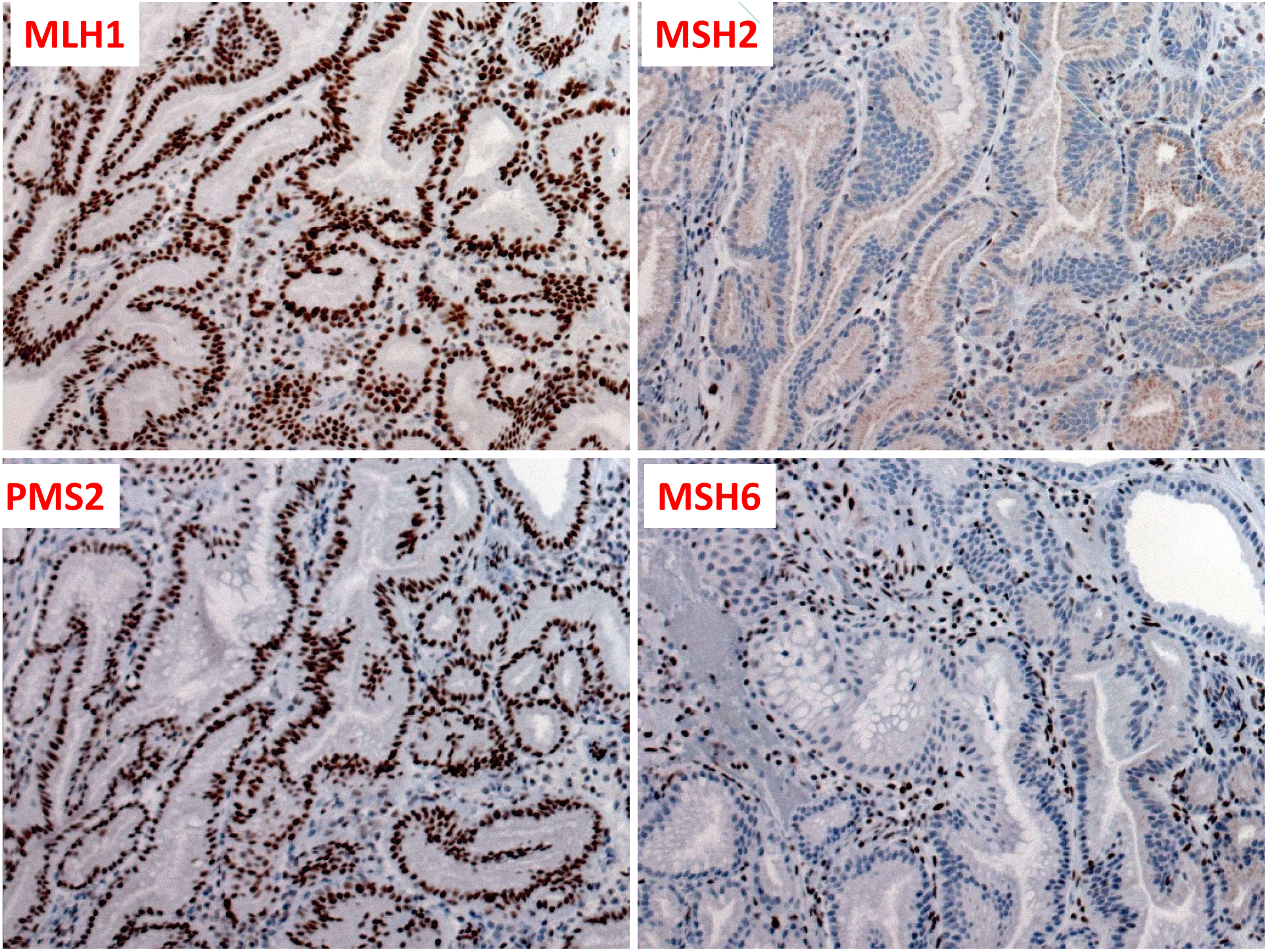
Muc 5



Muc 6



And the Lynch Syndrome


MLH1
MSH2
PMS2
MSH6

Gastric cardia – Pyloric gland adenoma

MSH2/MSH6 deficient
Highly suggestive of a germline mutation in the MSH2 gene

Table 5 Relative cumulative incidence (RR) cancer at 75 years in carriers of *path_MMR* genes stratified by gene. 95% CIs are shown in parentheses. Significantly increased (p<0.05) RRs are highlighted in bold. Maximum RR by gene underlined

ICD9	Organ	Population incidence (%)	Relative cumulative incidence (95% CI)			
			path_MLH1	*path_MSH2*	*path_MSH6*	*path_PMS2*
Any cancer		24.4	3.1 (2.8 to 3.4)	3.3 (2.9 to 3.7)	2.5 (1.7 to 3.2)	2.1 (0 to 4.1)
In separate organs order by RR						
152	Duodenum	0.1	**64.7 (27.4 to 102.1)**	20.1 (0.6 to 39.6)	0	0
182	Endometrium	1.6	**26.7 (20.7 to 32.7)**	**35.5 (26.1 to 44.8)**	**28.9 (17.1 to 40.6)**	16.5 (0.5 to 32.4)
153	Colon	2.1	**22.3 (18.7 to 25.9)**	**20.2 (15.6 to 24.7)**	**6.8 (1.5 to 12.1)**	0
156	Bile duct and gall bladder	0.2	**18.7 (6.3 to 31.1)**	8.6 (0 to 25.4)	0	0
183	Ovary	1.0	**10.1 (4.8 to 15.4)**	**16.9 (5.7 to 28.0)**	13.1 (0 to 31.2)	0
189	Ureter and kidney	1.3	**3.5 (1.2 to 5.9)**	**13.7 (8.2 to 19.2)**	2.3 (0 to 5.4)	0
154	Sigmoid and rectum	1.4	**8.4 (5.2 to 11.7)**	**13.0 (7.8 to 18.3)**	3.3 (0 to 6.9)	0
191	Brain	0.5	1.9 (0 to 4.8)	10.5 (0.4 to 20.6)	2.9 (0 to 8.4)	0
151	Stomach	0.8	**8.9 (4.4 to 13.4)**	**9.7 (2.3 to 17.0)**	6.6 (0 to 16.4)	0
188	Urine bladder	1.0	**4.1 (1.5 to 6.7)**	**8.1 (2.8 to 13.3)**	8.2 (0 to 16.9)	0
157	Pancreas	0.8	**7.8 (3.3 to 12.3)**	0.6 (0 to 1.9)	1.8 (0 to 5.2)	0
185	Prostate	10	1.7 (0.9 to 2.7)	**3.2 (1.2 to 5.1)**	1.8 (0 to 4.4)	3.8 (0 to 9.6)
174	Breast	9.4	1.3 (0.7 to 1.8)	1.2 (0.5 to 2.0)	1.4 (0.2 to 2.6)	6.0 (0 to 10.6)
In anatomical regions ordered by RR						
Gynaecological		2.6	**19.1 (15.6 to 22.7)**	**25.3 (20.1 to 30.4)**	**20.8 (13.3 to 28.2)**	10.1 (0.3 to 20)
Colorectal		3.8	**12.1 (10 to 14.2)**	**11.3 (8.7 to 13.9)**	3.9 (0.9 to 7.0)	0
Upper gastrointestinal cancer		1.9	**11.2 (8.2 to 14.3)**	**5.4 (2.1 to 8.6)**	3.5 (0 to 7.8)	0
Urinary tract cancer		2.3	**3.5 (1.9 to 5.1)**	**10.8 (7.2 to 14.4)**	4.8 (0.7 to 8.8)	0

Møller P, *et al*. *Gut* 2018;**67**:1306–1316. doi:10.1136/gutjnl-2017-314057

European Hereditary Tumor Group

	Organ	Age	*path_MLH1*	*path_MSH2*	*path_MSH6*	*path_PMS2*
Upper gastrointestinal cancer						
151	Stomach	40	0.3 (0.0 to 0.9)	0	0	0
		50	0.8 (0.0 to 1.7)	0.5 (0.0 to 1.4)	0	0
		60	2.4 (0.7 to 4.0)	1.6 (0.0 to 3.4)	1.4 (0.0 to 4.2)	0
		70	6.3 (3.0 to 9.7)	4.1 (0.8 to 7.5)	1.4 (0.0 to 4.2)	0
		75	7.1 (3.5 to 10.8)	7.7 (1.9 to 13.6)	5.3 (0.0 to 13.1)	0
152	Duodenum	40	0.4 (0.0 to 1.1)	0	0	0
		50	1.1 (0.0 to 2.3)	1.0 (0.0 to 2.3)	0	0
		60	2.1 (0.5 to 3.7)	2.0 (0.1 to 4.0)	0	0
		70	4.1 (1.4 to 6.8)	2.0 (0.1 to 4.0)	0	0
		75	6.5 (2.7 to 10.2)	2.0 (0.1 to 4.0)	0	0
156	Bile duct and gall bladder	40	0	0	0	0
		50	0.3 (0.0 to 0.8)	0	0	0
		60	1.3 (0.0 to 2.5)	0	0	0
		70	3.7 (1.3 to 6.2)	0	0	0
		75	3.7 (1.3 to 6.2)	1.7 (0.0 to 5.1)	0	0
157	Pancreas	40	0.3 (0.0 to 0.9)	0	0	0
		50	1.1 (0.0 to 2.1)	0	0	0
		60	1.7 (0.3 to 3.1)	0.5 (0.0 to 1.5)	1.4 (0.0 to 4.2)	0
		70	3.9 (1.4 to 6.4)	0.5 (0.0 to 1.5)	1.4 (0.0 to 4.2)	0
		75	6.2 (2.6 to 9.8)	0.5 (0.0 to 1.5)	1.4 (0.0 to 4.2)	0

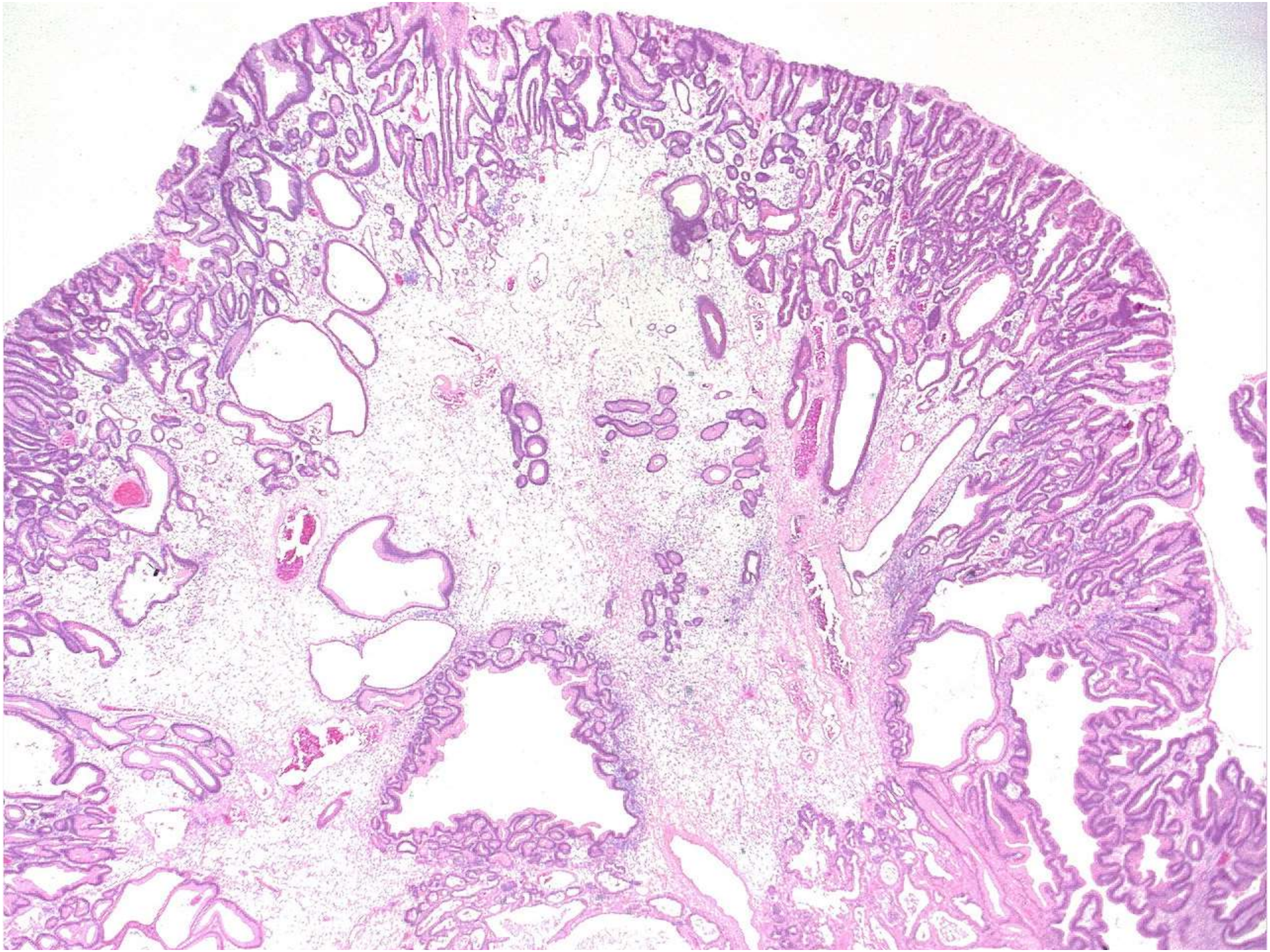
Møller P, *et al*. *Gut* 2018;**67**:1306–1316.

European Hereditary Tumor Group

Non-neoplastic polyps

- Fundic gland polyps
- Inflammatory/hyperplastic polyps spectrum
  - IPs – esp GEJ, & adjacent to prior ulcers
  - May be multiple – Hp, Meds, Cowden's,

- Polyposis syndromes
  - JPS,
  - PJS,
  - Cronkhite-Canada, Mentriers



Solitary polyp

- Hyperplastic polyp
- Possible Cowden's polyp
- (Healed inflammatory polyp)
  - What is going on in the background mucosa?

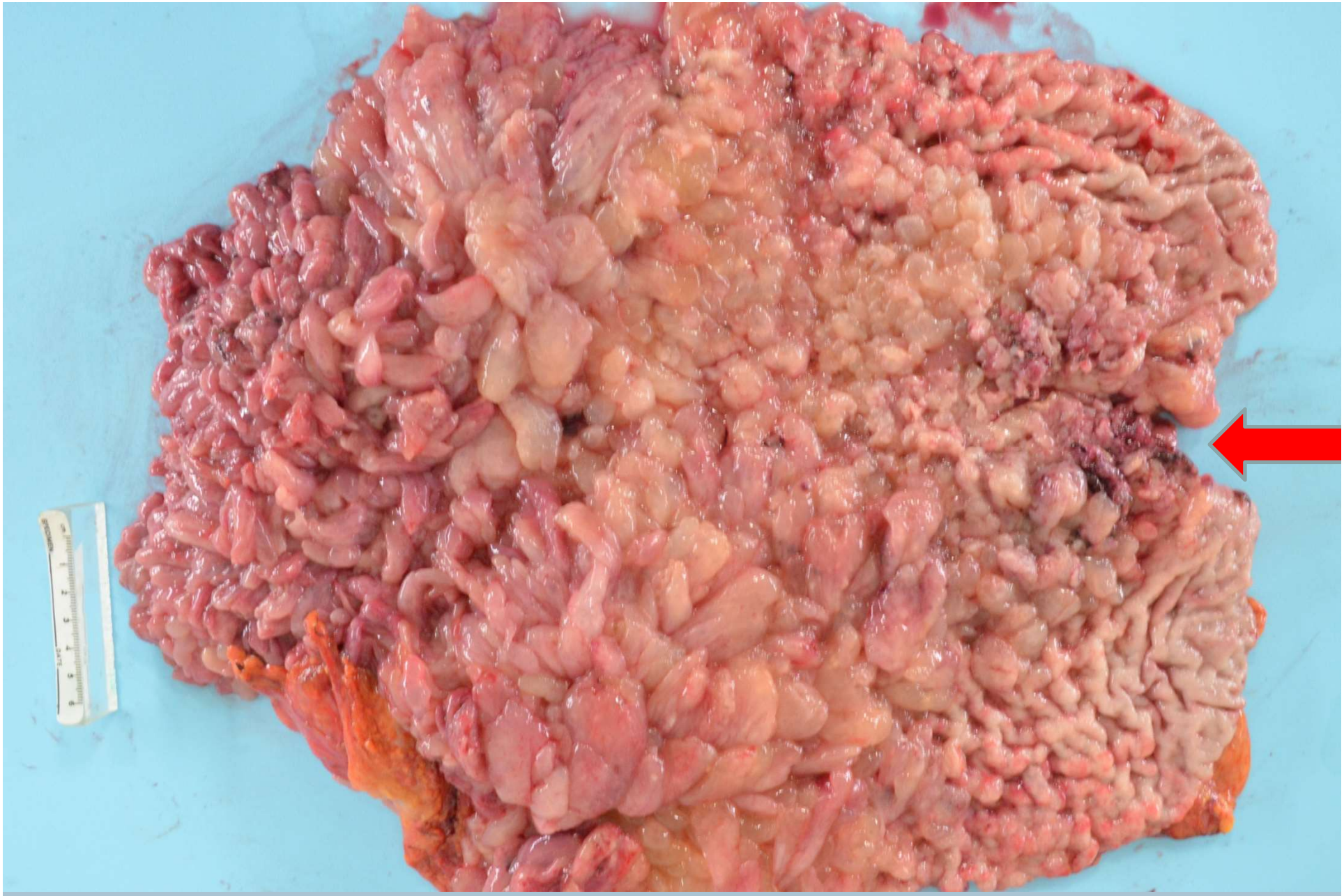
    Dysplasia relatively common - insignificant

- Need endoscopic appearances to exclude
  - Juvenile polyposis (myriad individual polyps)
  - Cronkhite –Canada syndrome (diffuse)
  - Ménétrier's (diffuse)

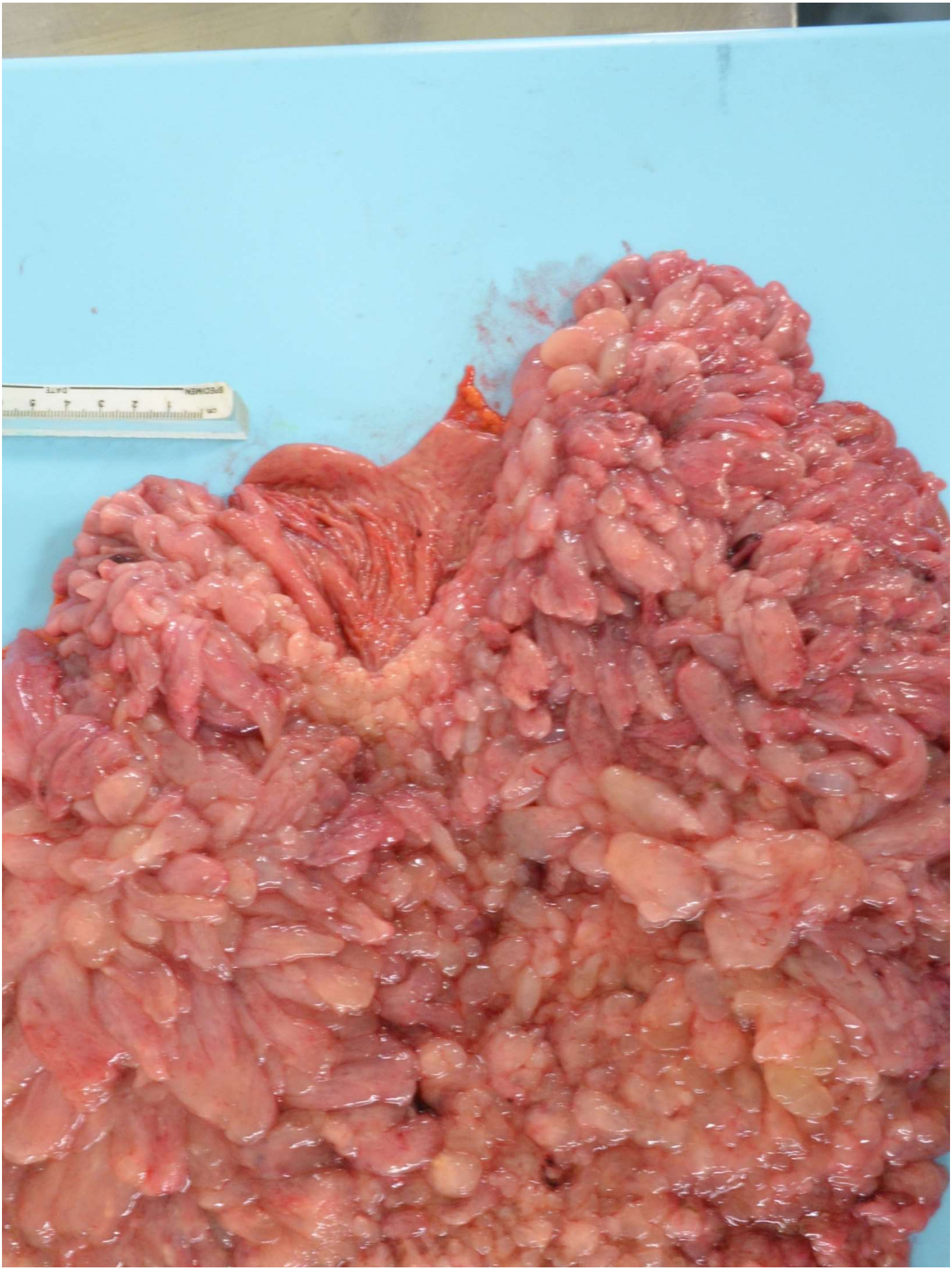
- Beware PJS if small
  - Smooth muscle is a late development

Non-neoplastic polyposis

- **Hyperplastic polyps**
  - Often numerous
  - Found throughout the stomach, especially near ulcers.
  - Associated with chronic gastritides (H. pylori, atrophic/autoimmune gastritis, & Cowden's syndrome.
  - Differential diagnosis includes:
- **Juvenile polyposis (often also large bowel polyps/ HHT/ SMAD4 > BMPR1A mutation in gastric JPS)**
- **Cronkhite-Canada syndrome**
  - Diffuse GI tract disease with little or no normal background mucosa. Protein loss
  - Hypoproteinemia, hypoalbuminemia resulting in hair and nail changes
- **Ménétrier's-** usually gastric body, rarely antrum

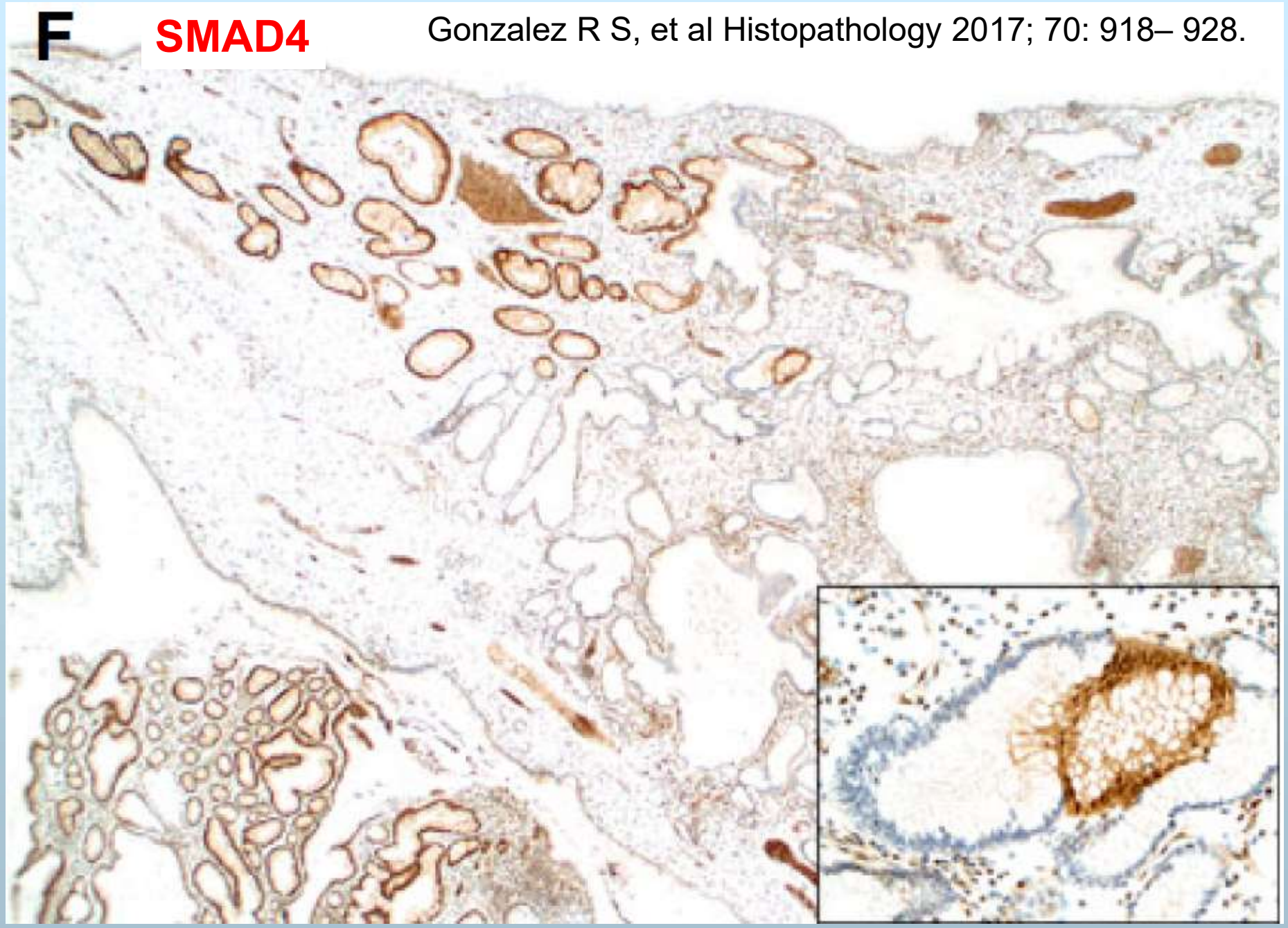


F 53 –known JPS – had right hemicolectomy age 20)


SPECIMEN
DATE
cm
1
2
3
4
5

F **SMAD4**

Gonzalez R S, et al Histopathology 2017; 70: 918– 928.



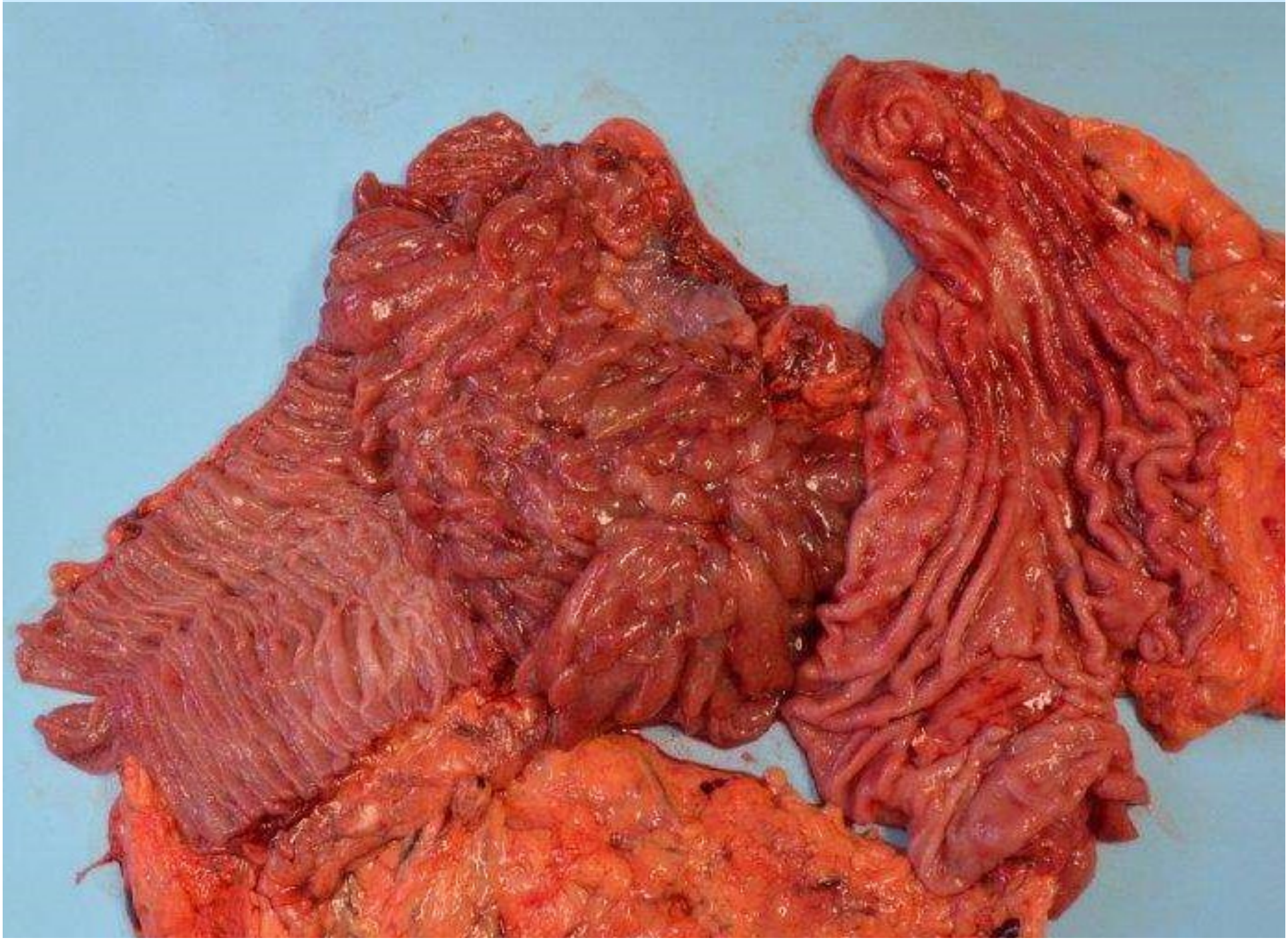
Insights into the pathogenesis of JPS

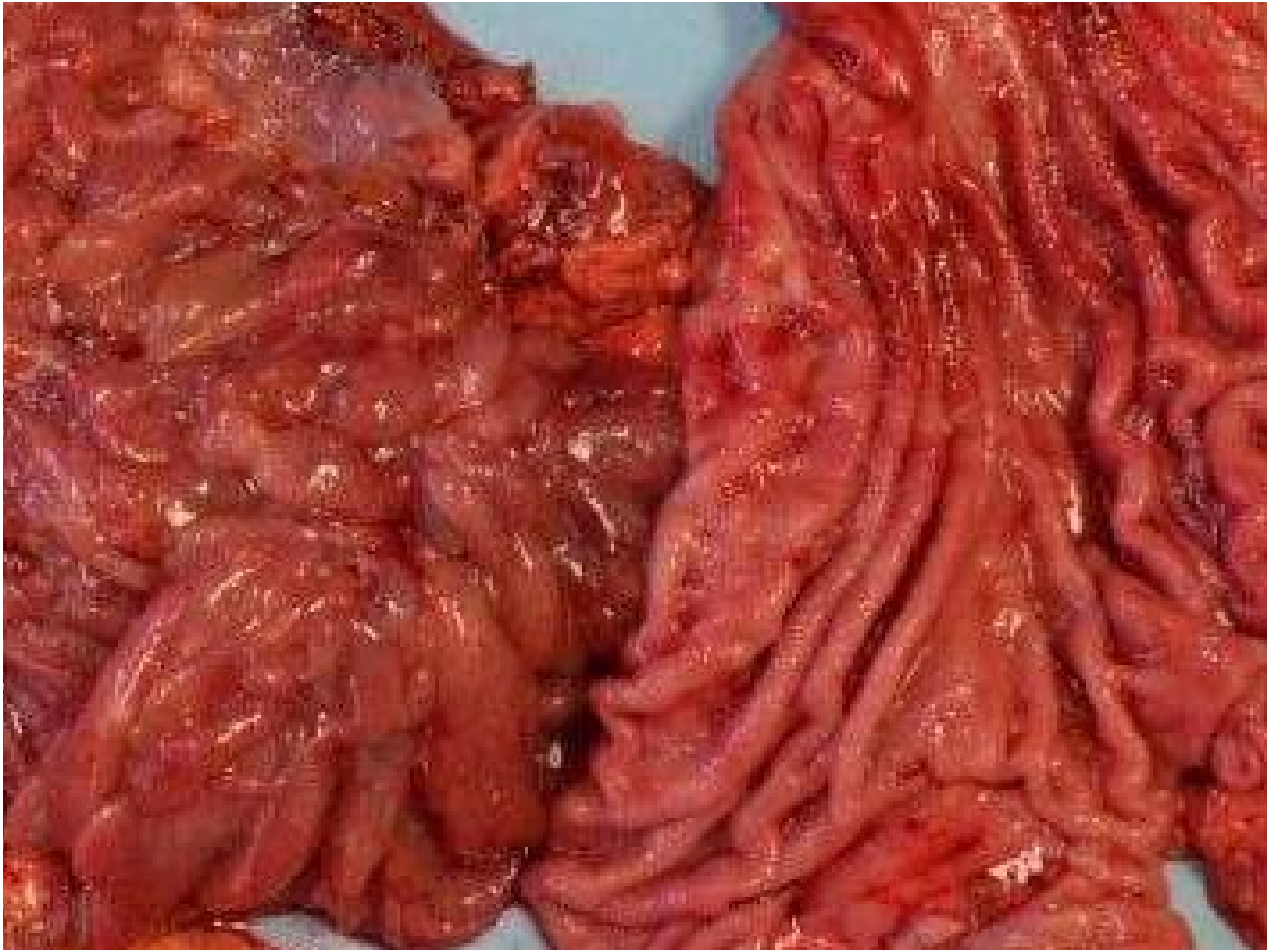
F54 Underwent Roux-en-Y gastric bypass for obesity c. 10 years previously

Son had recurrent nosebleeds -found to have HHT and SMAD4 mutation

Pt was found to have HHT/JPS – SMAD4 mutation

Gatroscopy showed myriad juvenile polyps so underwent gastrectomy.

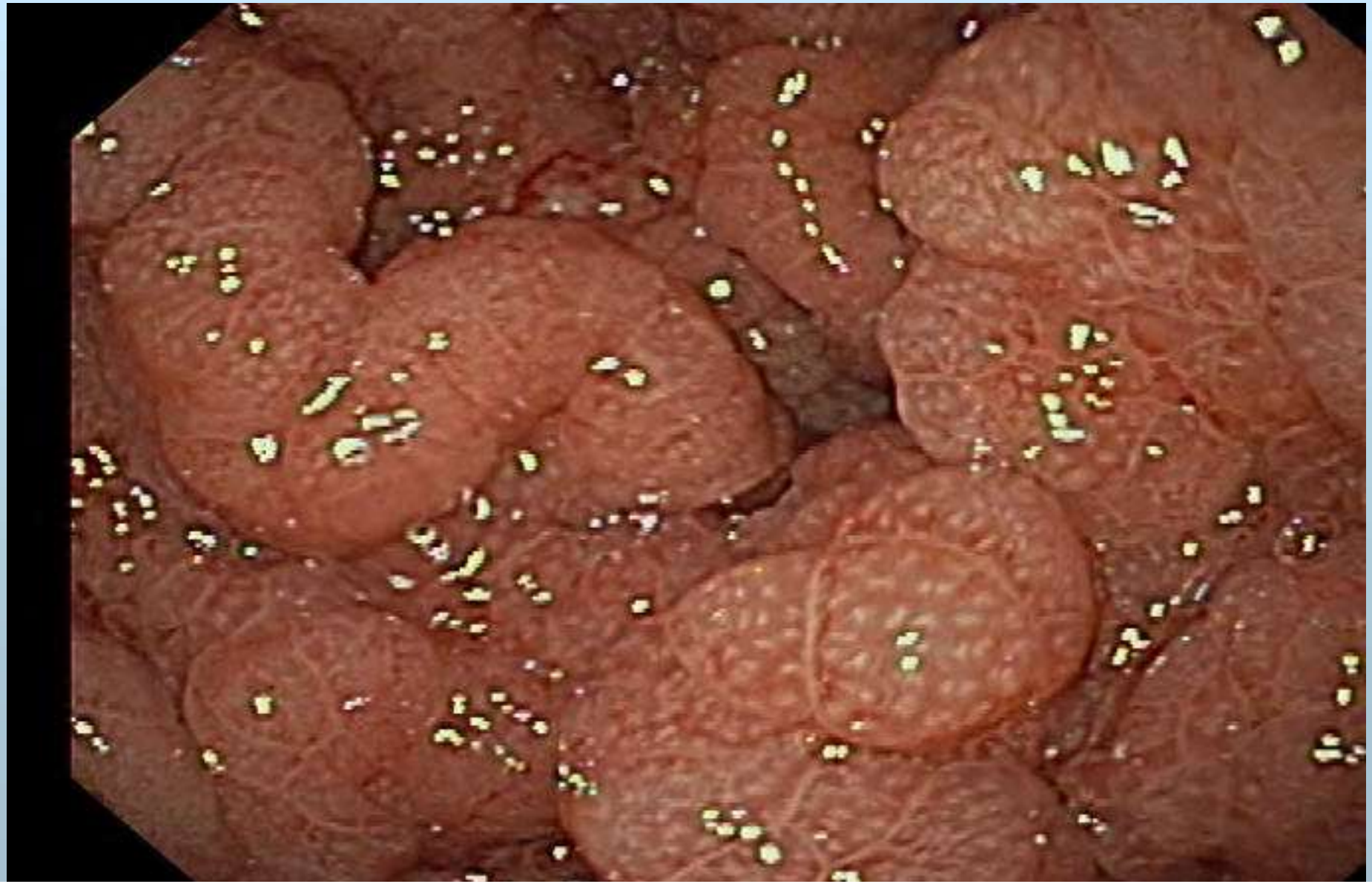




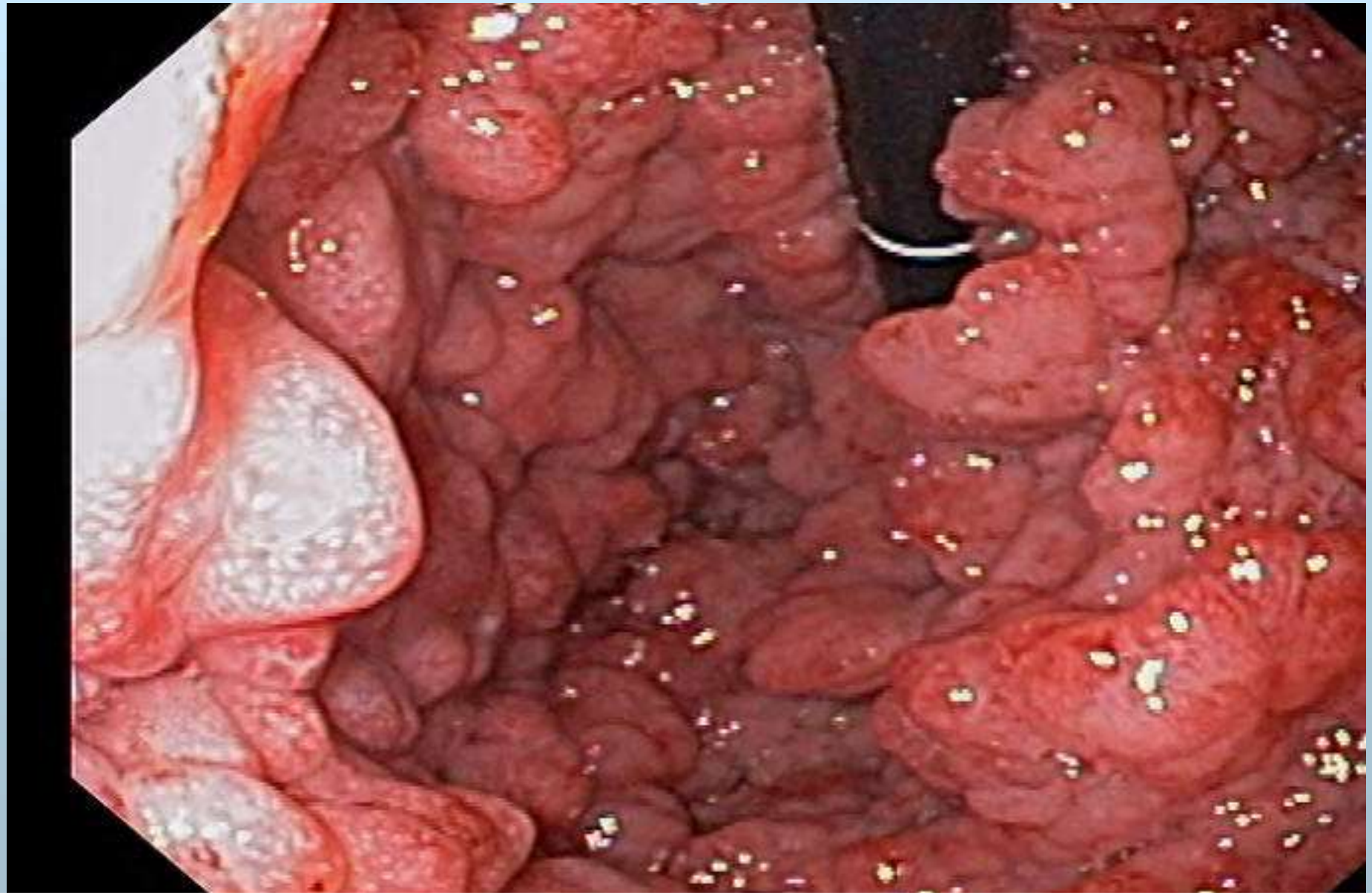
M 71 with diarrhea

- 6/day over a 2/12 period. Then nocturnal and became explosive.
- Lost 10 lbs and noticed leg edema
- Hb 125, MCV 100, Alb 14, protein 38.
- LFTs normal, C diff neg
- 2/12 later albumin 10
- Scoped x2 over 2months

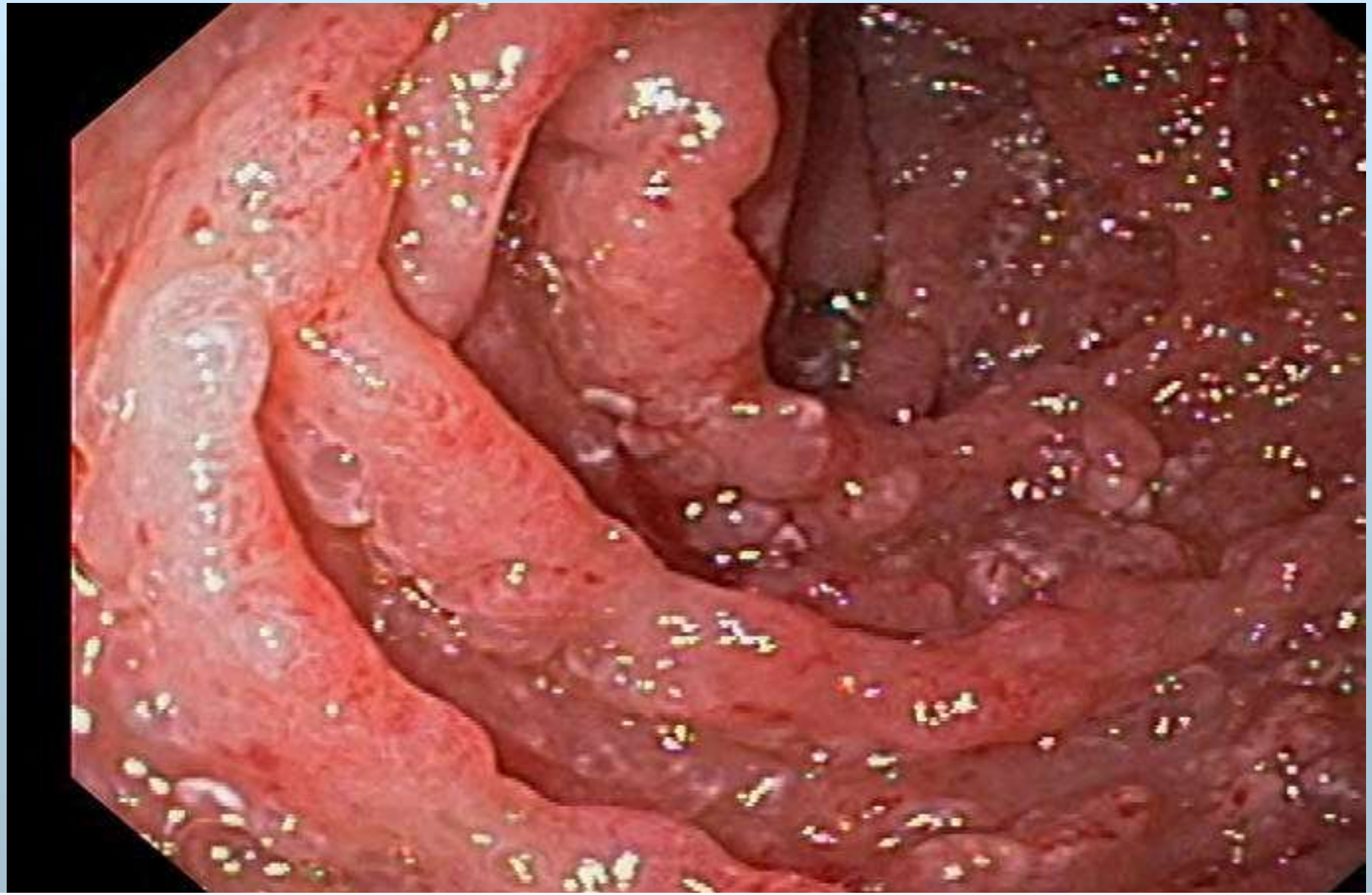
Gastric Corpus
(Courtesy Dr Sandra Nelles)

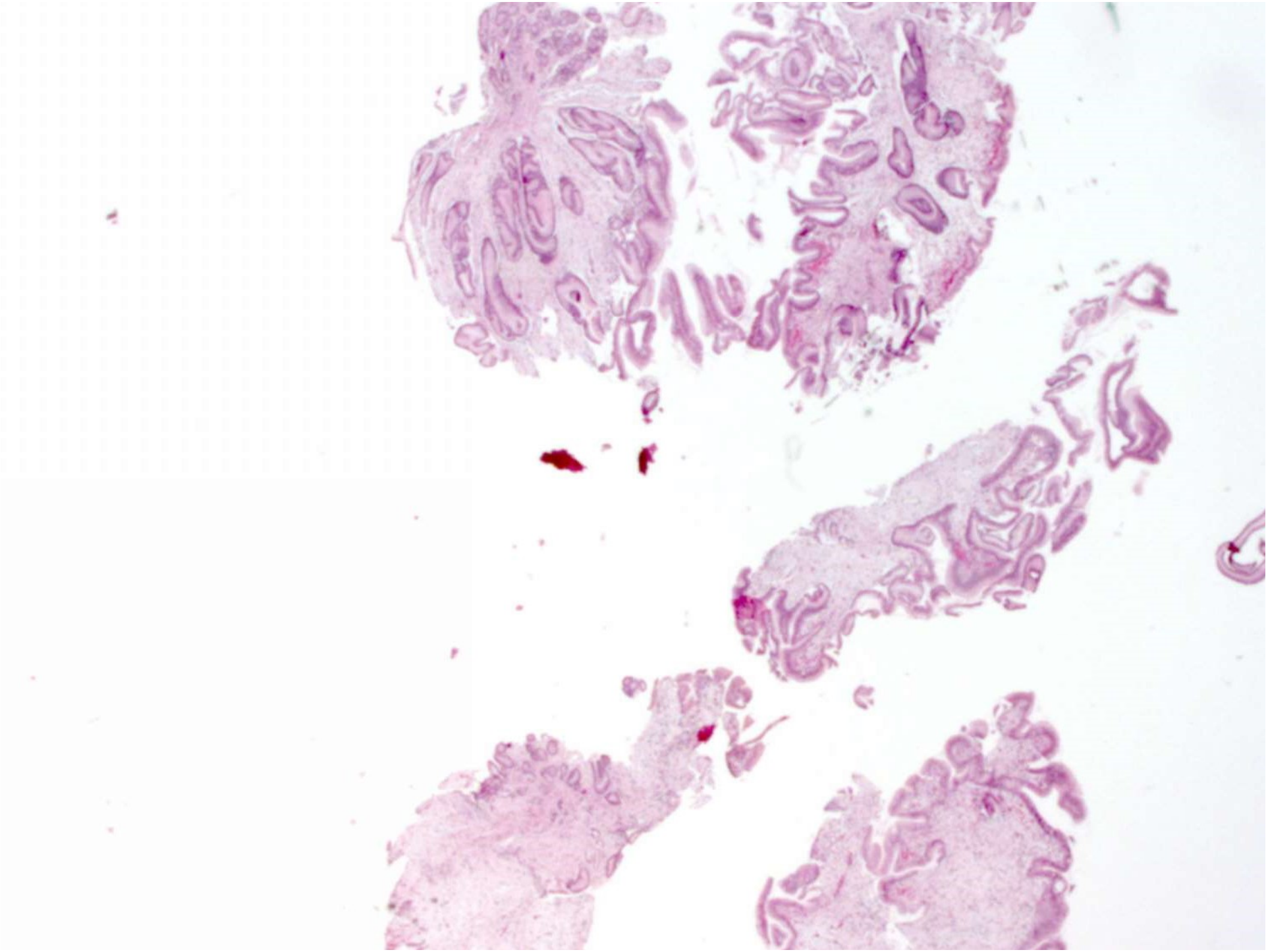


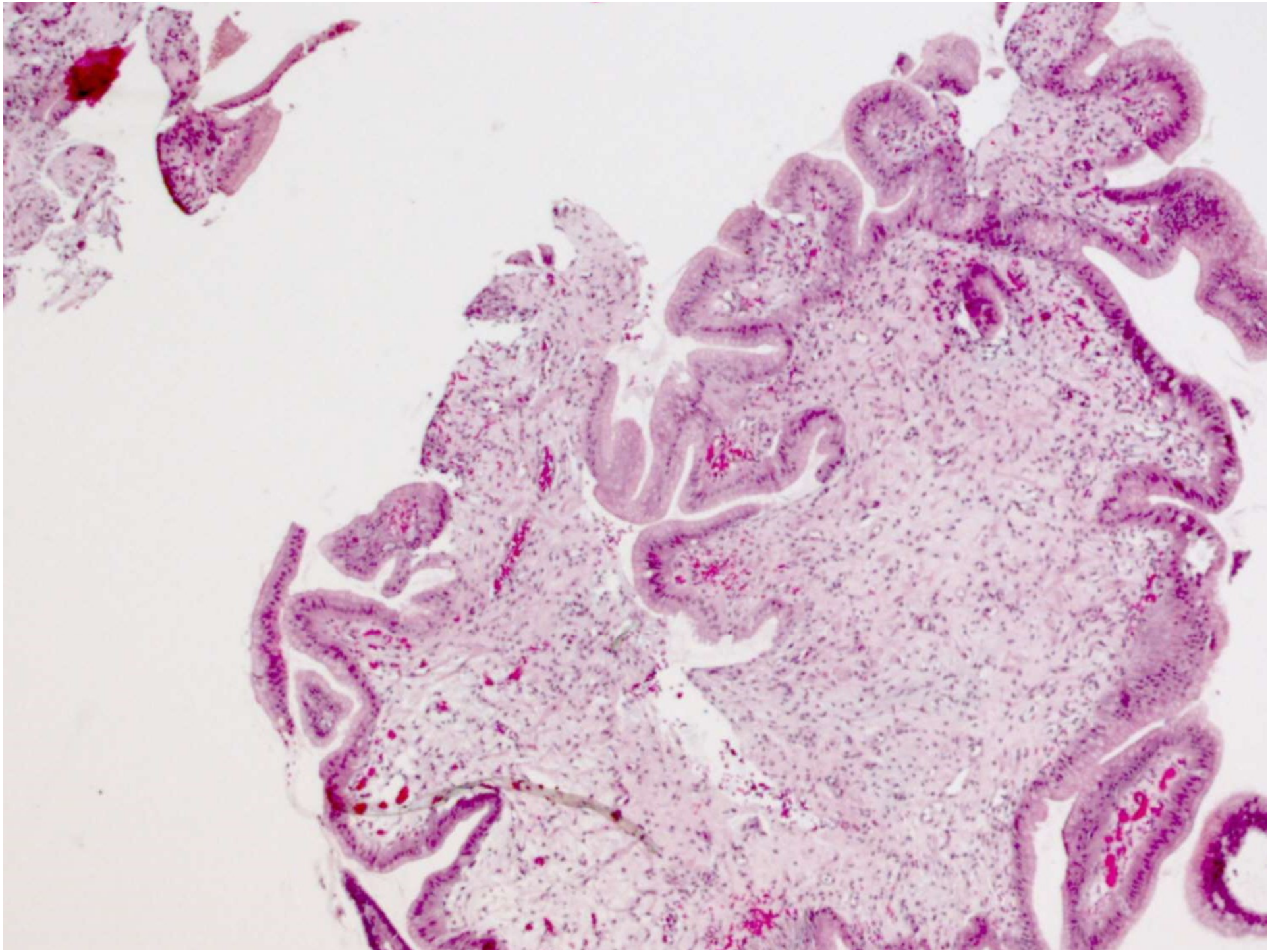
Fundus

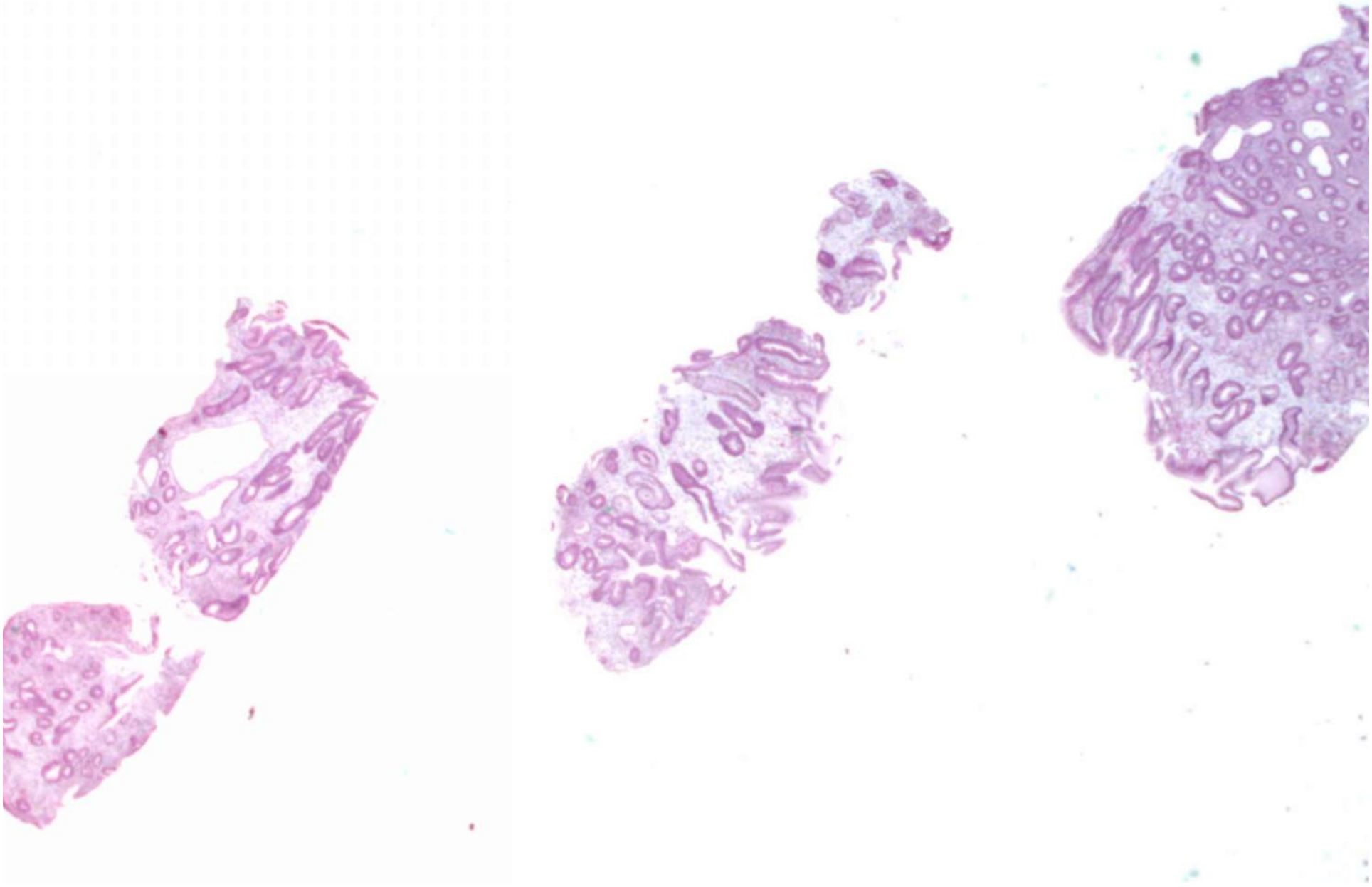


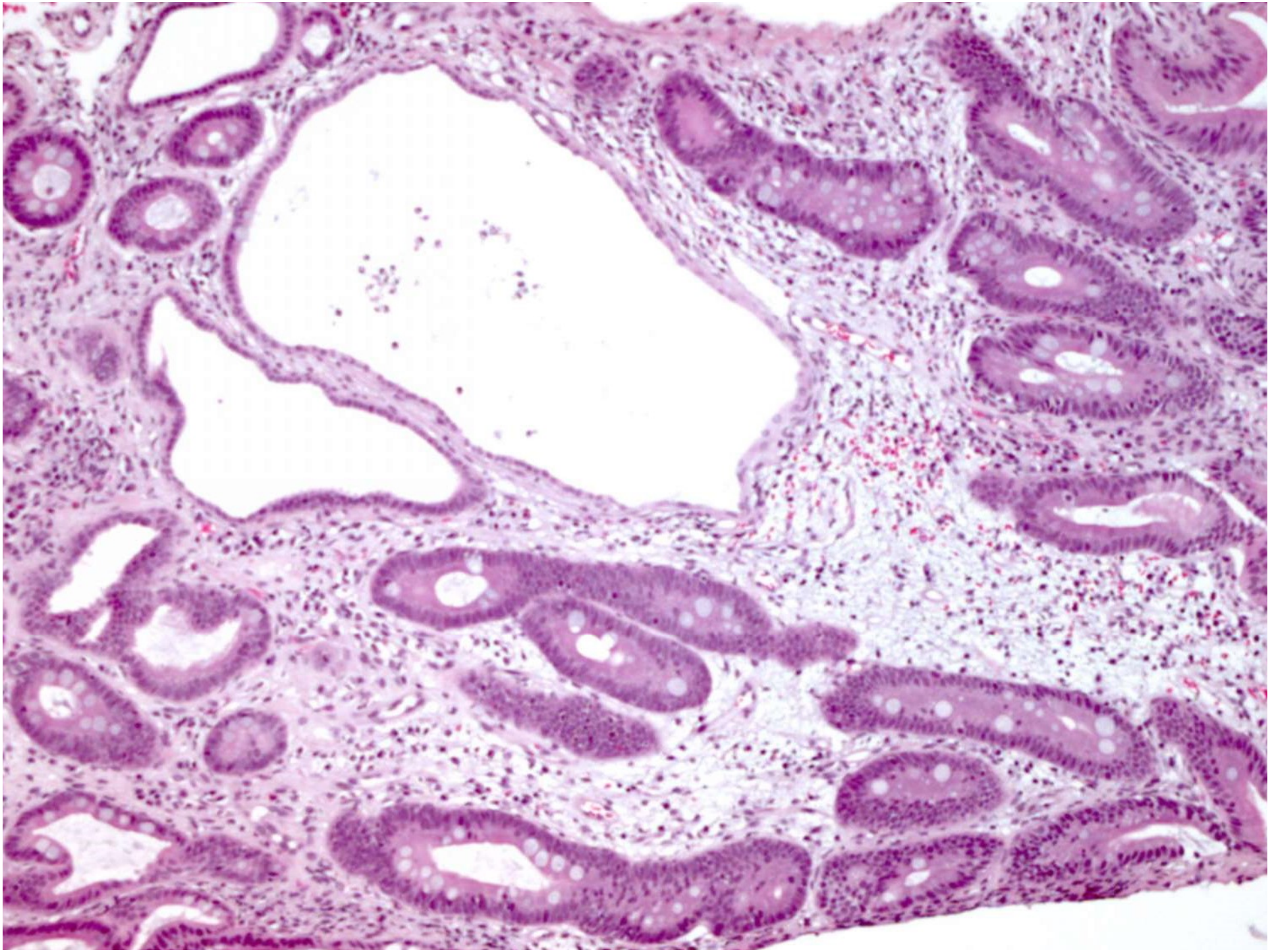
Duodenum











Questions – was there any…

- ?Hair loss (bald)
- ? Nail changes (no nails – had fallen off – apparently 2ndary to malnutrition)
- Skin pigmentation – yes

- Clinicians thought of Cronkhite-Canada syndrome and got in a Derm consult. All changes said to be 2ndary to malnutrition

Hypertrophic gastropathies

1. Ménétrier "primary": Mucous cell hyperplasia—epithelial hyperplasia of surface and foveolar mucous cells;

   Usually oxyntic glands - can be normal or atrophic.

2. Protein-losing hypertrophic conditions "2ary Ménétrier"
   a. CMV-associated hypertrophic gastritis (infants)
   b. Hypertrophic lymphocytic gastritis
   c. *H. pylori*–associated hypertrophic gastritis
3. Zollinger–Ellison syndrome
4. Polyposis syndrome:, Cronkhite–Canada syndrome, JPS
5. Inflammatory: syphilis, histoplasmosis, and granulomatous diseases involving the mucosa and submucosa
6. Diffuse neoplasia (carcinoma, lymphoma)