Dysplasia Topics – Top to Bottom

Elizabeth Montgomery, MD

Disclosures

- Consultation for Olympus
- Consultant for Johnson and Johnson
- Consultant for Merck
- Received honorarium and travel expense money from ARUP Laboratories

Objectives

- To discuss squamous dysplasia of the esophagus
- To consider esophageal columnar dysplasia and gastric dysplasia
- To avoid the small bowel as much as possible since everything is colonization by metastatic malignant neoplasms
- To address issues in colitis-associated dysplasia
- To save the anus for LAST (but not really talk about that 10 year old stuff).

Esophagus

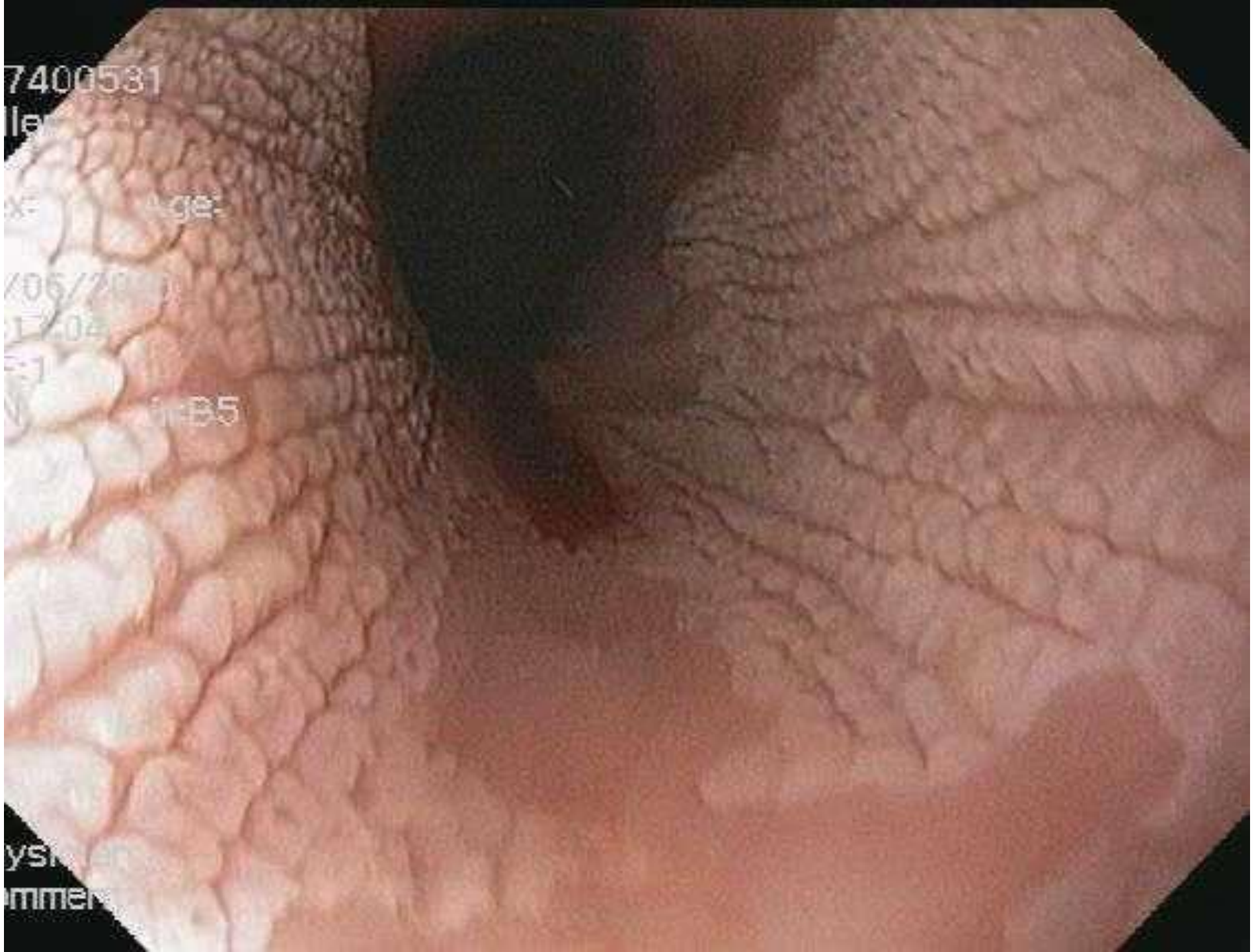
Precursors to Squamous Cell Carcinoma

- Basal cell hyperplasia – fails to retain Lugol's iodine; >15% basal cell thickness – controversial
- "Leukoplakia" (orthokeratotic dysplasia/epidermoid metaplasia) – probably a precursor
- Low-grade Intra-epithelial neoplasia/ squamous dysplasia (lower half of epithelium – mild cytologic alteration).
- High-grade (over half thickness; more striking cytologic alterations)

Leukoplakia (orthokeratotic dysplasia/epidermoid metaplasia)

Leukoplakia refers to a persistent white patch usually encountered in the buccal mucosa that corresponds histologically to areas of hyperkeratosis.

Corresponding esophageal lesions are rarely encountered and are sporadically mentioned in the literature.



Private Information

Epidermoid Metaplasia

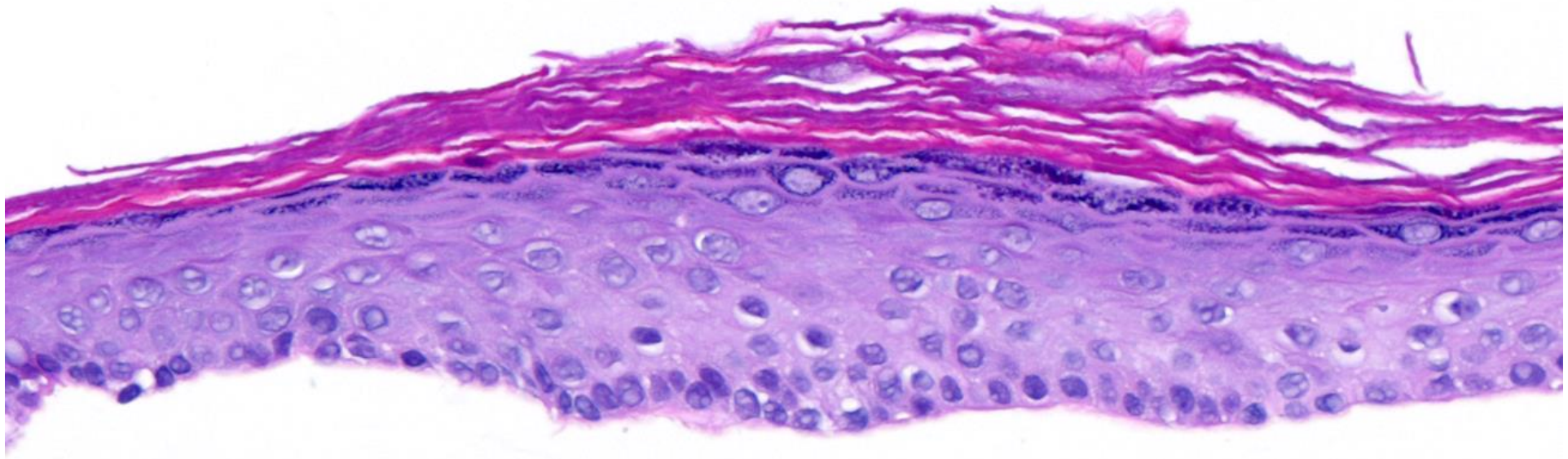
- Plaques of white, thickened mucosa, or red areas which are typically more prominent toward the distal third of the esophagus.
- Biopsies show epithelial hyperplasia and hyperkeratosis and a granular layer just like skin.

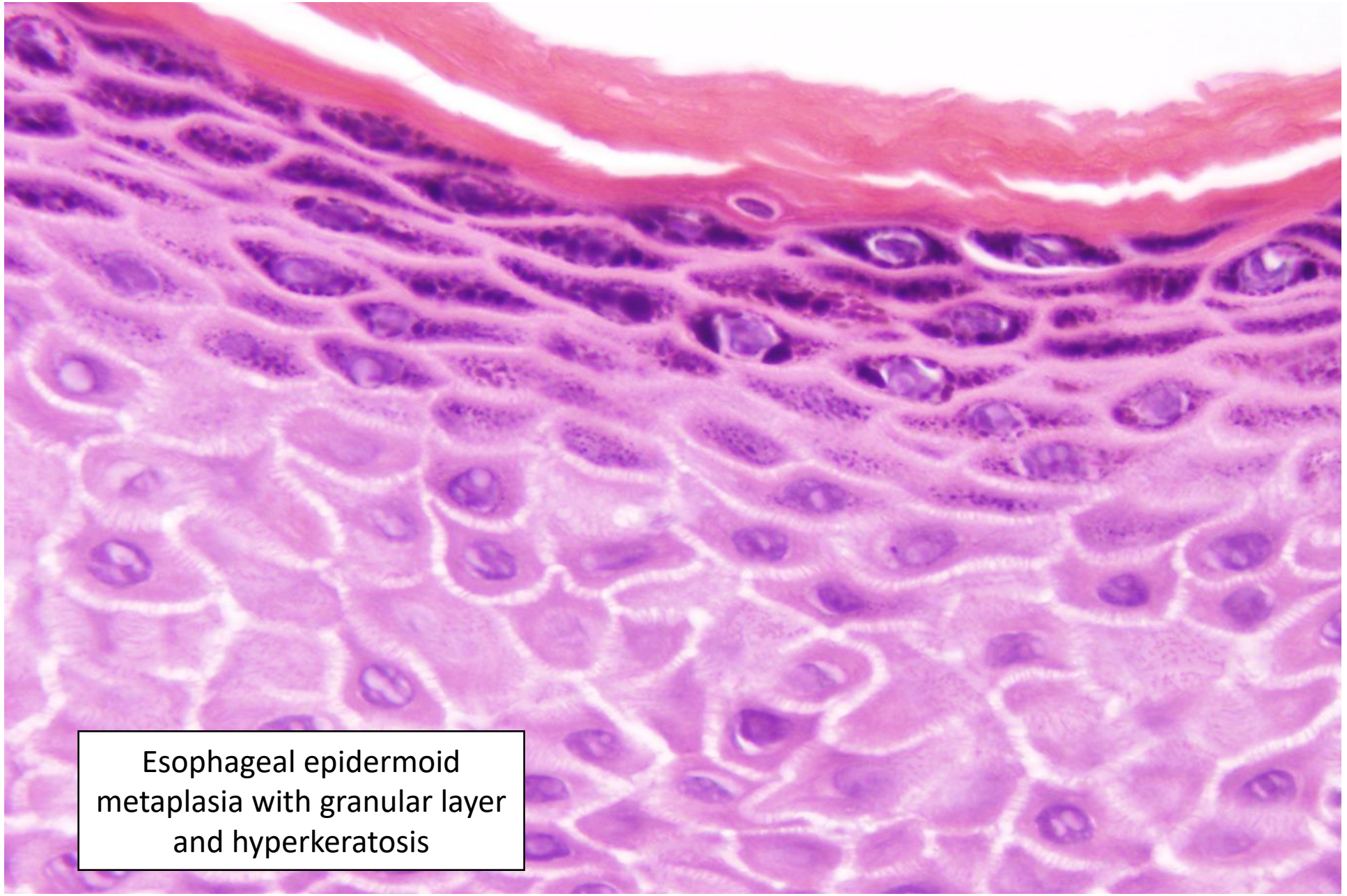
Leukoplakia (orthokeratotic dysplasia/epidermoid metaplasia)

- Significantly greater history of alcohol consumption, head and neck pathology (squamous carcinoma/dysplasia, leukoplakia, and lichen planus), esophageal squamous dysplasia and/or squamous carcinoma when compared to those surveyed due to Barrett esophagus.
- Our cases were also associated with squamous neoplasia but we had far fewer

- Singhi AD, Arnold CA, Crowder CD, Lam-Himlin DM, Voltaggio L, Montgomery EA. Esophageal leukoplakia or epidermoid metaplasia: a clinicopathological study of 18 patients. Mod Pathol. 2014 Jan;27(1):38-43.
- Taggart MW, Rashid A, Ross WA, Abraham SC. Oesophageal hyperkeratosis: clinicopathological associations. Histopathology. 2013 Oct;63(4):463-73.

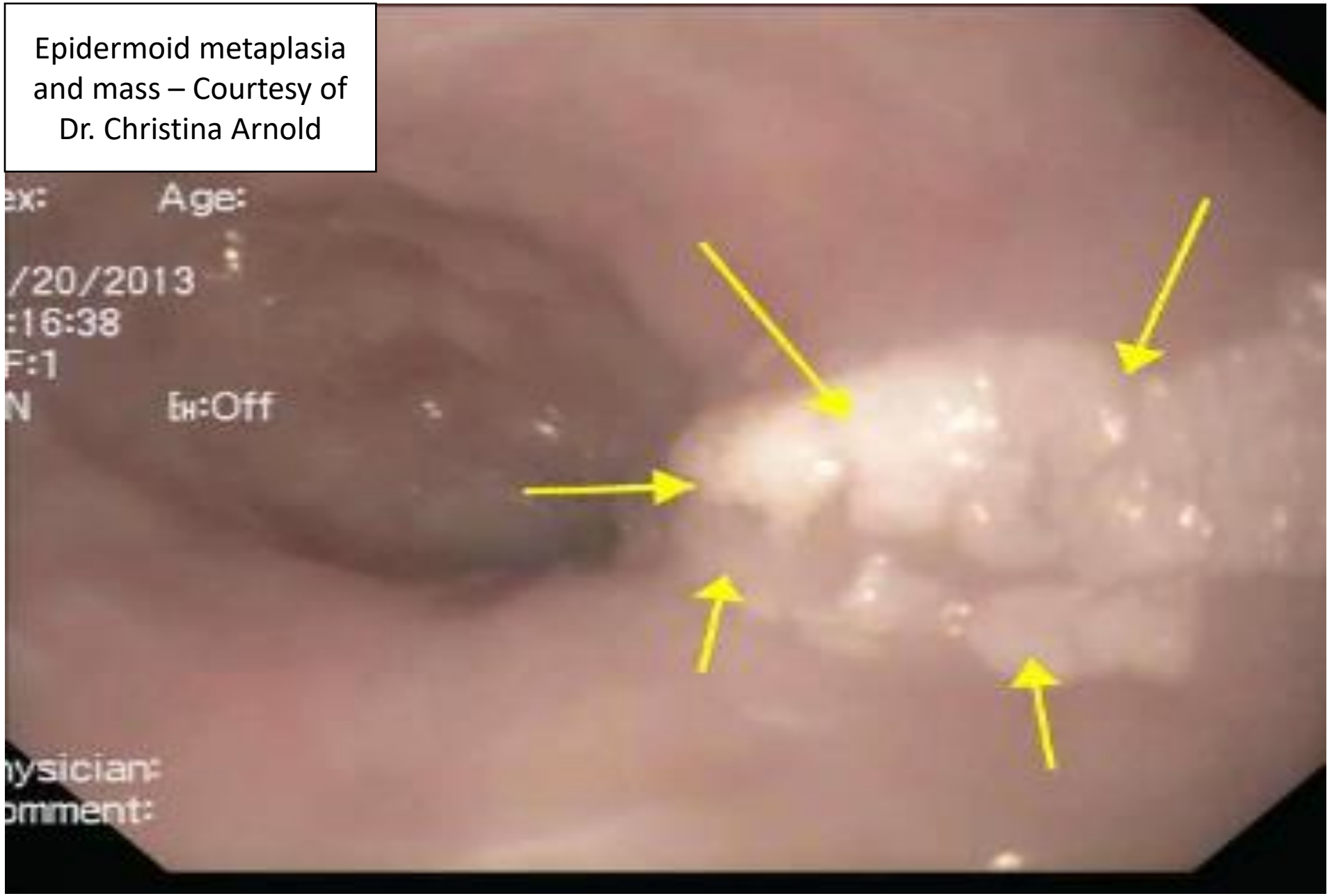
Esophageal epidermoid metaplasia – note granular layer and hyperkeratosis – presents as a plaque to the endoscopist

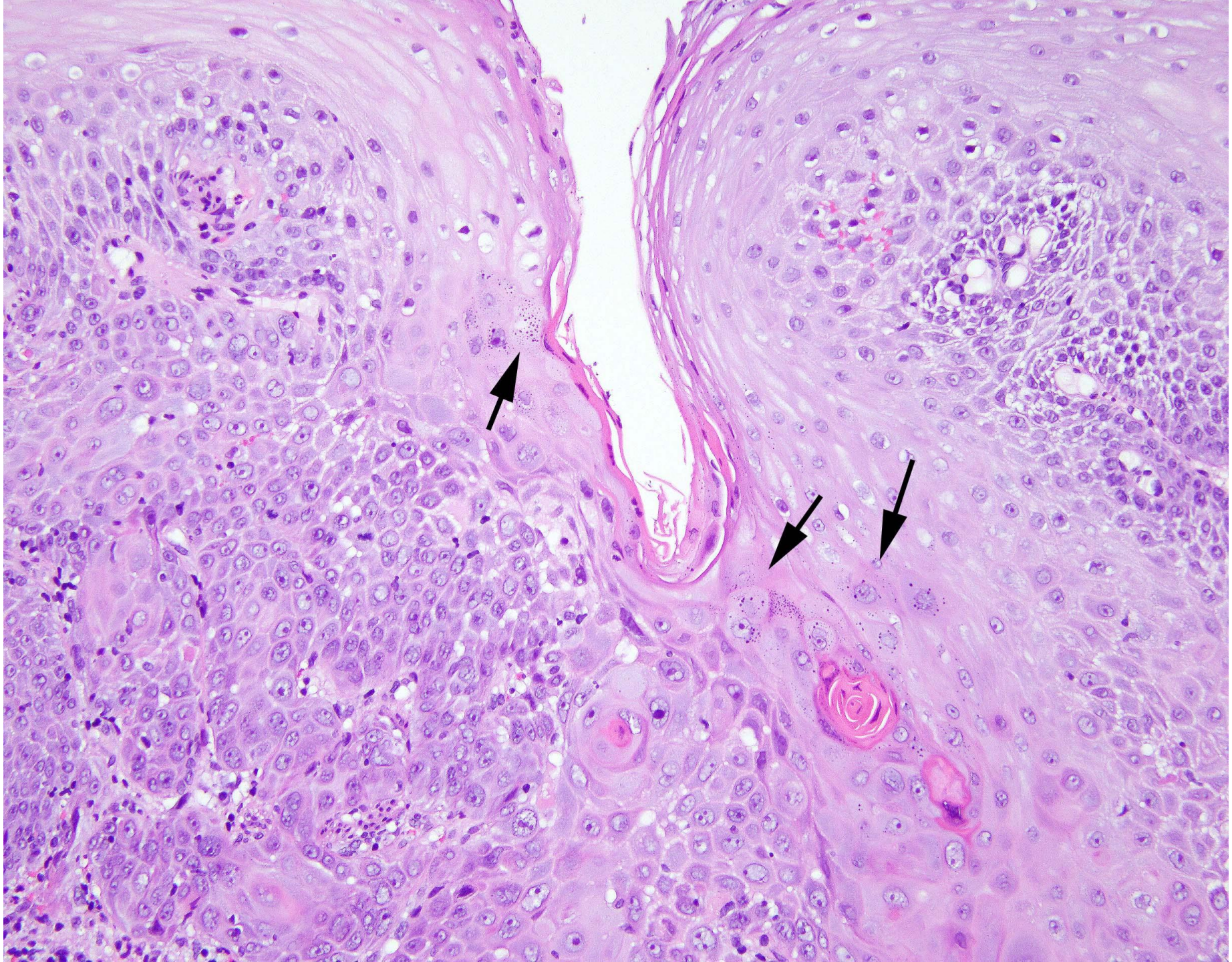




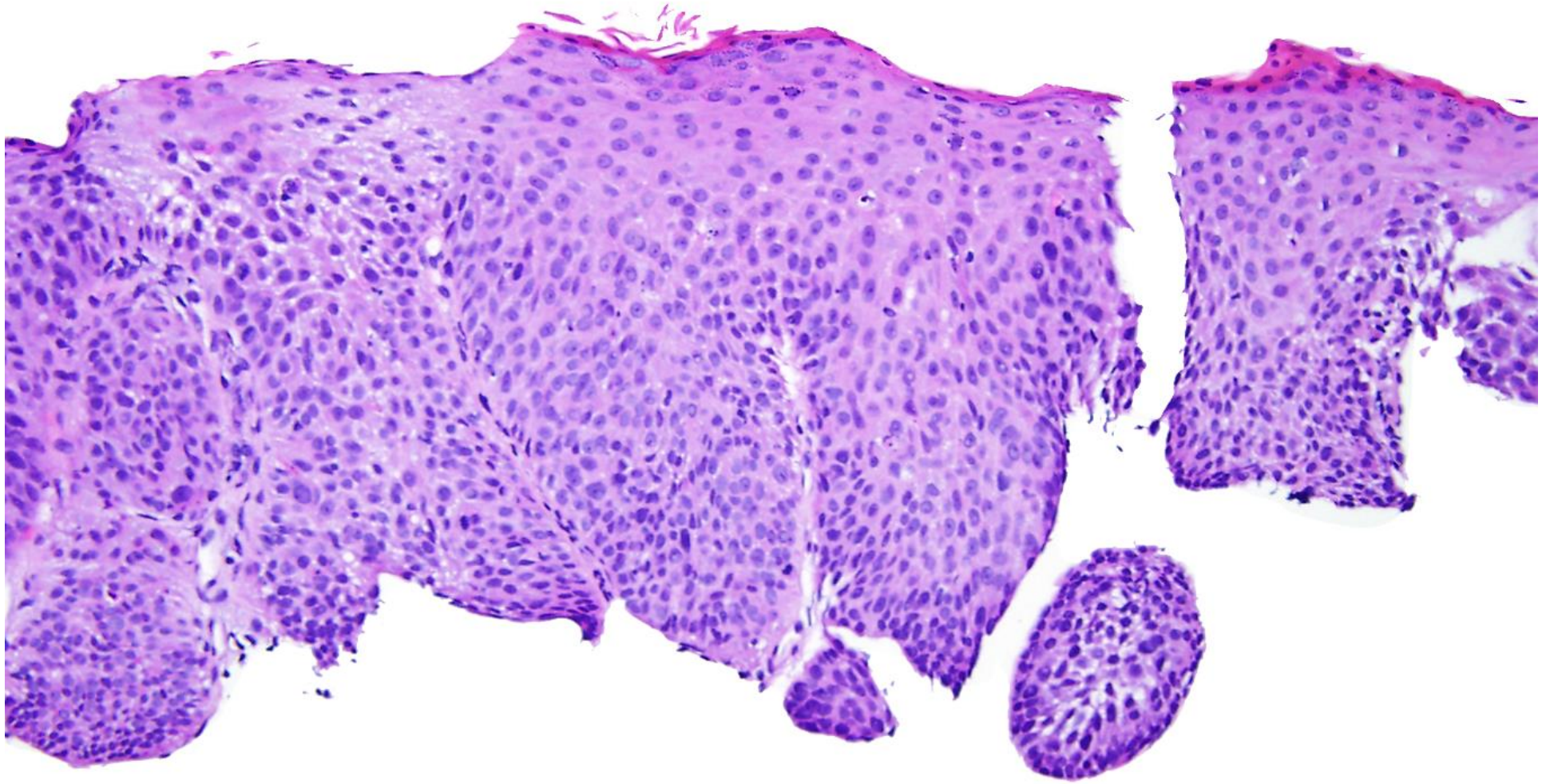
Esophageal epidermoid metaplasia with granular layer and hyperkeratosis

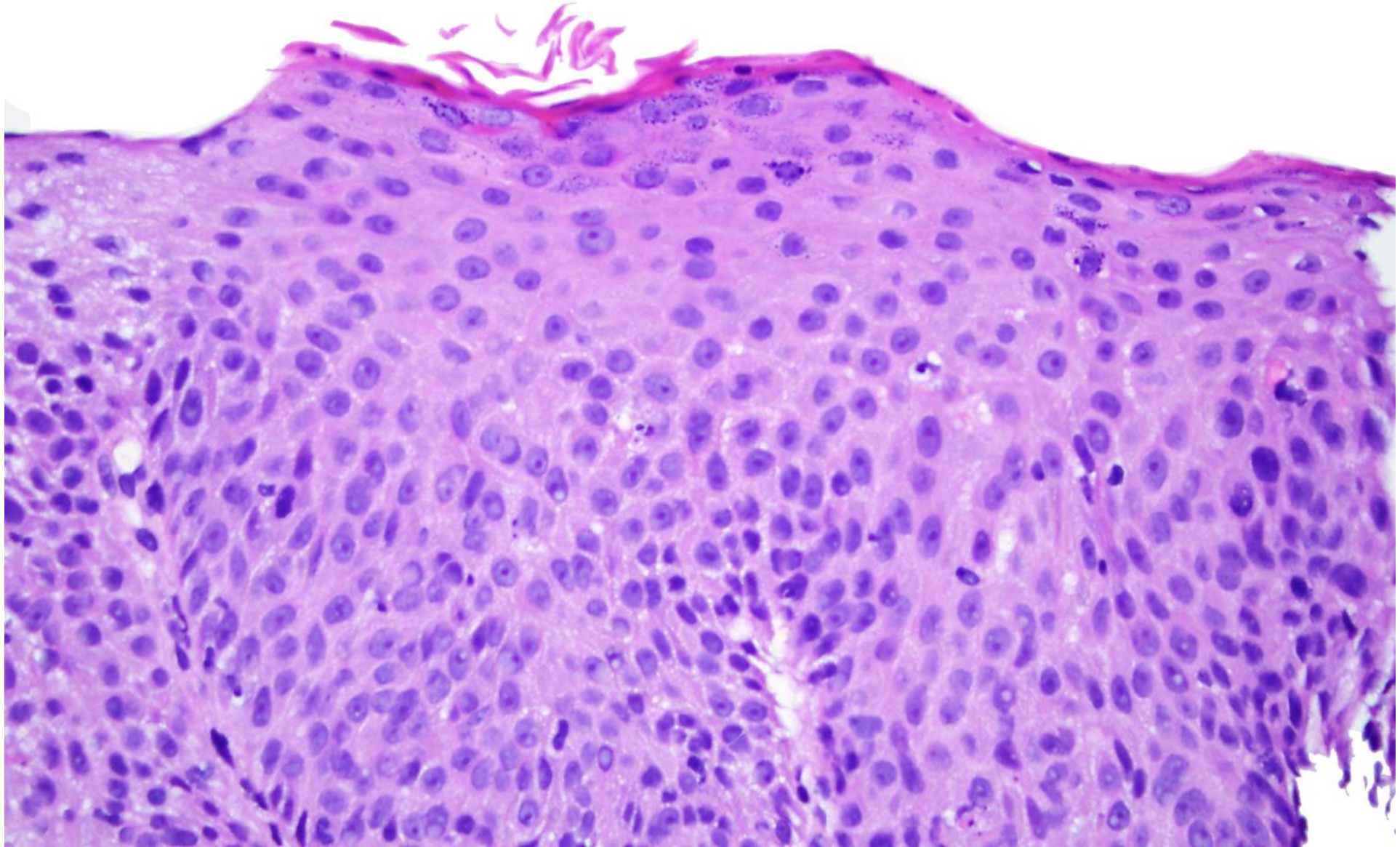
Epidermoid metaplasia and mass – Courtesy of Dr. Christina Arnold





Epidermoid metaplasia and squamous dysplasia





Epidermoid Metaplasia

- The molecular alterations are identical to those in the associated squamous cell carcinomas!

Singhi AD, Arnold CA, Lam-Himlin DM, Nikiforova MN, Voltaggio L, Canto MI, McGrath KM, Montgomery EA. Targeted next-generation sequencing supports epidermoid metaplasia of the esophagus as a precursor to esophageal squamous neoplasia. Mod Pathol. Mod Pathol. 2017 Nov;30(11):1613-1621. PubMed PMID: 28731047.

Oral proliferative verrucous hyperplasia NOT associated with HPV
Key mutation: *TP53*

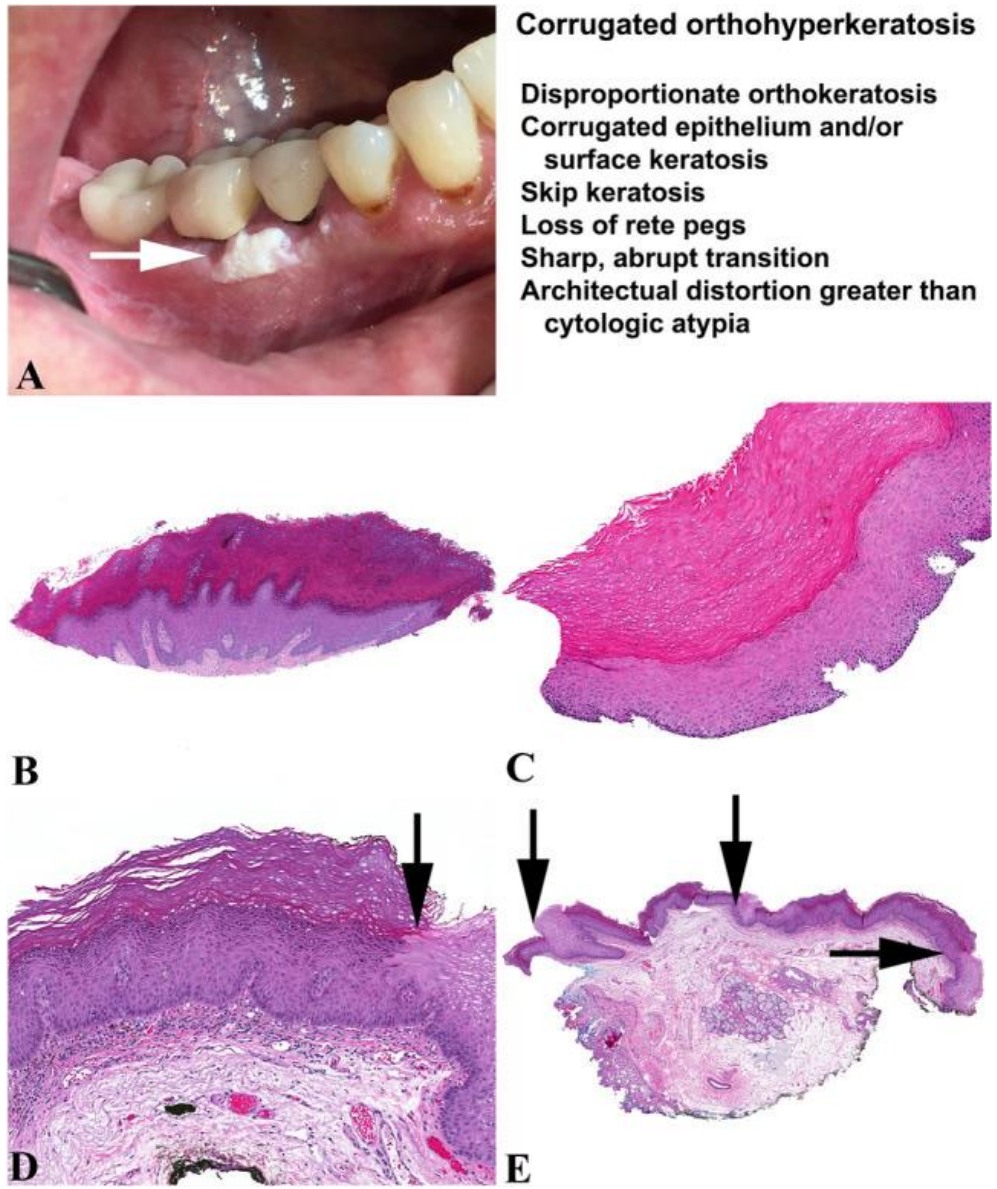
1: Herreros-Pomares A, Hervás D, Bagan-Debon L, Proaño A, Garcia D, Sandoval J, Bagan J. Oral cancers preceded by proliferative verrucous leukoplakia exhibit distinctive molecular features. Oral Dis. 2023 Mar 9. doi: 10.1111/odi.14550. Epub ahead of print. PMID: 36892444.

2: Afkhami M, Maghami E, Gernon TJ, Villaflor V, Bell D. Wolf in sheep's clothing - Oral proliferative verrucous leukoplakia: Progression with longitudinal molecular insights. Ann Diagn Pathol. 2023 Apr;63:152104. PMID: 36640643.

3: Thompson LDR, Fitzpatrick SG, Müller S, Eisenberg E, Upadhyaya JD, Lingen MW, Vigneswaran N, Woo SB, Bhattacharyya I, Bilodeau EA, Carlos R, Islam MN, Leon ME, Lewis JS Jr, Magliocca KR, Mani H, Mehrad M, Purgina B, Richardson M, Wenig BM, Cohen DM. Proliferative Verrucous Leukoplakia: An Expert Consensus Guideline for Standardized Assessment and Reporting. Head Neck Pathol. 2021 Jun;15(2):572-587:33415517; PMCID: PMC8134585.

Similar laryngeal findings:

Hutchings, D, Windon AL, Assarzadegan N, Salimian KJ, Voltaggio L, Montgomery EA, Rooper LM. Epidermoid/Orthokeratotic Metaplasia of the Larynx: Toward a Unifying Concept for Pre-Dysplastic Lesions of the Upper Aerodigestive Tract", USCAP Annual meeting 2020 (platform presentation).



From Thompson et al.

Table 1.

Table 1. Estimated risk of ESCC and surveillance recommendations

Condition	ESCC risk	Proposed surveillance recommendations
Fanconi anemia	Estimated incidence risk: 1,200–6,200 (12–14)	Endoscopic surveillance beginning at age 15–20 years in 1–2-yr intervals
Lichen planus	6.1% developed esophageal cancer in cohort of 132 patients (24)	Endoscopic surveillance 6 mo after diagnosis and then continued surveillance every 1–2 yr
Chronic mucocutaneous candidiasis	6.5% of 92 patients with APECED developed oral or esophageal SCC by age 44 (33)	Consider endoscopic surveillance for both detection of esophageal candidiasis and for ESCC
Esophageal epidermoid metaplasia	3% of 40 patients developed ESCC after EEM diagnosis (44) 20% had previous or concurrent ESCC or squamous high-grade dysplasia (44)	Endoscopic surveillance 6 mo after diagnosis and then yearly if no dysplasia. Four-quadrant biopsies throughout the affected esophagus with p53 staining
Epidermolysis bullosa	7.1% of 42 patients with RDEB older than 30 yr developed ESCC (54)	Limited because of mucosal fragility. Consider endoscopic evaluation with symptom changes
Tylosis	Lifetime risk of ESCC of up to 95% by age 65 in large family pedigrees (59,60)	Endoscopic surveillance annually starting at age 20 yr with Lugol iodine solution with both targeted biopsies and random 4-quadrant biopsies with p53 staining
Esophageal atresia	0.7% of 289 patients developed ESCC (108-fold risk) (70)	Endoscopic surveillance beginning at age 15 yr in 3–5-yr intervals
Achalasia	Esophageal cancer risk was 5-fold higher in 1,863 person cohort with achalasia compared with matched cohort of 7,452 without achalasia. Esophageal cancer incidence of 1.4 per 1,000 person-years (91)	Consider endoscopic surveillance in those with longstanding disease, dilation of the esophagus, male sex, alcohol use, tobacco use, older age

APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; EEM, esophageal epidermoid metaplasia; ESCC, esophageal squamous cell carcinoma; RDEB, recessive dystrophic epidermolysis bullosa; SCC, squamous cell carcinoma.

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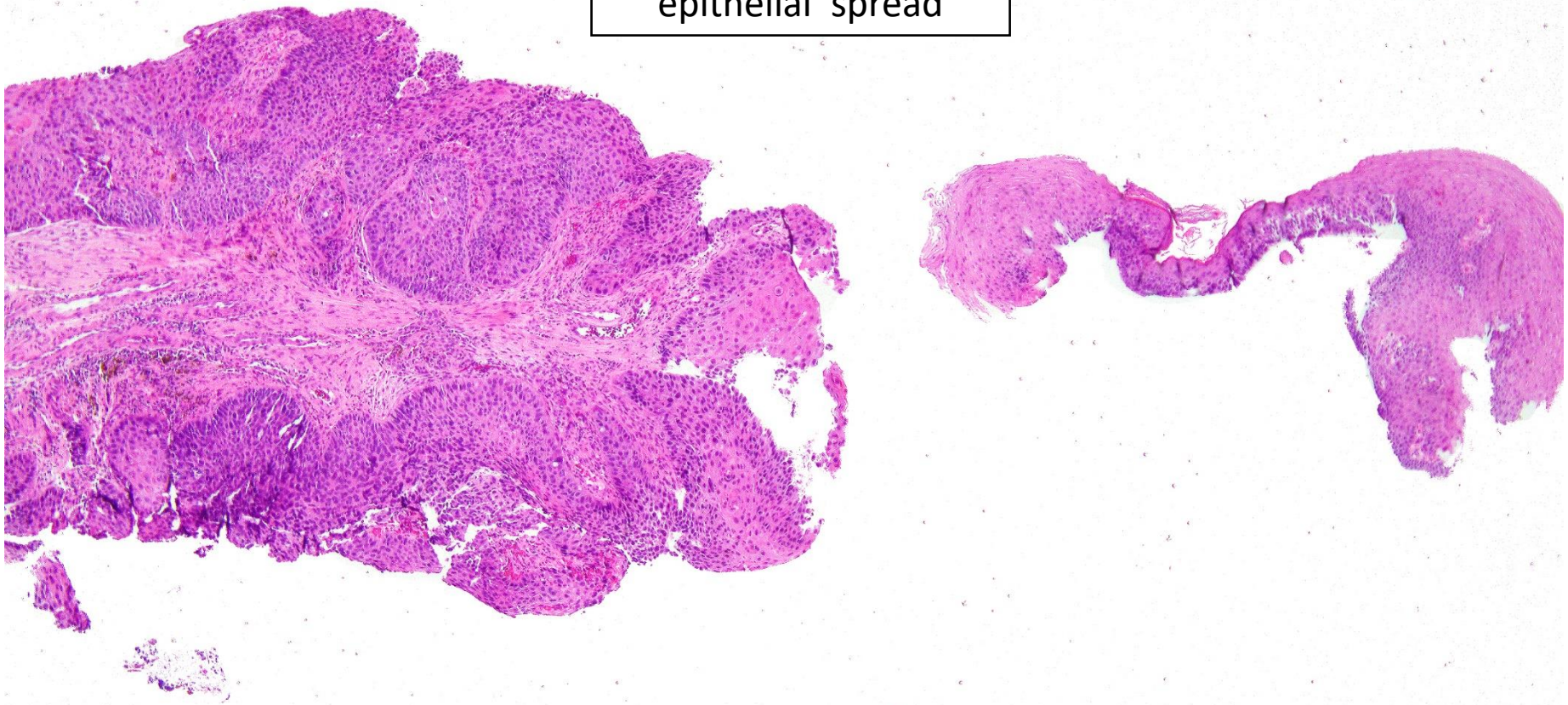
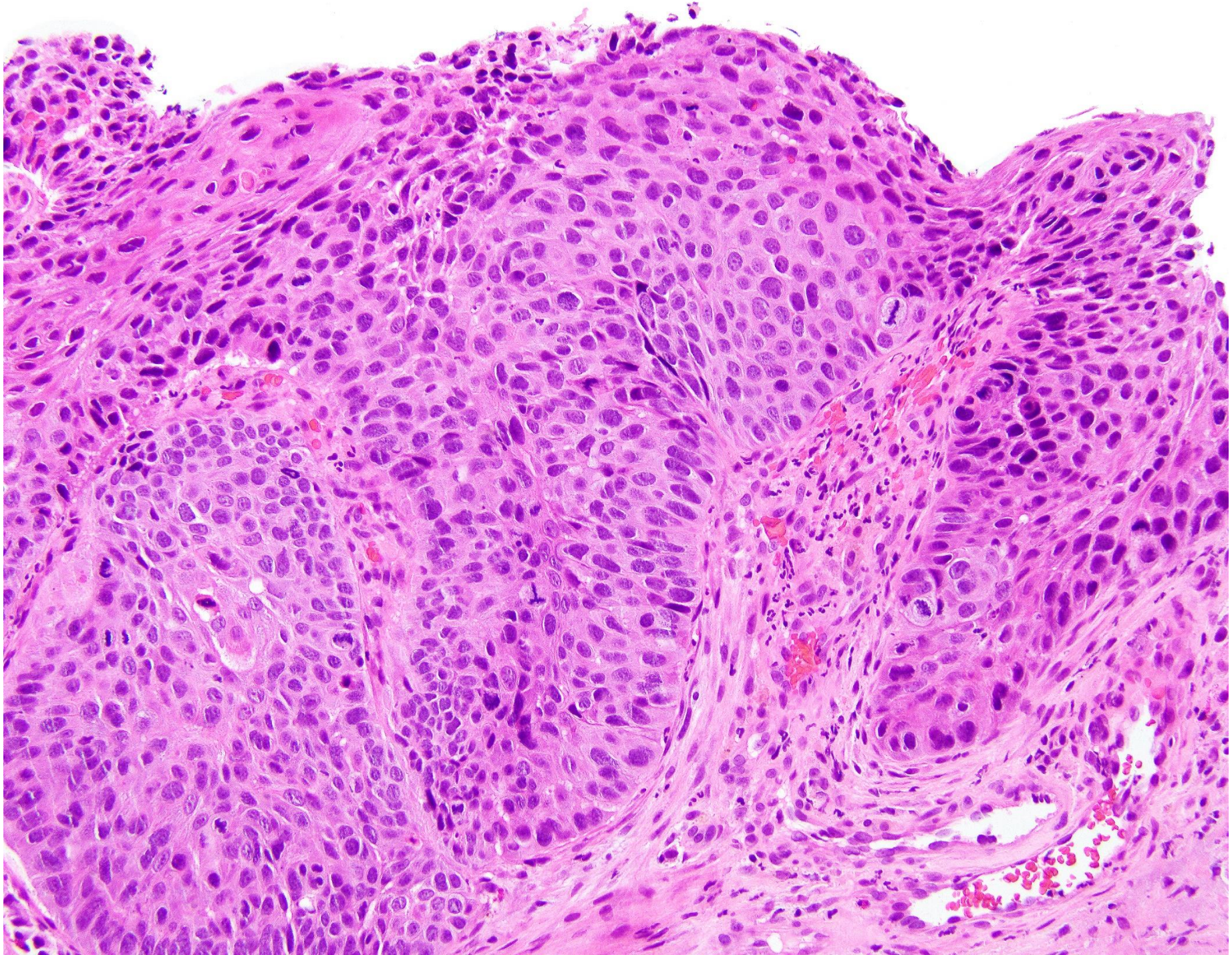
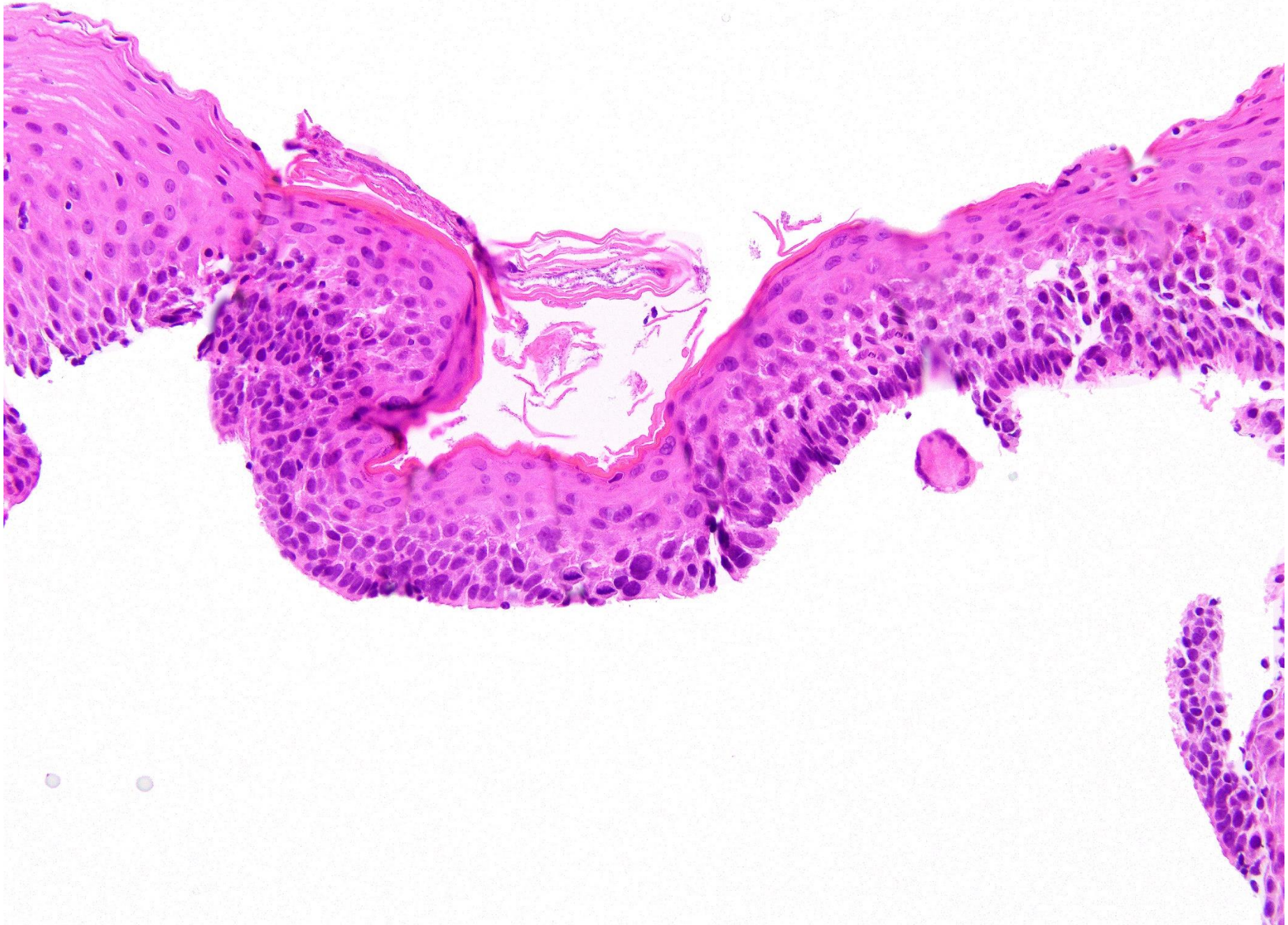
Kamboj AK, Gibbens YY, Hagen CE, Wang KK, Iyer PG, Katzka DA. Esophageal Epidermoid Metaplasia: Clinical Characteristics and Risk of Esophageal Squamous Neoplasia. Am J Gastroenterol. 2021 Jul 1;116(7):1533-1536. PMID: 33734117.

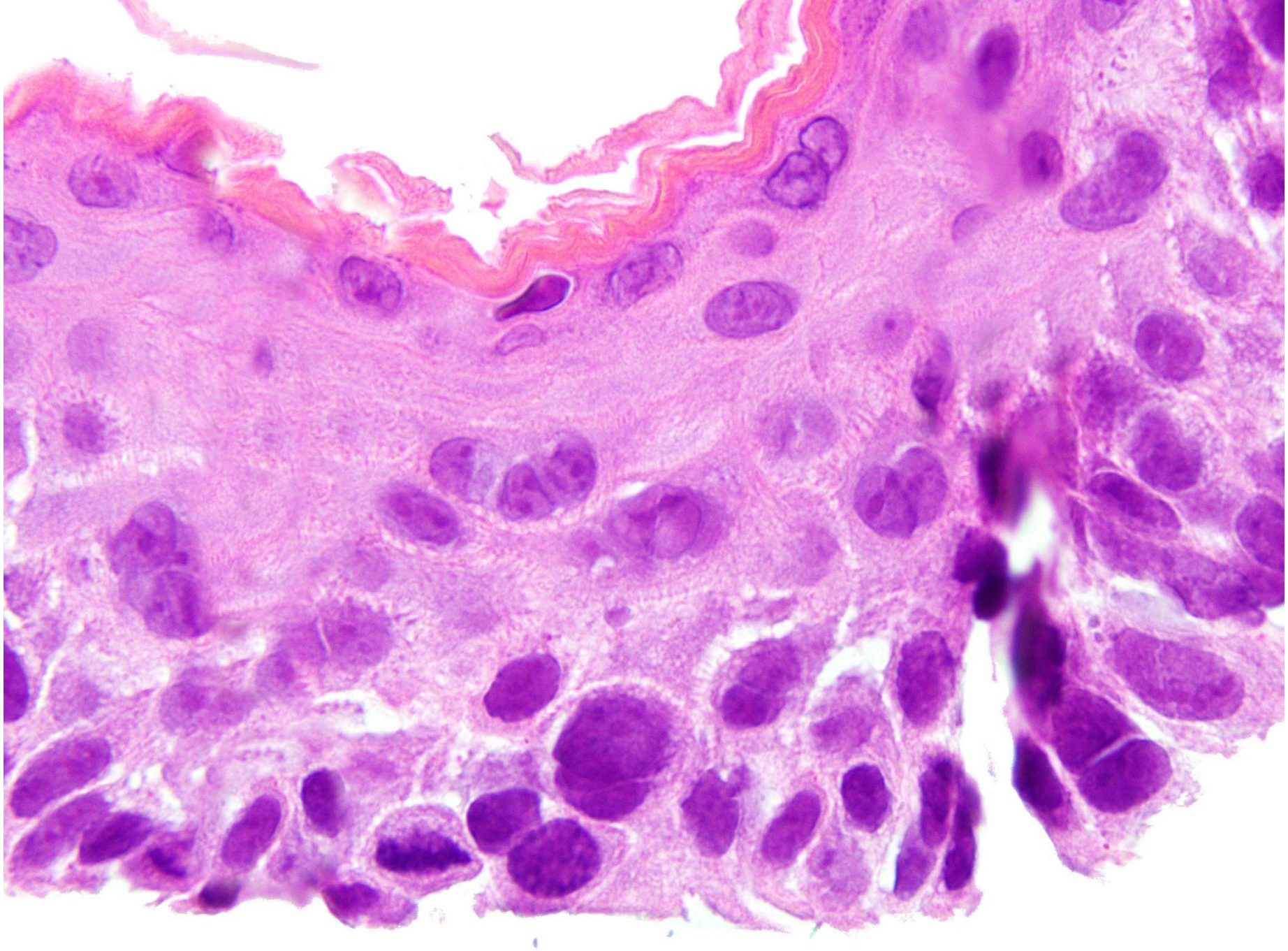
Pomenti SF, Flashner SP, Del Portillo A, Nakagawa H, Gabre J, Rustgi AK, Katzka DA. Clinical and Biological Perspectives on Noncanonical Esophageal Squamous Cell Carcinoma in Rare Subtypes. Am J Gastroenterol. 2024 Dec 1;119(12):2376-2388. PMID: 39166765.

Squamous cell carcinoma – intra-epithelial spread









Columnar esophagus and stomach

FAQ: How is Barrett's Esophagus Defined?

British (and Japanese) definition of Barrett's esophagus 2014:

- Columnar epithelium with or without goblet cells extending ≥1 cm above the gastric folds

American Gastroenterological Association definition of Barrett's esophagus 2011:

- Columnar epithelium in the esophagus that contains goblet cells – no length requirement

American College of Gastroenterologists' definition of Barrett's esophagus 2016:

- Columnar epithelium with goblet cells extending ≥1 cm above the top of the gastric folds

Fitzgerald RC, di Pietro M, Ragunath K, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut.* 2014;63(1):7-42.

American Gastroenterological Association Medical Position Statement on the Management of Barrett's Esophagus. *Gastroenterology.* 2011;140(3):1084-1091.

Shaheen NJ, Falk GW, Iyer PG, Souza RF, Yadlapati RH, Sauer BG, Wani S. Diagnosis and Management of Barrett's Esophagus: An Updated ACG Guideline. Am J Gastroenterol. 2022 Apr 1;117(4):559-587. PMID: 35354777.

2012 and 2016 Studies from University of Southern California

- ONLY FOUND DYSPLASIA OR CARCINOMA IN PATIENTS WITH INTESTINAL METAPLASIA AND EARLY CANCERS WERE ACCOMPANIED BY INTESTINAL METAPLASIA
- BUT these patients were all biopsied using systematic protocols ("perfect world") by highly experienced colleagues

Chandrasoma P, Wijetunge S, DeMeester S, Ma Y, Hagen J, Zamis L, DeMeester T. Columnar-lined esophagus without intestinal metaplasia has no proven risk of adenocarcinoma. Am J Surg Pathol. 2012 Jan;36(1):1-7.

Smith J, Garcia A, Zhang R, DeMeester S, Vallone J, **Chandrasoma P**. Intestinal Metaplasia is Present in Most if Not All Patients Who Have Undergone endoscopic Mucosal Resection for Esophageal Adenocarcinoma. Am J Surg Pathol. 2016 Apr;40(4):537-43. PubMed PMID: 26813746.

Cases with staging data – Johns Hopkins

- In our material at Johns Hopkins, we found that >92% of patients with treatment naïve esophageal adenocarcinomas had background intestinal metaplasia

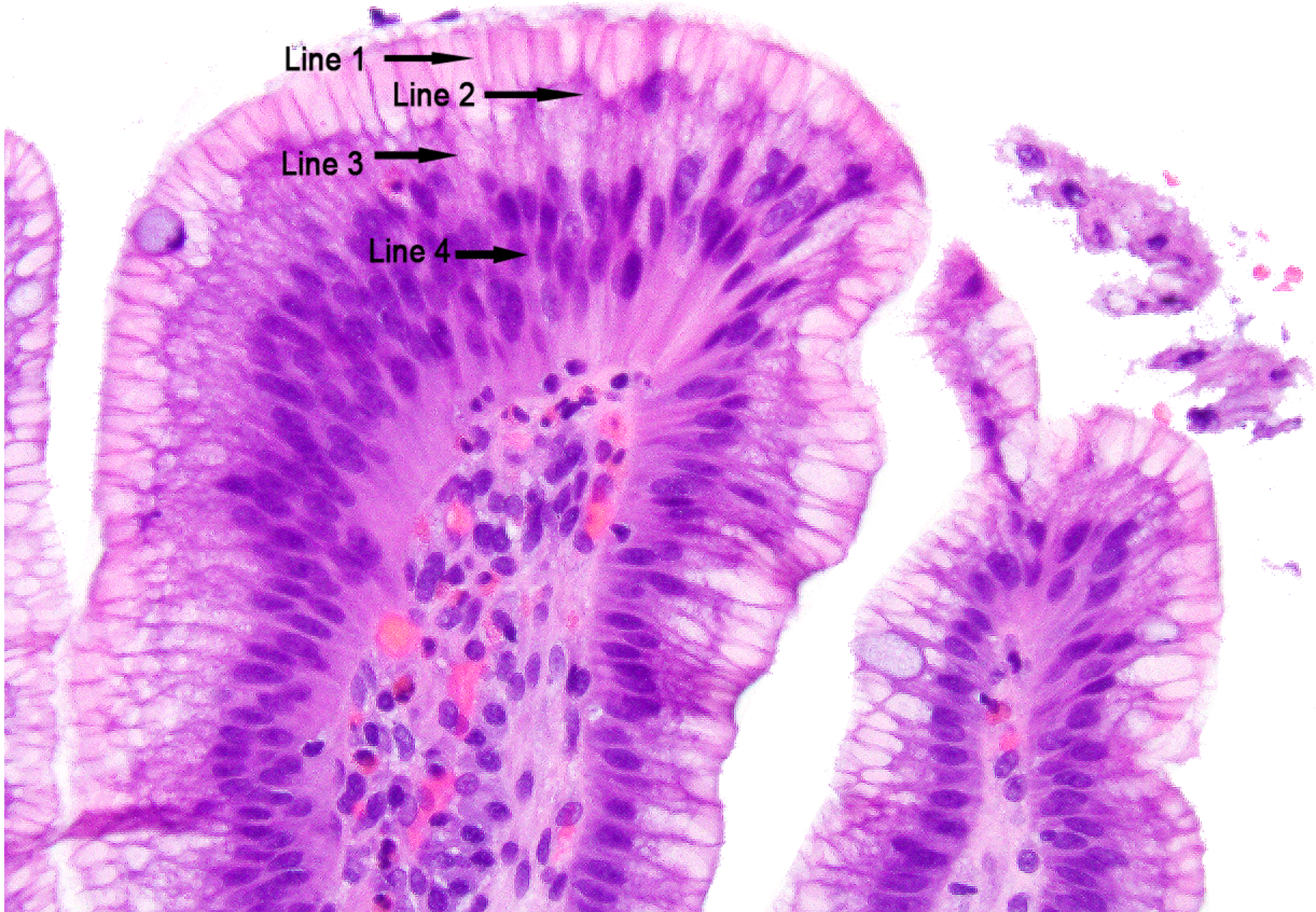
Salimian KJ, Waters KM, Eze O, Pezhouh MK, Tarabishy Y, Shin EJ, Canto MI, Voltaggio L, Montgomery EA. Definition of Barrett Esophagus in the United States: Support for Retention of a Requirement for Goblet Cells. Am J Surg Pathol. 2018 Feb;42(2):264-268. PubMed PMID: 29016405.

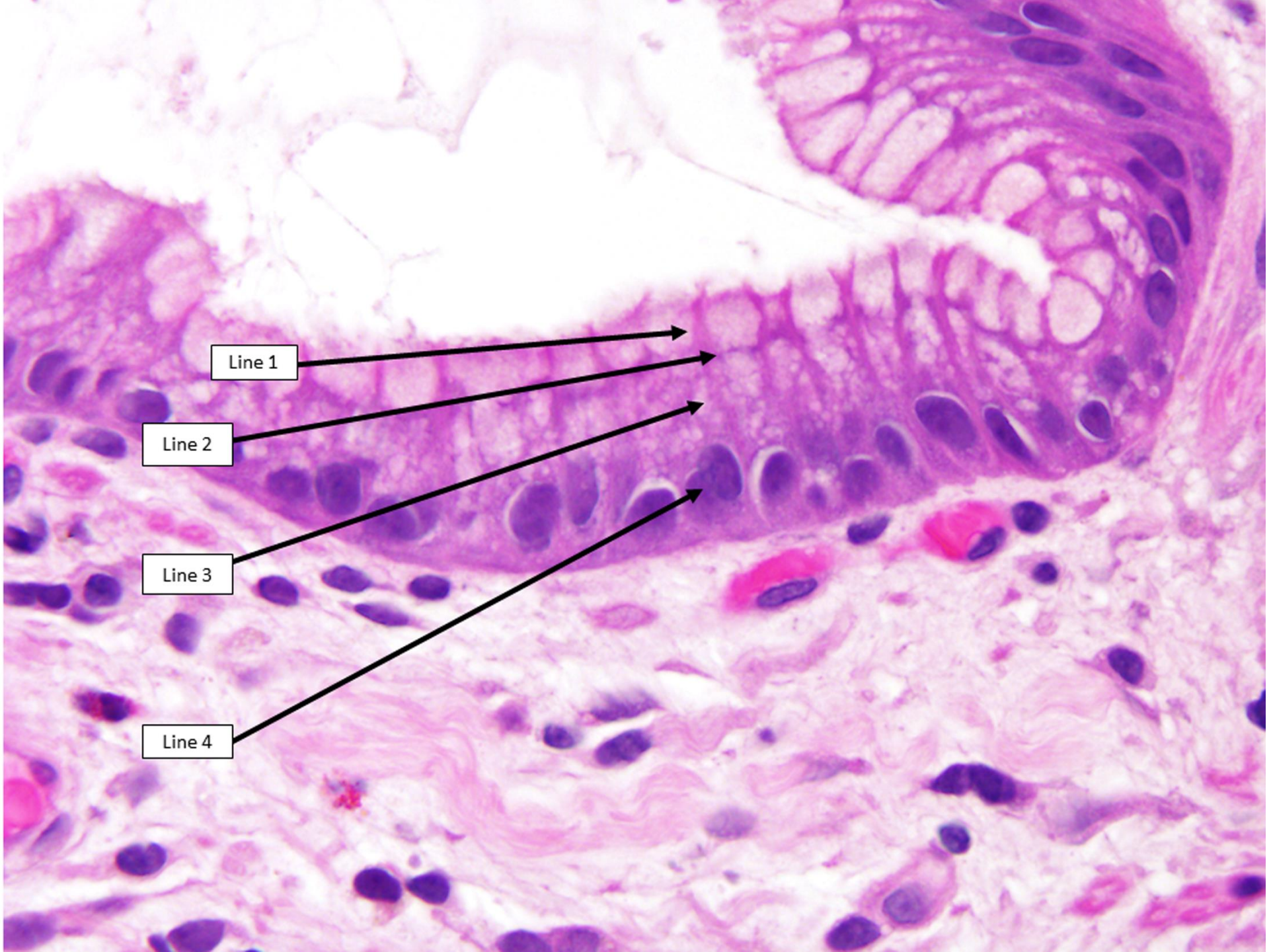
Avoiding overdiagnosis of dysplasia

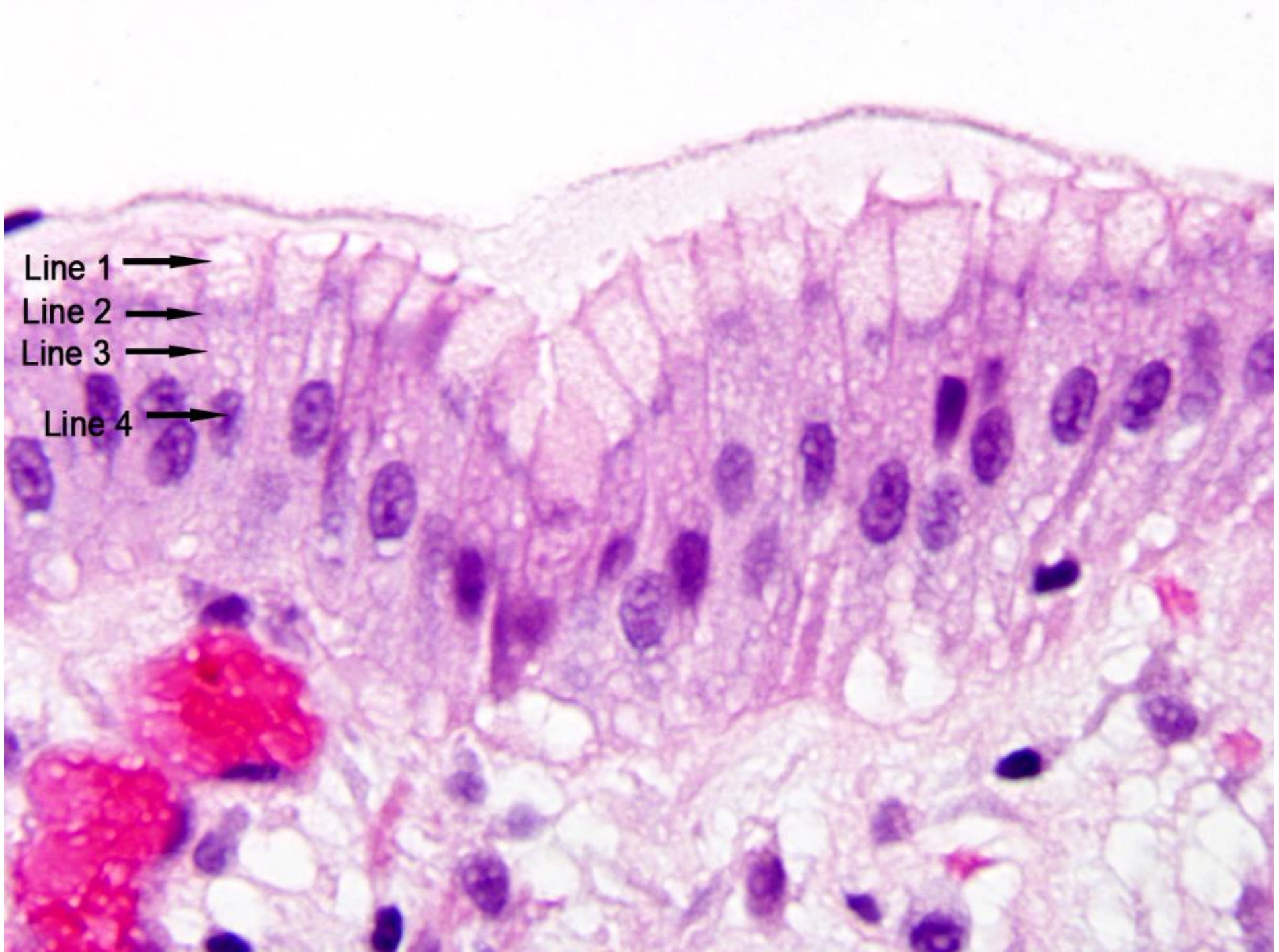
A fantastic clue

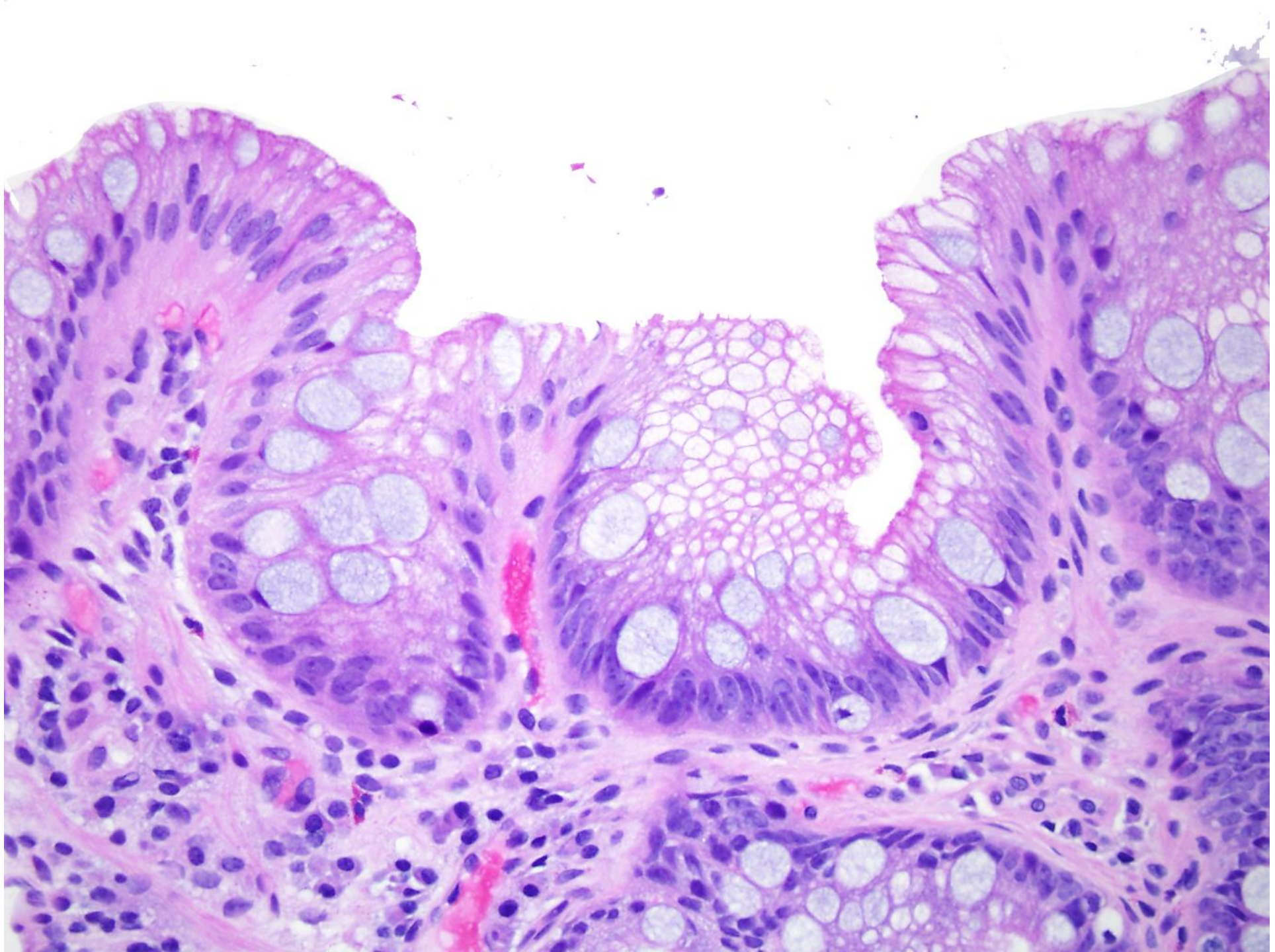
- A great clue to reactive epithelium in Barrett mucosa is looking for “the four lines”
- This feature is present in gastric cardiac mucosa and remains in Barrett mucosa

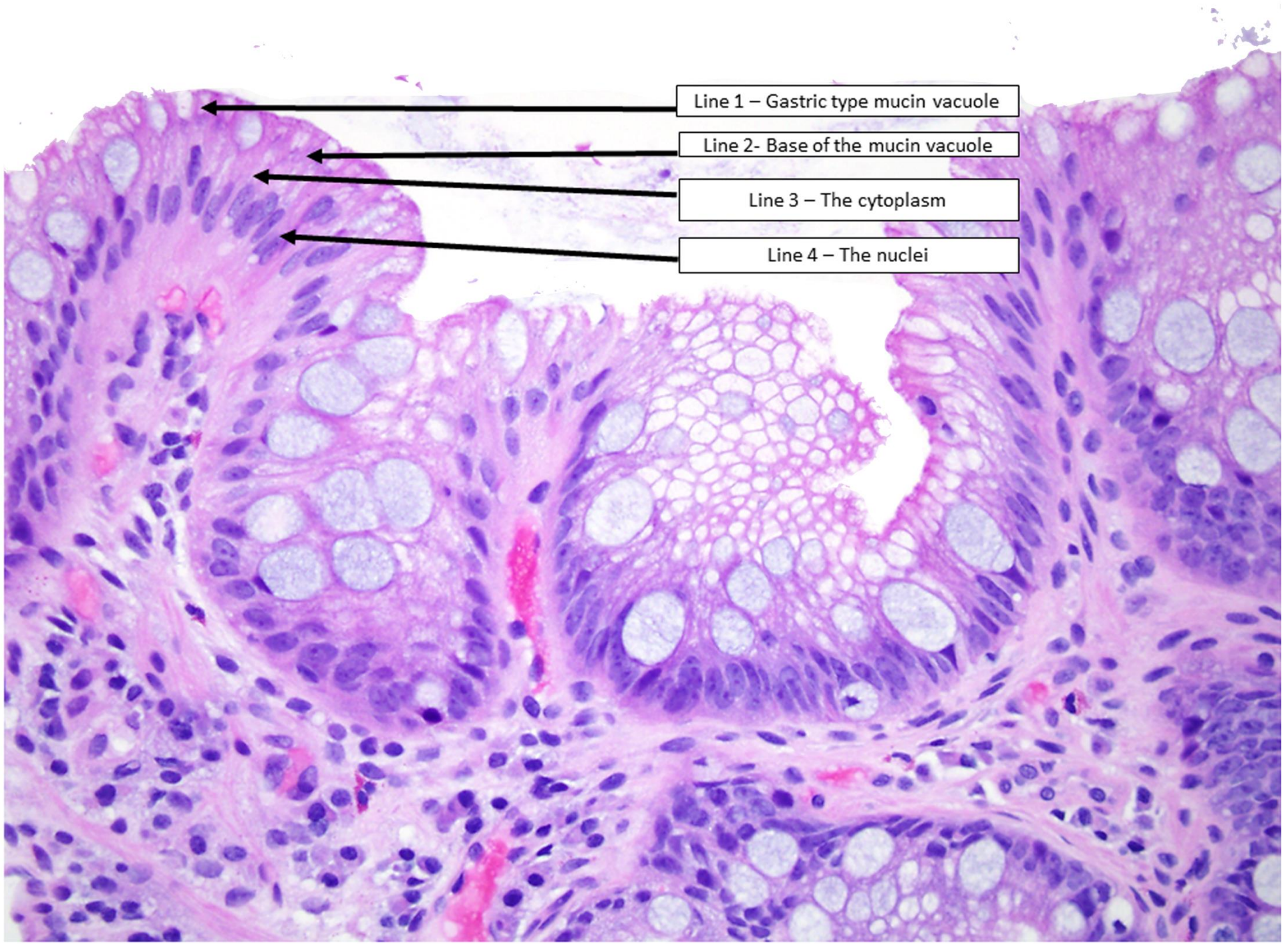
- Let’s have a look











Indefinite for dysplasia

- Originally defined in IBD and diagnosed by answering the questions…
- a) Is this epithelium unequivocally benign or reactive?
- b) Is this epithelium unequivocally neoplastic/adenomatous
- The answer “NO” to both questions = IFD

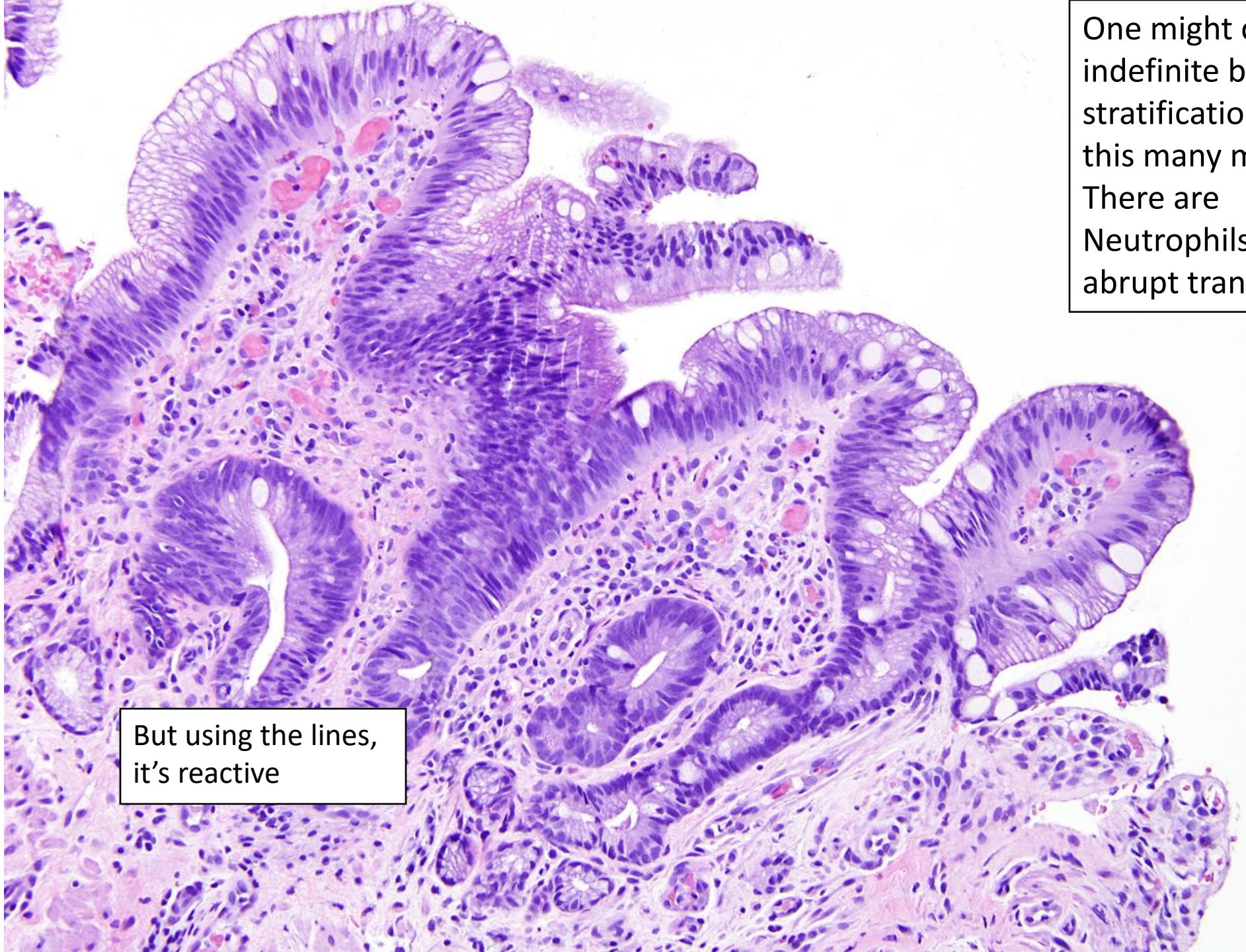
But…..

- 2001 – study on dysplasia in BE (oops)
- Deliberately defined any epithelium that looked dysplastic in the bases of the pits but had surface maturation as IFD
- i.e. impossible to have dysplasia with maturation

Montgomery E, Bronner MP, Goldblum JR, Greenson JK, Haber MM, Hart J, Lamps LW, Lauwers GY, Lazenby AJ, Lewin DN, Robert ME, Toledano AY, Shyr Y, Washington K. Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. Hum Pathol. 2001 Apr;32(4):368-78. PubMed PMID: 11331953.

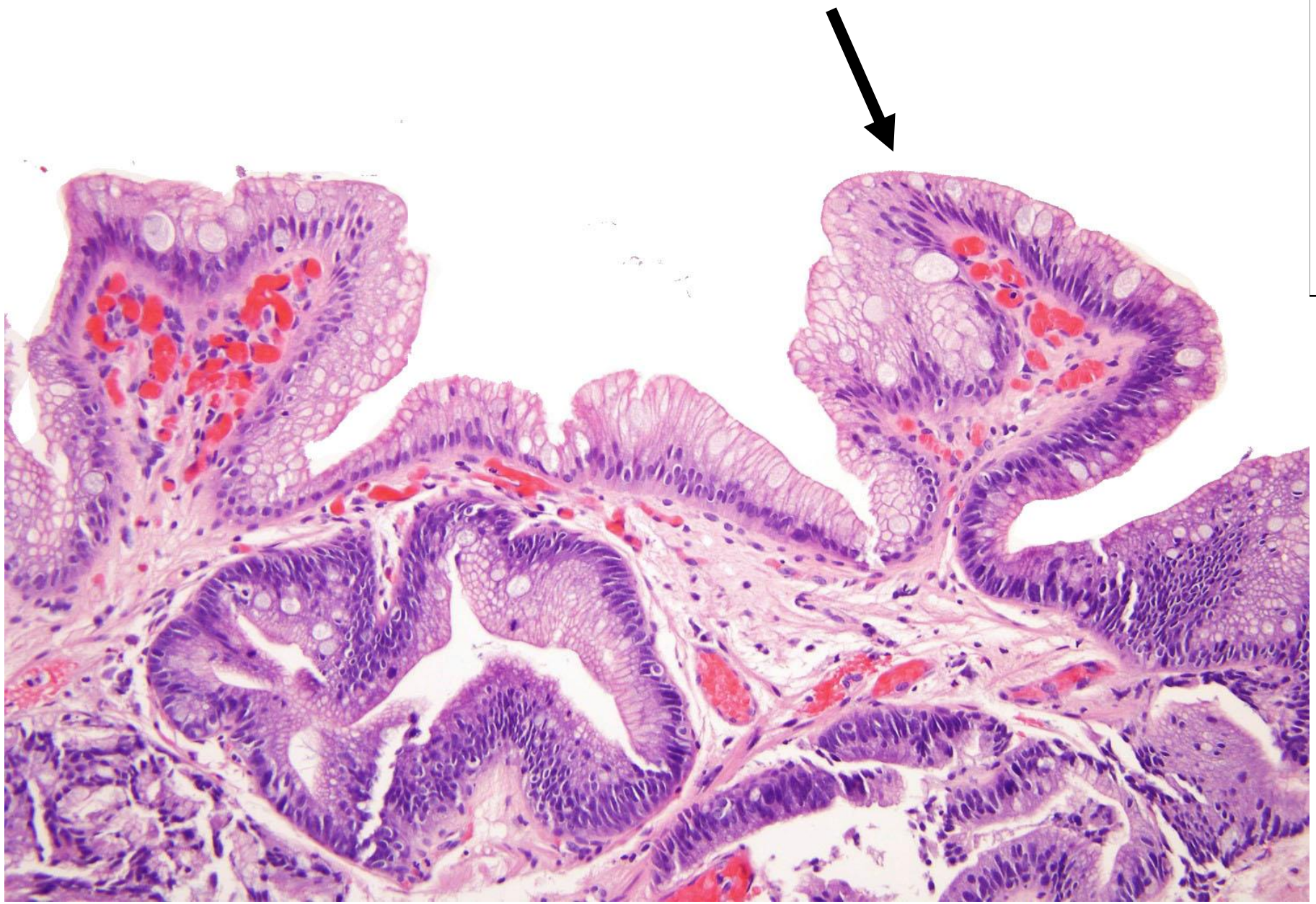
BE, Indefinite for Dysplasia

- Surface – often more mature than glands
- Architecture - slight glandular crowding
- Cytology - hyperchromasia, nuclear membrane irregularities, increased mitoses in deep glands. Maintained nuclear polarity
- Inflammation - Frequently a factor
- **Nice to see an abrupt transition to be sure something is dysplastic – and thus clonal**

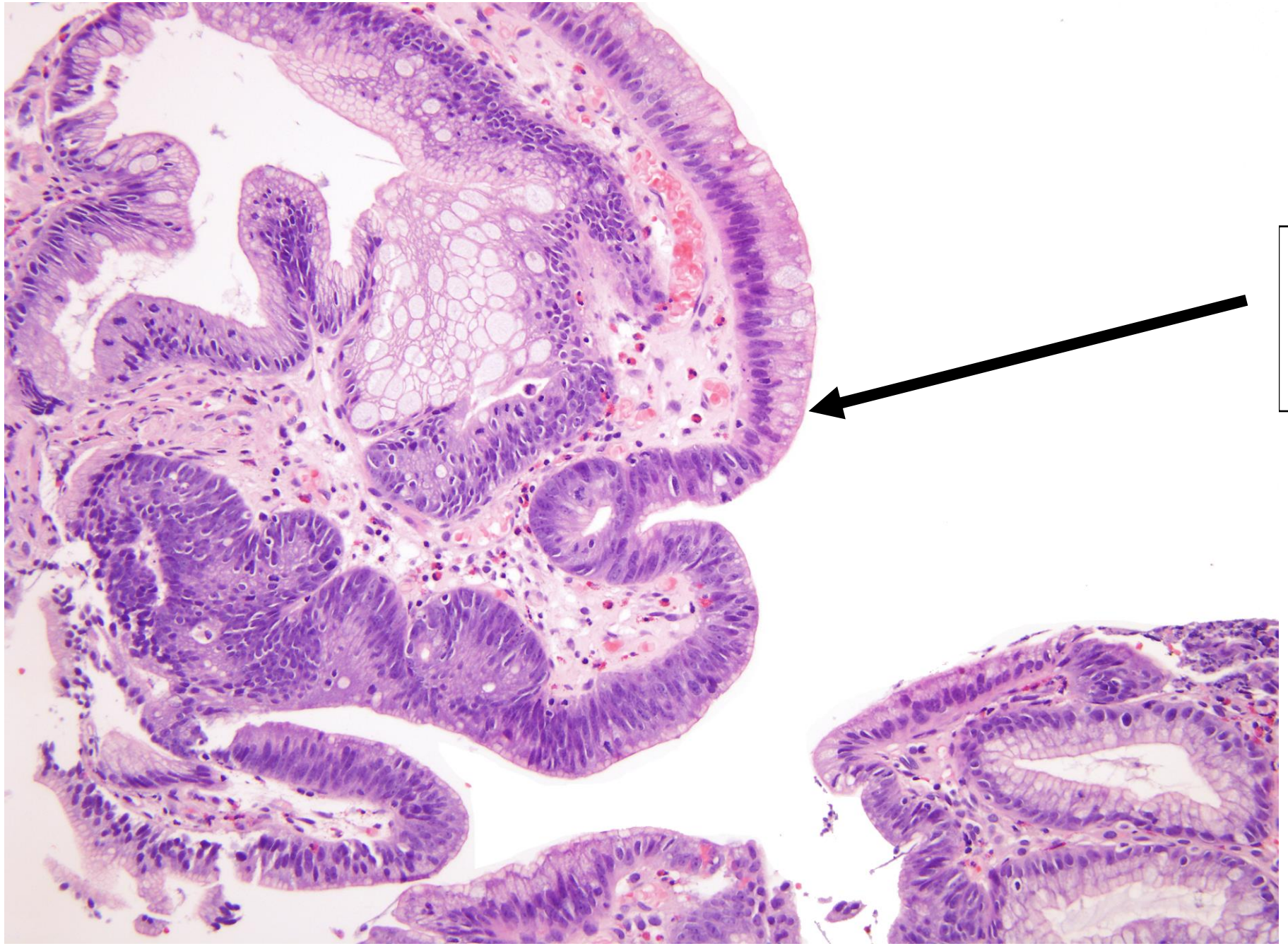


One might call indefinite because of stratification (we did this many many times). There are Neutrophils and no abrupt transition

But using the lines, it's reactive



Reactive - Unclear, gradual demarcation between zone of monolayered nuclei and stratification AND LINES

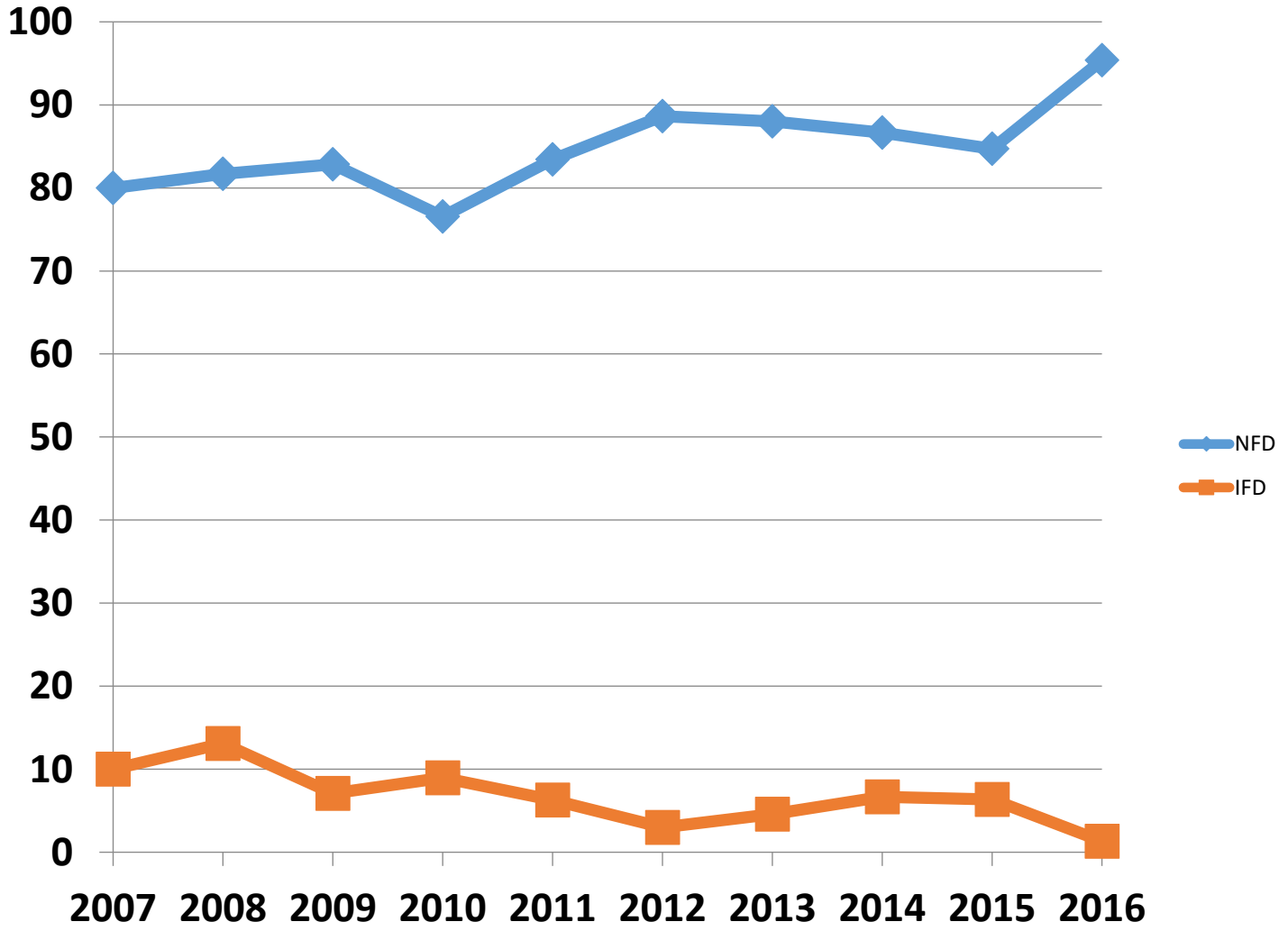


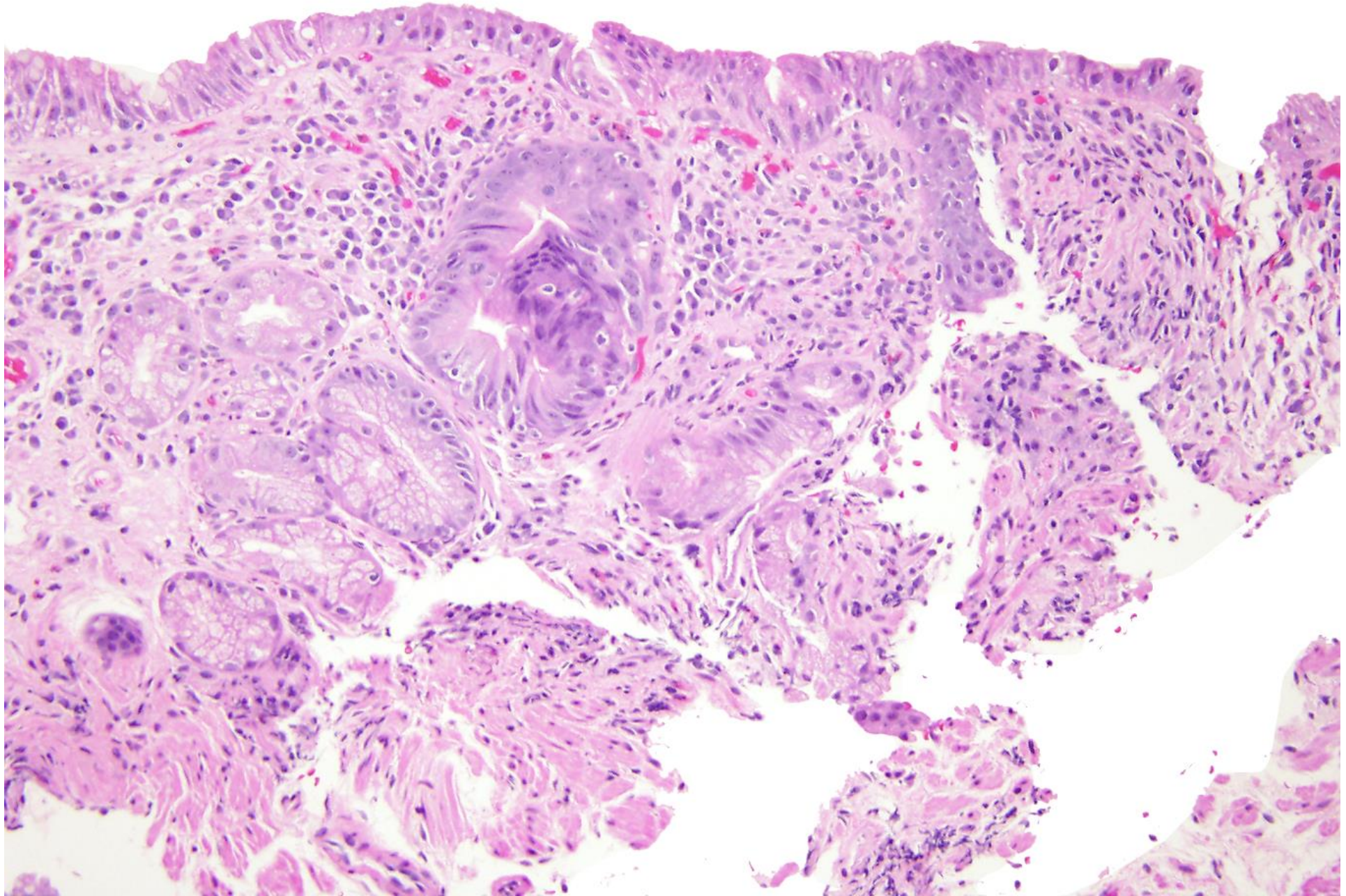
Dysplasia - Sharp demarcation of zone of abnormal nuclei

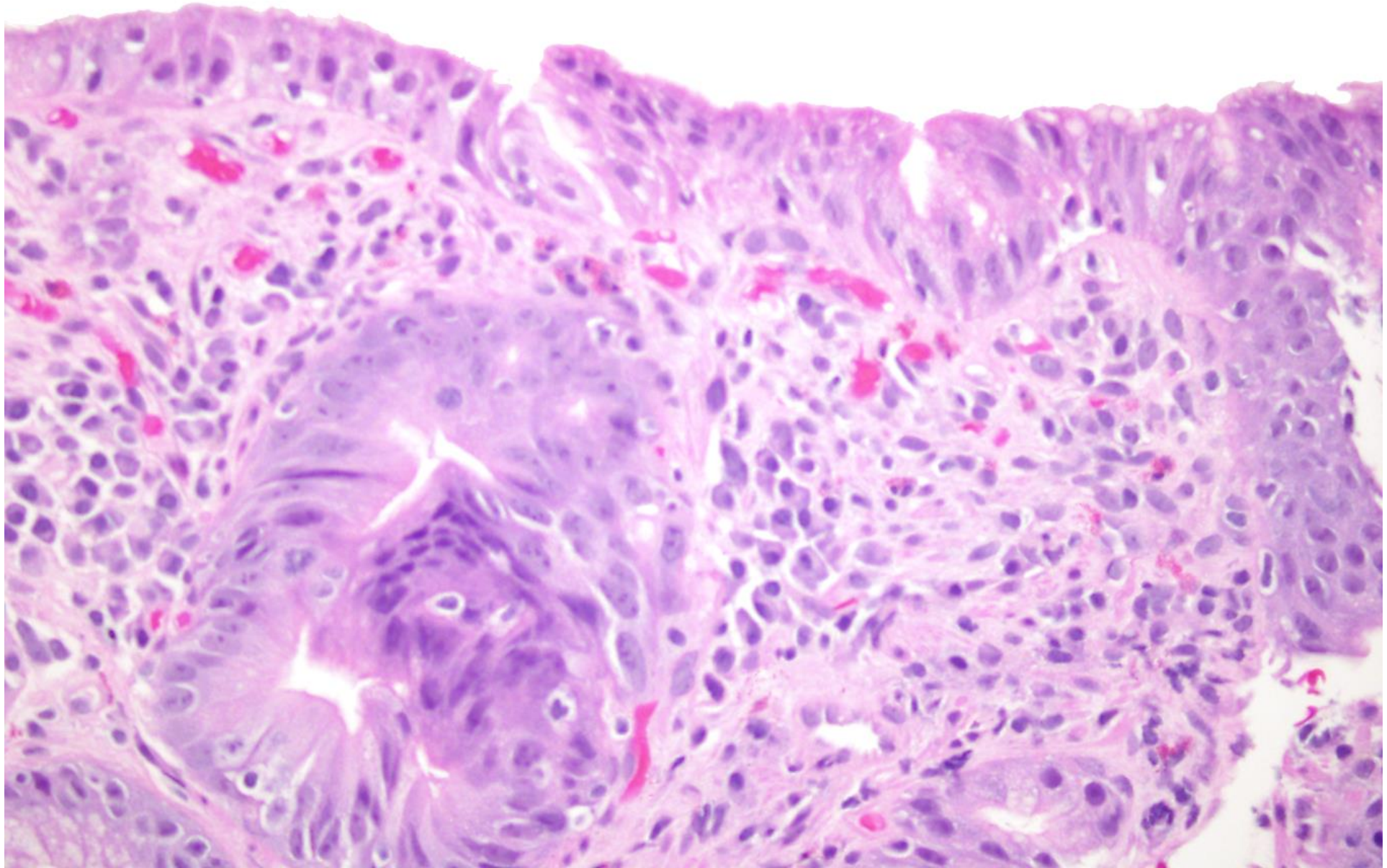
Our dirty laundry

Waters KM, Salimian KJ, Voltaggio L, Montgomery EA. Refined Criteria for Separating Low-grade Dysplasia and Nondysplastic Barrett Esophagus Reduce Equivocal Diagnoses and Improve Prediction of Patient Outcome: A 10-Year Review. Am J Surg Pathol. 2018 Dec;42(12):1723-1729 PubMed PMID: 30234520.

Changes in Proportion of NFD and IFD





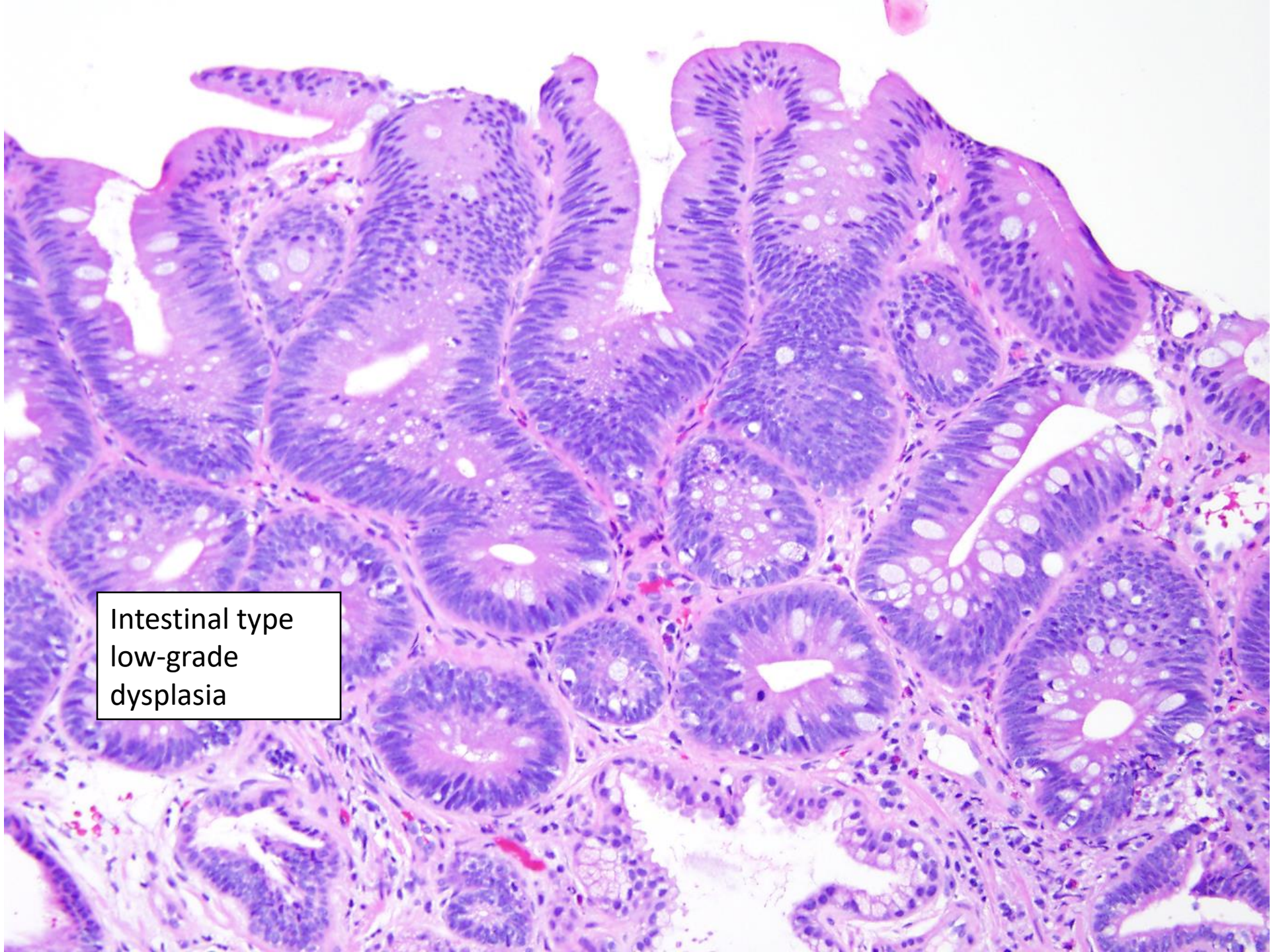


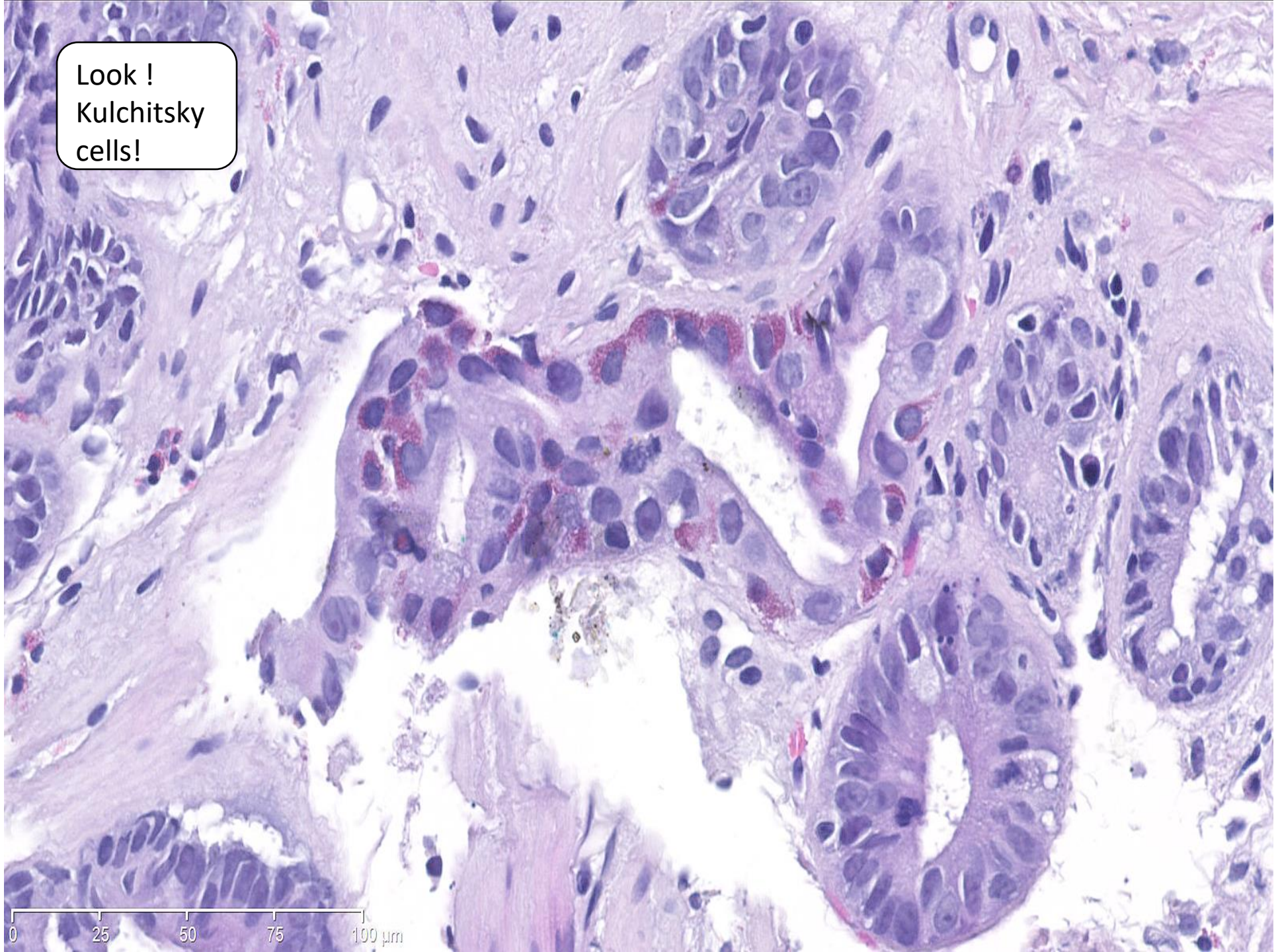
Ideally: Quality Assurance in A Typical Pathology Practice

- <5% LGD (2-3%)
- <5% IFD (2-3% better)
- <5% HGD (2-3% better)
- Waters KM, Salimian KJ, Voltaggio L, Montgomery EA. Refined Criteria for Separating Low-grade Dysplasia and Nondysplastic Barrett Esophagus Reduce Equivocal Diagnoses and Improve Prediction of Patient Outcome: A 10-Year Review. Am J Surg Pathol. 2018 Dec;42(12):1723-1729 PubMed PMID: 30234520.
- Curvers WL, ten Kate FJ, Krishnadath KK, et al. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. Am J Gastroenterol. 2010;105:1523–1530.

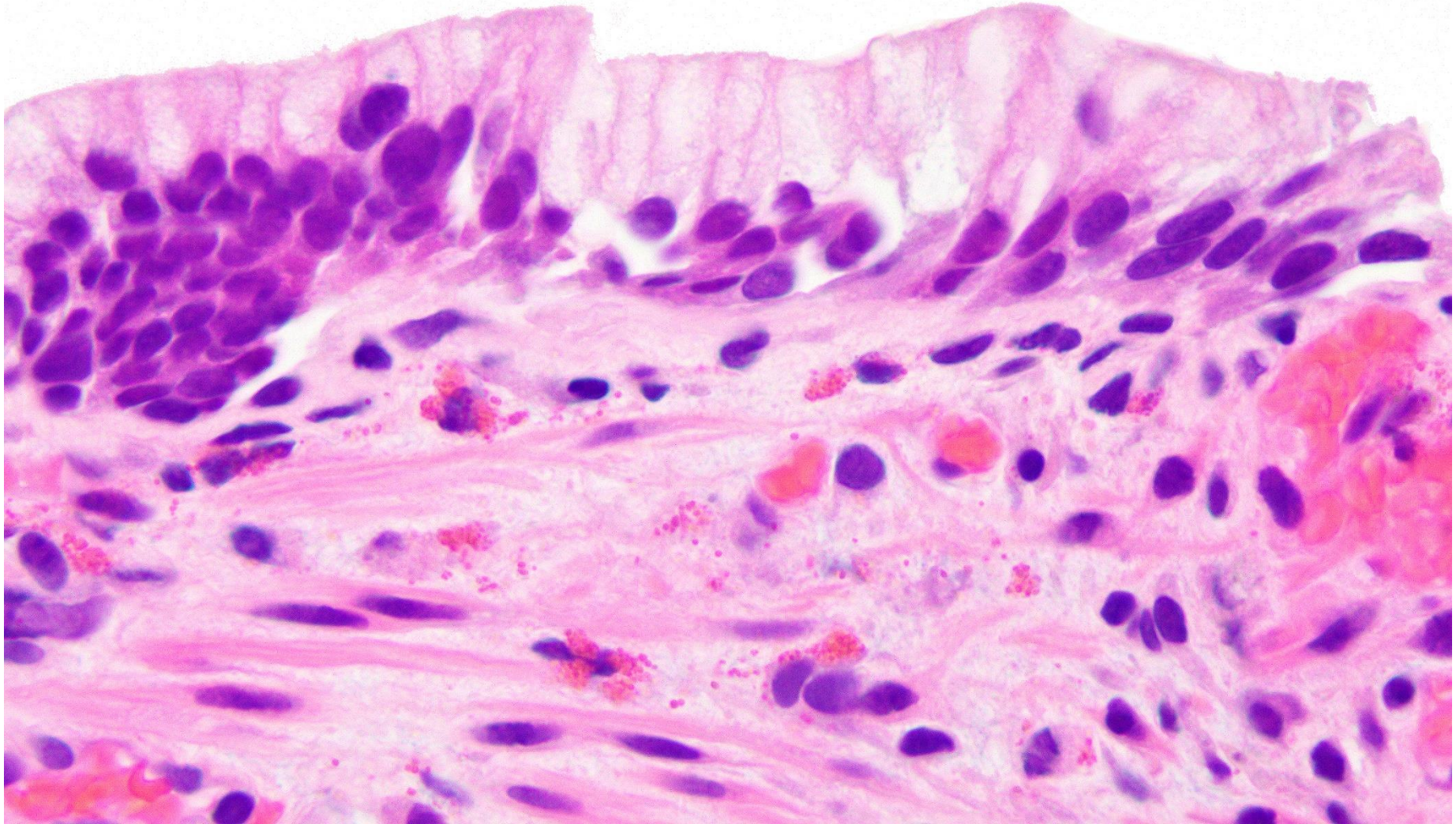
Additionally

- There are variant forms of dysplasia – initial studies were all using criterial for intestinal type dysplasia but variant patterns are less well recognized and less well understood

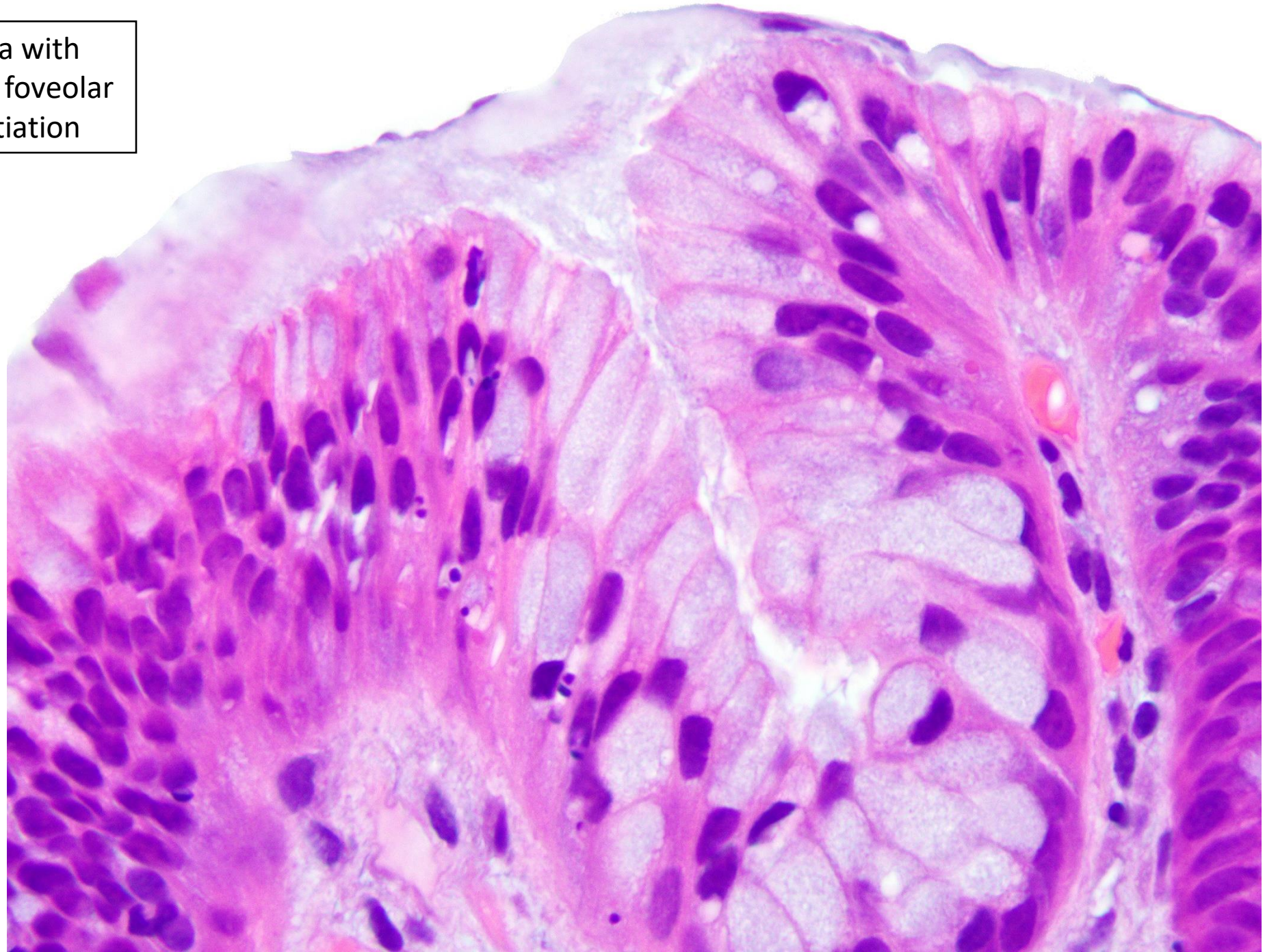




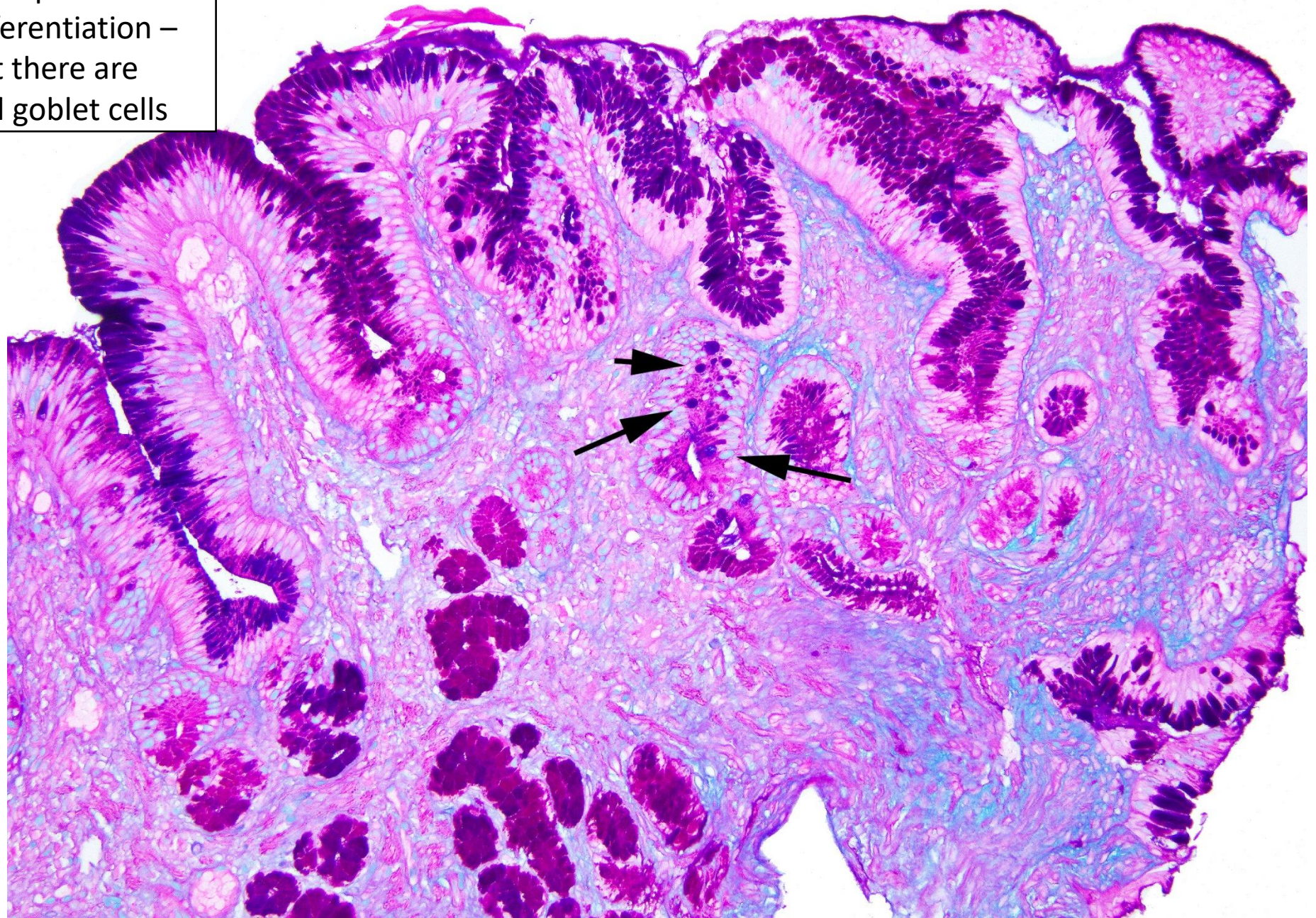
Dysplasia with prominent foveolar differentiation



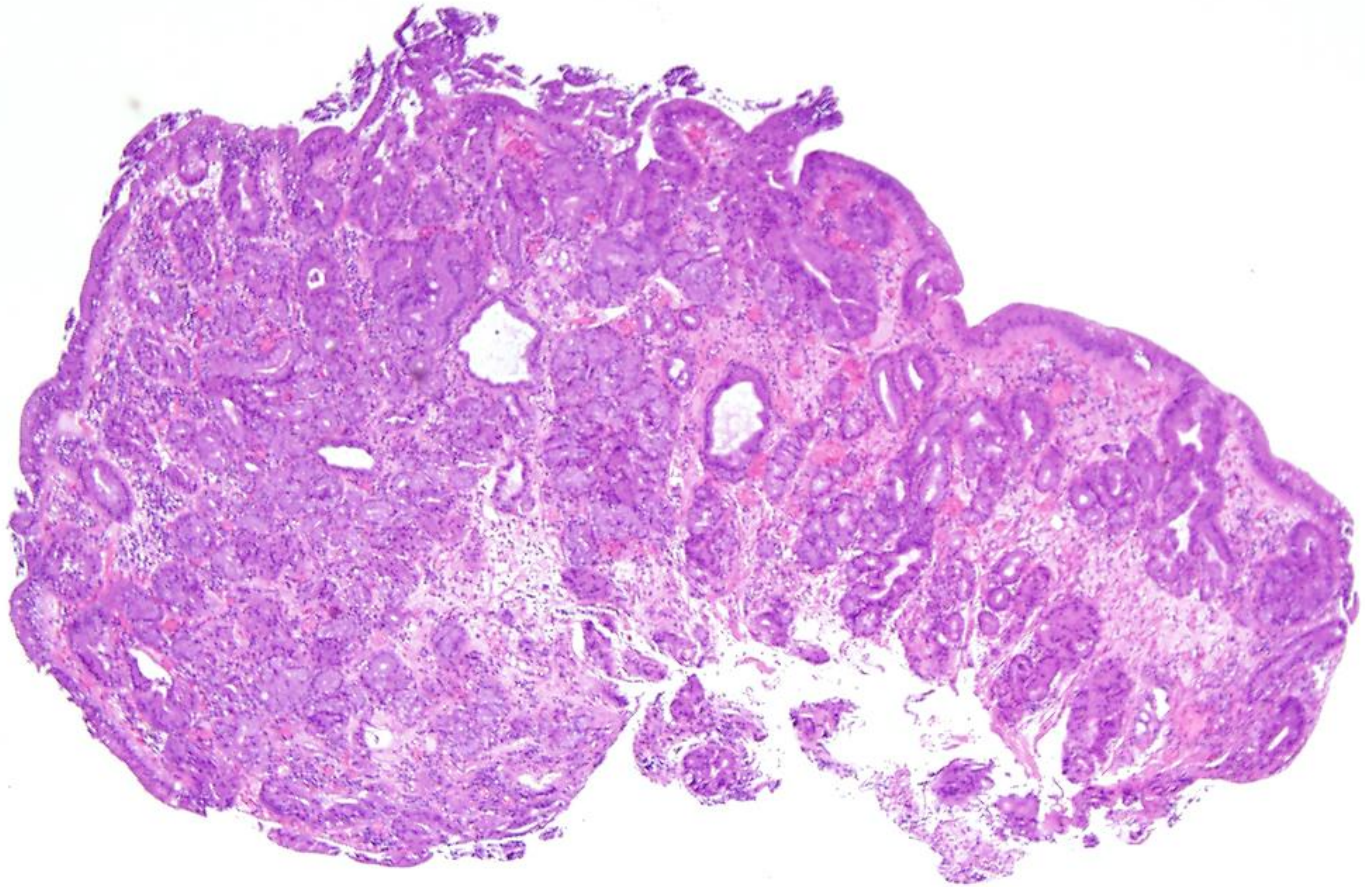
Dysplasia with prominent foveolar differentiation

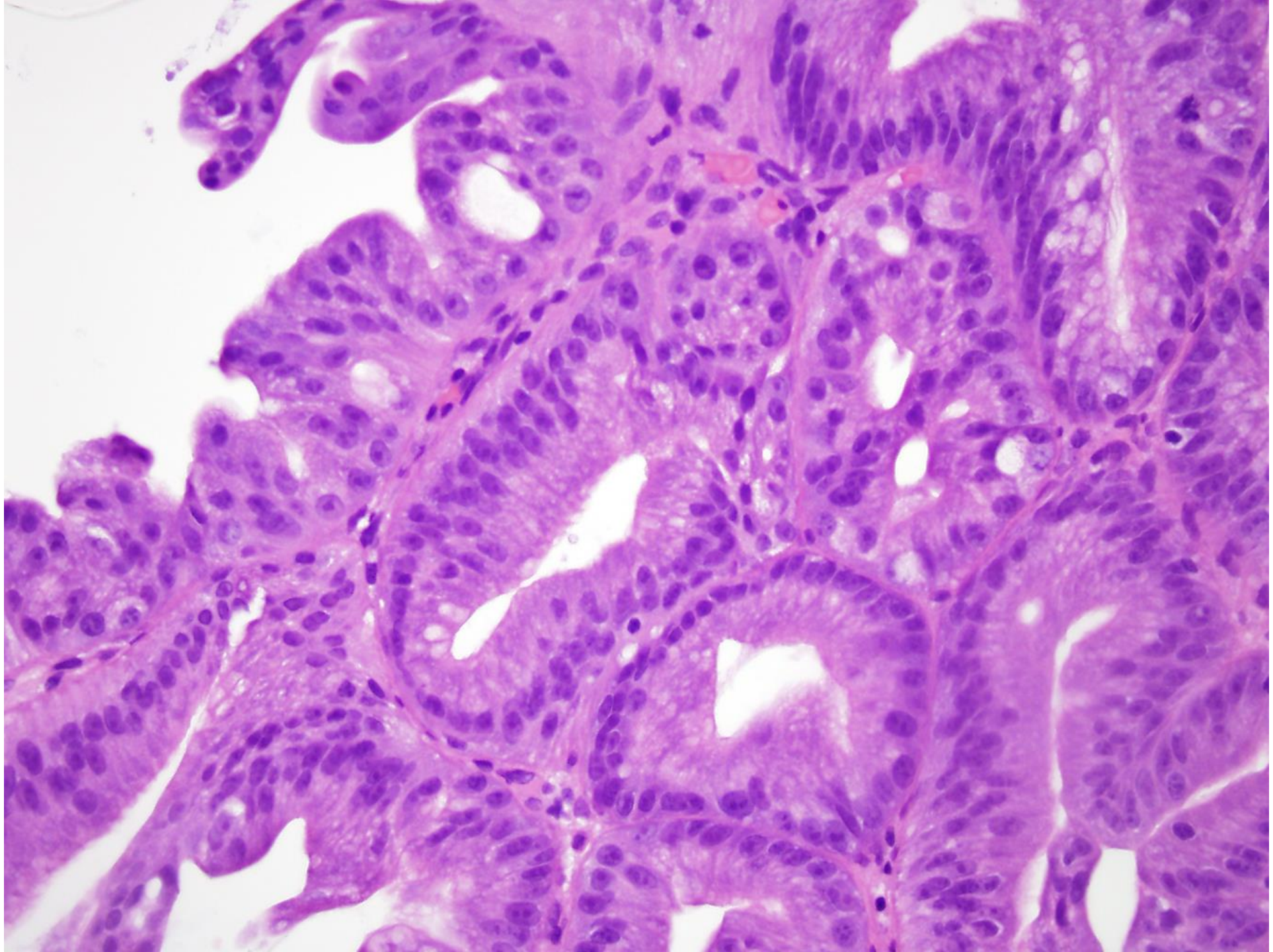


Dysplasia with prominent foveolar differentiation – Note that there are background goblet cells



Pyloric type



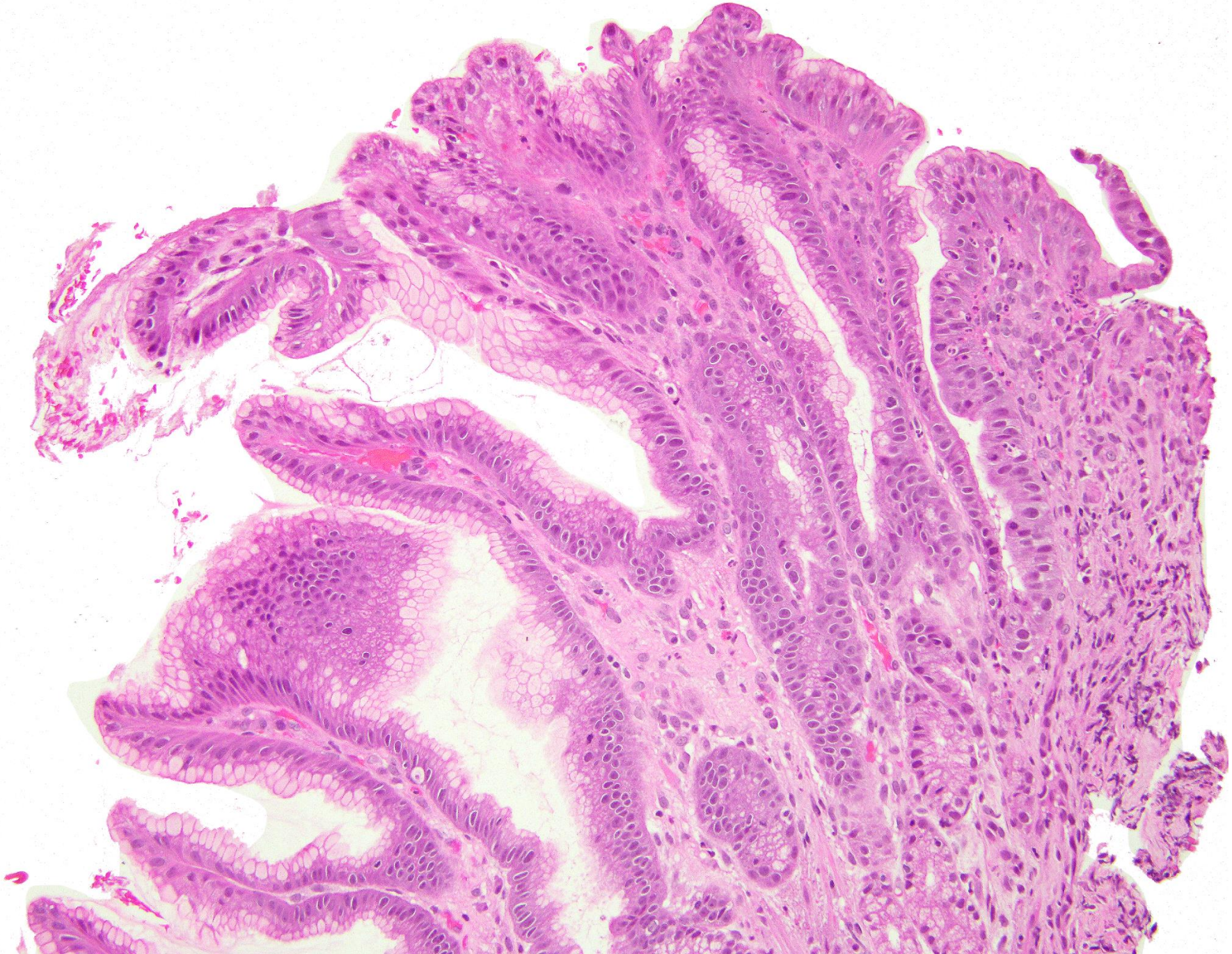


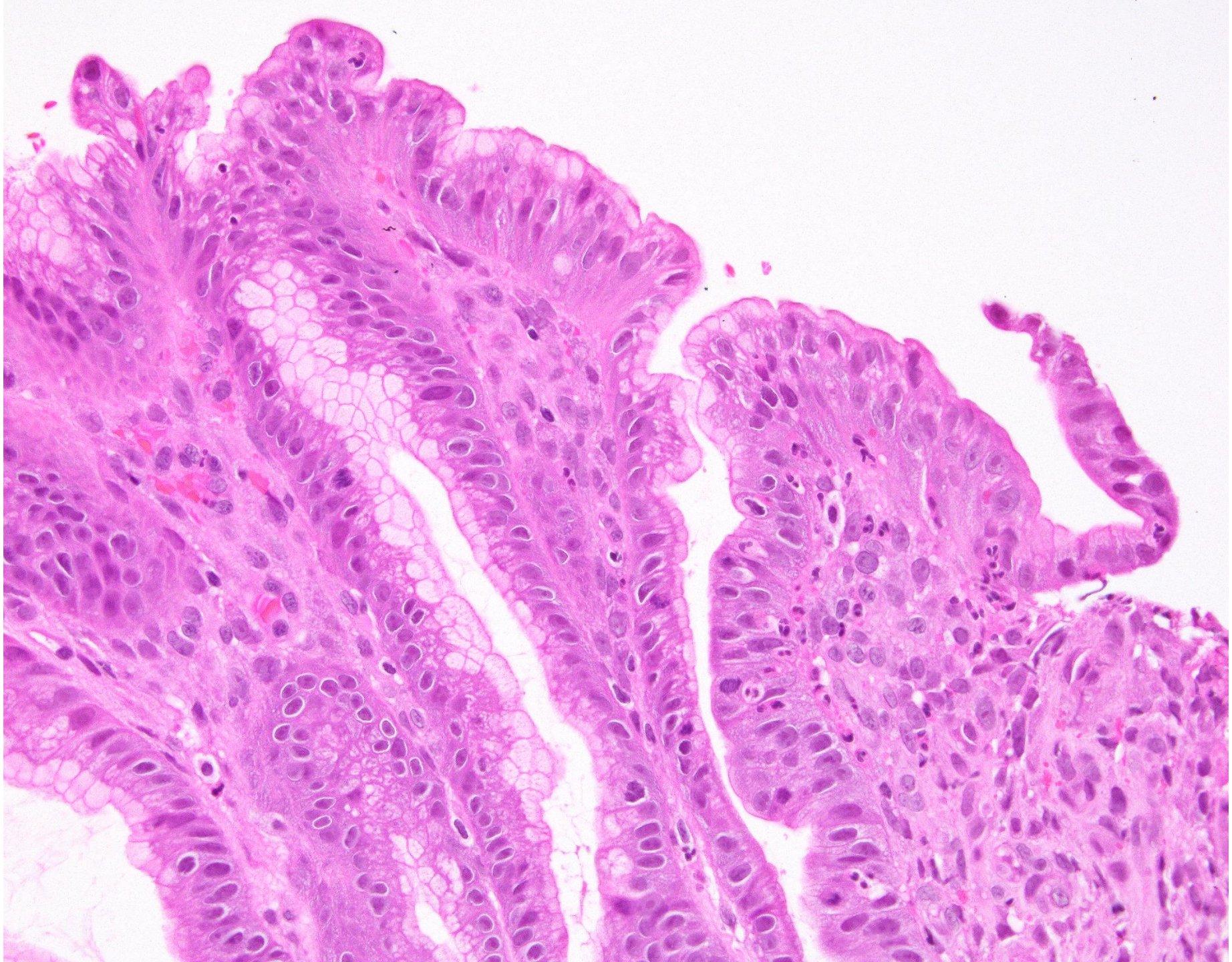
A few comments on stomach

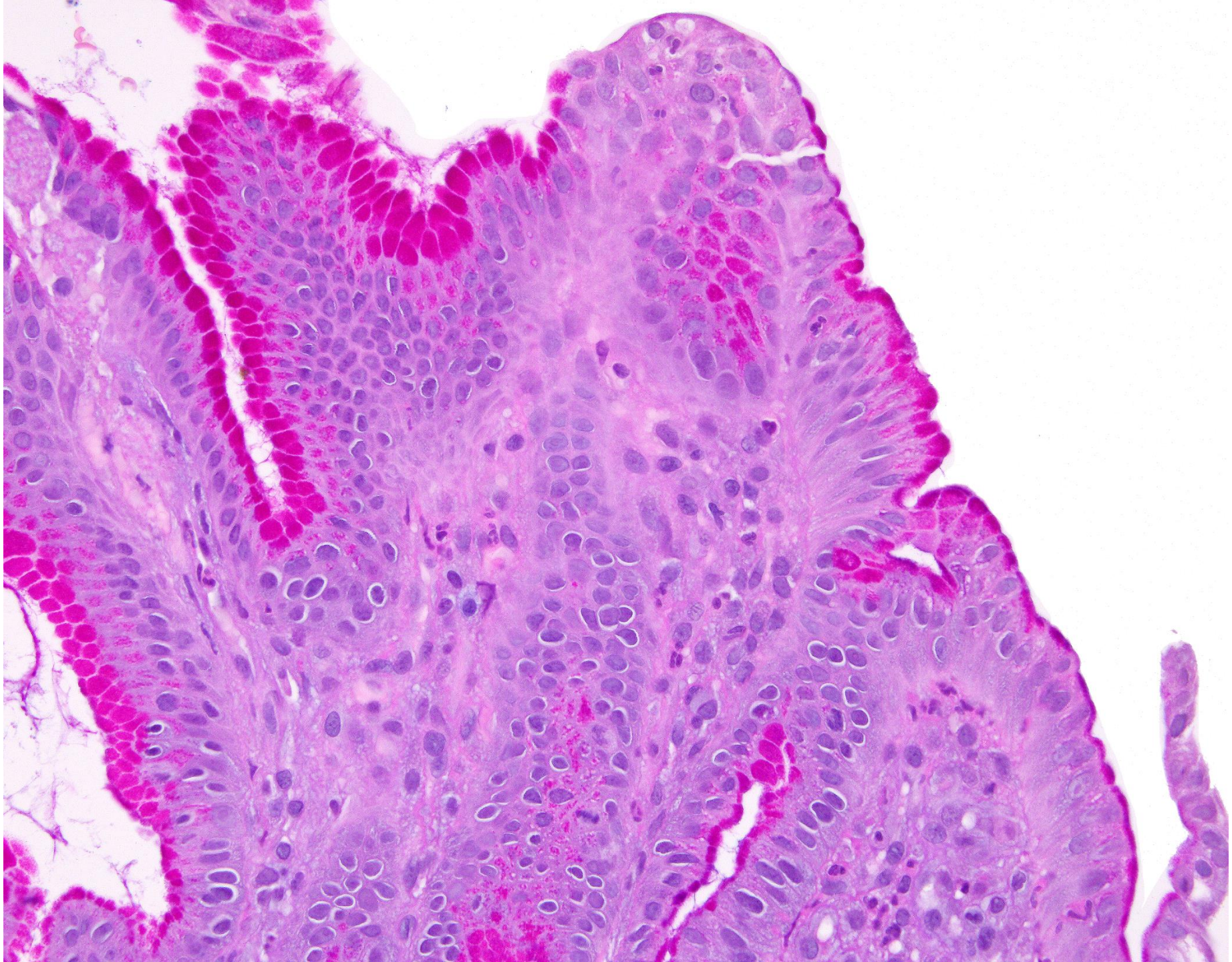
Can we use “the lines” for gastric biopsies?

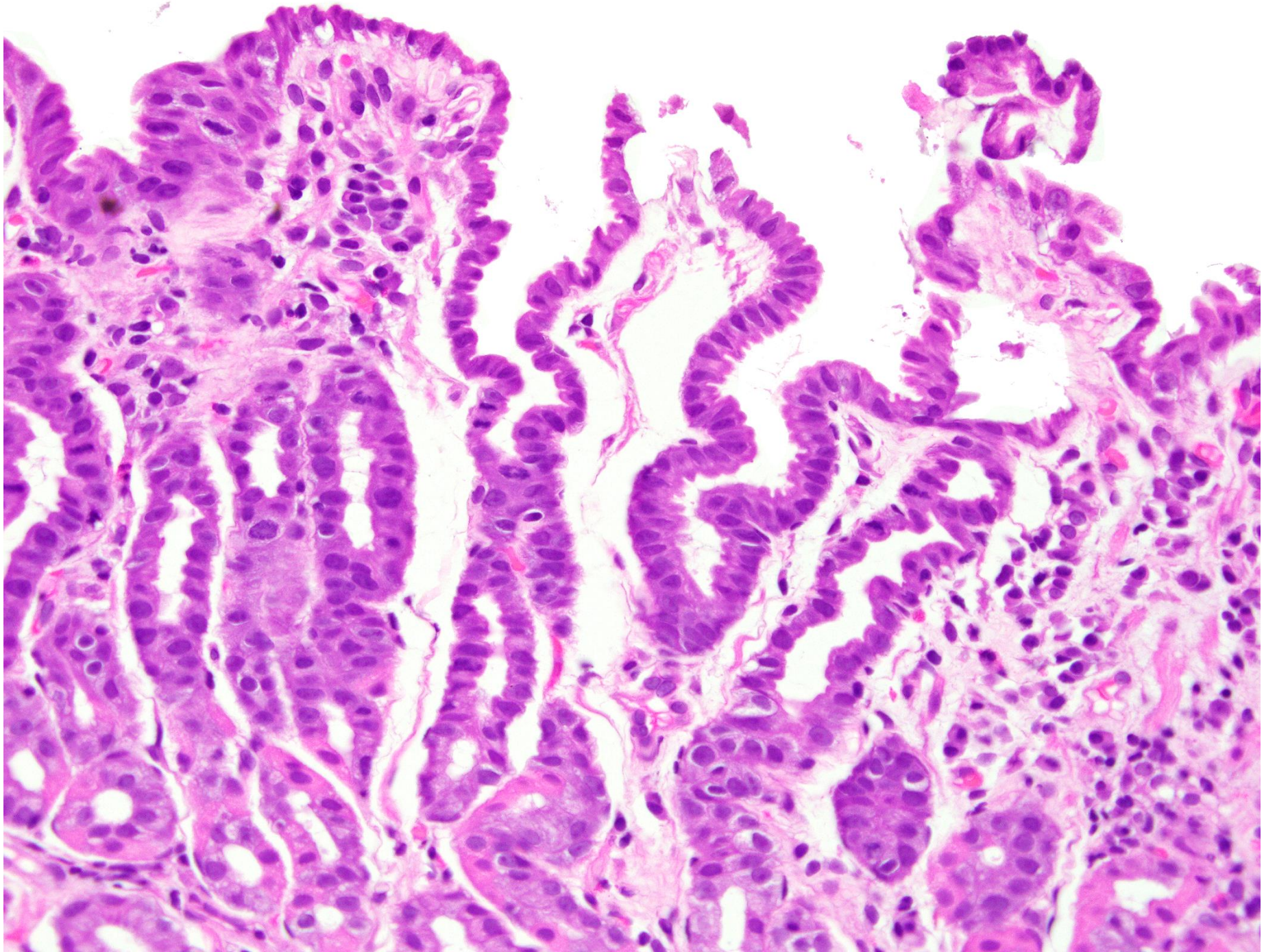
- Not as nicely as in the esophagus but in general – YES!

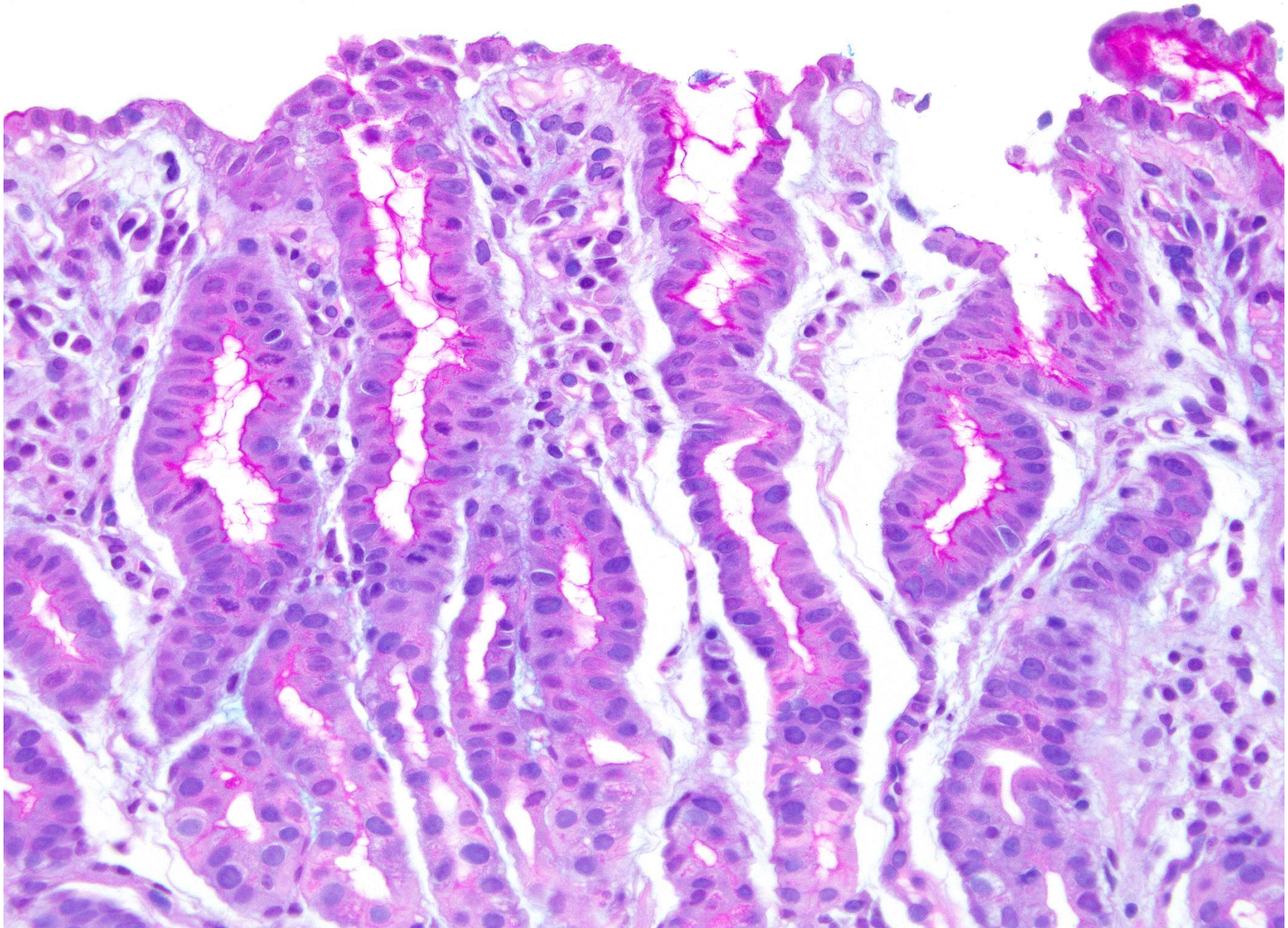
- Waters KM, Salimian KJ, Assarzadegan N, Hutchings D, Makhoul EP, Windon AL, Wong MT, Voltaggio L, Montgomery EA. Cell polarity (the 'four lines') distinguishes gastric dysplasia from epithelial changes in reactive gastropathy. Histopathology. 2021 Feb;78(3):453-458. PMID: 32841414; PMCID: PMC9281539.





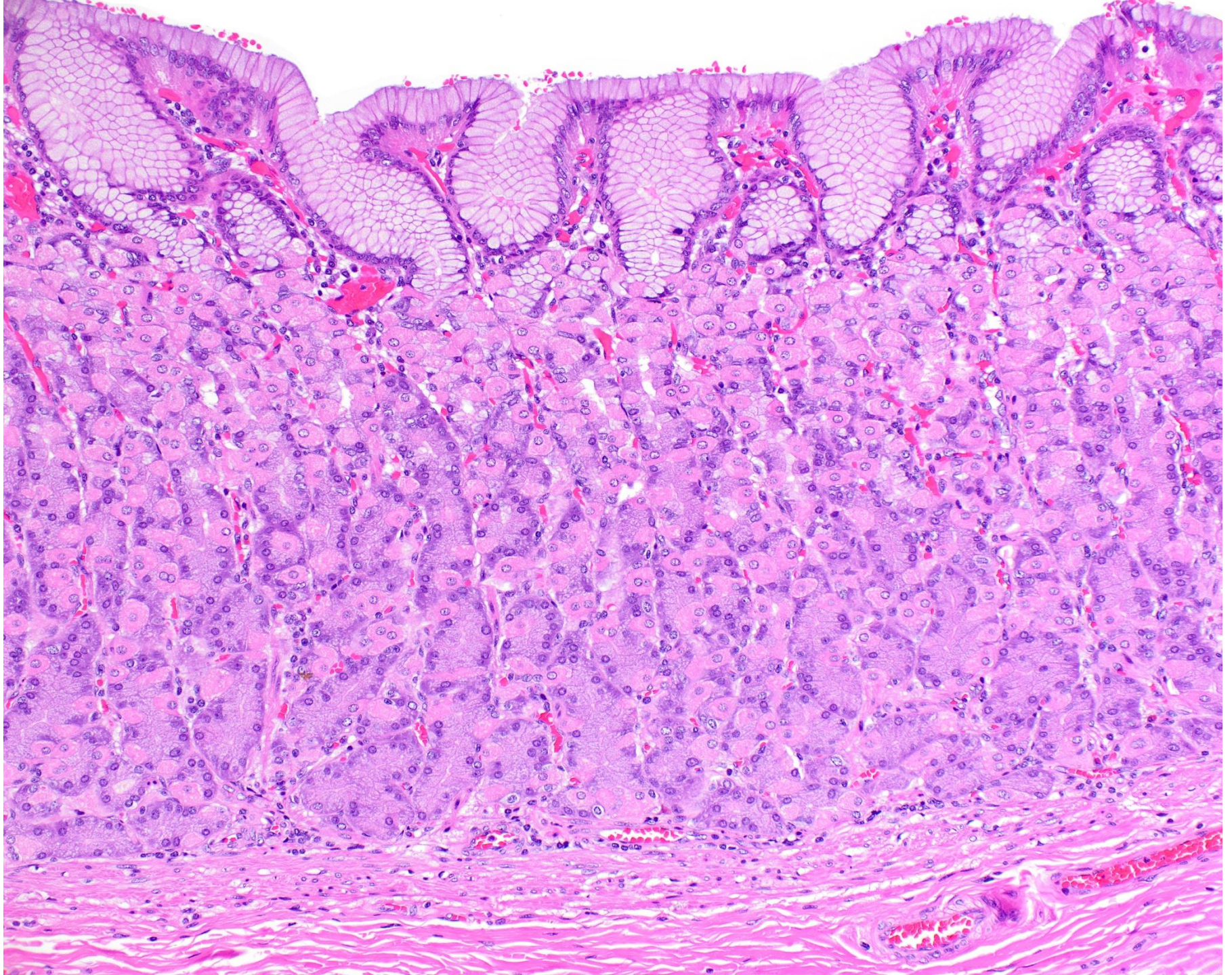




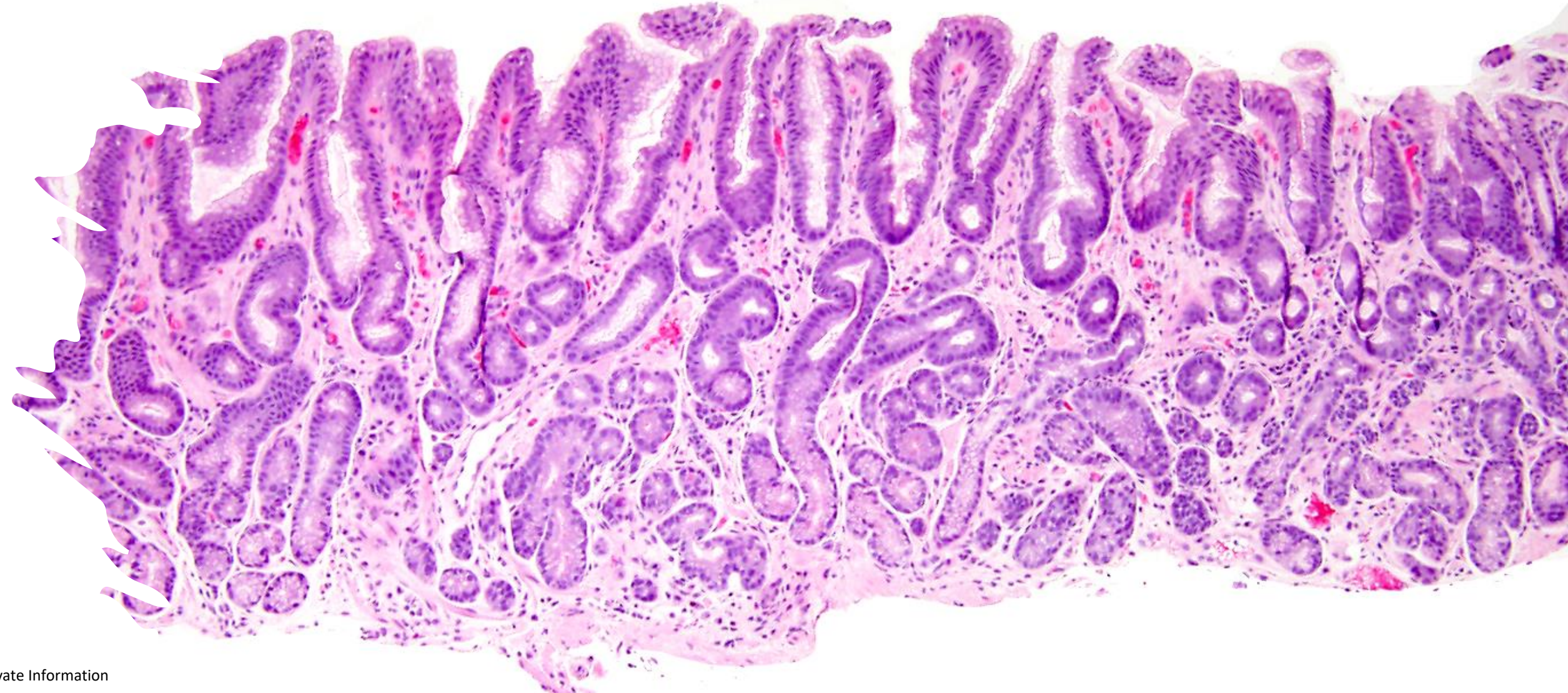


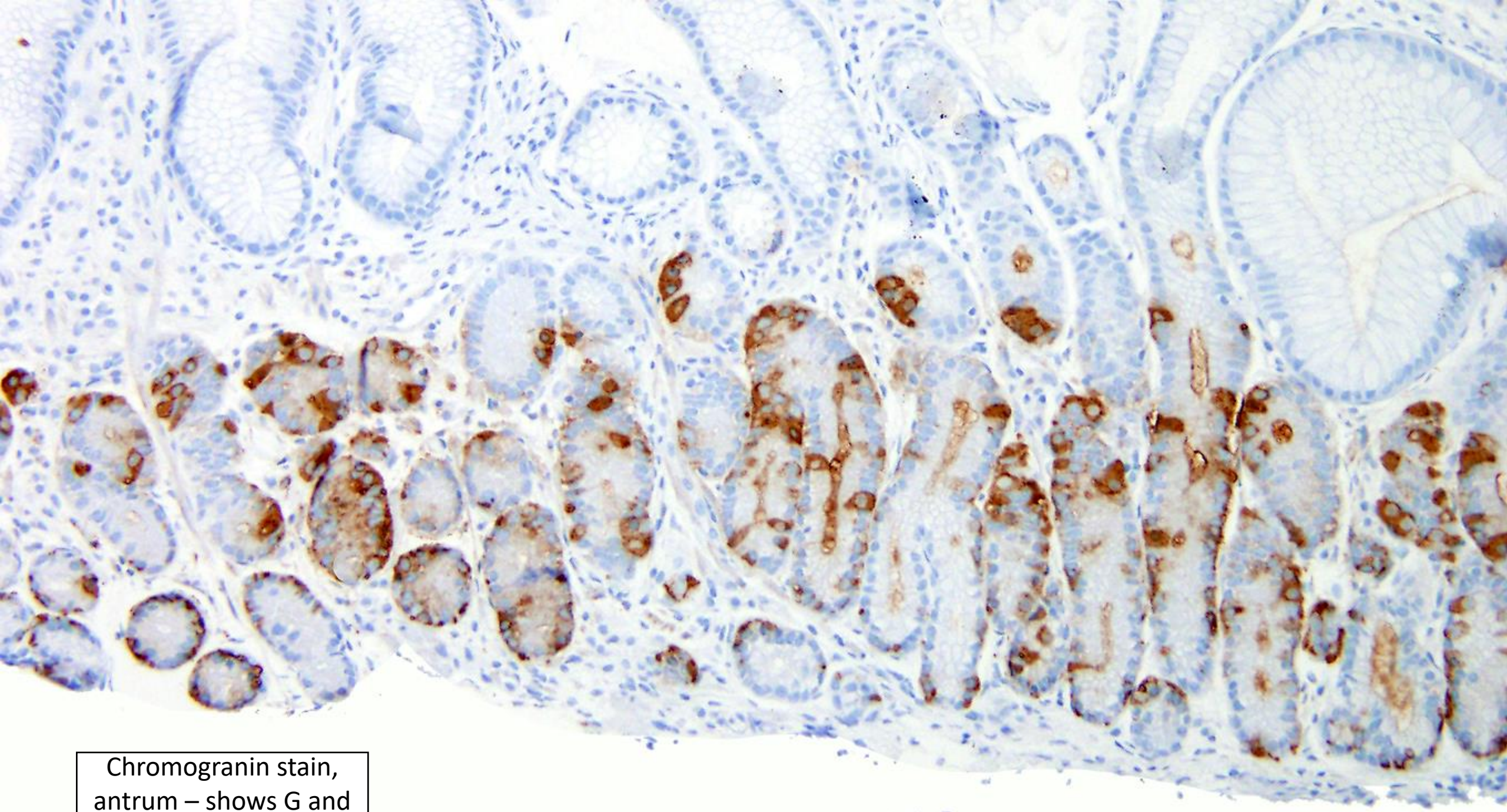
Gastric dysplasia

Oxyntic mucosa
Pink parietal cells
Purplish chief cells

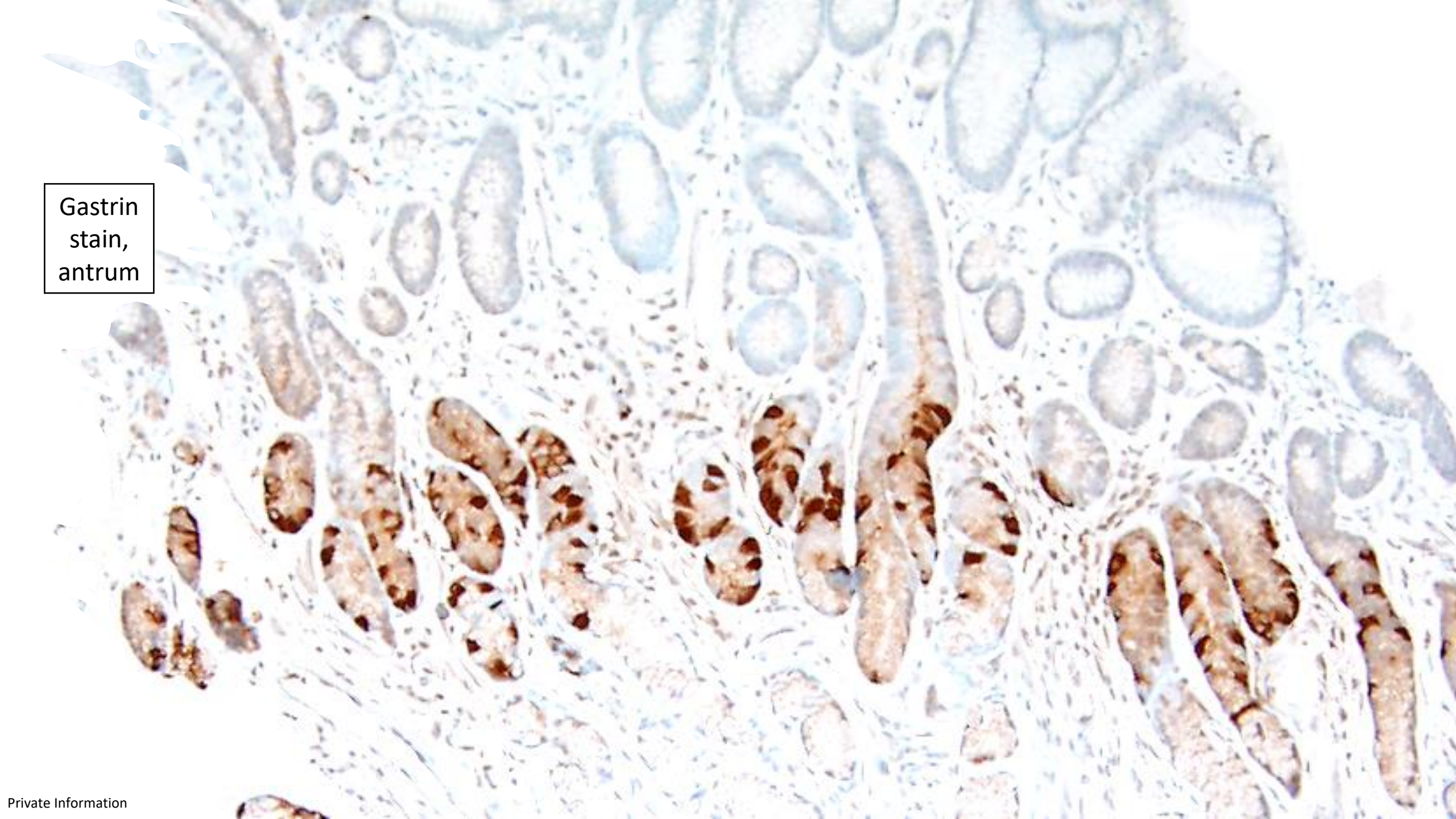


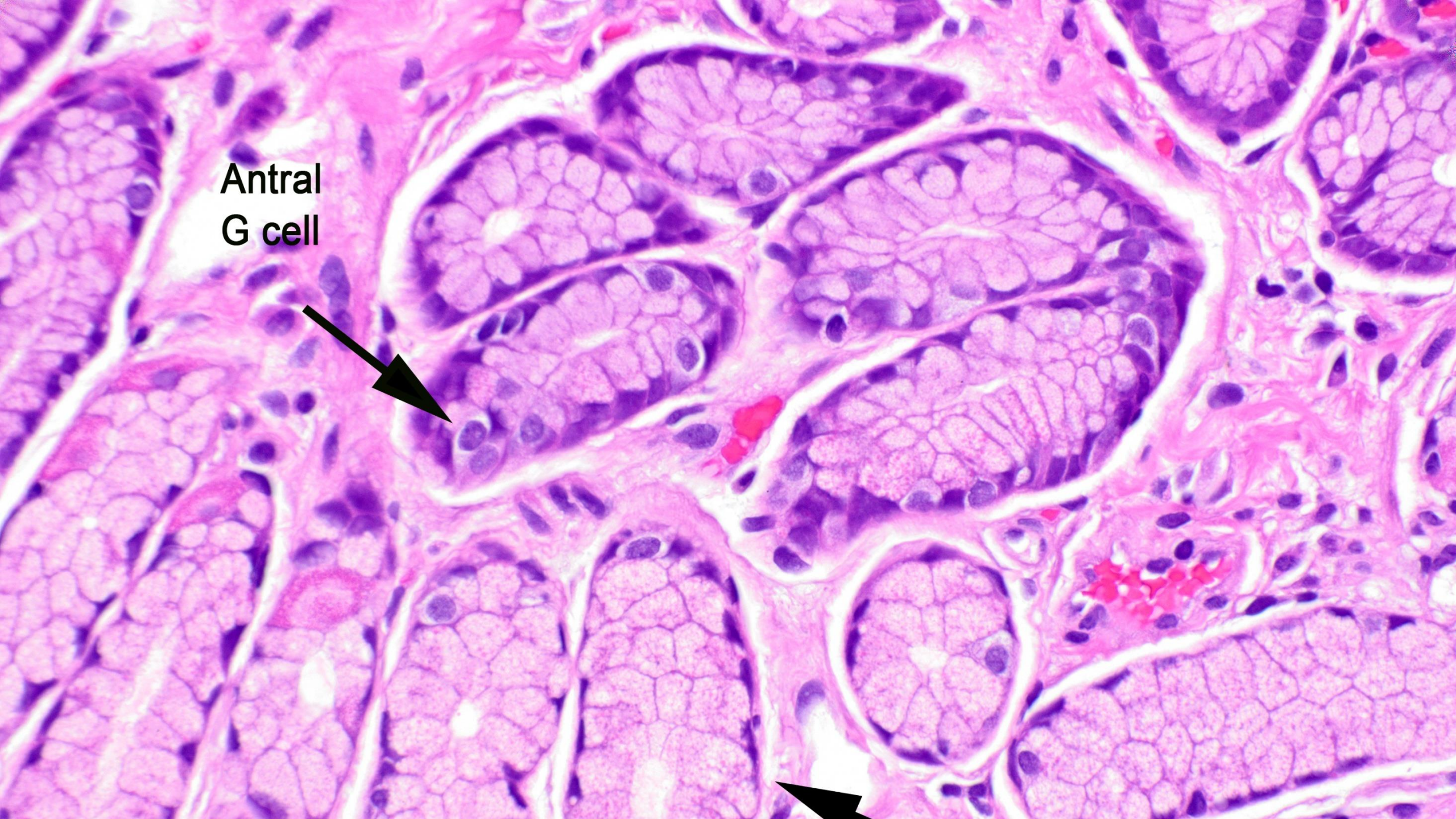
Antrum

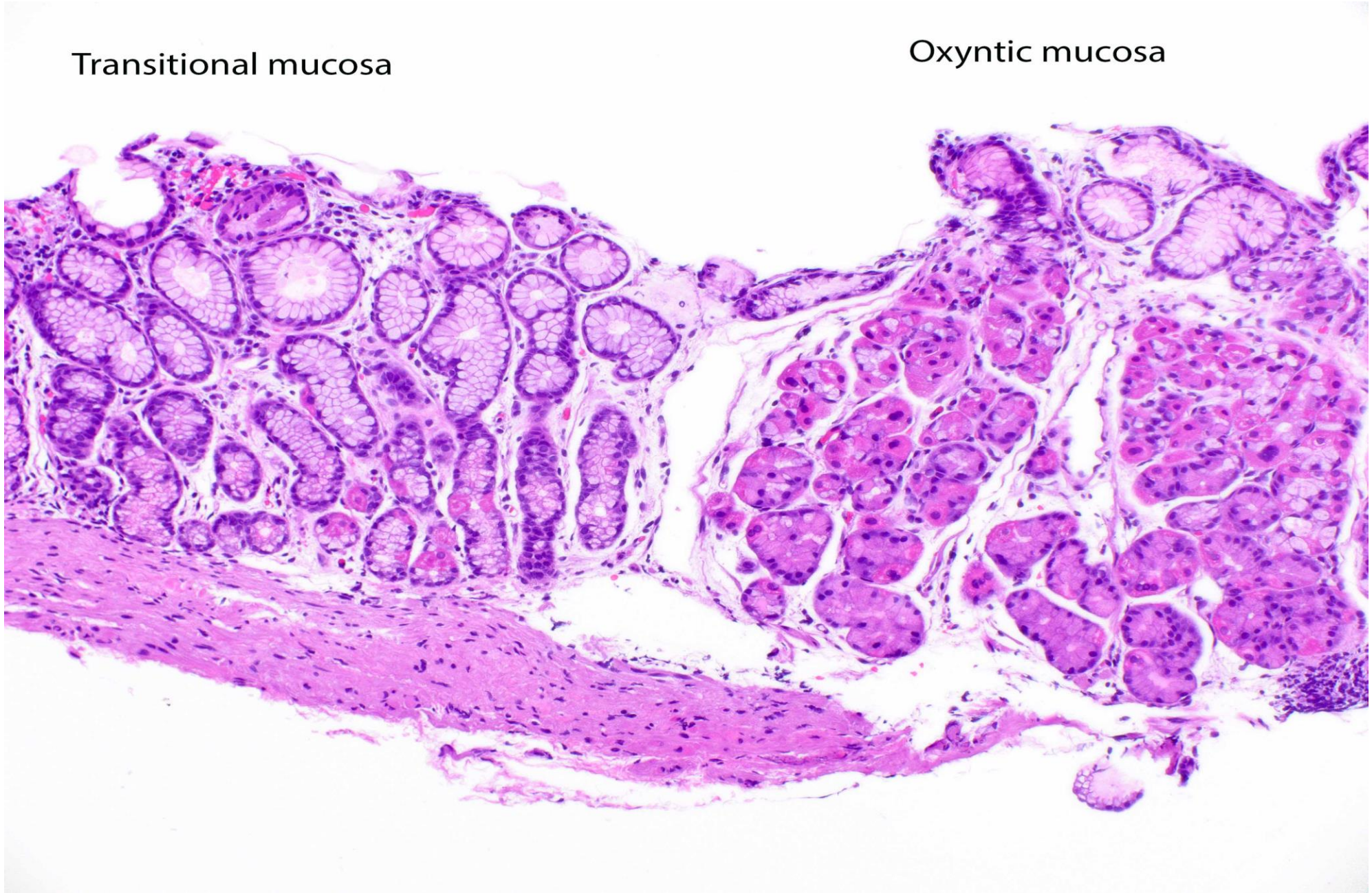




Chromogranin stain, antrum – shows G and D cells




Antral
G cell



What Happens to Produce Gastric Dysplasia?

- Many cycles of injury and repair
- The so-called Correa cascade of damage of glands with atrophy - metaplasia – dysplasia – carcinoma
- The metaplasia is often intestinal – of either the complete of incomplete type
- In general, autoimmune gastritis and reactive gastropathy/chemical gastritis are associated with complete type intestinal metaplasia and *Helicobacter pylori* gastritis can be associated with either type.
- Interestingly, patients with autoimmune gastritis are unlikely to develop gastric carcinoma UNLESS THEY HAD PRIOR *H. PYLORI* GASTRITIS

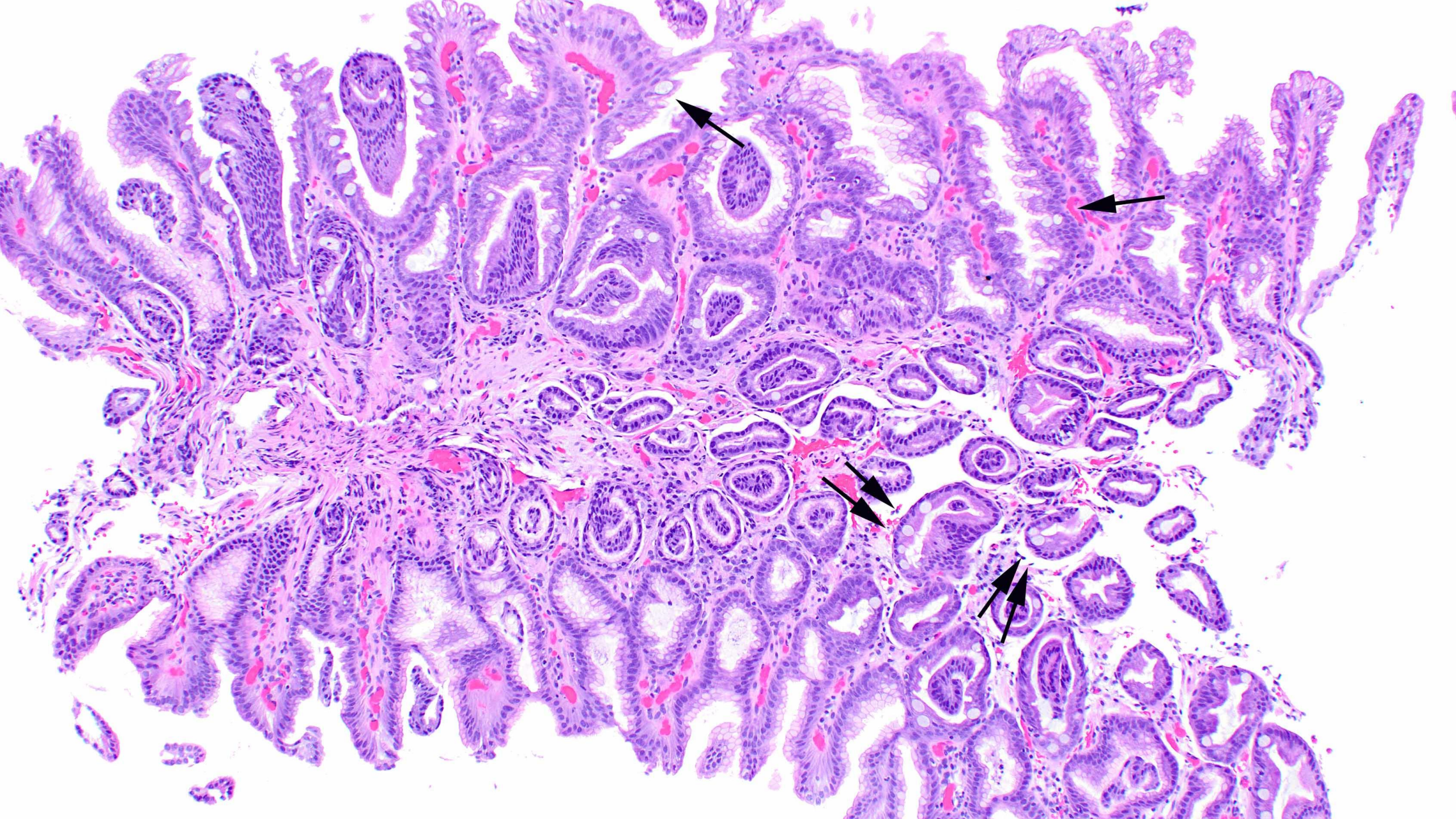
Rugge M, Bricca L, Guzzinati S, Sacchi D, Pizzi M, Savarino E, Farinati F, Zorzi M, Fassan M, Dei Tos AP, Malfertheiner P, Genta RM, Graham DY. Autoimmune gastritis: long-term natural history in naïve *Helicobacter pylori*-negative patients. Gut. 2023 Jan;72(1):30-38. PMID: 35772926.

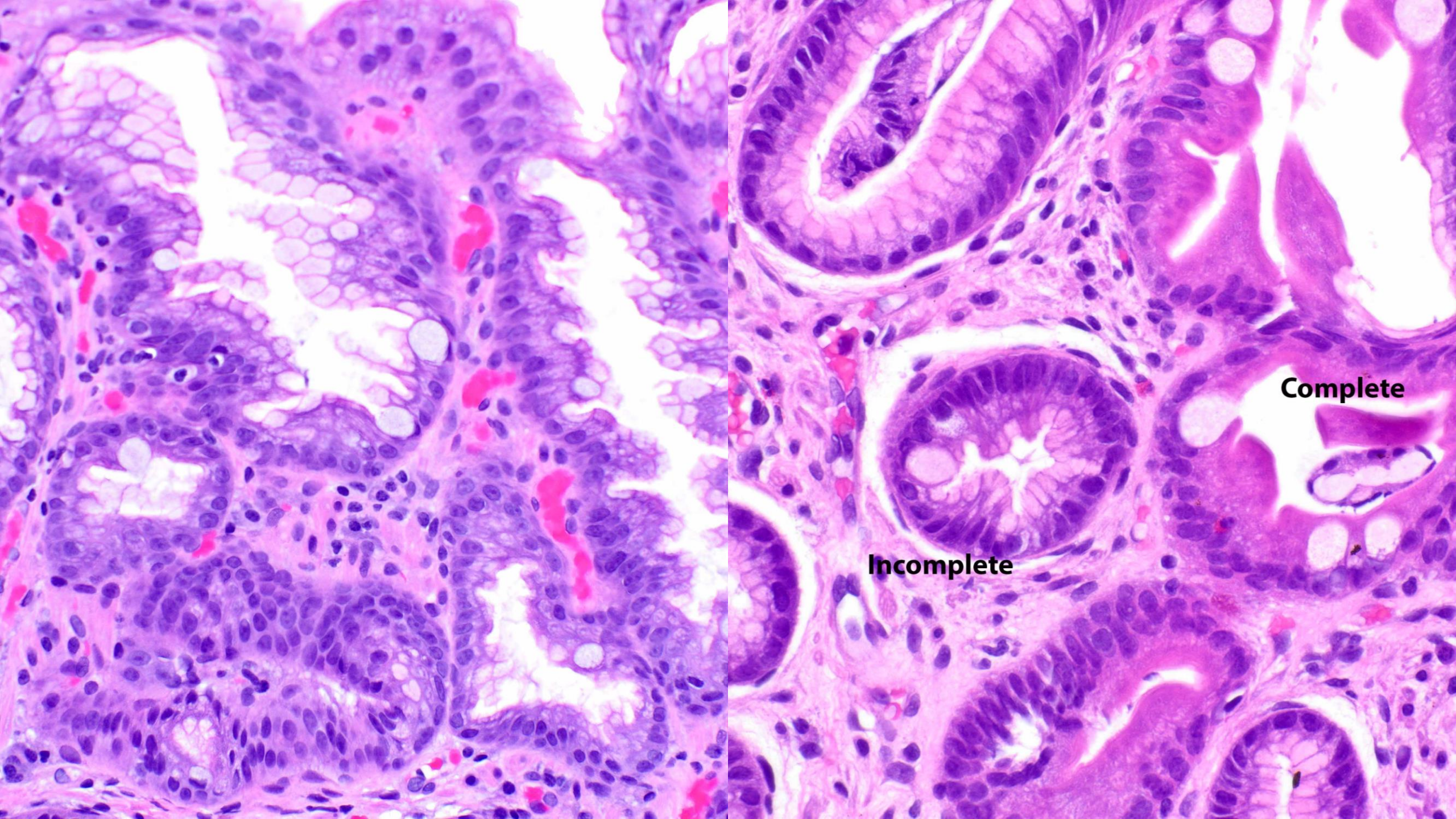
Poveda JC, Chahar S, Garcia-Buitrago MT, Montgomery EA, McDonald OG. The Morphologic Spectrum of Gastric Type 1 Enterochromaffin-Like Cell Neuroendocrine Tumors. Mod Pathol. 2023 Apr;36(4):100098. PMID: 36913909; PMCID: PMC10121960.

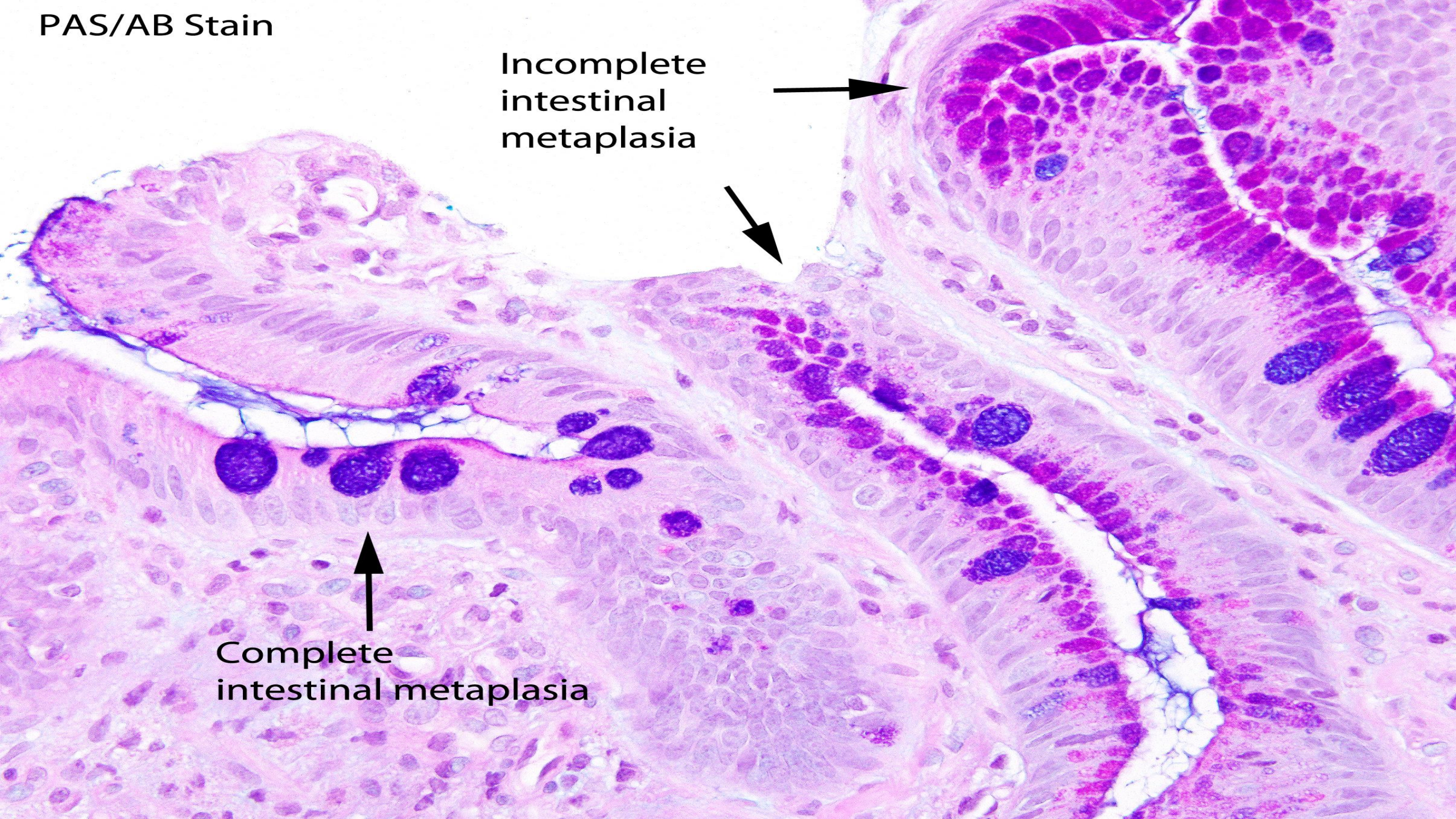
Oh Dear, Yet Another New Demand

- In 2020, the American Gastroenterological Association made a fuss about reporting incomplete IM versus complete IM – the data are supportive in high-risk countries
- New demands when probably overkill…. No US data
- Especially since colleagues often only biopsy the antrum and not the transition zone and body

Gupta S, Li D, El Serag HB, Davitkov P, Altayar O, Sultan S, Falck-Ytter Y, Mustafa RA. AGA Clinical Practice Guidelines on Management of Gastric Intestinal Metaplasia. Gastroenterology. 2020 Feb;158(3):693-702. PMID: 31816298.




Complete
Incomplete


PAS/AB Stain
Incomplete intestinal metaplasia
Complete intestinal metaplasia


Incomplete
Complete

Gastric adenomas and dysplasias

- In most instances, lesions that we have designated as gastric adenomas are simply polypoid gastritis associated dysplasia.
- Very few gastric polyps with dysplasia are truly adenomatous lesions arising in a background of normal mucosa.
- The situation is very much analogous to that for inflammatory bowel disease.
- Over time, we have regarded lesions as adenomas when they produce a visible polyp and as dysplasia when they are flat or difficult to see endoscopically.

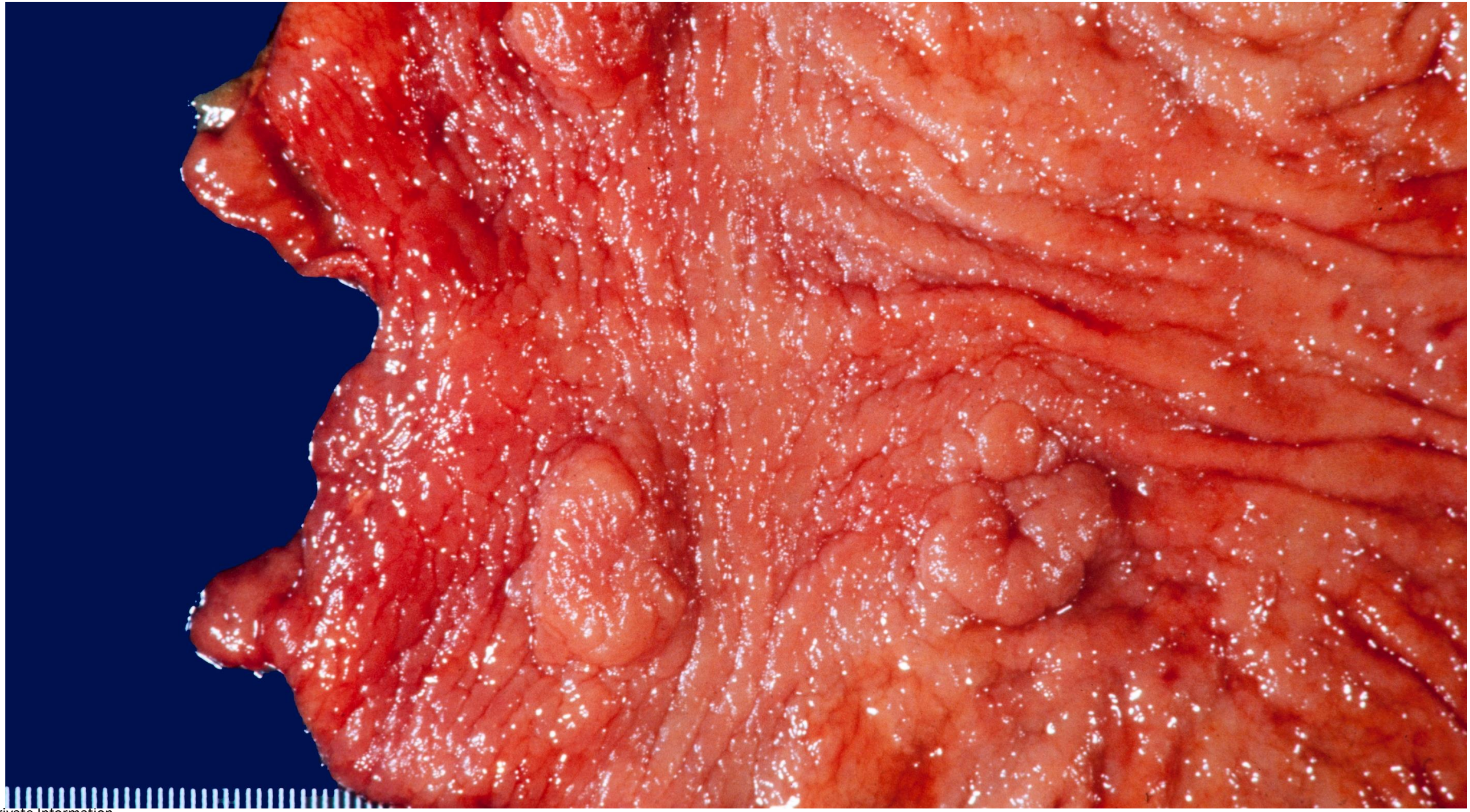
Gastric Dysplasia

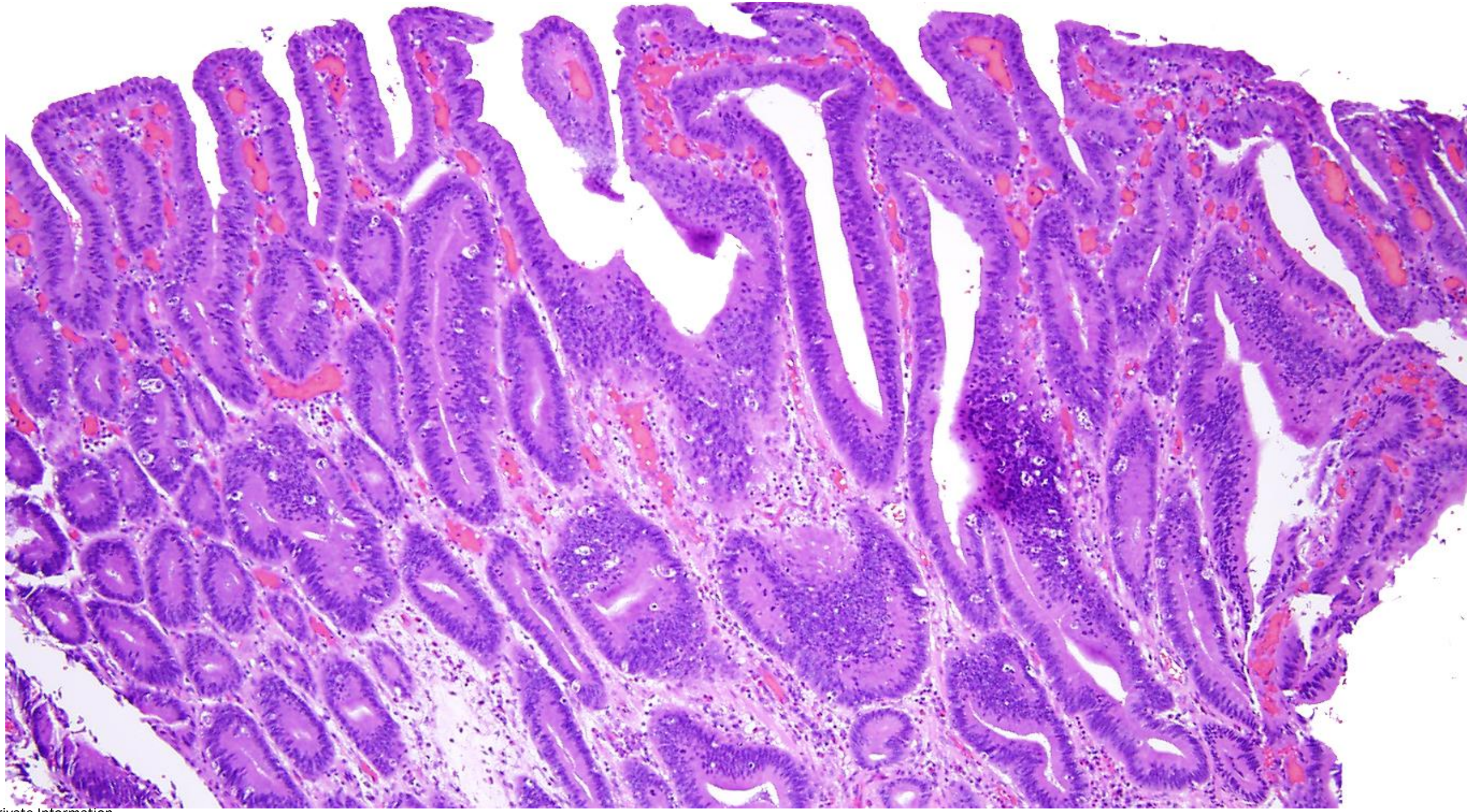
- Dysplasia is typically encountered in the setting of atrophy as a result of long-standing injury (usually *Helicobacter* infection)

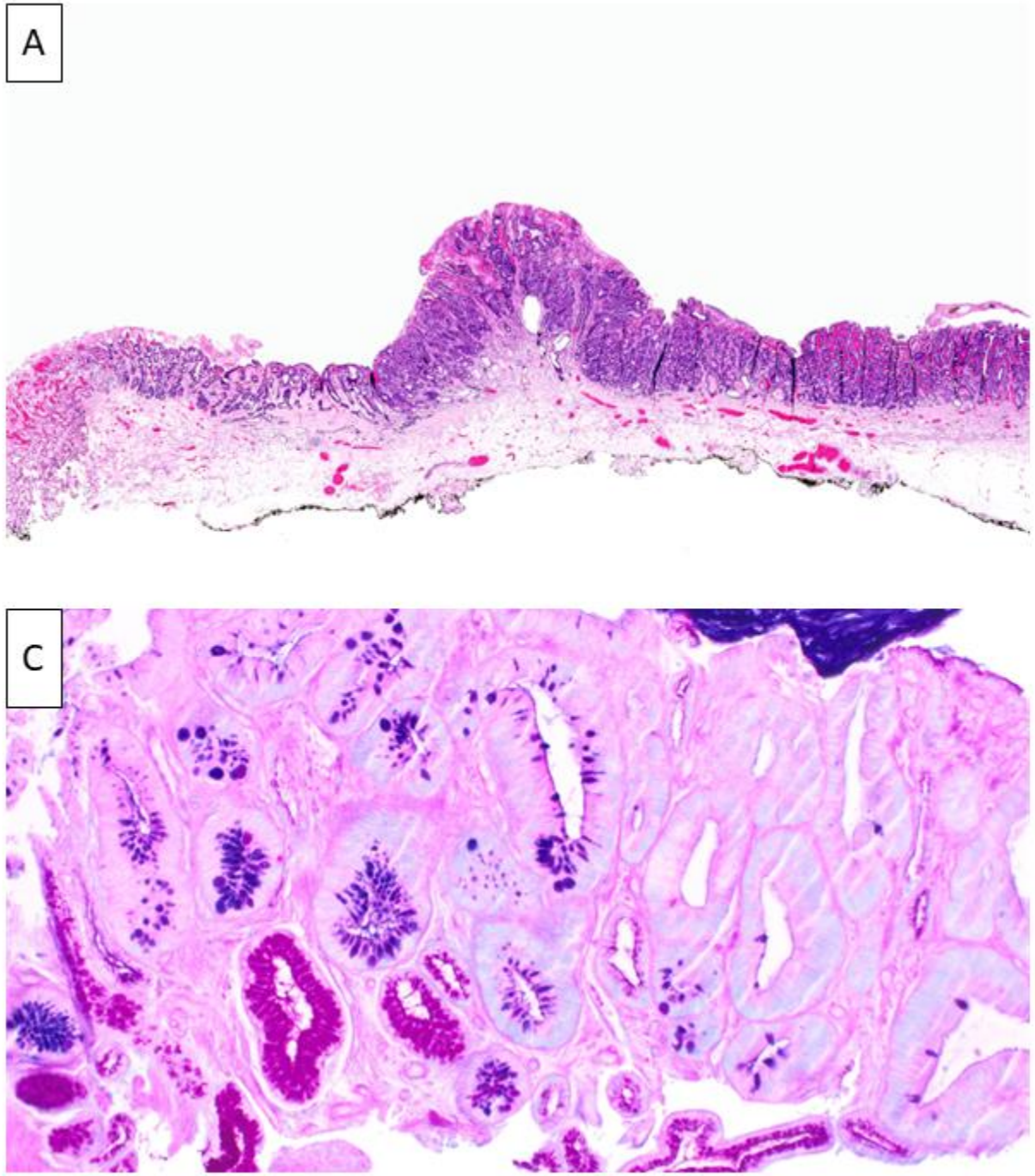
- Low-grade dysplasia has been reported to “regress”, persist, and progress to a higher grade dysplastic lesion/adenocarcinoma in 53.3%, 31.1%, and 6.6%/8.8% of cases, respectively (Data from Rugge et al).

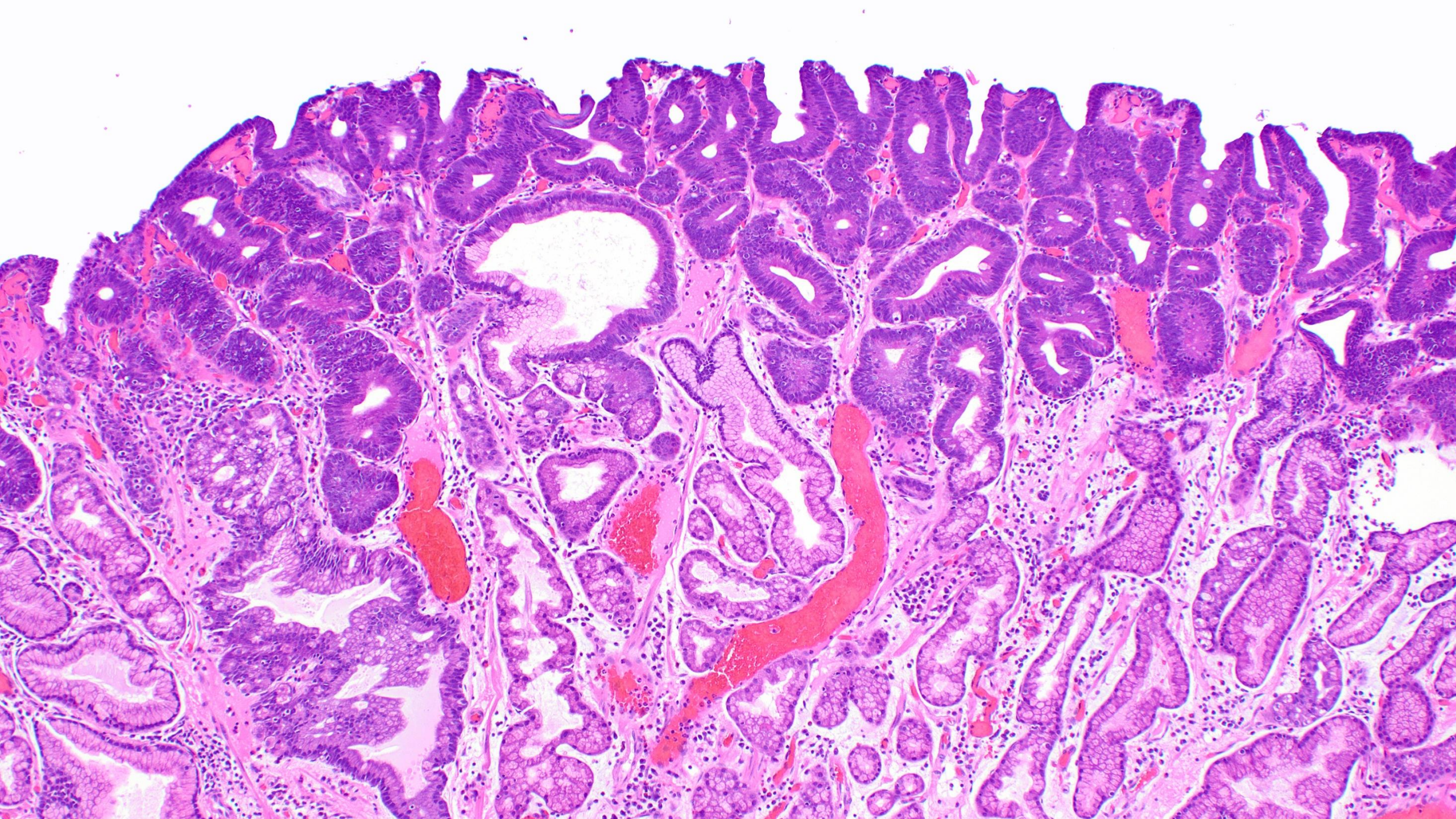
- High grade lesions are unlikely to regress and are associated with about 70% chance of progression.

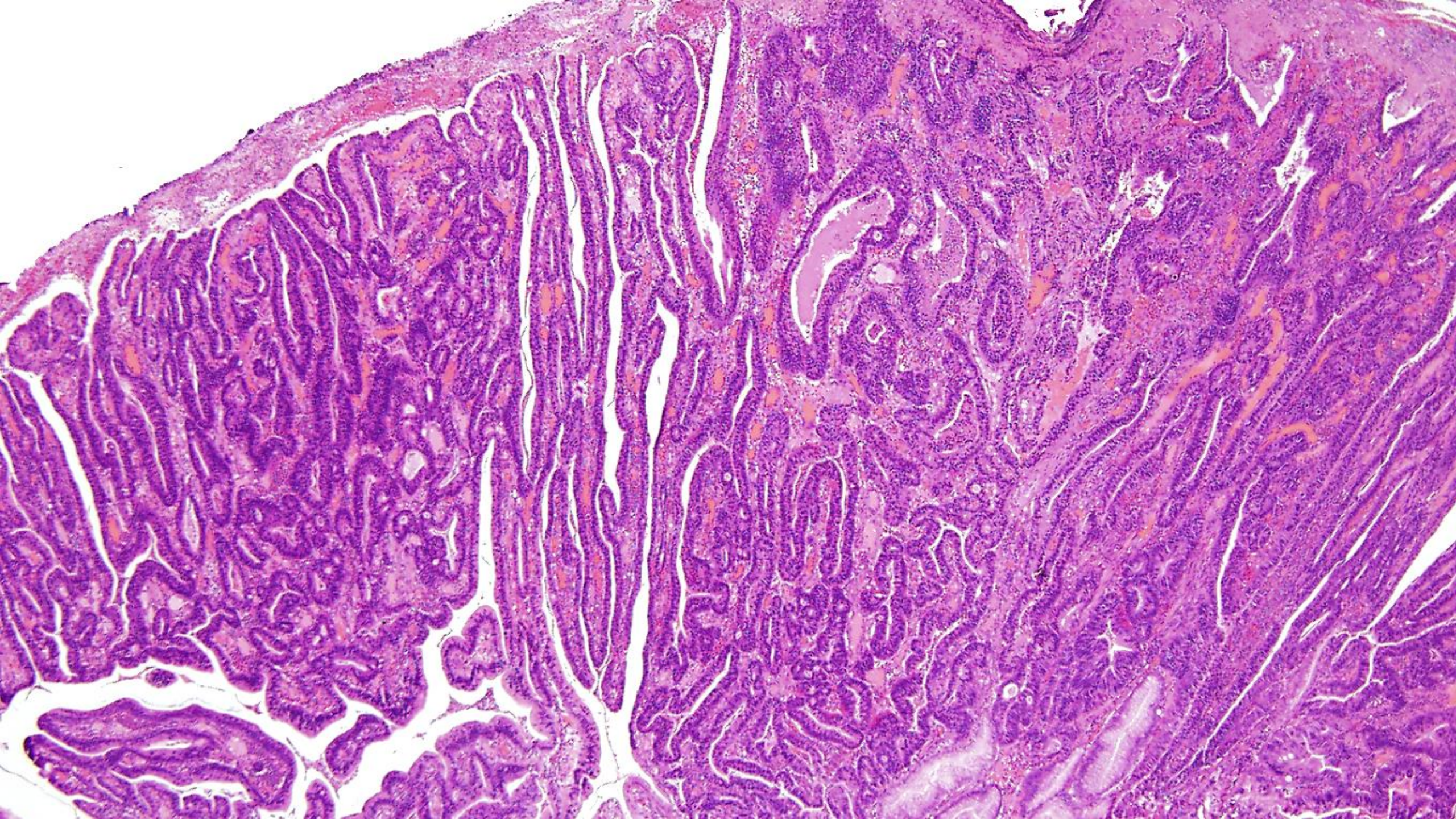
- These patients are typically followed endoscopically and their stomachs mapped with multiple biopsies. High-grade dysplastic lesions are typically managed with endoscopic mucosal resection (EMR) or surgical resection.

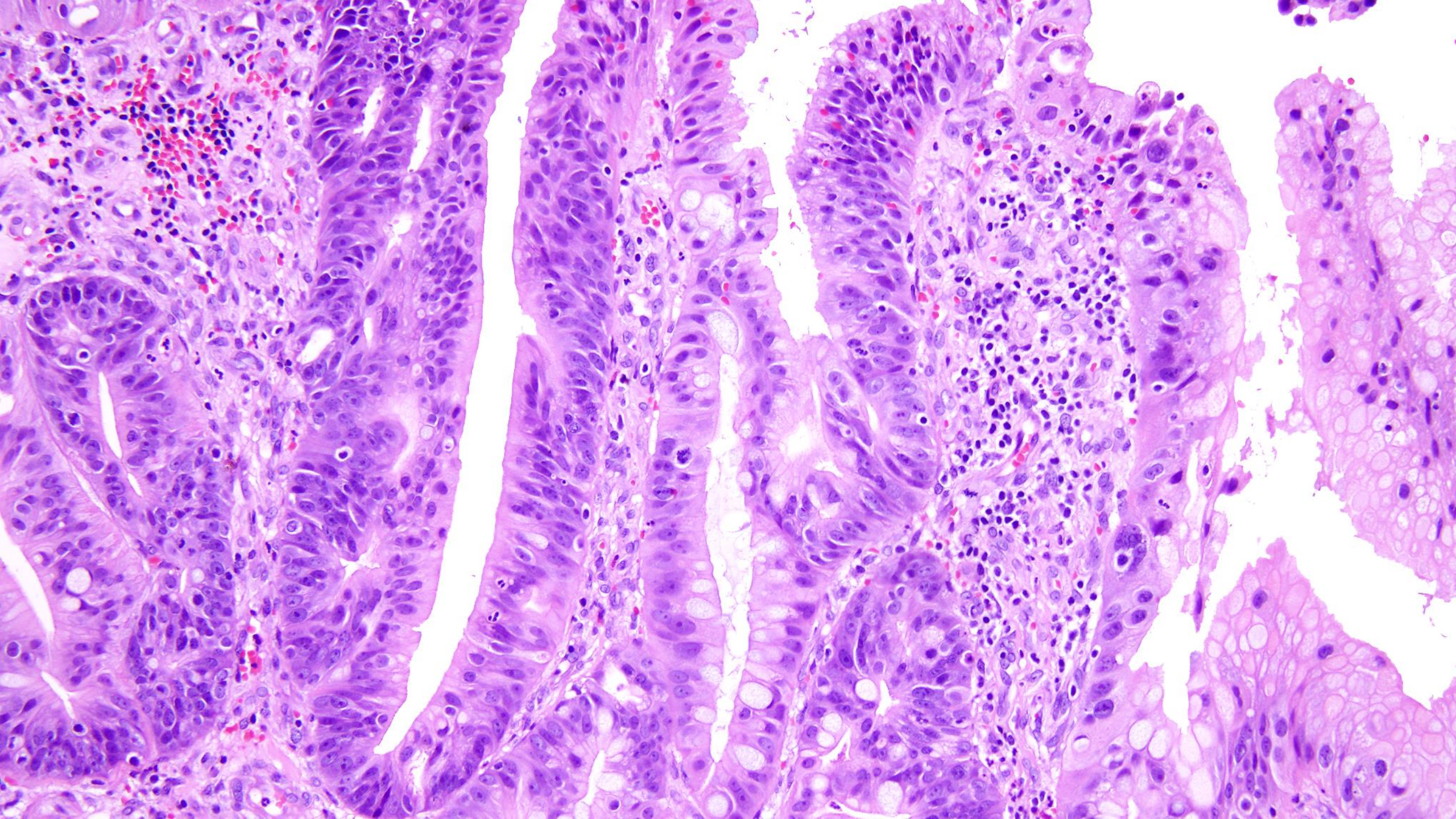





A
B
C







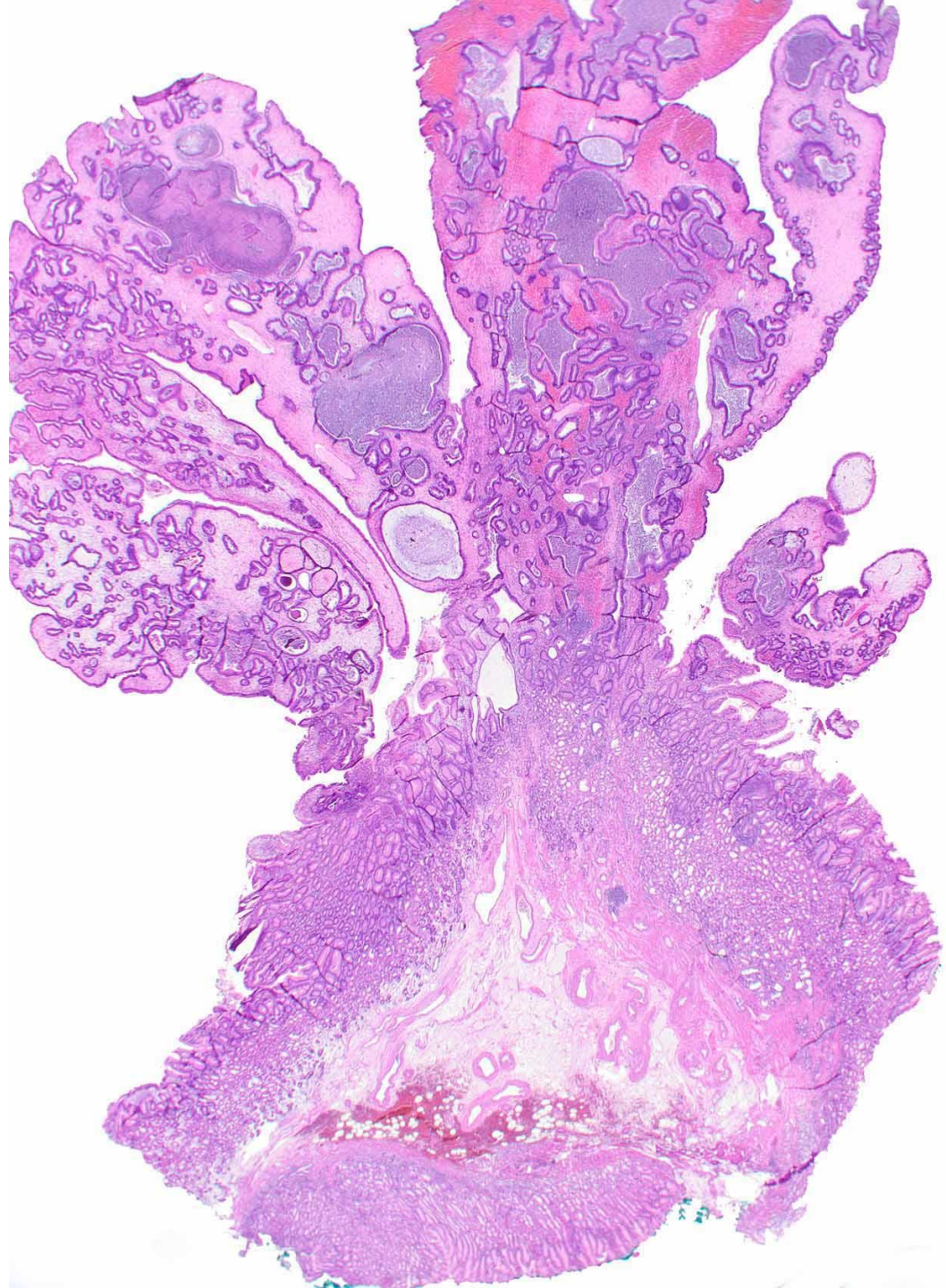
Gastric Adenomas in a Western Population

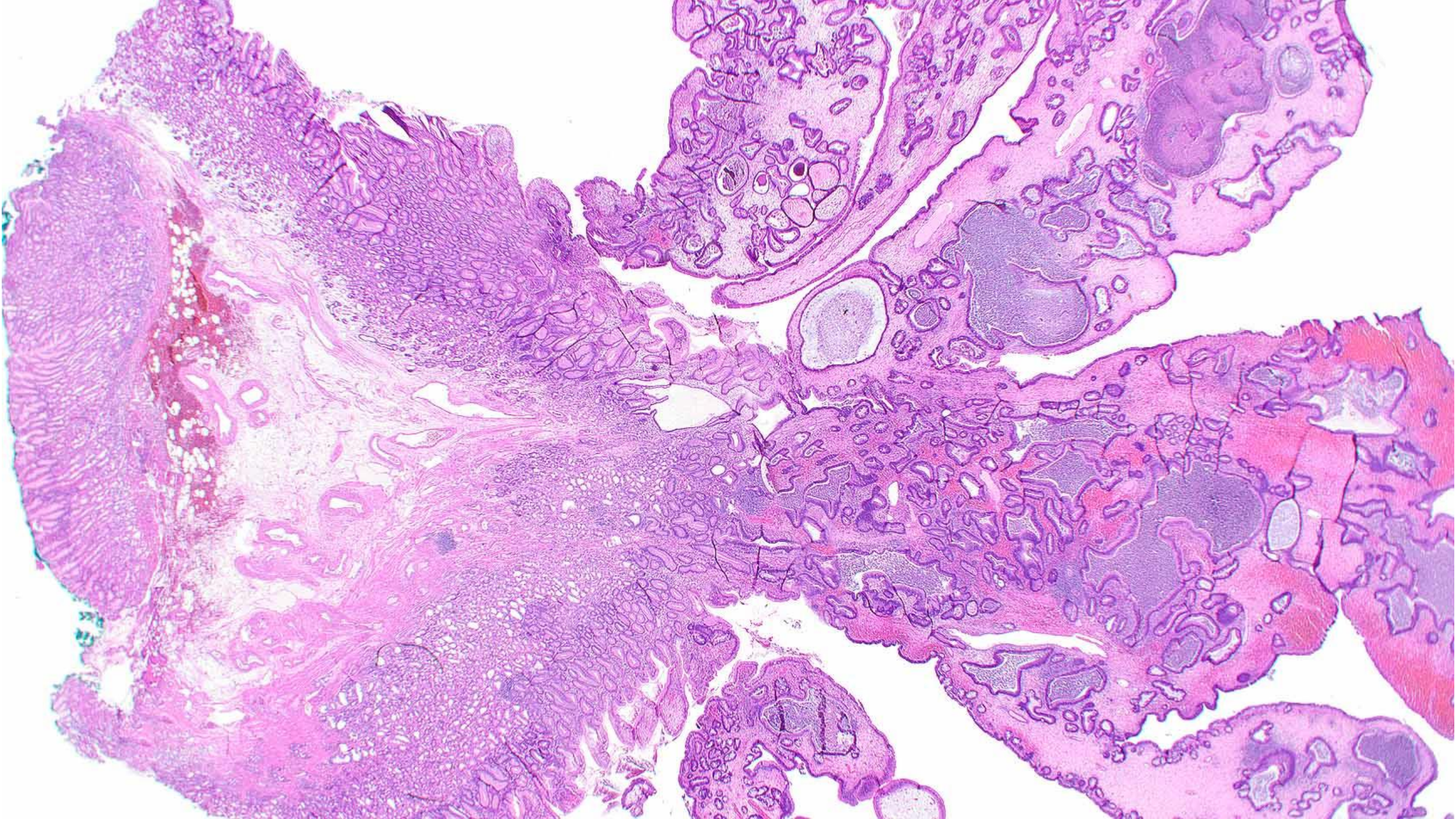
- Intestinal type (AKA polypoid gastric dysplasia)
- Gastric foveolar type
- Pyloric gland adenoma (has *GNAS* mutations whether gastritis-associated or syndromic with familial adenomatous polyposis)
- Oxyntic gland/chief cell adenoma – evolving concept since very rare (has *GNAS* mutations)
- MOVE TO REGARD GASTRITIS-ASSOCIATED POLYPOID DYSPLASIA AS “LESION” RATHER THAN ADENOMA
- Ref; Pimentel-Nunes P, Libânio D, Marcos-Pinto R, Areia M, Leja M, Esposito G, Garrido M, Kikuste I, Megraud F, Matysiak-Budnik T, Annibale B, Dumonceau JM, Barros R, Fléjou JF, Carneiro F, van Hooft JE, Kuipers EJ, Dinis-Ribeiro M. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. Endoscopy. 2019 Apr;51(4):365-388. PMID: 30841008.

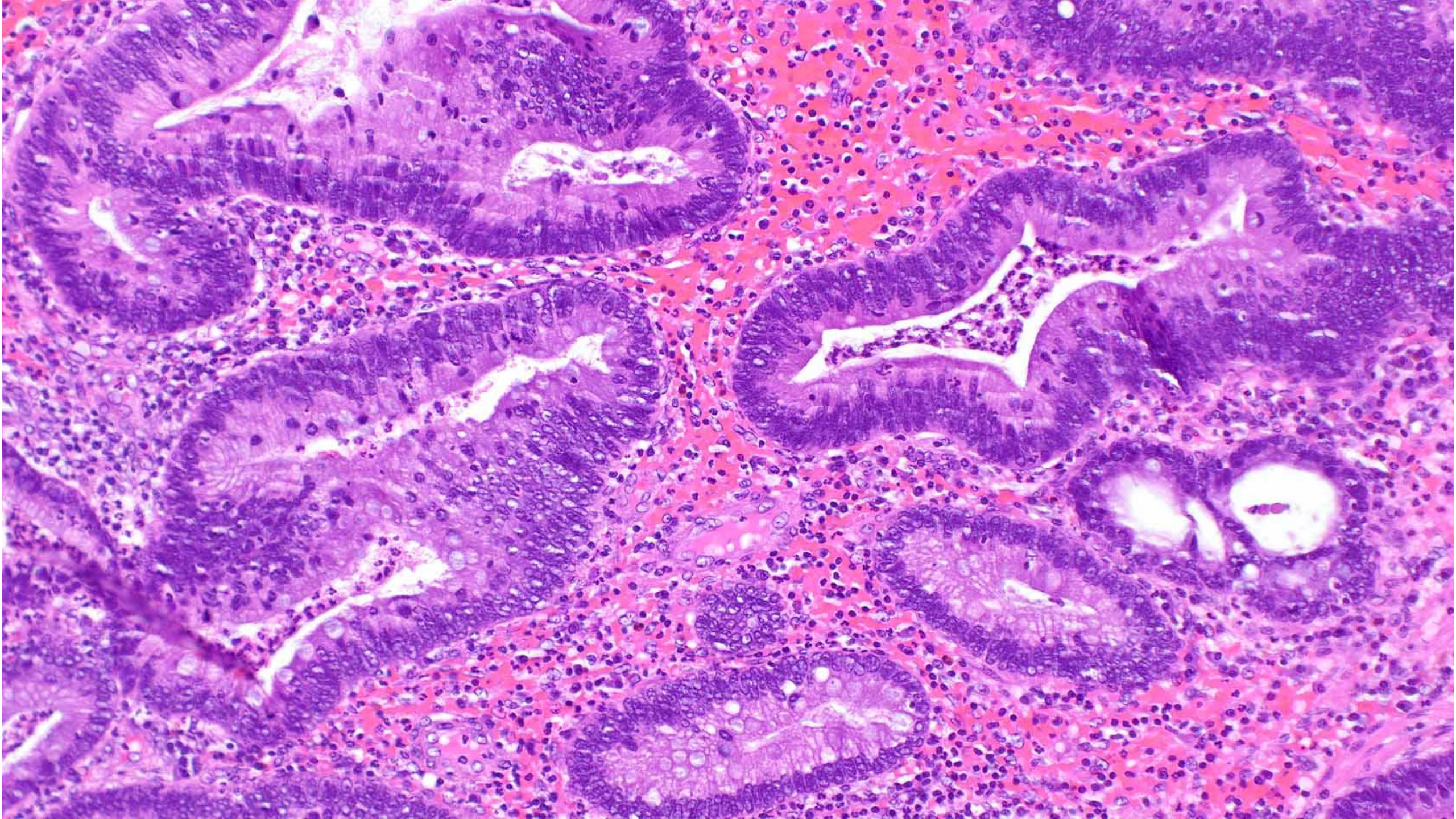
Hmmm

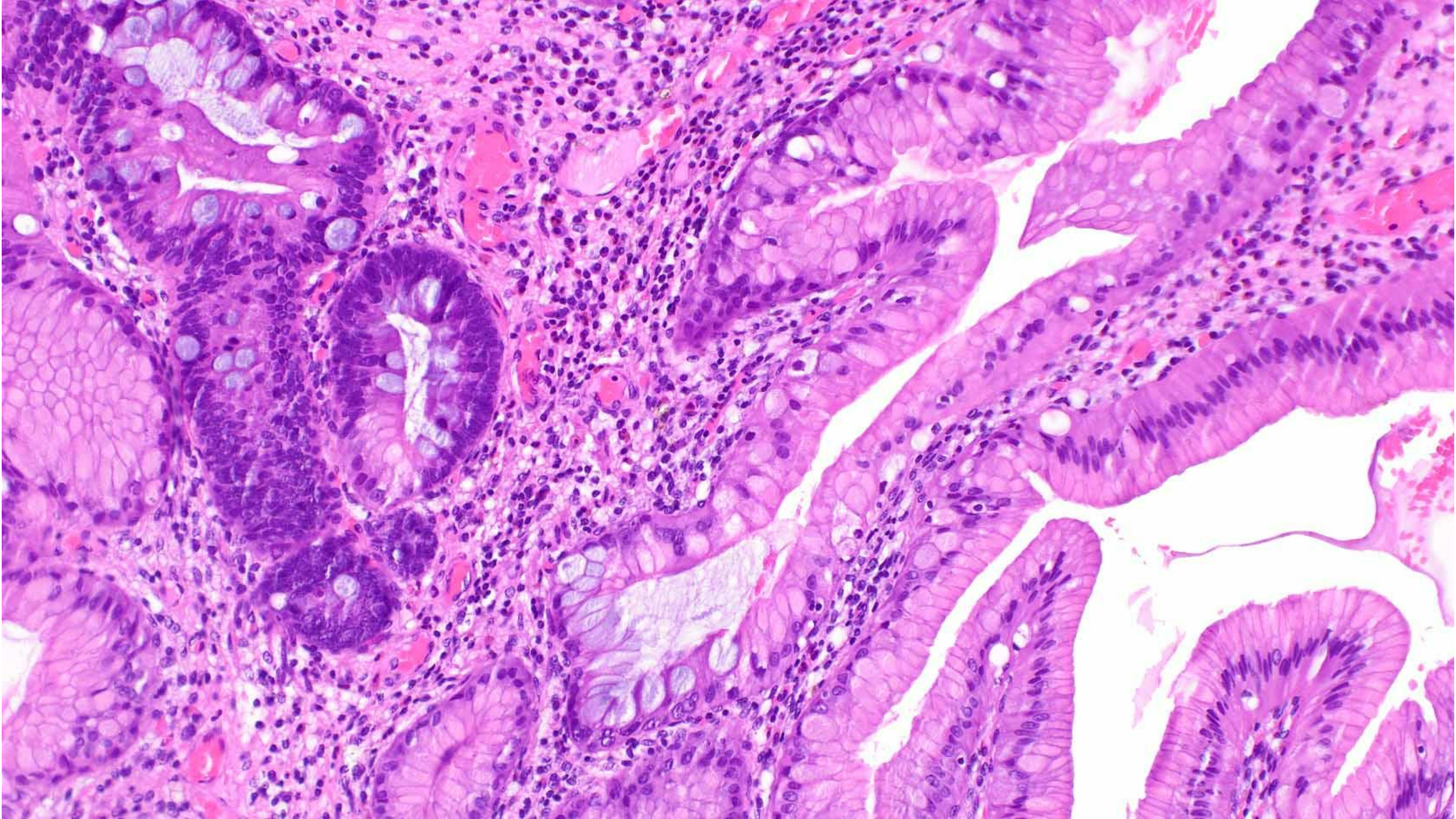
- So if a polyp with pyloric gland differentiation is found in a patient with autoimmune gastritis it is not an adenoma and the same polyp in a patient with familial adenomatous polyposis and no gastritis is an adenoma?
- So if a polyp with intestinal differentiation is found in a patient with autoimmune gastritis it is not an adenoma and the same polyp in a patient with familial adenomatous polyposis and no gastritis is an adenoma?

Wood LD, Salaria SN, Cruise MW, Giardiello FM, Montgomery EA. Upper GI tract lesions in familial adenomatous polyposis (FAP): enrichment of pyloric gland adenomas and other gastric and duodenal neoplasms. Am J Surg Pathol. 2014 Mar;38(3):389-93. PubMed PMID: 24525509.

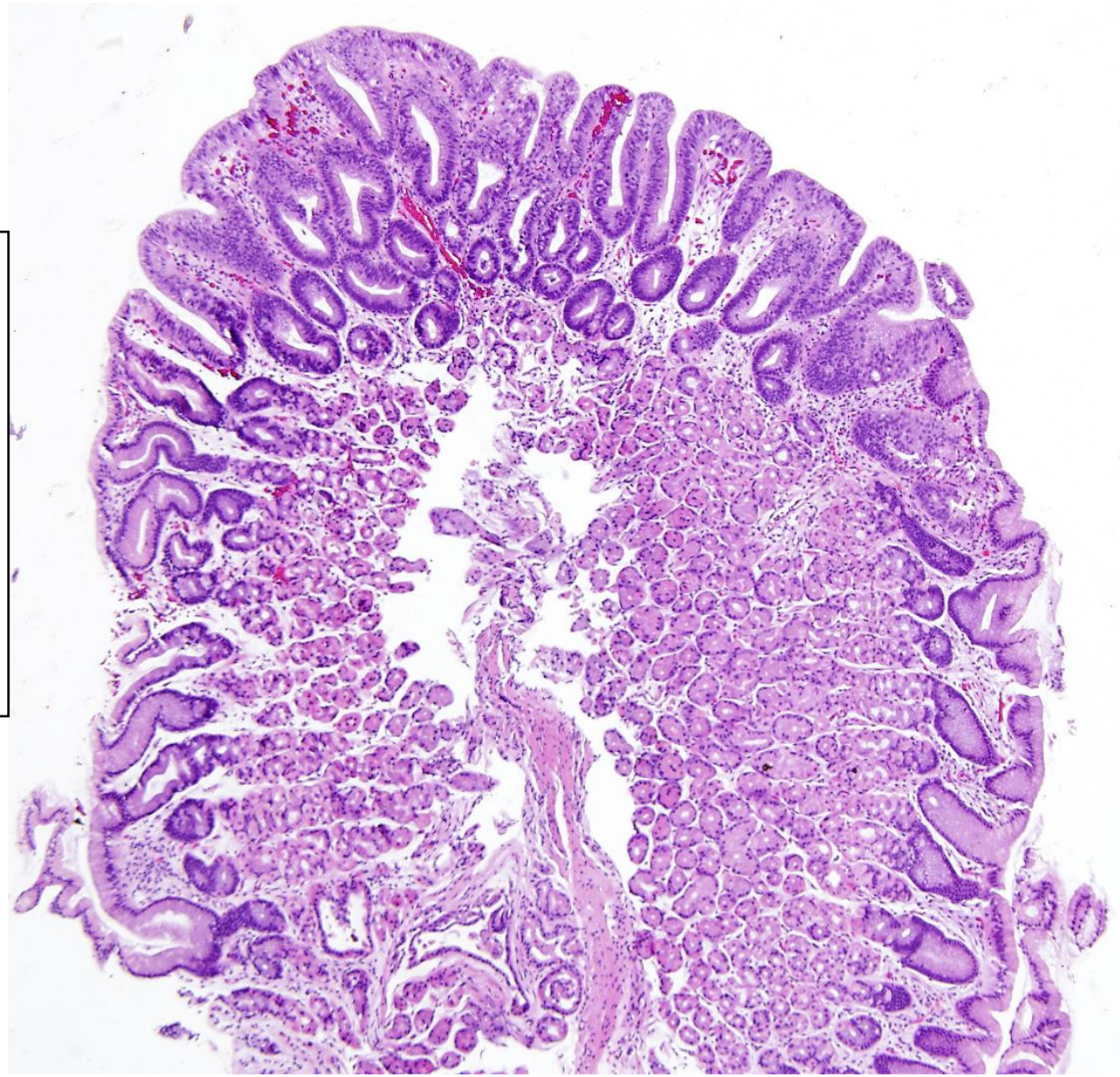


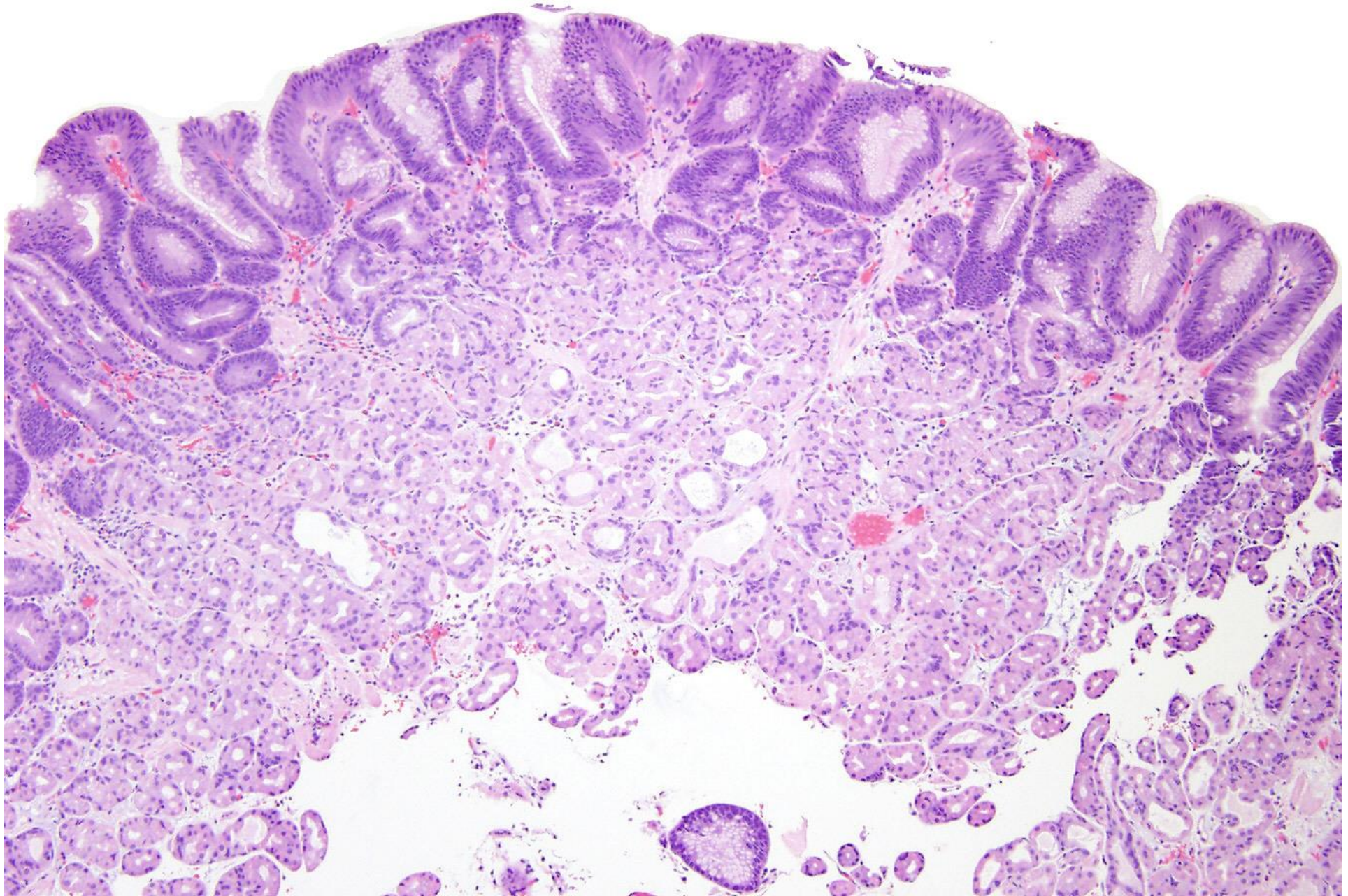


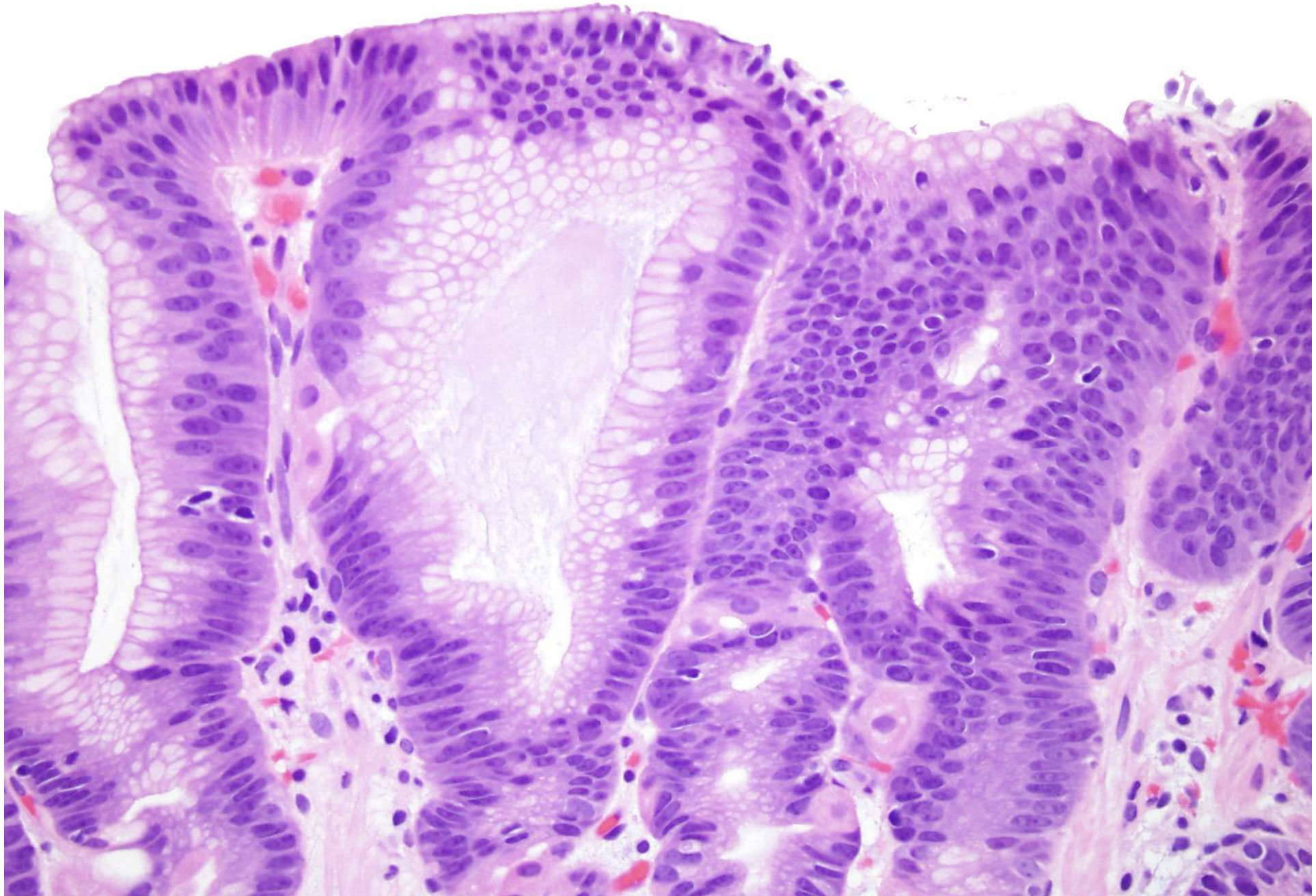


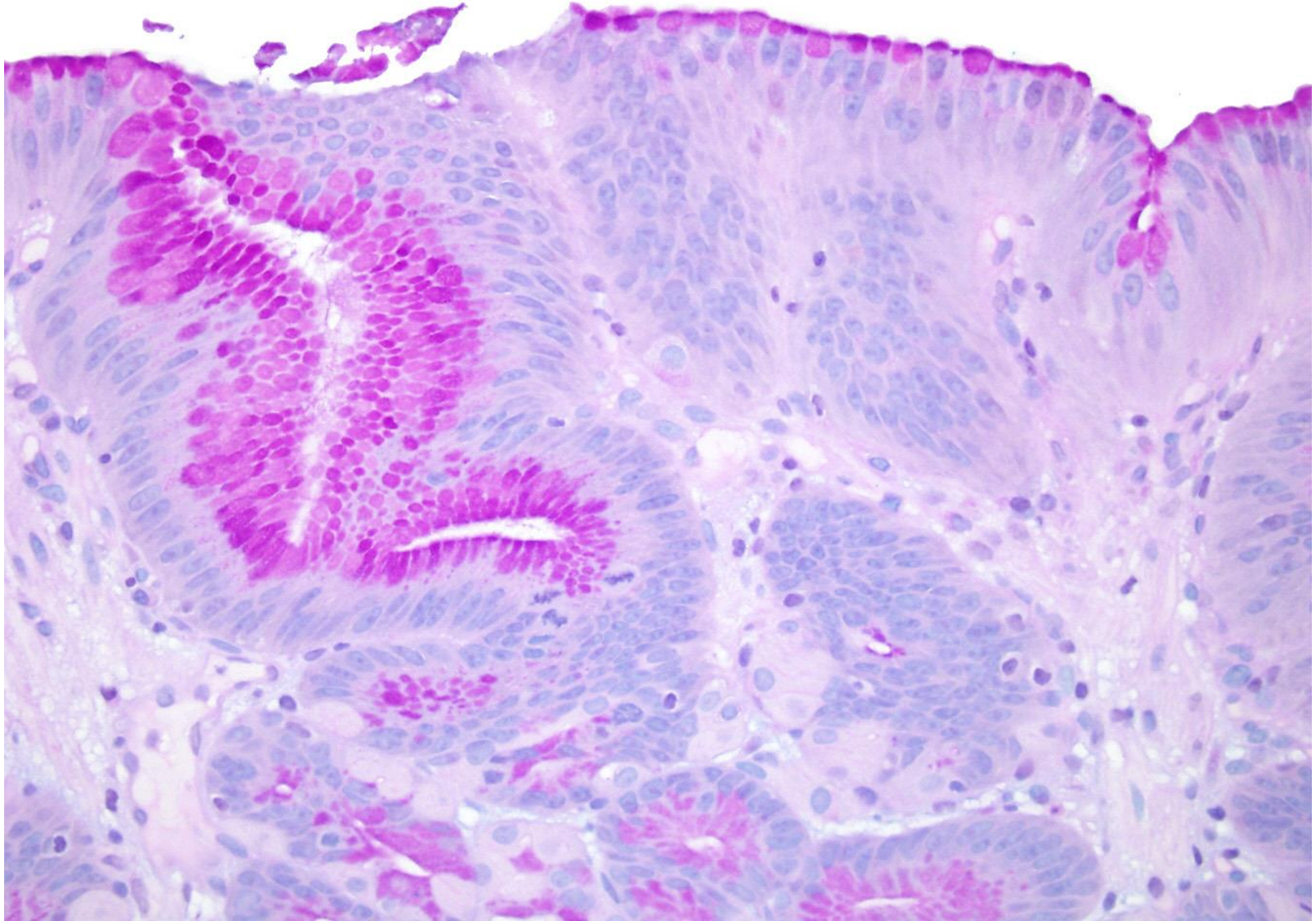


Gastric adenoma, gastric foveolar type – pristine background mucosa, NO intestinal metaplasia anywhere. The cells have apical neutral mucin
In Many ways equivalent to colorectal adenomas





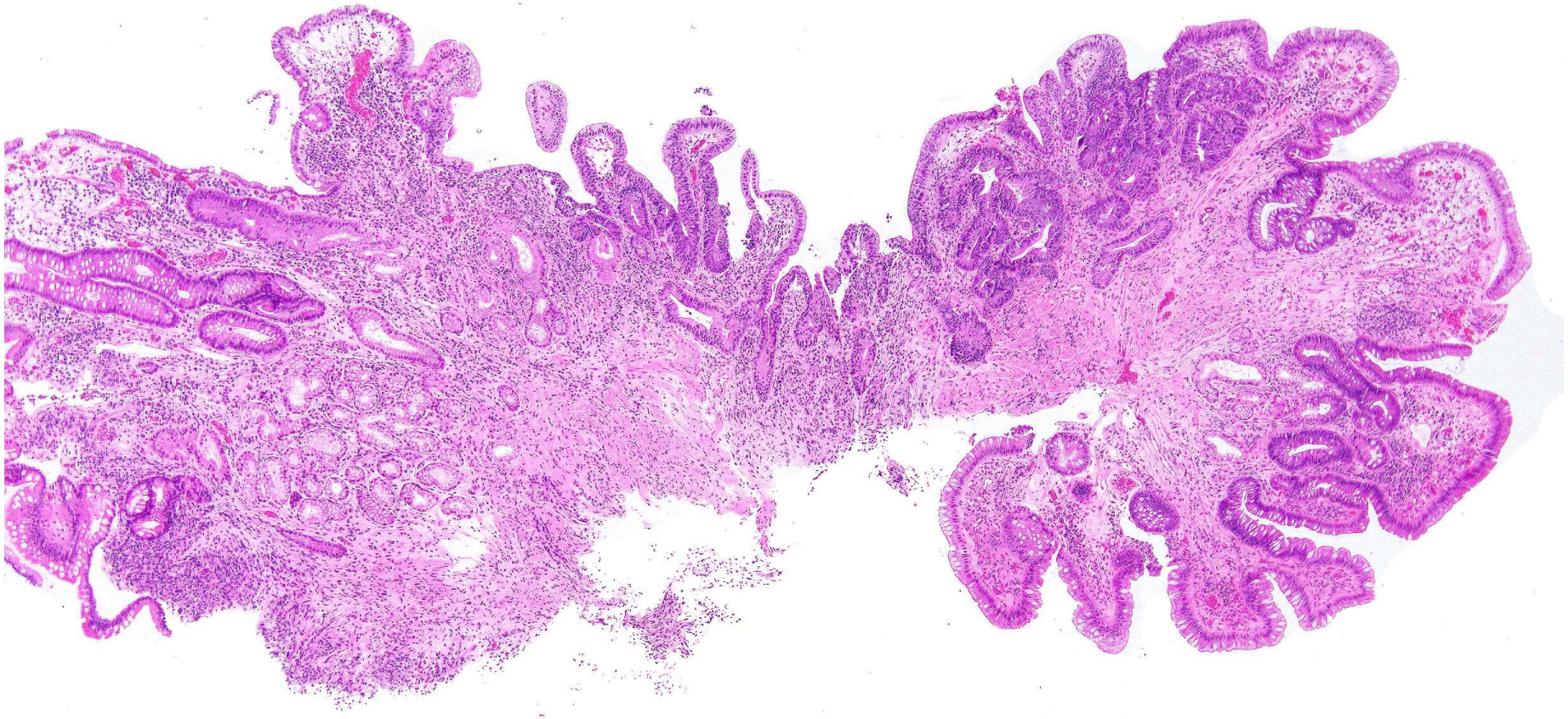




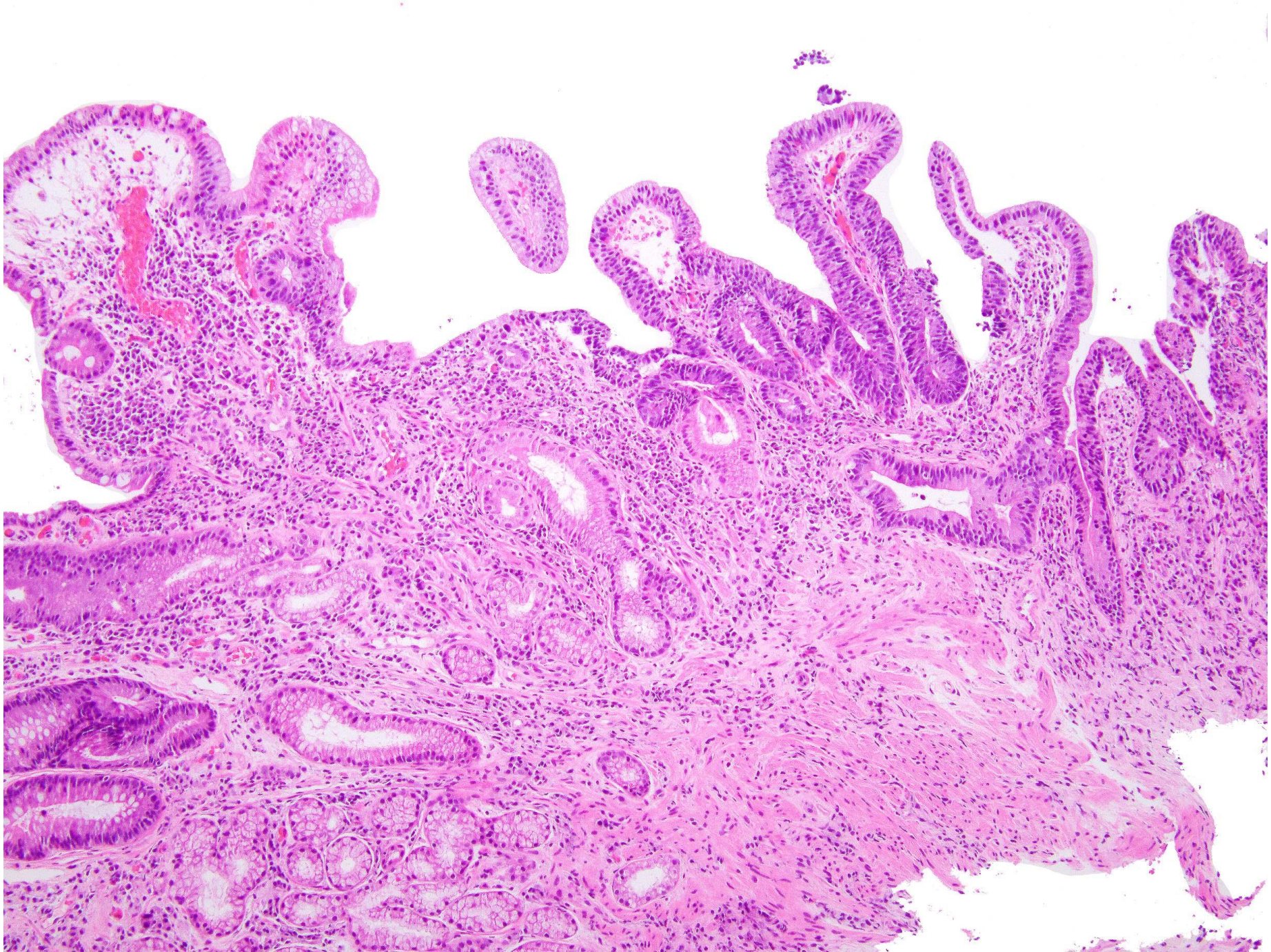
Small bowel

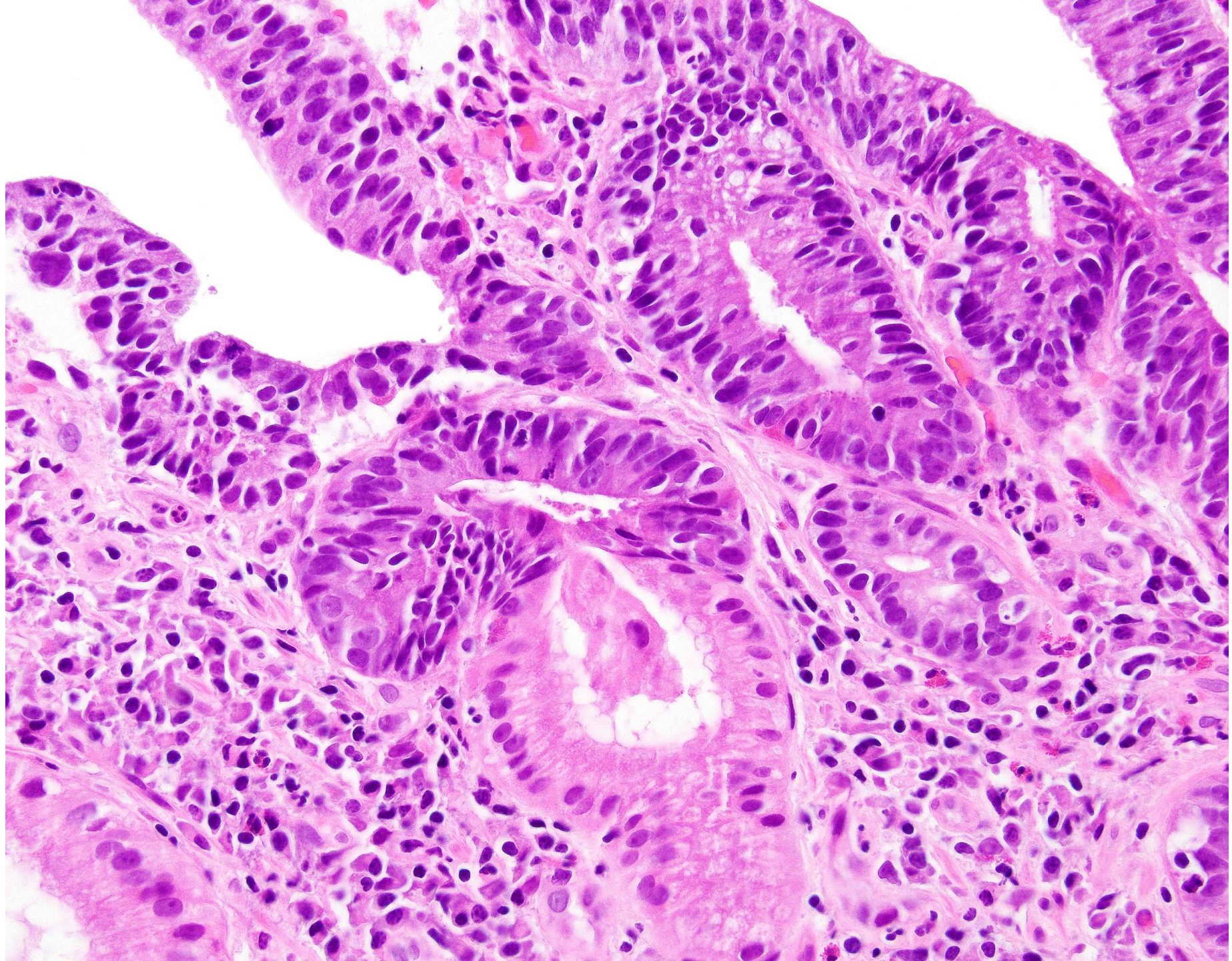
- Less real estate, less dysplasia
- COLONIZATION!!!

- Estrella JS, Wu TT, Rashid A, Abraham SC. Mucosal colonization by metastatic carcinoma in the gastrointestinal tract: a potential mimic of primary neoplasia. Am J Surg Pathol. 2011 Apr;35(4):563-72. PubMed PMID: 21412071.



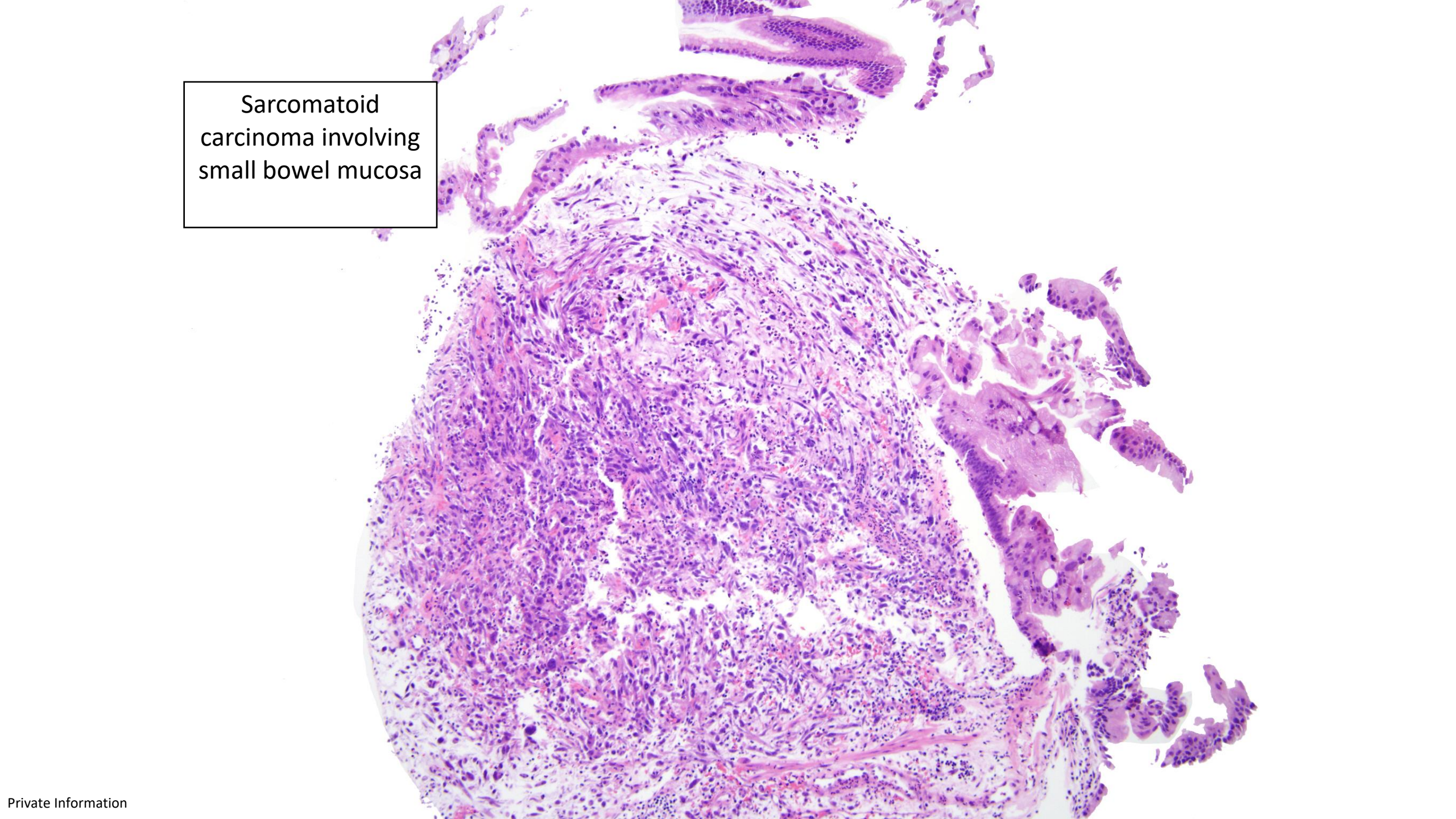
Crohn disease associated with dysplasia

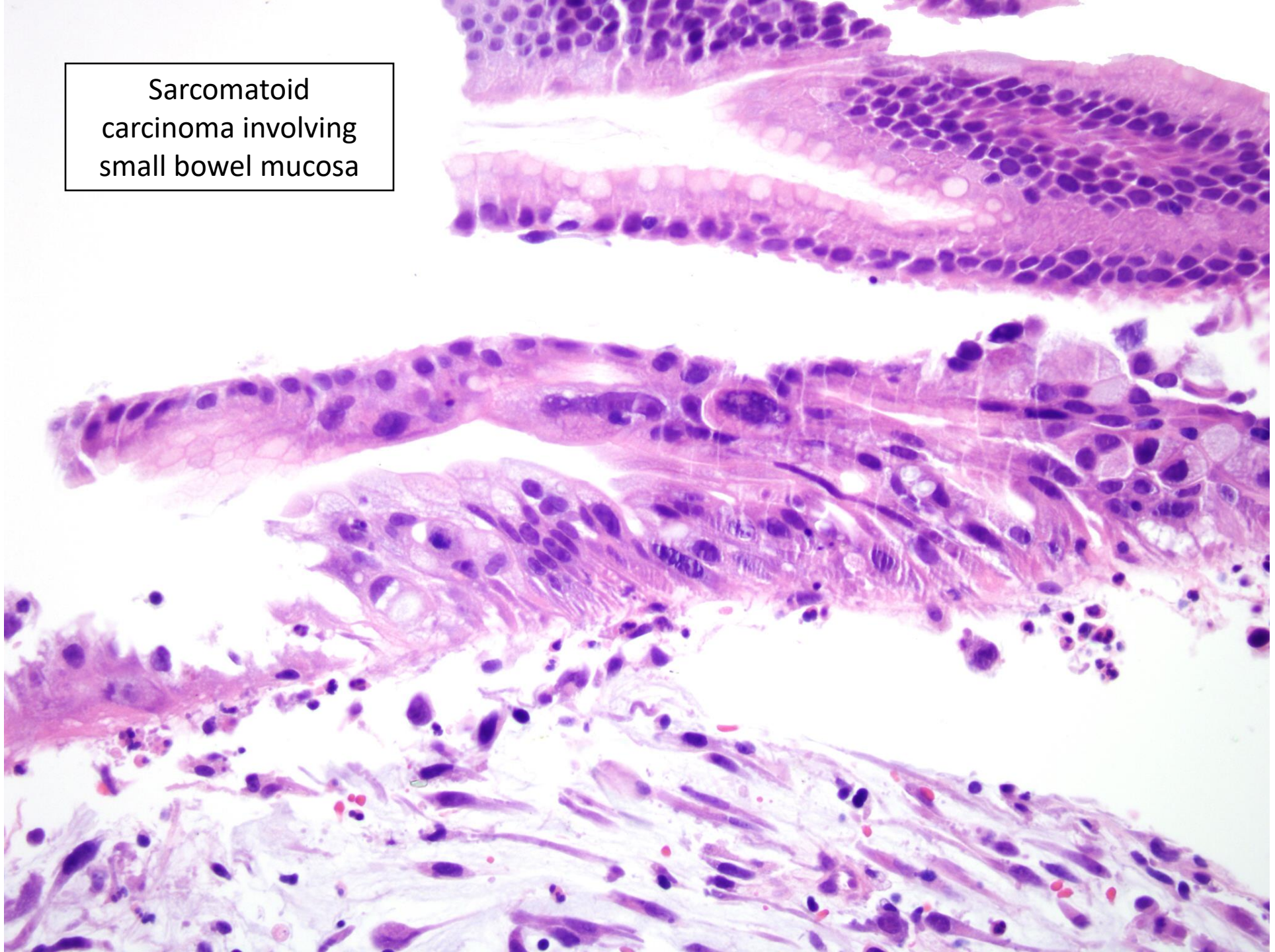


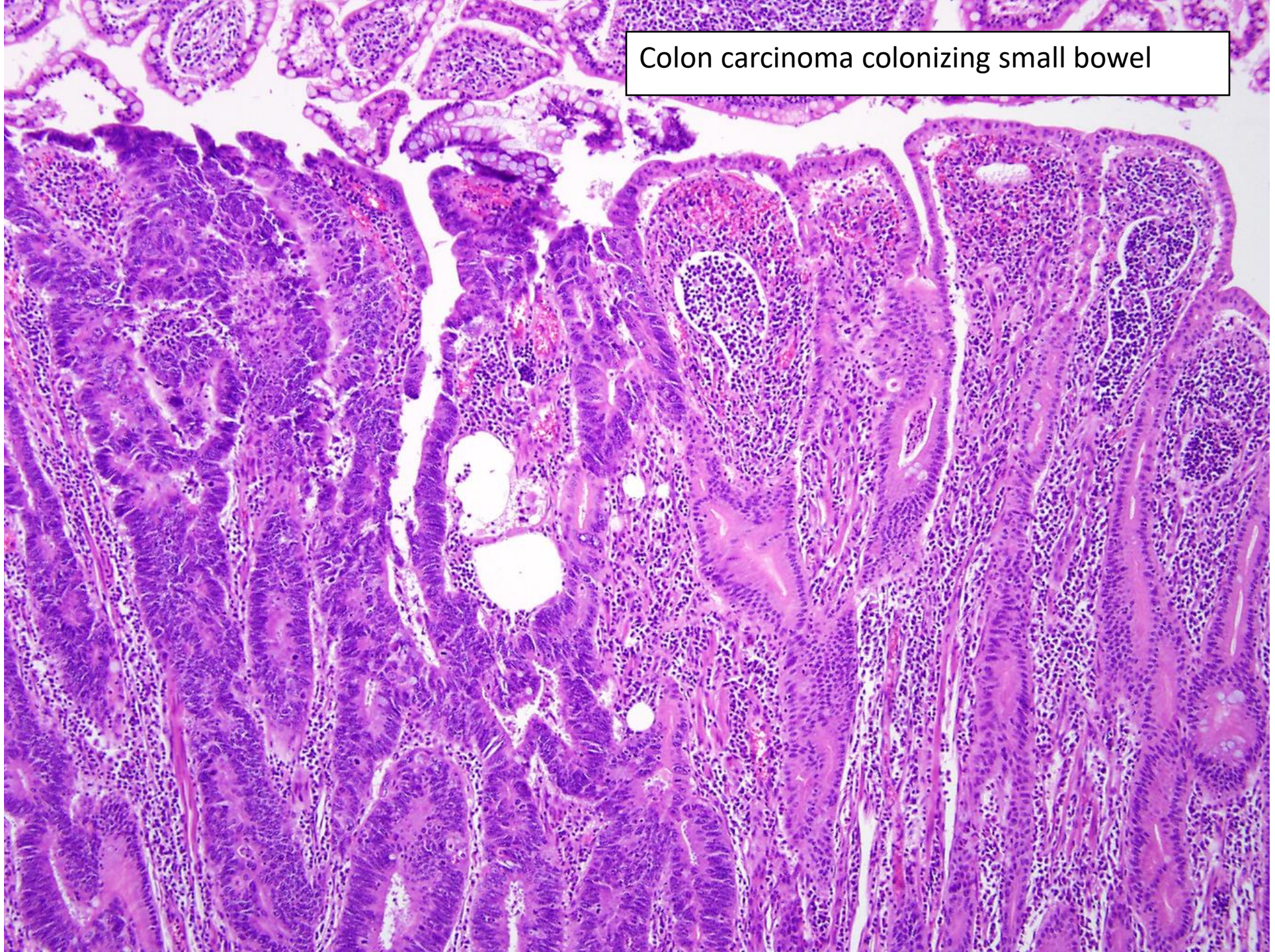


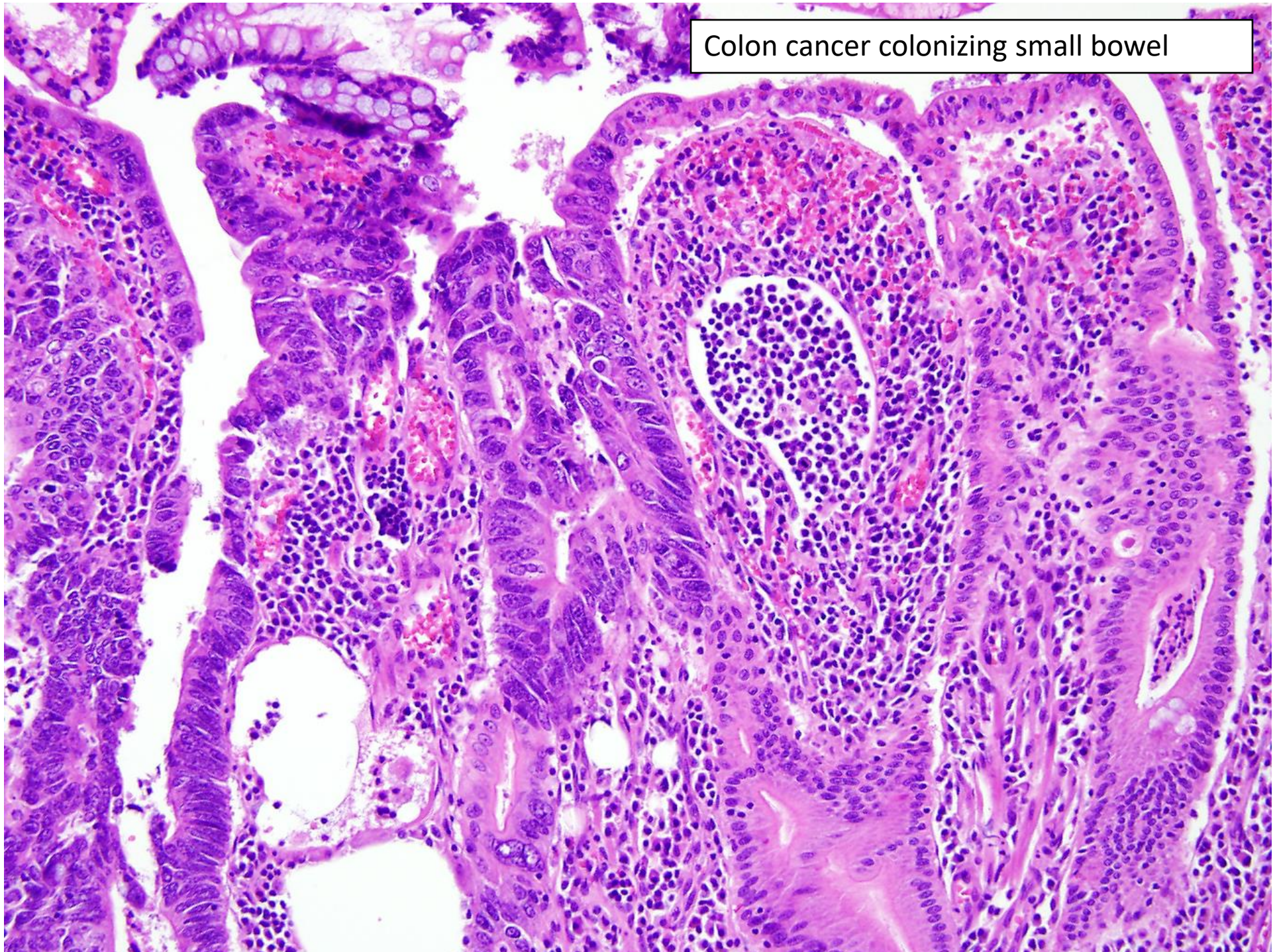
An Important Thing to Recall

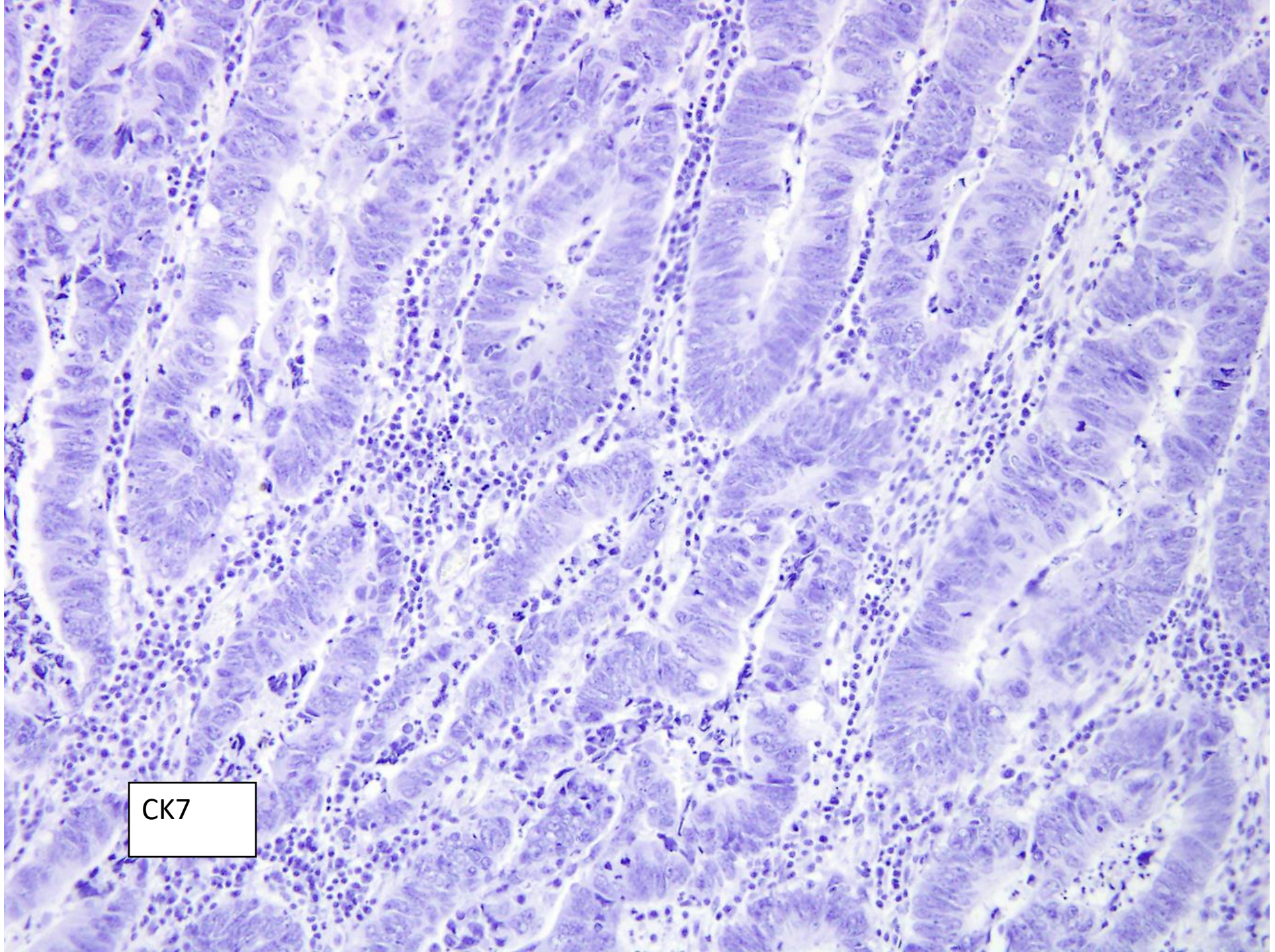
- The small bowel is treacherous since it metastases are so common there and they can “colonize” the surface and mimic an *in situ* component
- Metastases outnumber primary lesions over 2:1
- Immunostaining can really save the day
- Bellizzi AM, Montgomery EA, Hornick JL. American Registry of Pathology Expert Opinions: Evaluation of poorly differentiated malignant neoplasms on limited samples - Gastrointestinal mucosal biopsies. Ann Diagn Pathol. 2019 Nov 15;44:151419. PubMed PMID: 31786484.

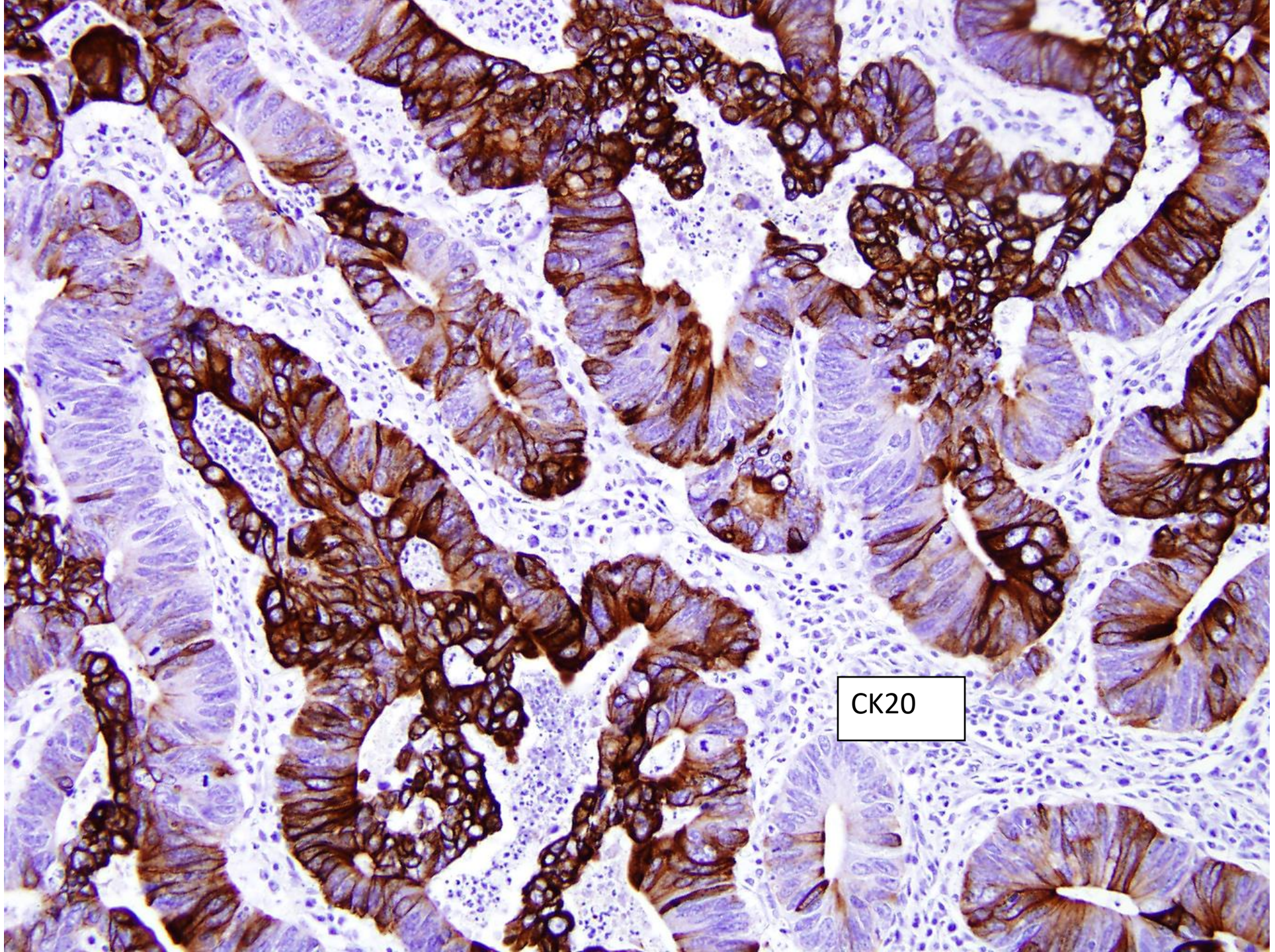




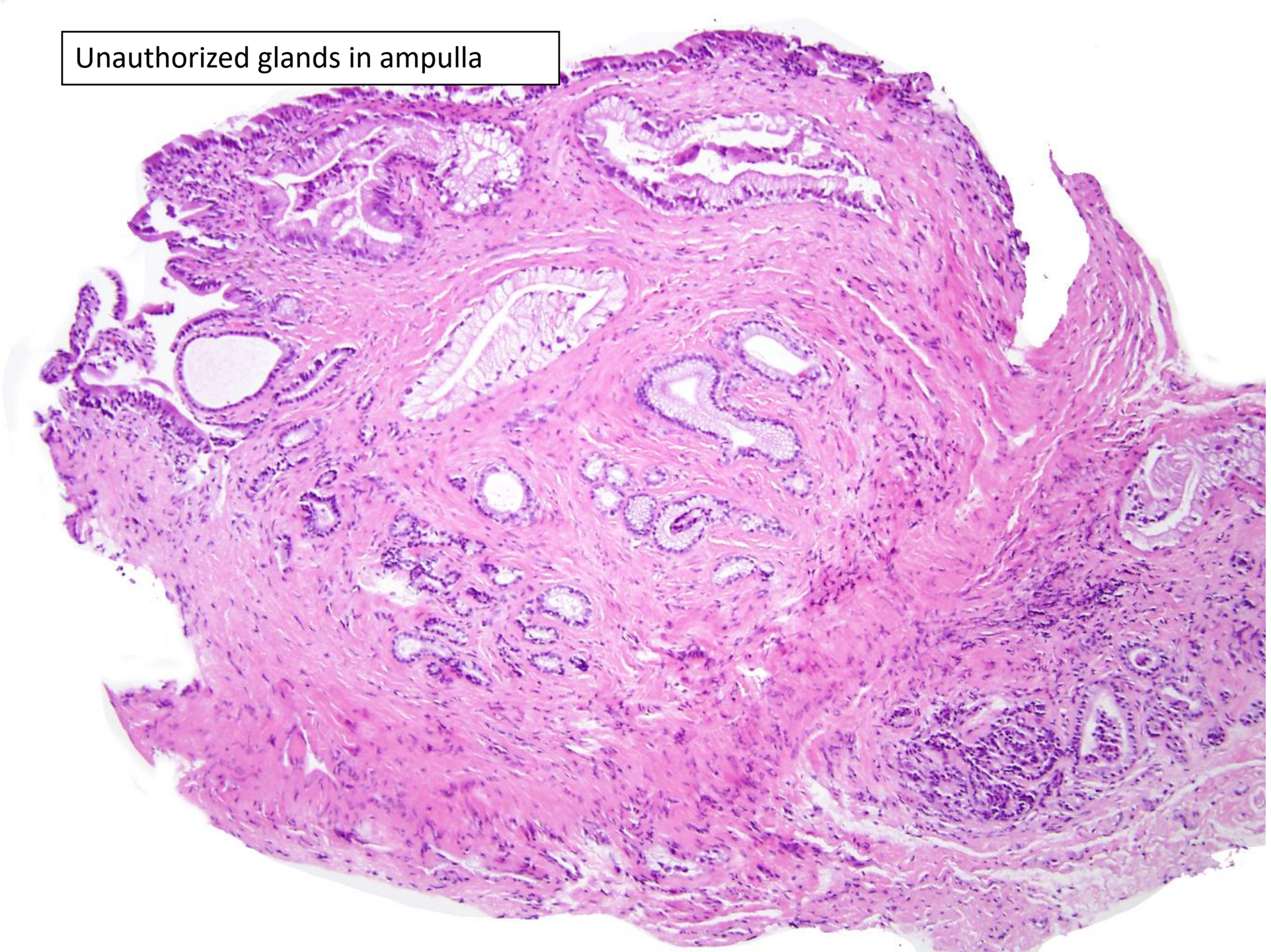


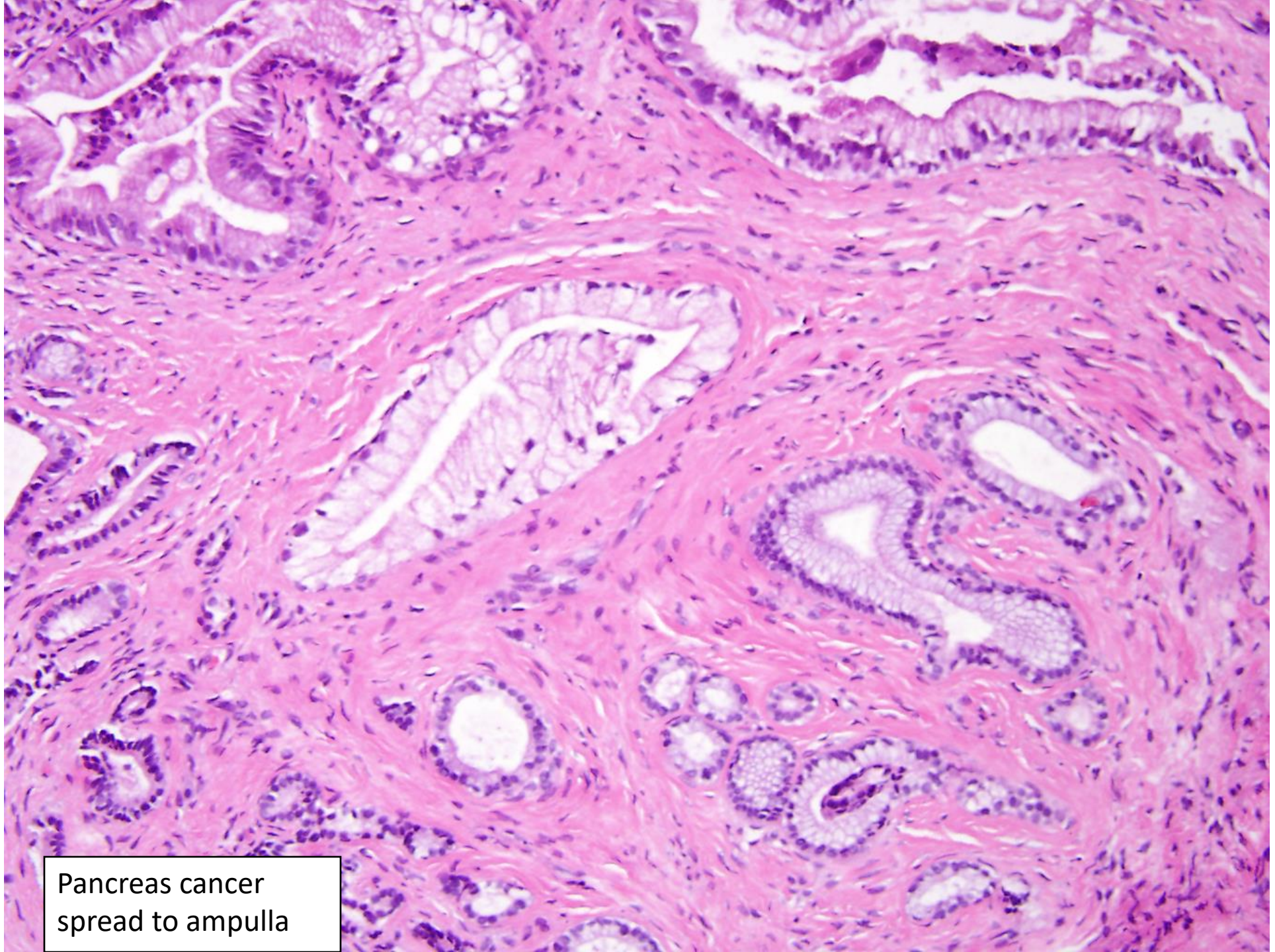


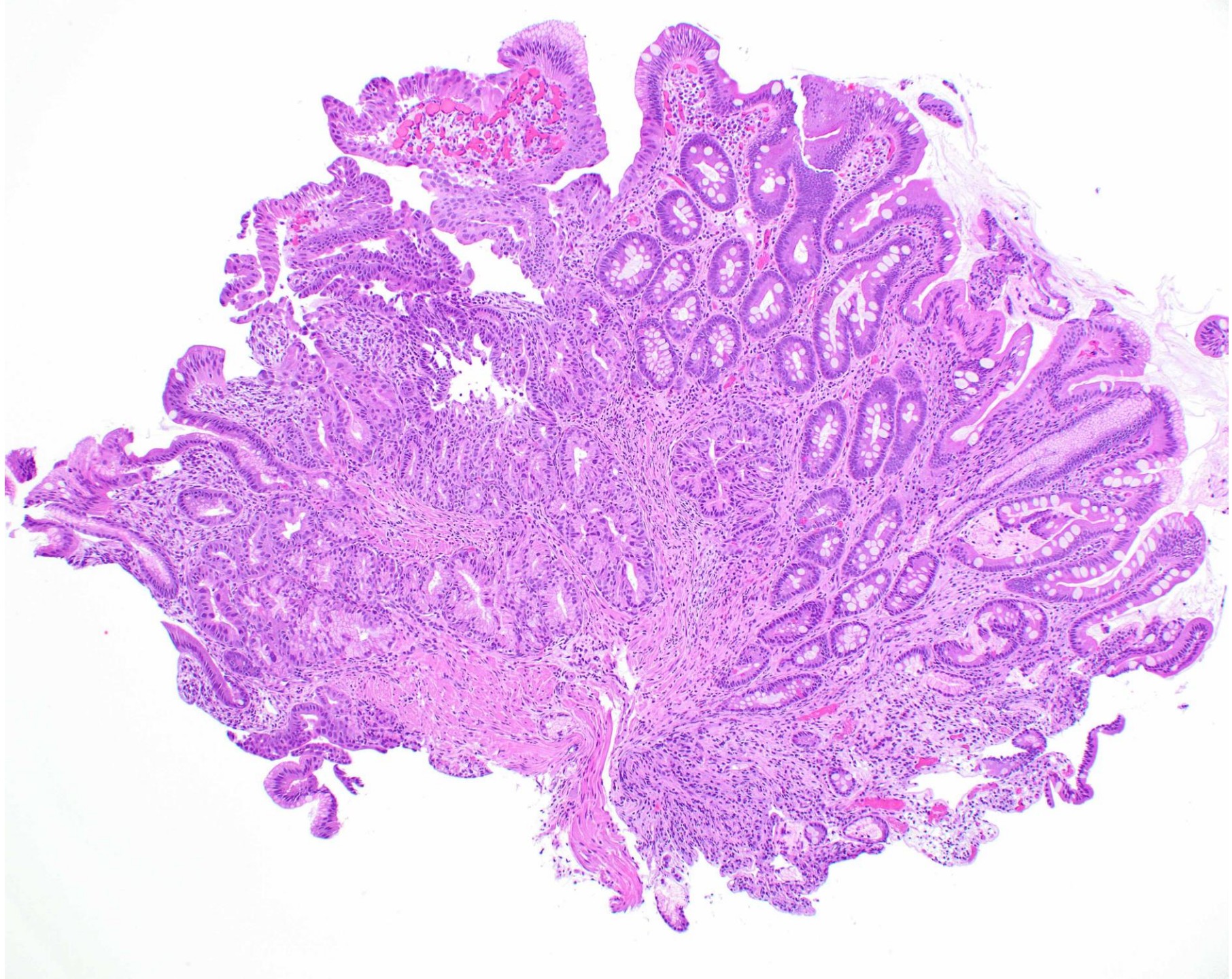


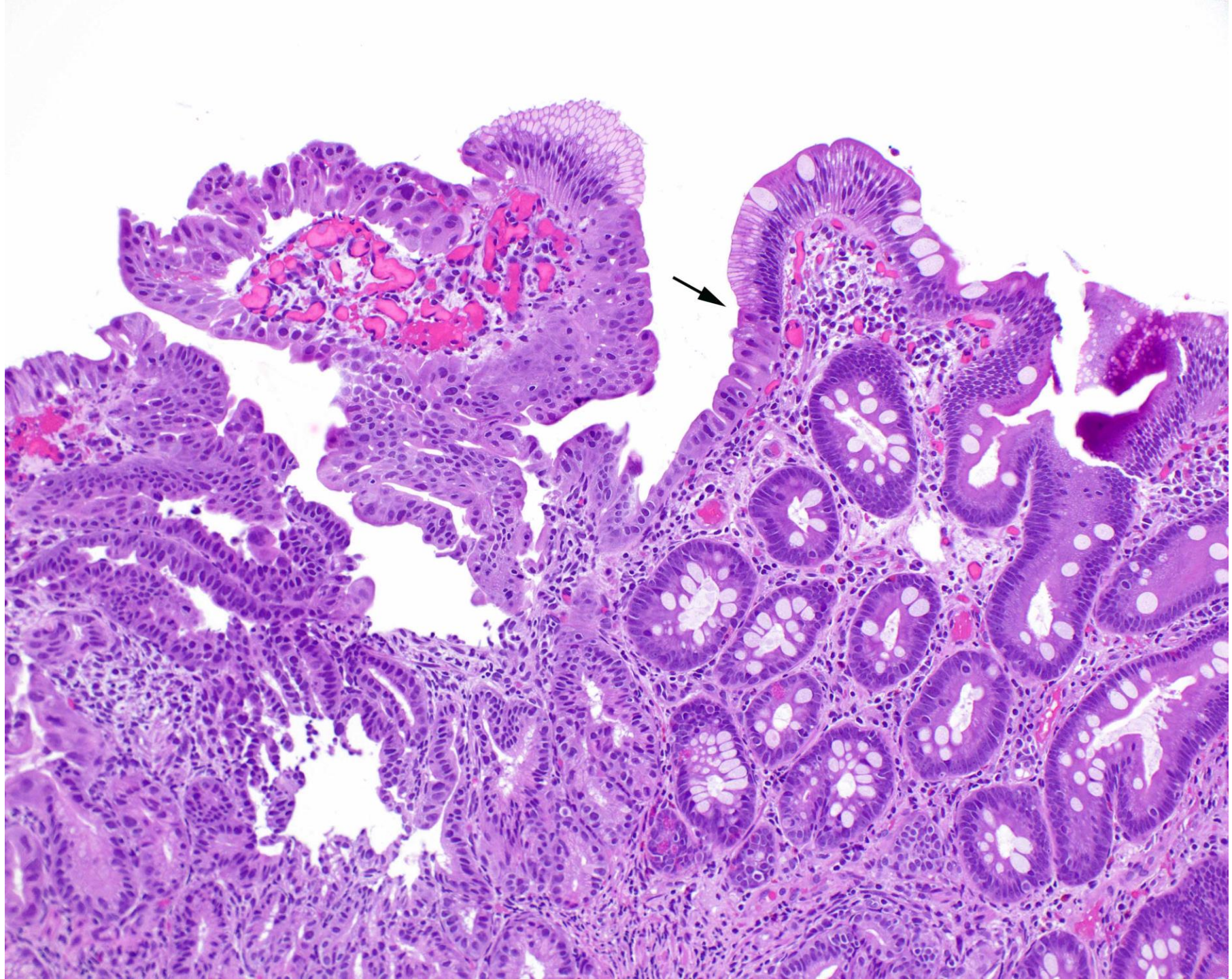


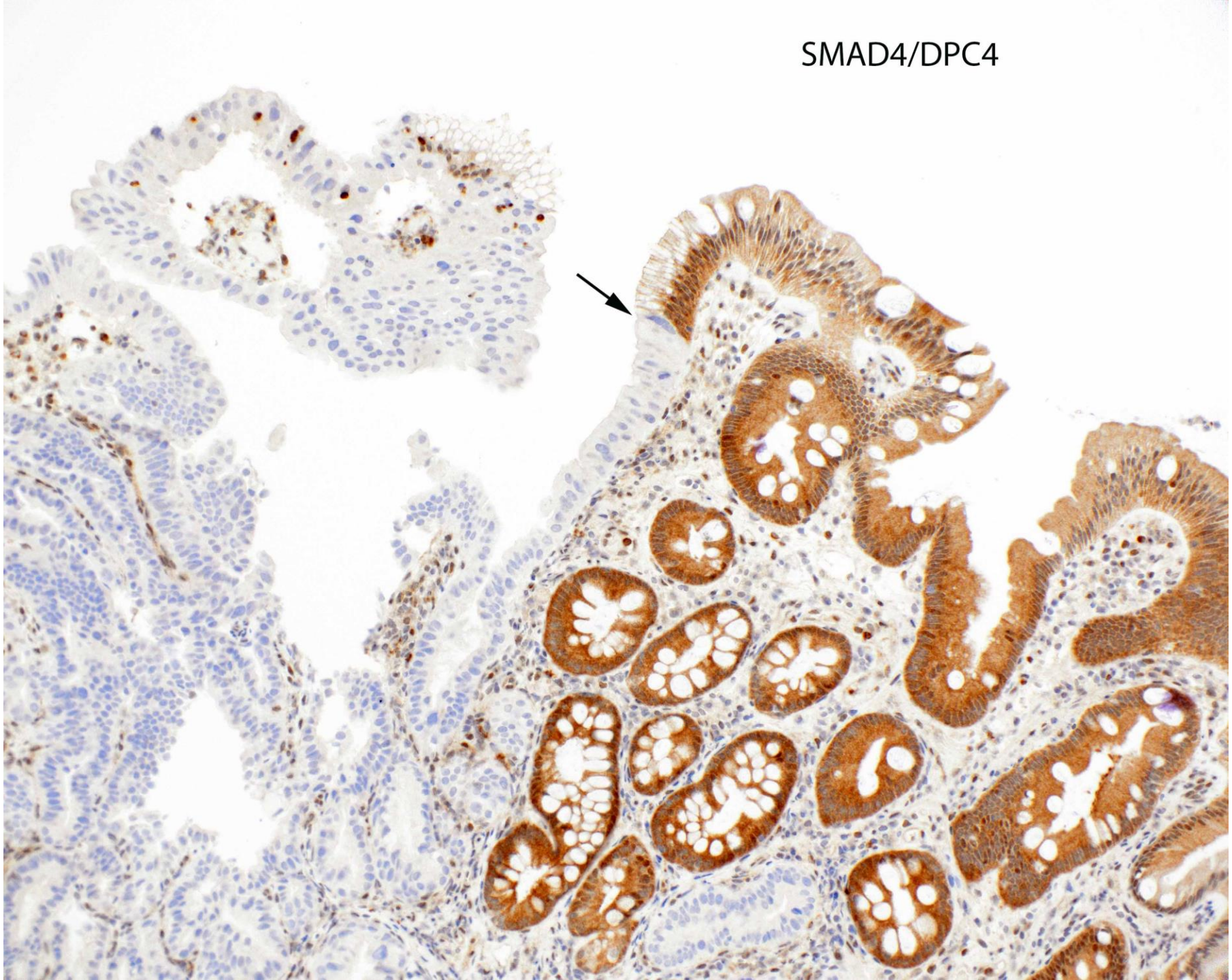
Unauthorized glands in ampulla











Colon

- The big issue is dysplasia associated with inflammatory bowel disease

Dysplasia

Classically defined as “adenoma-like” but early observers noted variant patterns

Riddell RH, Goldman H, Ransohoff DF, Appelman HD, Fenoglio CM, Haggitt RC, Ahren C, Correa P, Hamilton SR, Morson BC, et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. Hum Pathol. 1983 Nov;14(11):931-68. PubMed PMID: 6629368.

Over time, variant patterns better described

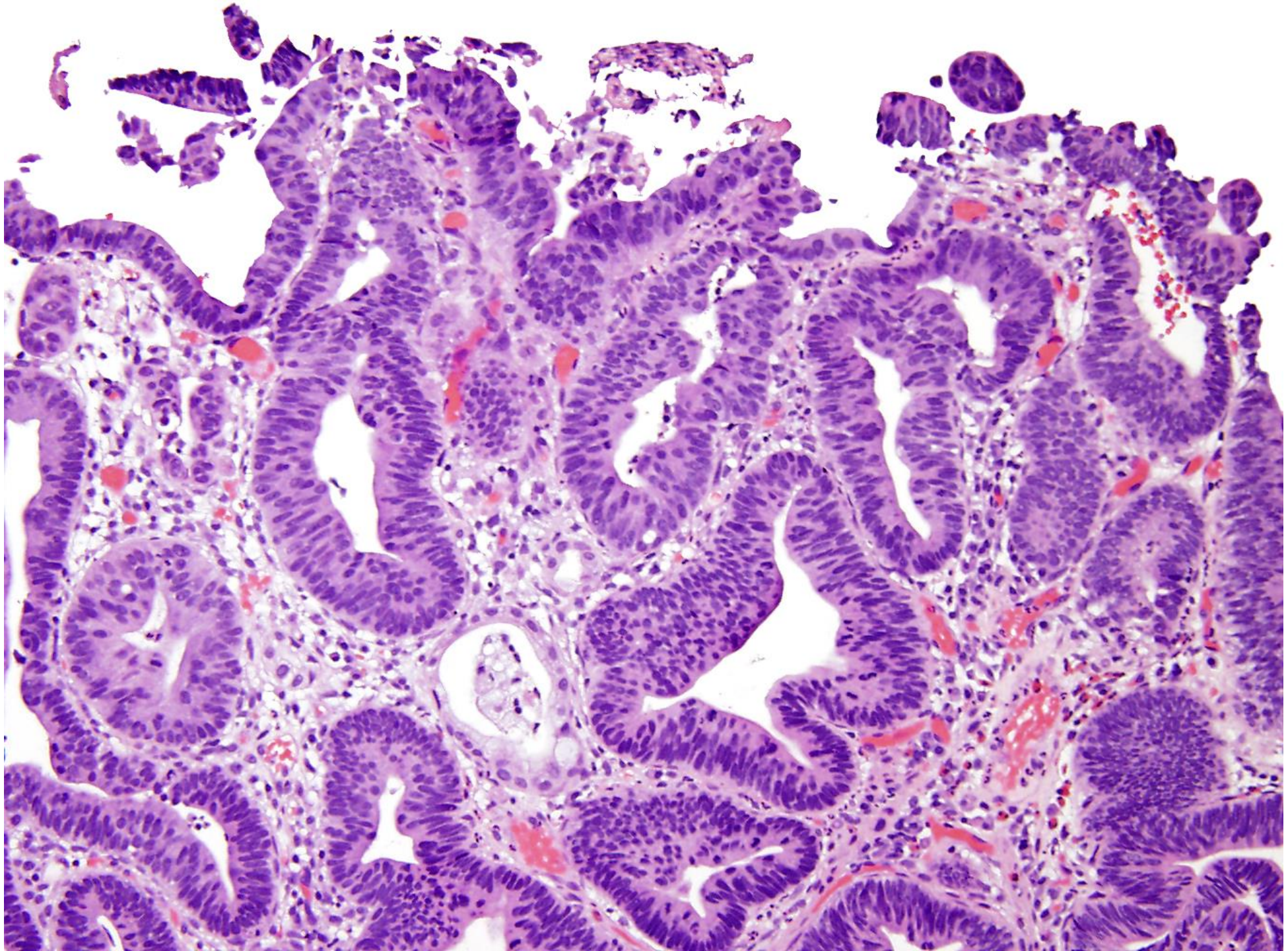
Choi WT, Yozu M, Miller GC, Shih AR, Kumarasinghe P, Misdraji J, Harpaz N, Lauwers GY. Nonconventional dysplasia in patients with inflammatory bowel disease and colorectal carcinoma: a multicenter clinicopathologic study. Mod Pathol. 2020 May;33(5):933-943. PMID: 31822800.

Colleagues also noted unusual serrated changes

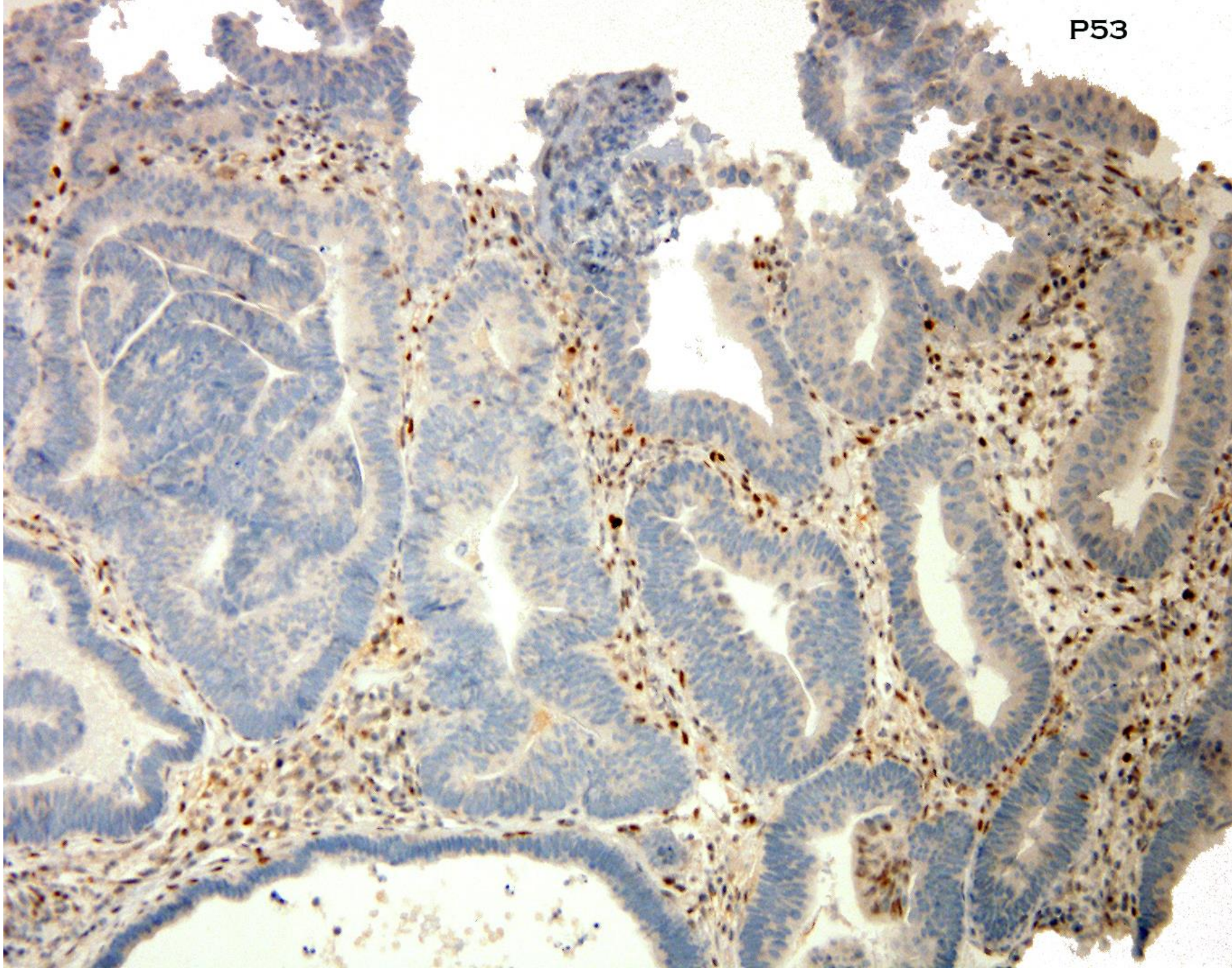
Kilgore SP, Sigel JE, Goldblum JR. Hyperplastic-like mucosal change in Crohn's disease: an unusual form of dysplasia? Mod Pathol. 2000 Jul;13(7):797-801. PubMed PMID: 10912940.

Parian A, Koh J, Limketkai BN, Eluri S, Rubin DT, Brant SR, Ha CY, Bayless TM, Giardiello F, Hart J, Montgomery E, Lazarev MG. Association between serrated epithelial changes and colorectal dysplasia in inflammatory bowel disease. Gastrointest Endosc. 2016 Jul;84(1):87-95. PMID: 26709112

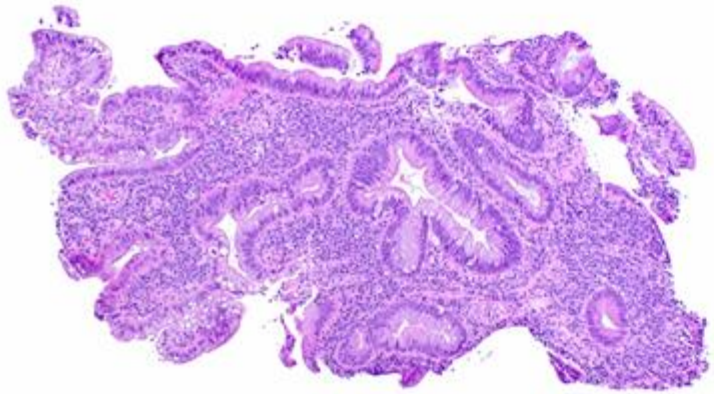
Colitis-associated high-grade dysplasia; the pattern is similar to that seen in colorectal adenoma

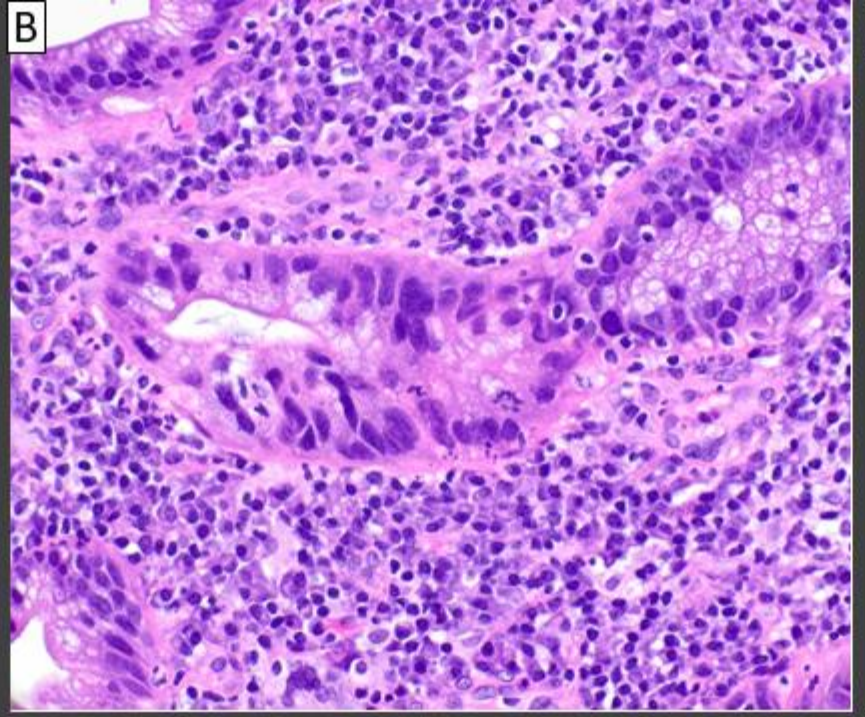


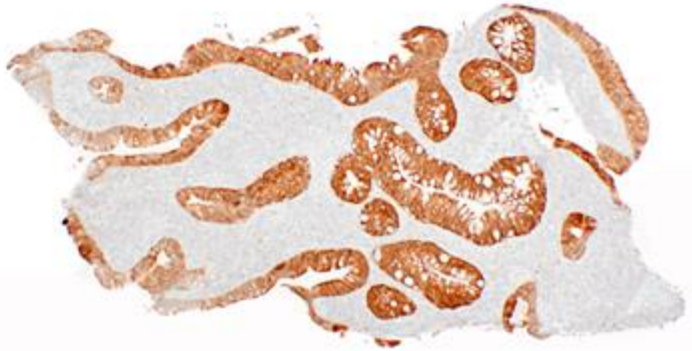
Colitis-associated high-grade dysplasia; this example shows a p53 “null” pattern

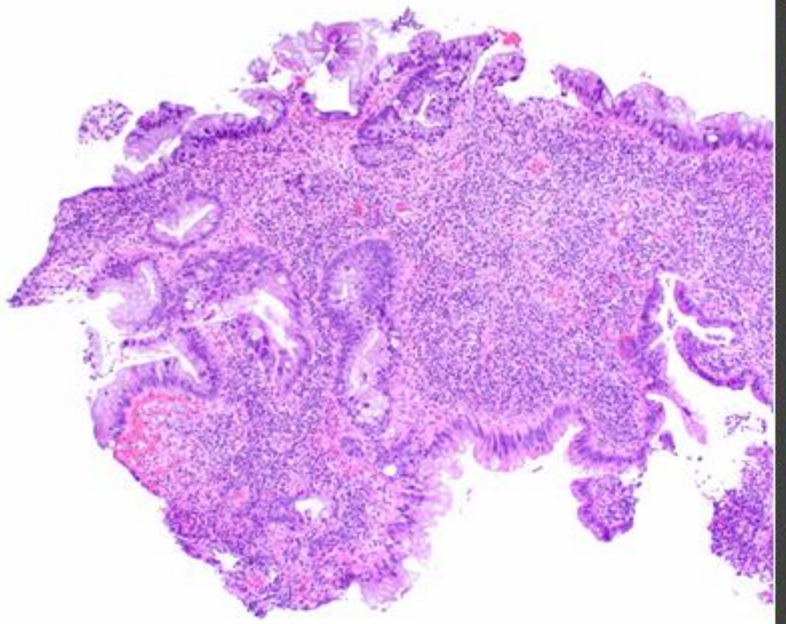


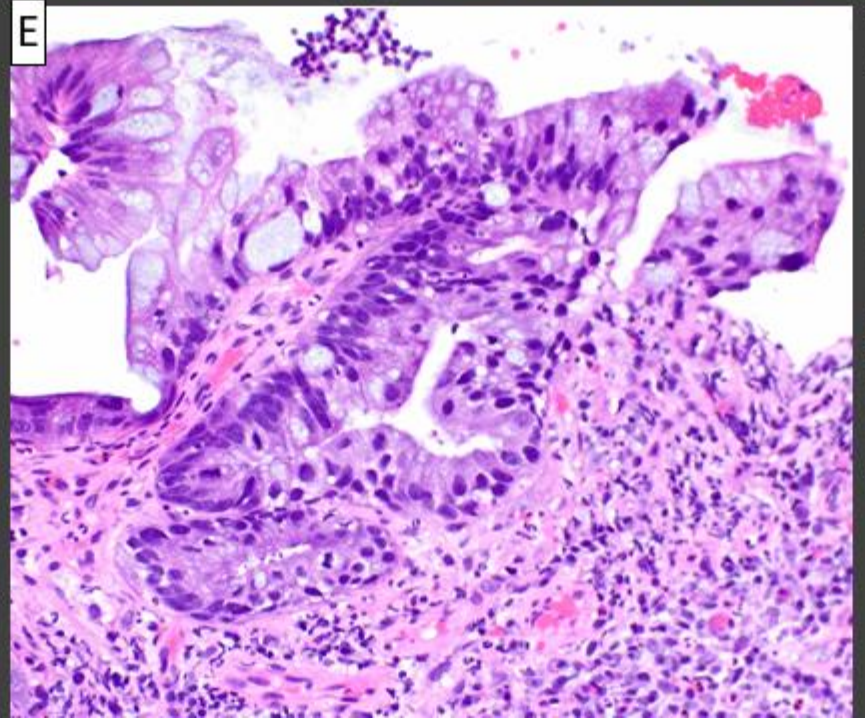
Other p53 staining patterns

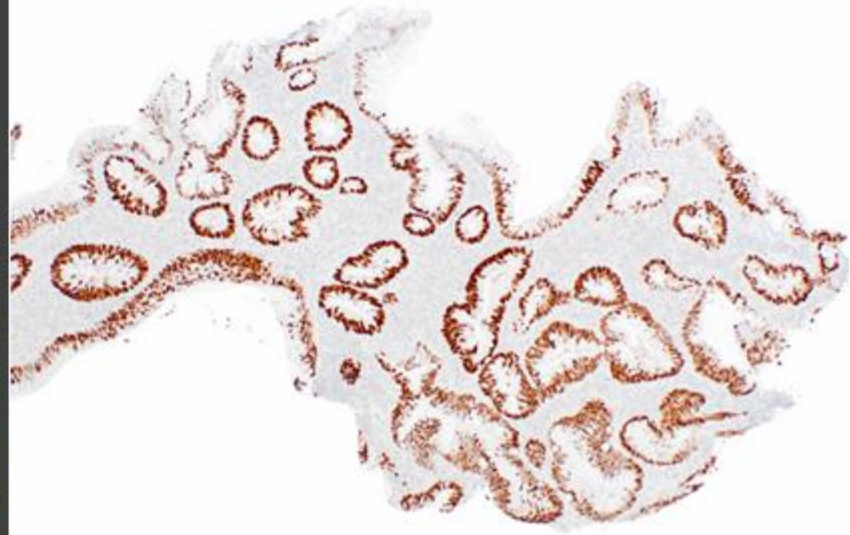












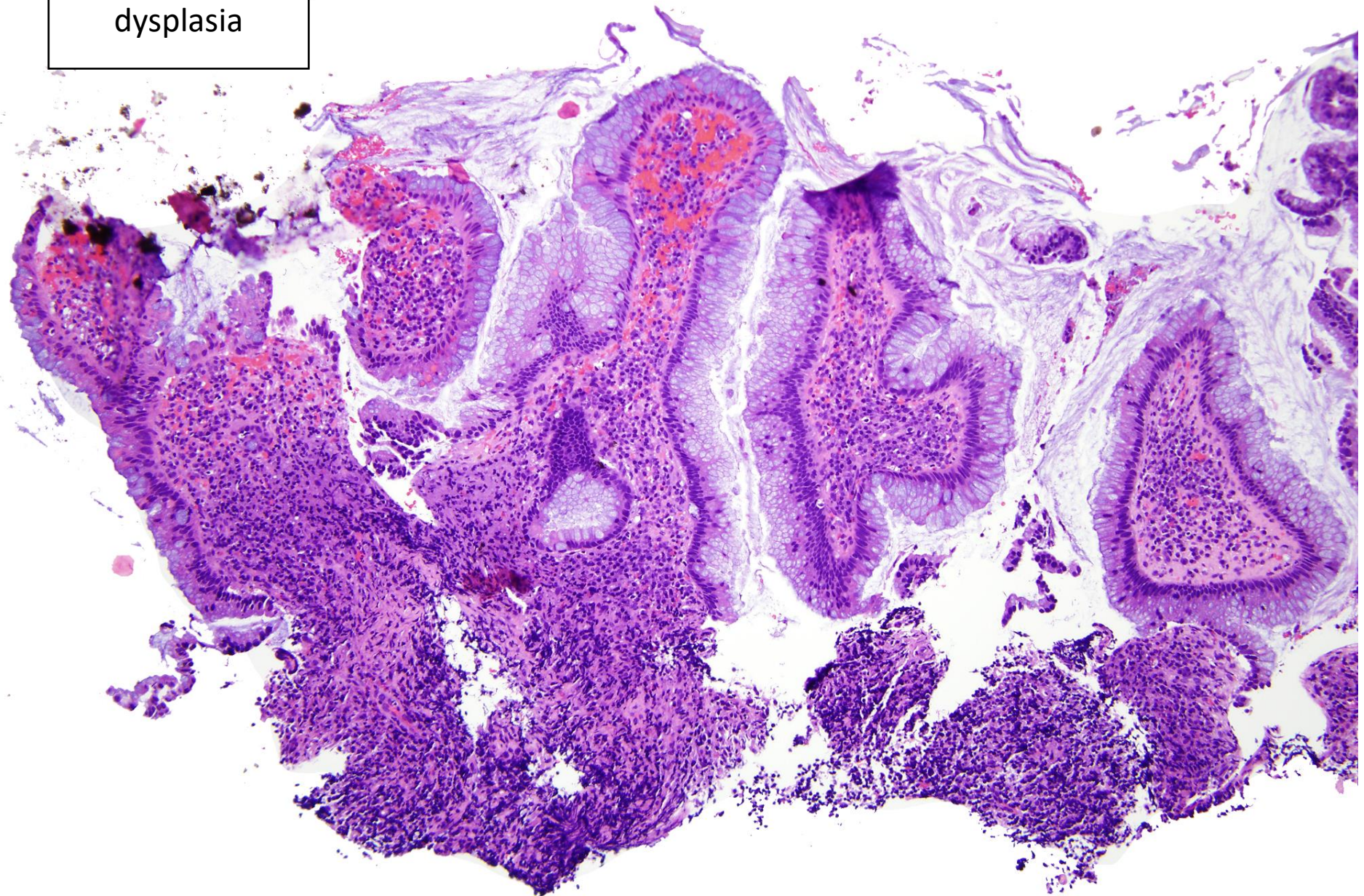
“Non-conventional dysplasia”

- **Hypermucinous**
- “Serrated lesions” – TSA-like, SSA-like, “NOS”*
- Dysplasia with increased Paneth cell differentiation
- Goblet cell deficient dysplasia

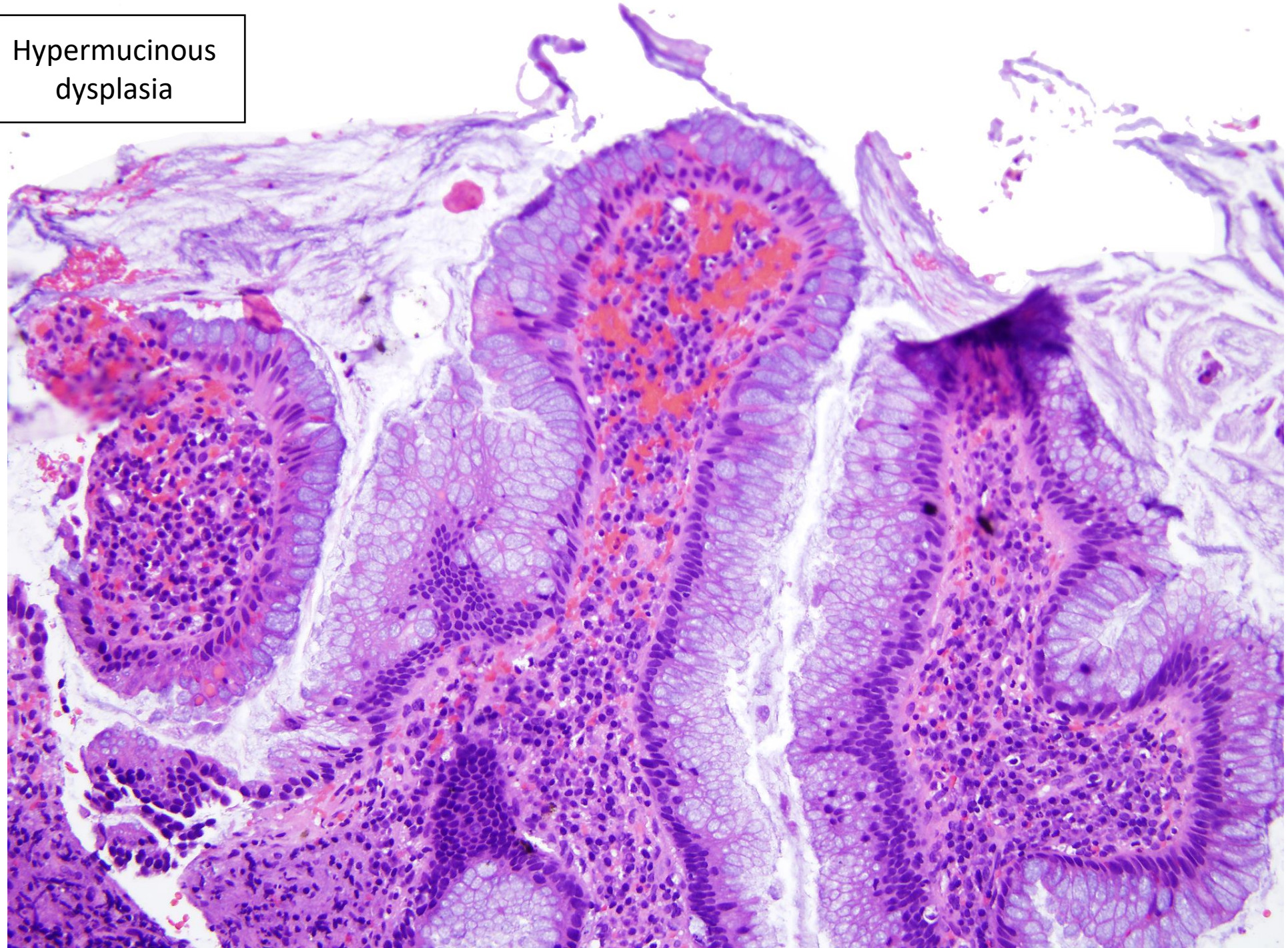
- * Said to have BRAF mutations – these are often simply serrated polyps that happen to arise in inflammatory bowel disease (in my opinion)

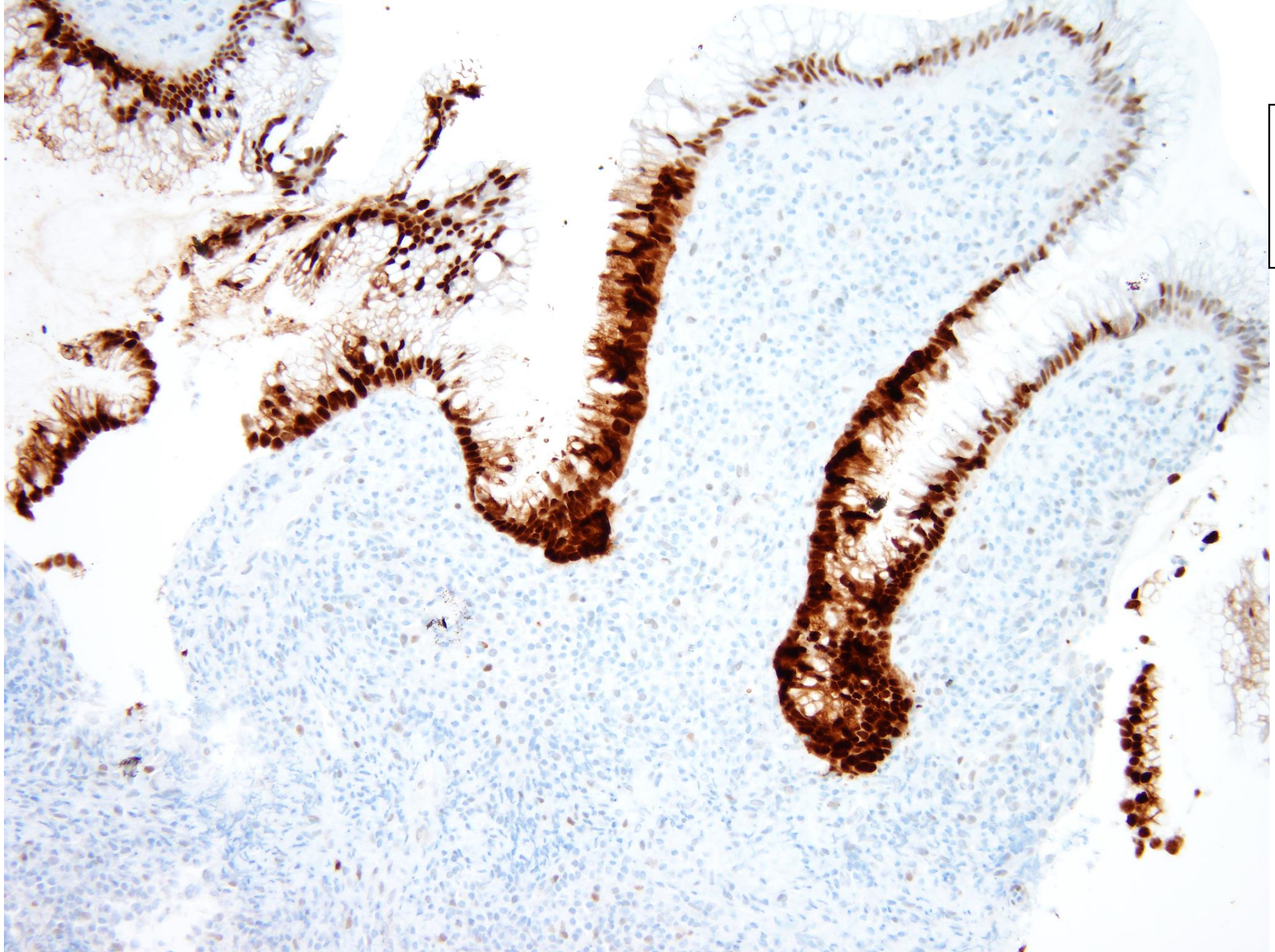
*Ko HM, Harpaz N, McBride RB, Cui M, Ye F, Zhang D, Ullman TA, Polydorides AD. Serrated colorectal polyps in inflammatory bowel disease. Mod Pathol. 2015 Dec;28(12):1584-93. PMID: 26403785.

Hypermucinous dysplasia



Hypermucinous dysplasia





P53, point mutation pattern

Serrated epithelial change (SEC)

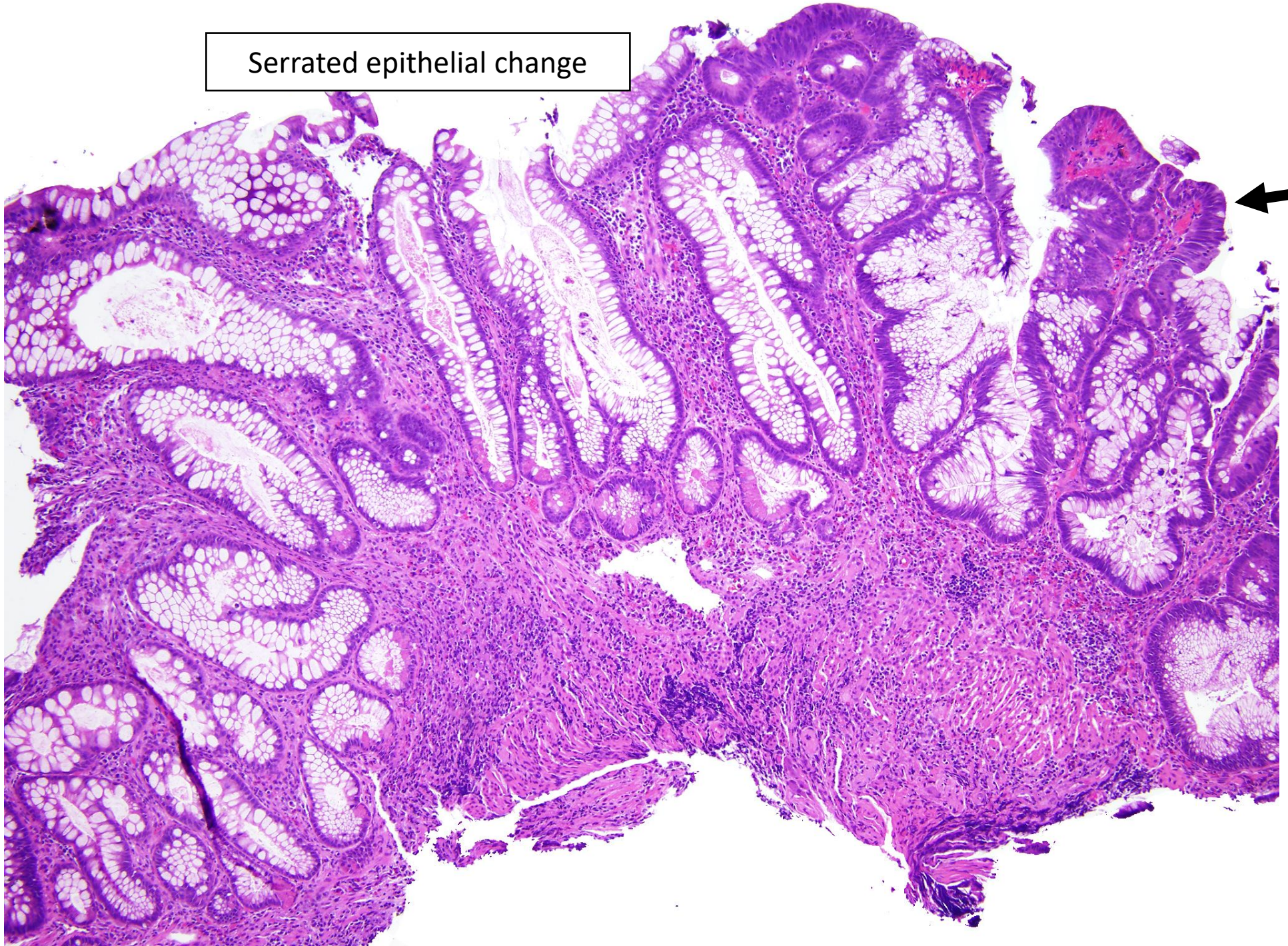
- Distorted architecture without dysplasia
- In contrast to those in hyperplastic polyps, the crypts in SEC lose orientation to the lumen and are no longer perpendicular to the muscularis mucosae nor do they necessarily reach the muscularis mucosae.
- Serrations of the epithelium and enlarged goblet cells both extend to the base of the crypts.
- SEC is goblet-cell rich, in contrast to most hyperplastic polyps, which typically display microvesicular cytoplasm.

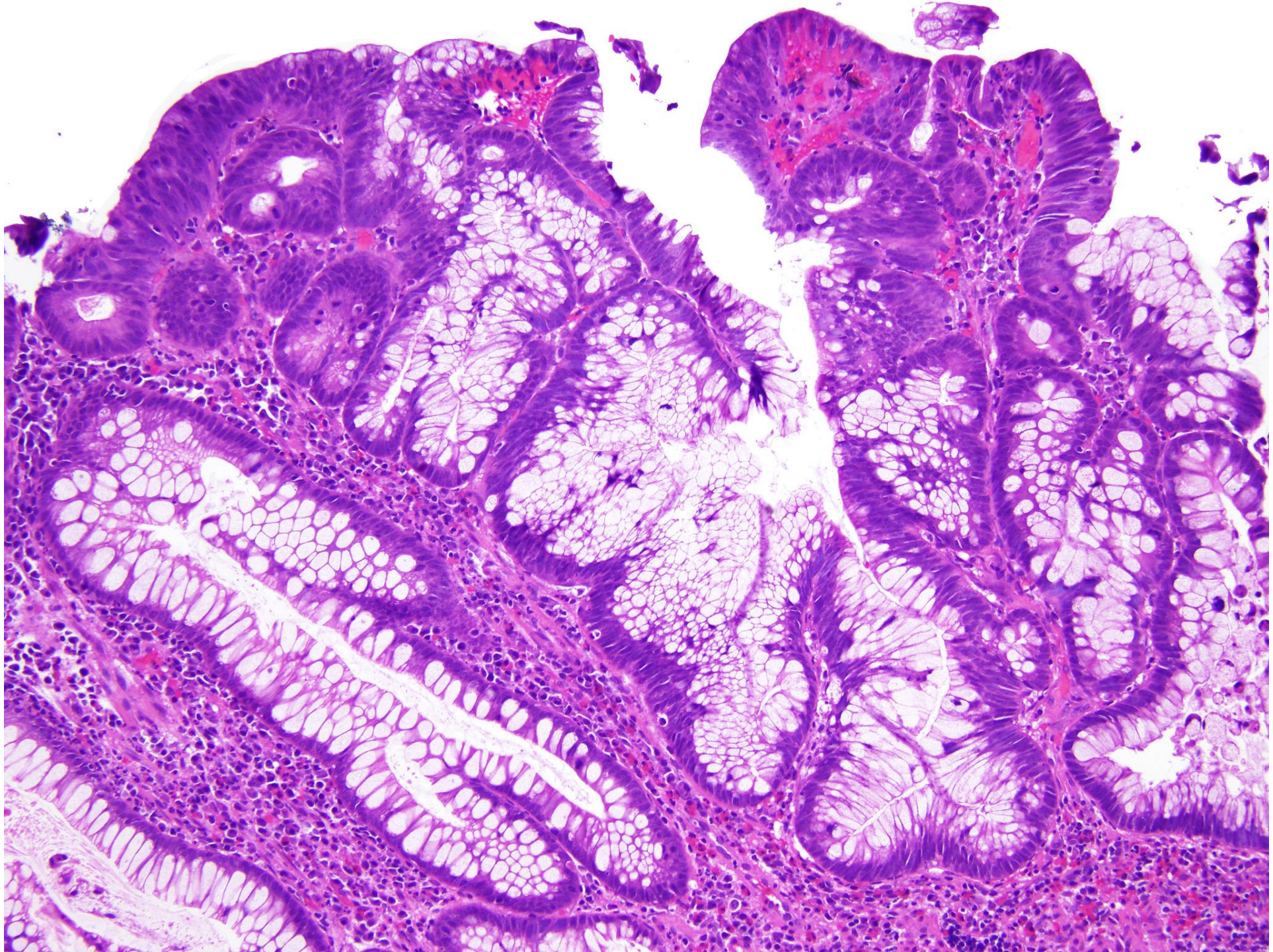
- Parian A, Koh J, Limketkai BN, Eluri S, Rubin DT, Brant SR, Ha CY, Bayless TM, Giardiello F, Hart J, Montgomery E, Lazarev MG. Association between serrated epithelial changes and colorectal dysplasia in inflammatory bowel disease. Gastrointest Endosc. 2016 Jul;84(1):87-95. PMID: 26709112
- Singhi AD, Waters KM, Makhoul EP, Parian A, Lazarev MG, Proksell SS, Dueker JM, Schwartz MB, Wald AI, Nikiforova MN, Montgomery EA. Targeted next-generation sequencing supports serrated epithelial change as an early precursor to inflammatory bowel disease-associated colorectal neoplasia. Hum Pathol. 2021 Jun;112:9-19. PMID: 33727167.
- Waters KM, Singhi AD, Montgomery EA. Exploring the spectrum of serrated epithelium encountered in inflammatory bowel disease. Hum Pathol. 2023 Feb;132:126-134. PMID: 35753410.
- Bahceci D, Alpert L, Storozuk T, Liao X, Yozu M, Westerhoff M, Kővári BP, Lauwers GY, Choi WT. Dysplasia Detected in Patients With Serrated Epithelial Change Is Frequently Associated With an Invisible or Flat Endoscopic Appearance, Nonconventional Dysplastic Features, and Advanced Neoplasia. Am J Surg Pathol. 2024 Oct 1;48(10):1326-1334. PMID: 38907614.

Serrated epithelial change (SEC)

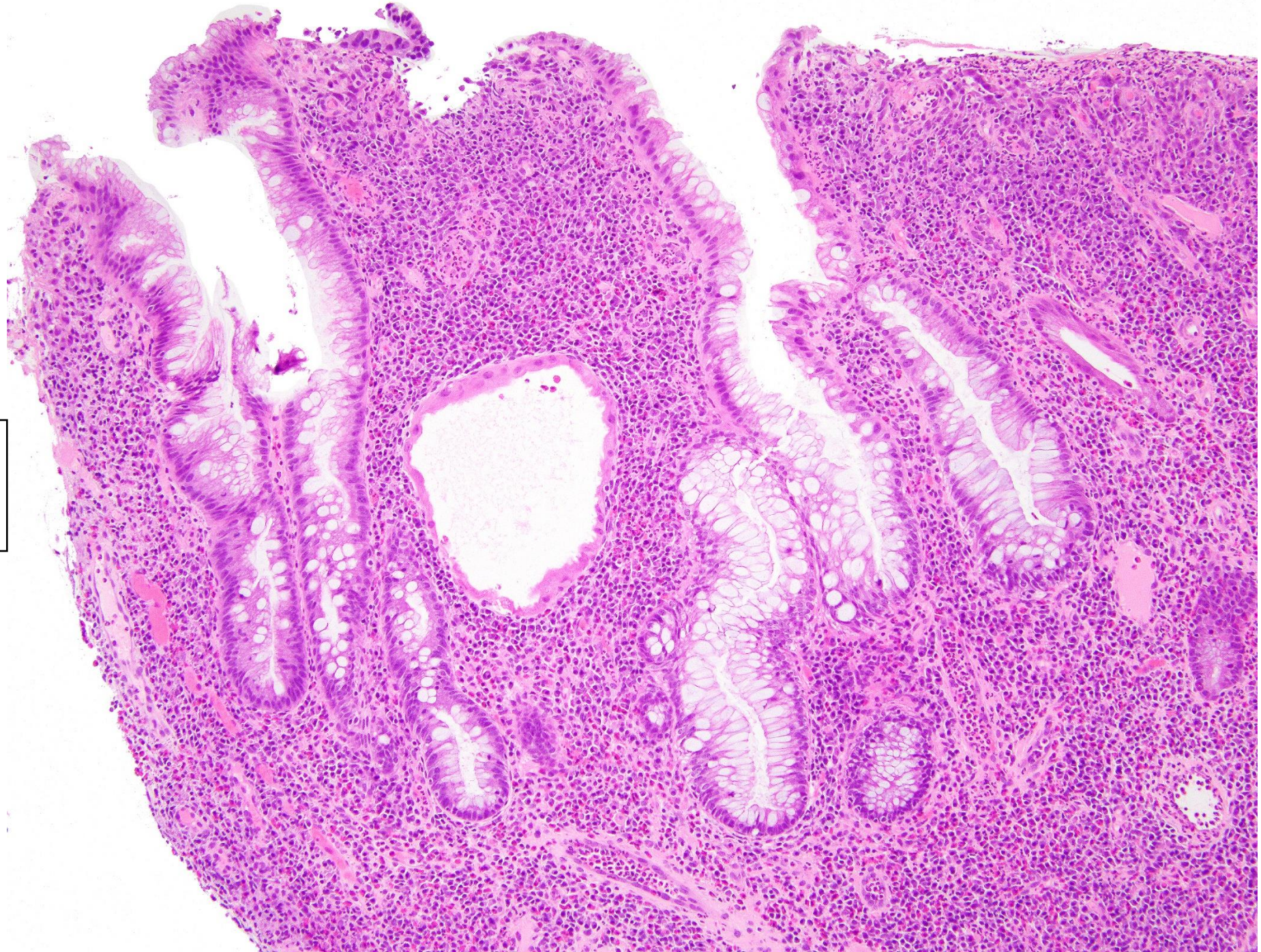
- *TP53* mutations are found in 50% of SEC cases (without point mutation pattern of staining of immunohistochemistry)
- In cases with associated dysplasia, same mutations as in the dysplasia/carcinoma!
- It's probably the "field effect" noted that scientists who don't interpret slides describe *

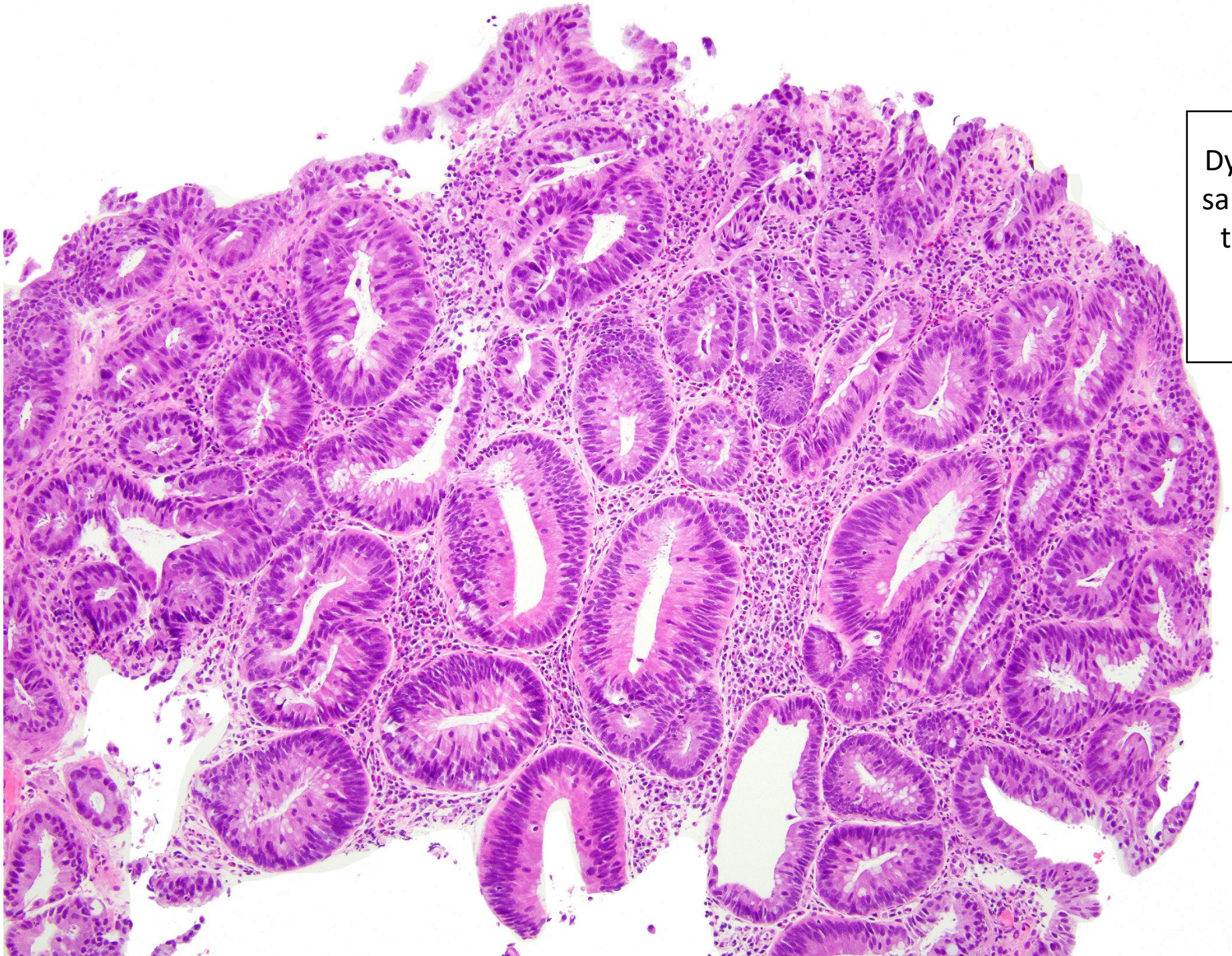
*Galandiuk S, Rodriguez-Justo M, Jeffery R, Nicholson AM, Cheng Y, Oukrif D, Elia G, Leedham SJ, McDonald SA, Wright NA, Graham TA. Field cancerization in the intestinal epithelium of patients with Crohn's ileocolitis. Gastroenterology. 2012 Apr;142(4):855-864.e8. PMID: 22178590; PMCID: PMC4446968.





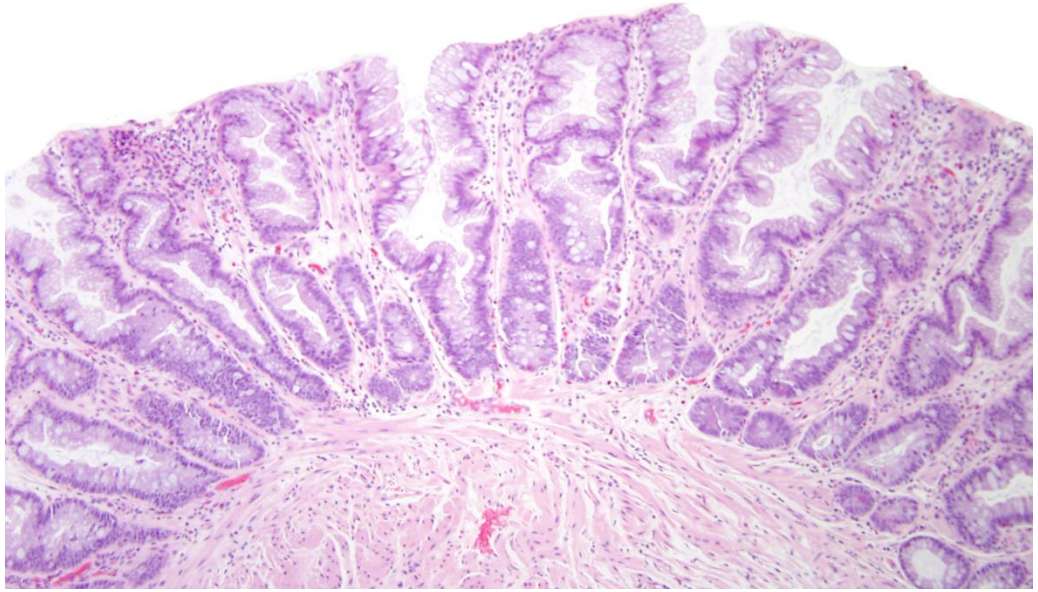
Serrated epithelial change



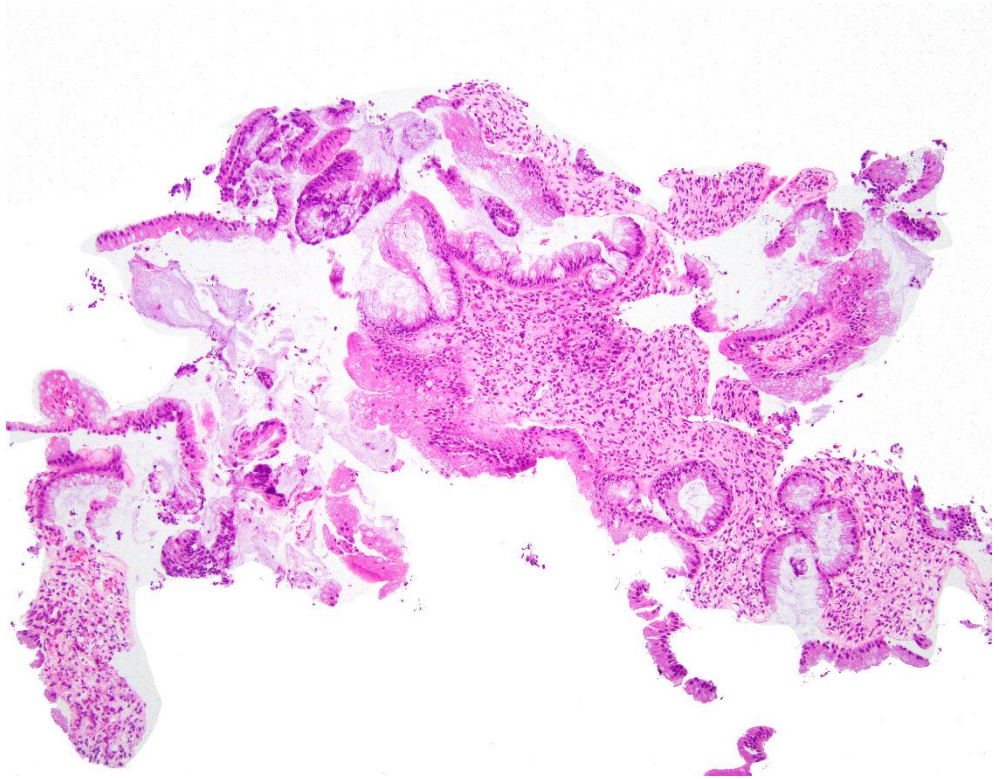


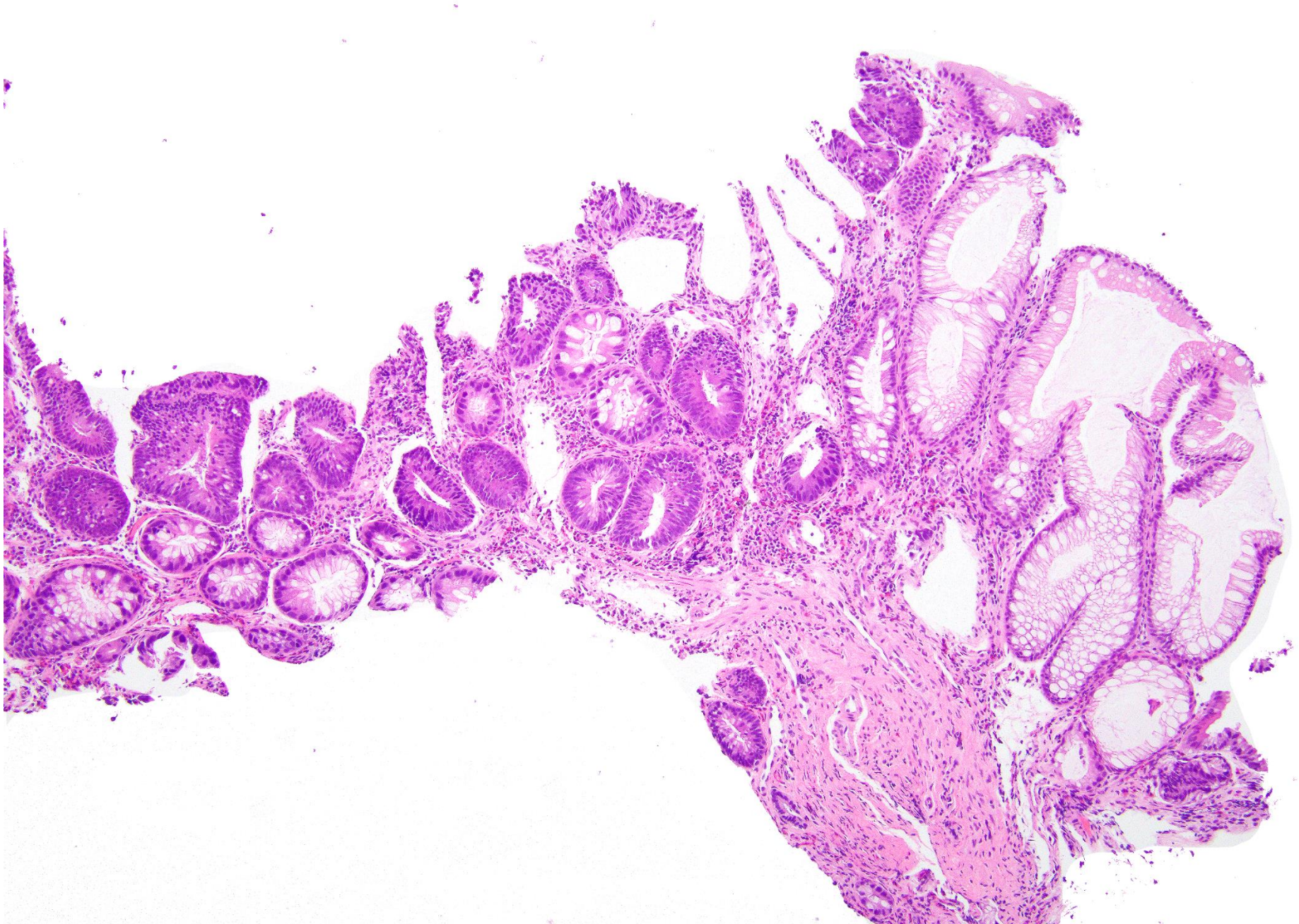
Dysplasia from same biopsy as the serrated epithelial change

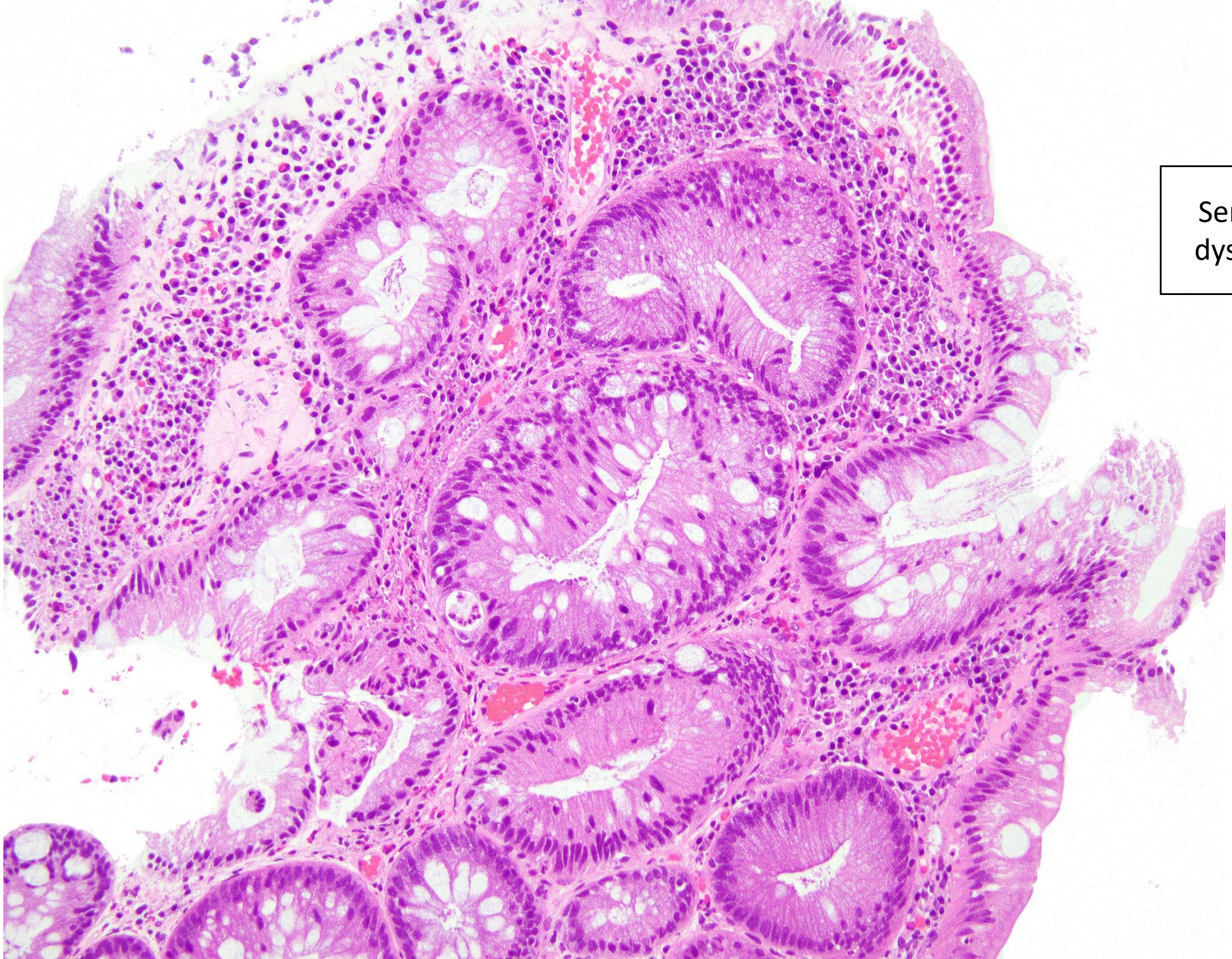
Hyperplastic polyp or sessile serrated adenoma has basically normal architecture with crypt bases landing on muscularis mucosae



Serrated epithelial change has serrated crypts but the architecture is a hot mess

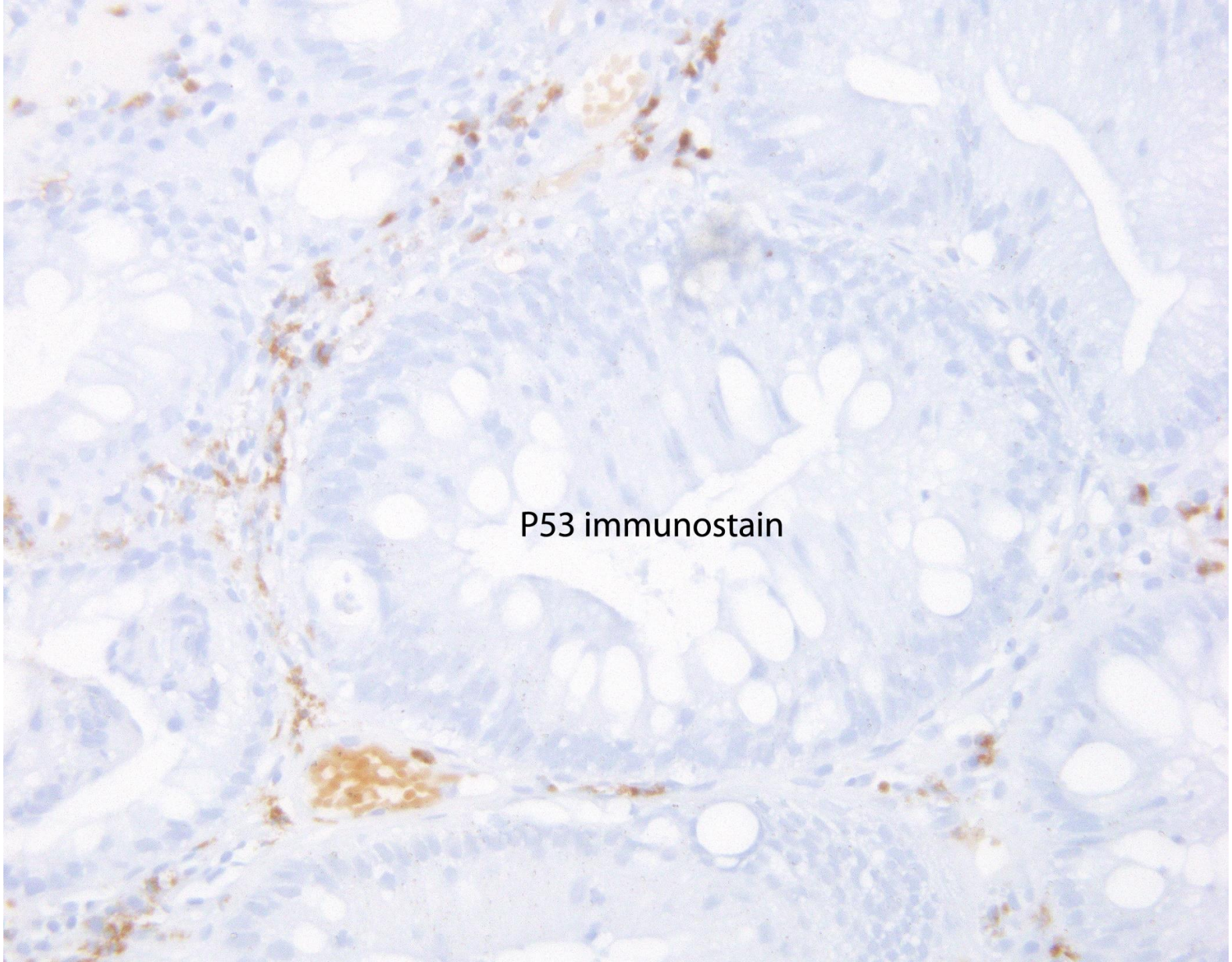


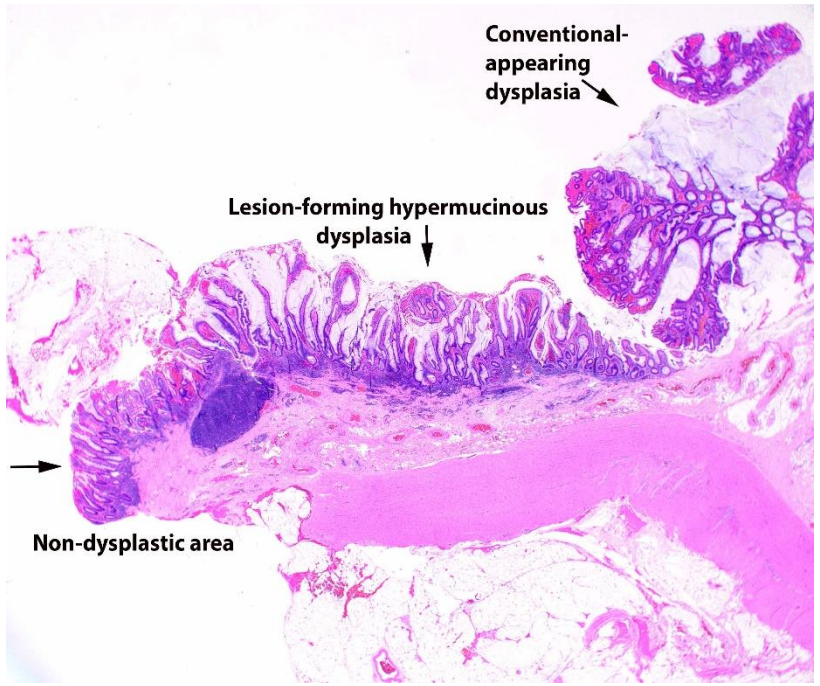


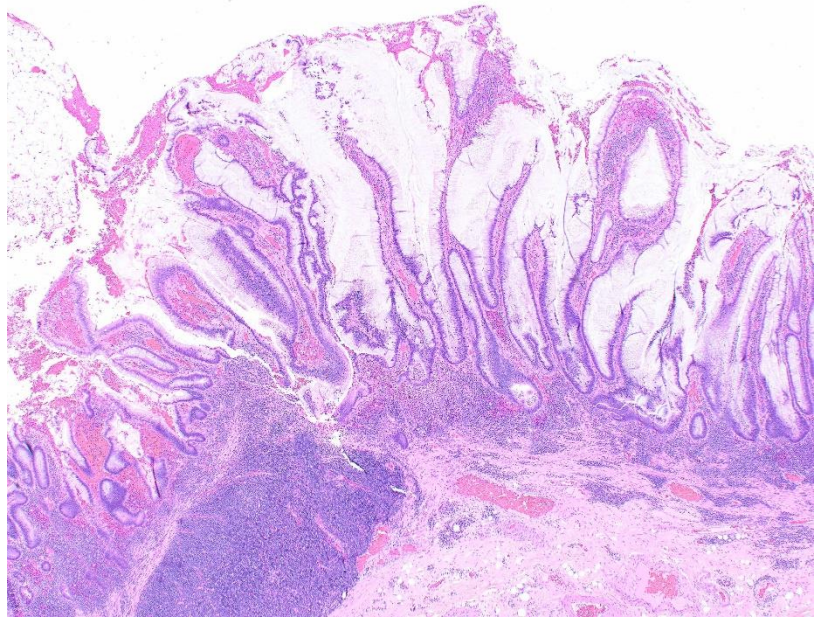


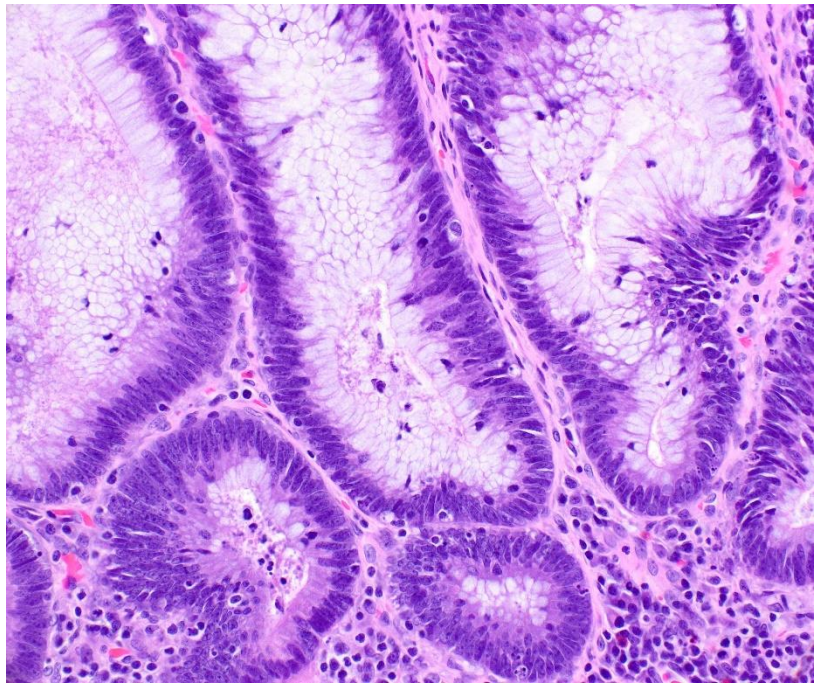
Serrated dysplasia

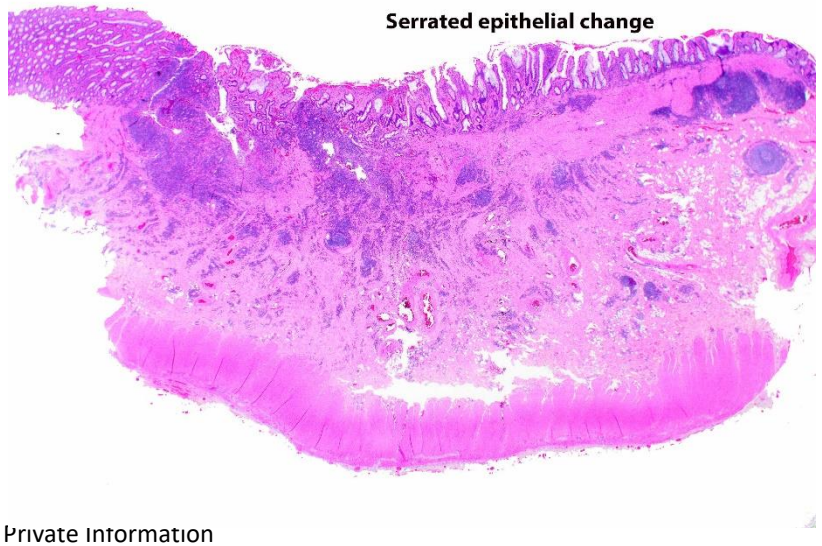
Null pattern p53

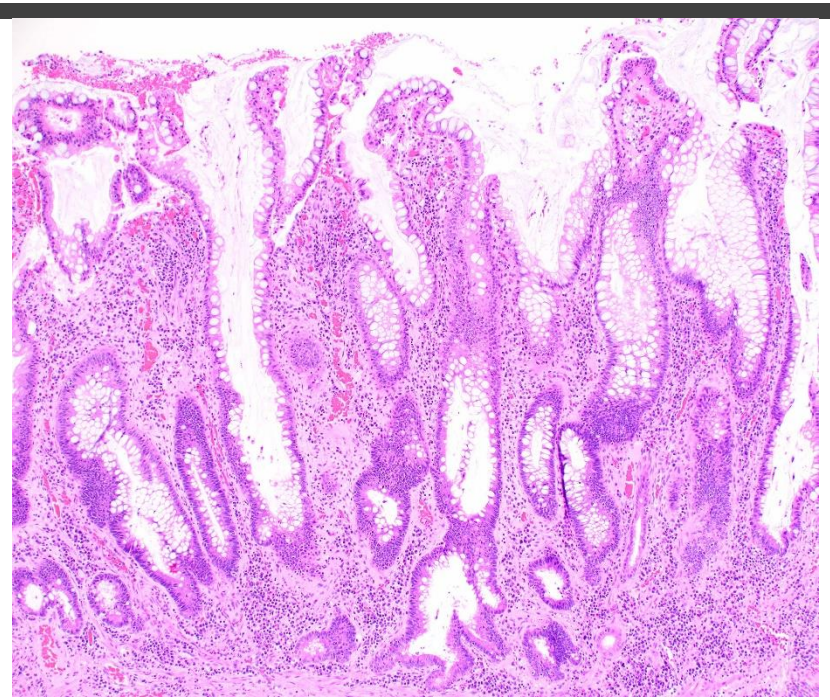


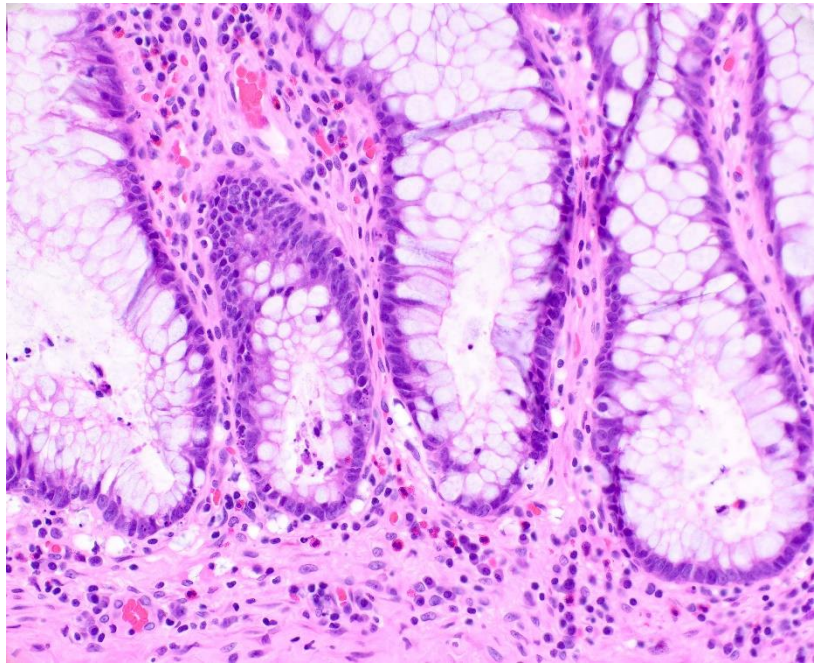












Treatment has changed over time

- Laine L, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R; SCENIC Guideline Development Panel. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastroenterology. 2015 Mar;148(3):639-651.e28. PubMed PMID: 25702852.

Anus

- We are all sick of squamous HPV-associated lesions. It's the LAST thing some of us want to hear about - Lower Anogenital Squamous Terminology (LAST) Standardization Project for human papilloma virus (HPV)-associated lesions
- LAST was published in 2012 – time to move along

Darragh TM, Colgan TJ, Cox JT, et al. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med. 2012;136:1266–1297.

Soooooooo

- Let’s try some new and cool things:

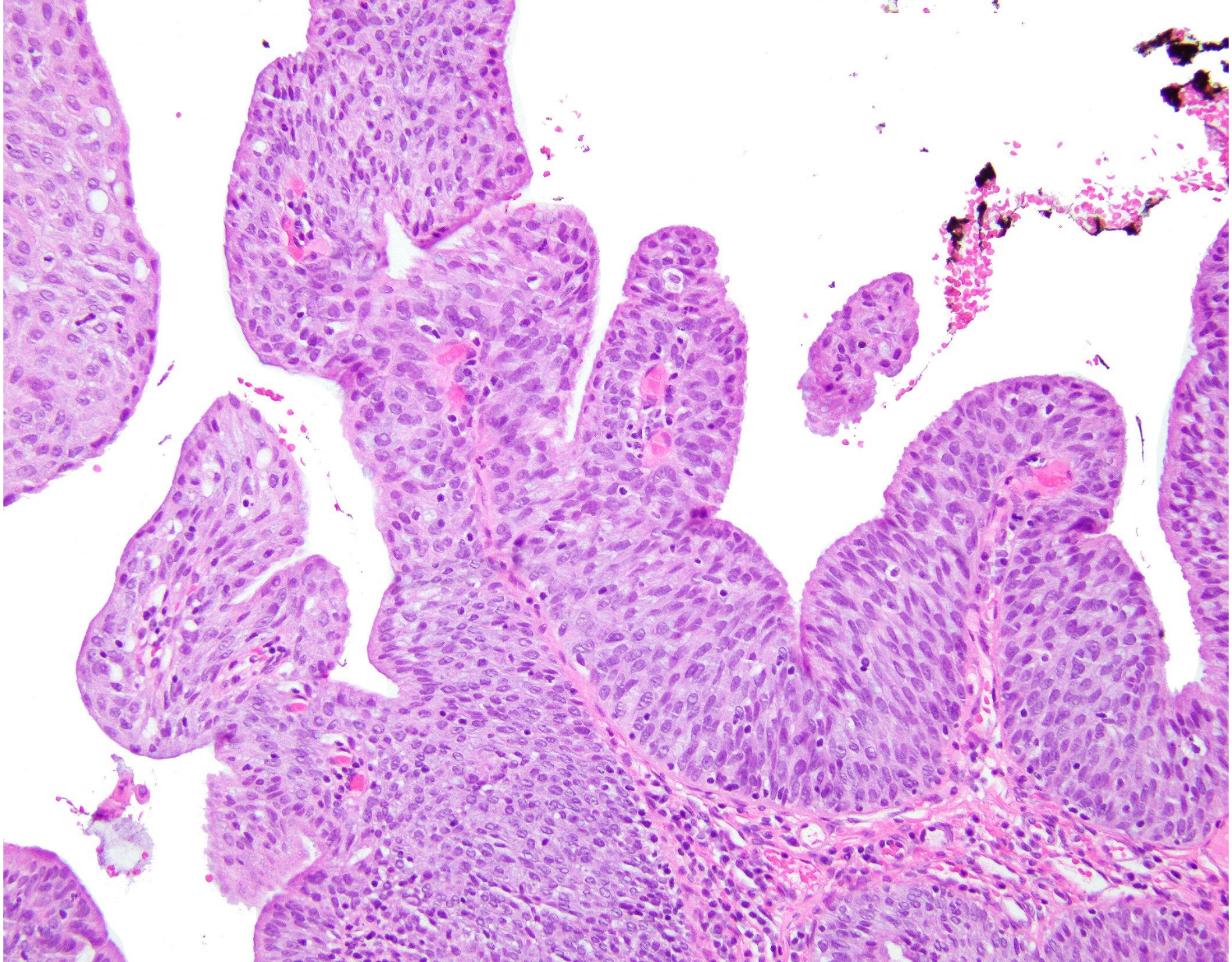
An odd bird

- Papillary immature squamous metaplasia
- Looks like HSIL on a peek; biologically less horrible than LSIL
- But no mitotic activity; negative p16

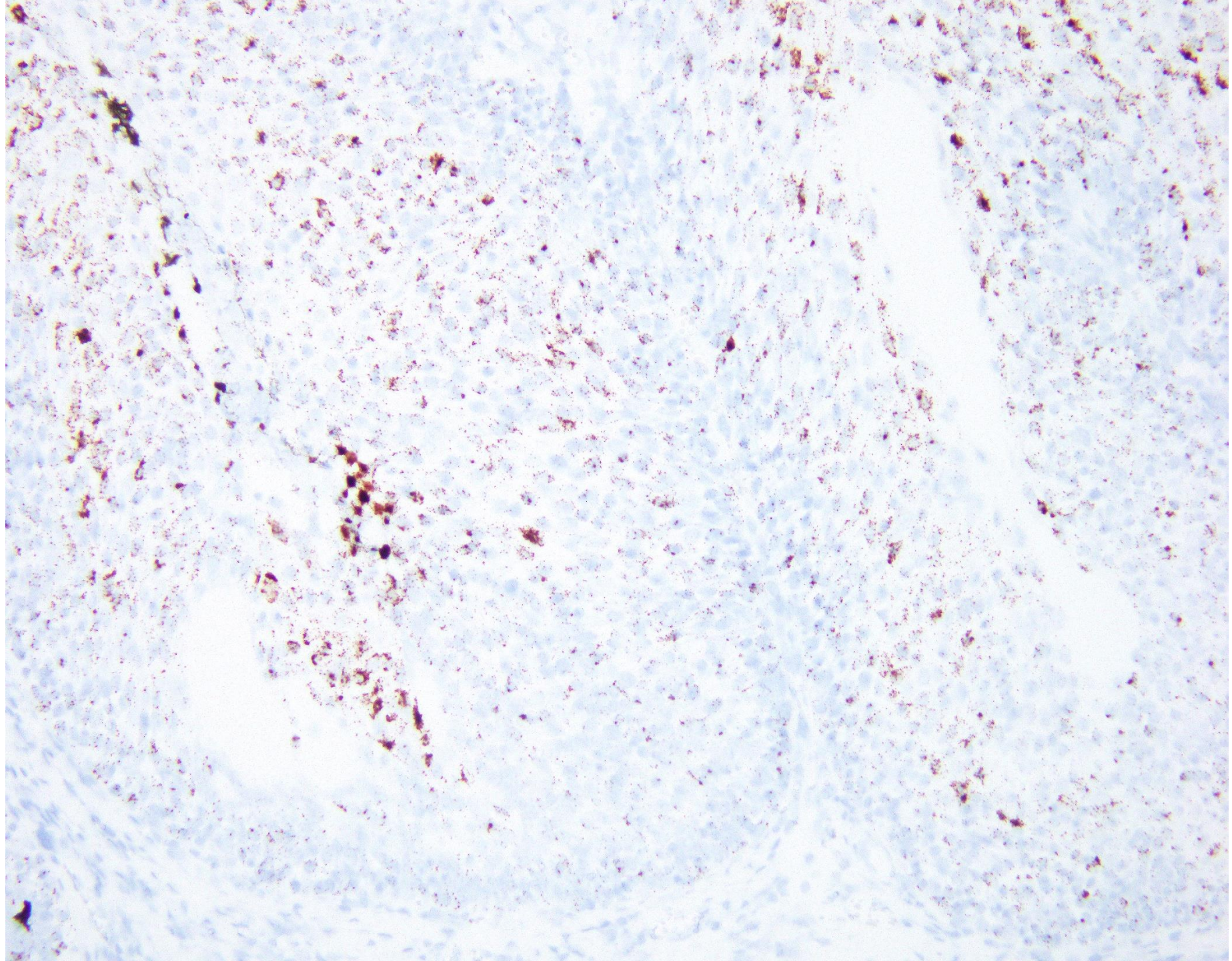
- Lifrange F, Gomez Galdon M, Van Gossum M, Pau L, Verset L, Demetter P. Papillary immature squamous metaplasia of the anal canal: a rare but probably underdiagnosed entity. *Histopathology.* 2021.

- Roberts JM, Cornall AM, Ekman D, et al. Papillary Immature Metaplasia of the Anal Canal: A Low-grade Lesion That Can Mimic a High-grade Lesion. *Am J Surg Pathol.* 2016;40(3):348-353.

Papillary immature squamous metaplasia in transitional mucosa



HPV
6/11



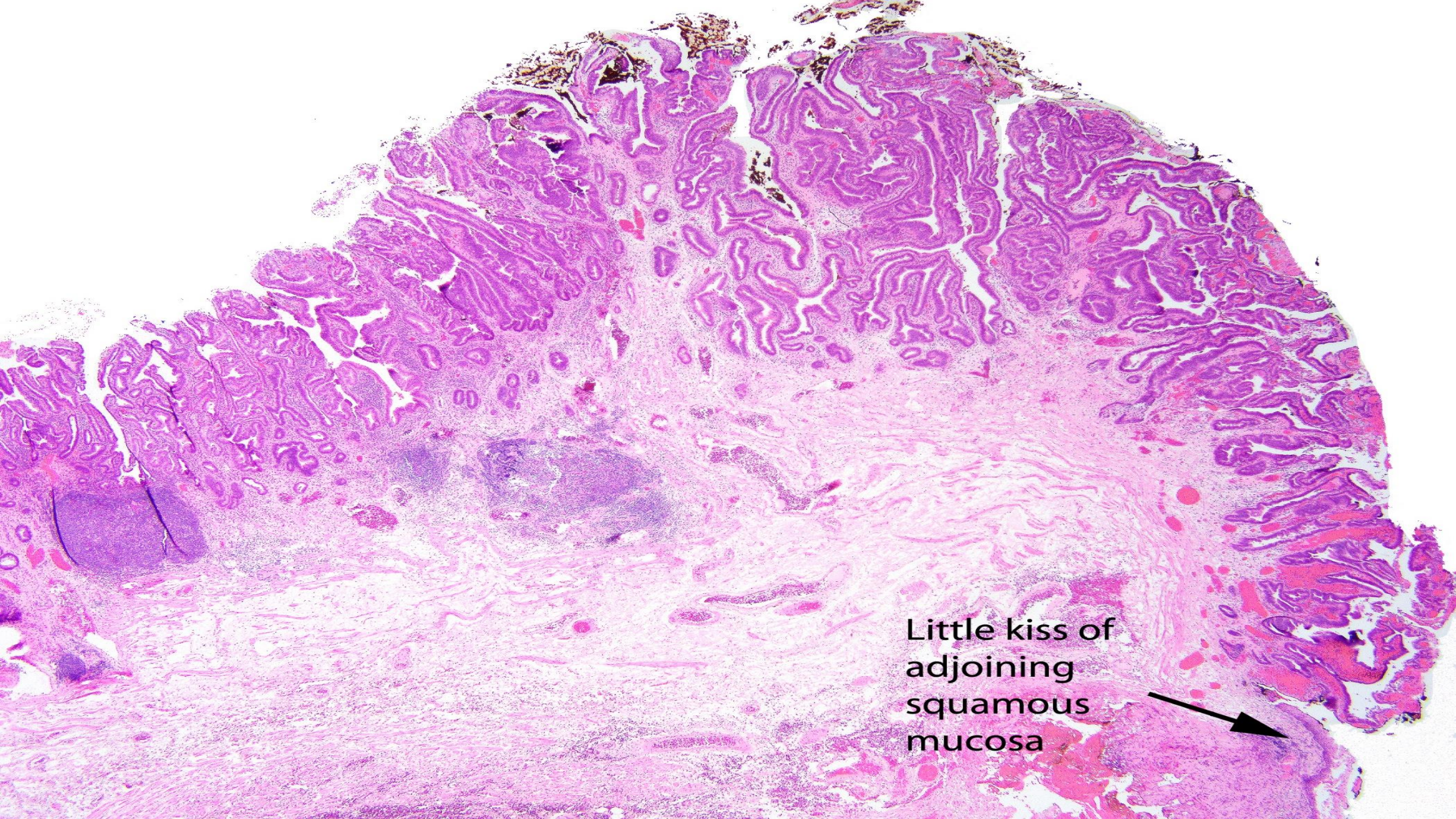
Something in the anus analogous to cervical lesions

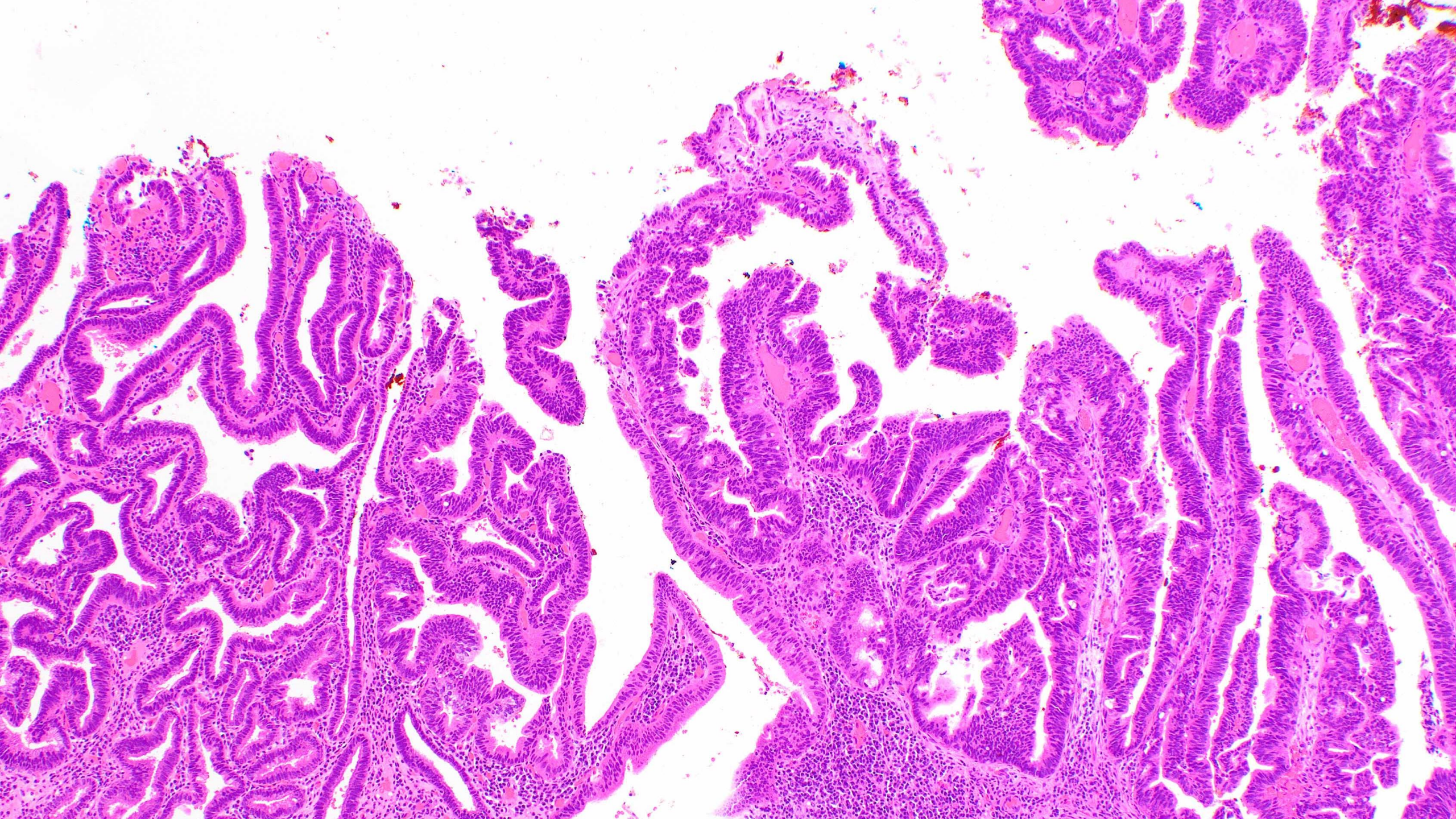
- Voltaggio L, McCluggage WG, Iding JS, Martin B, Longacre TA, Ronnett BM. A novel group of HPV-related adenocarcinomas of the lower anogenital tract (vagina, vulva, and anorectum) in women and men resembling HPV-related endocervical adenocarcinomas. Mod Pathol. 2020 May;33(5):944-952. PMID: 31857682.

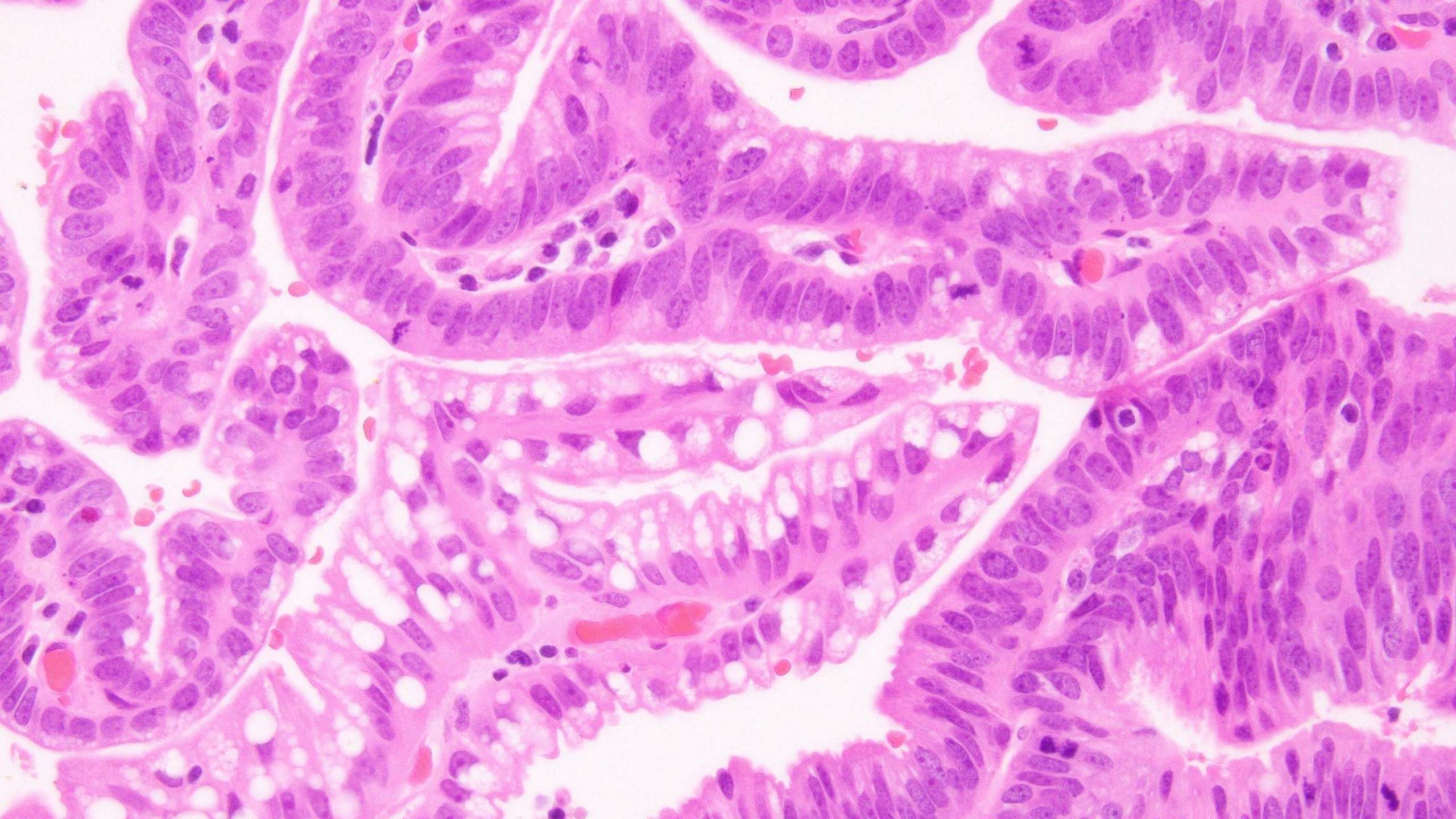
Lysandra Voltaggio

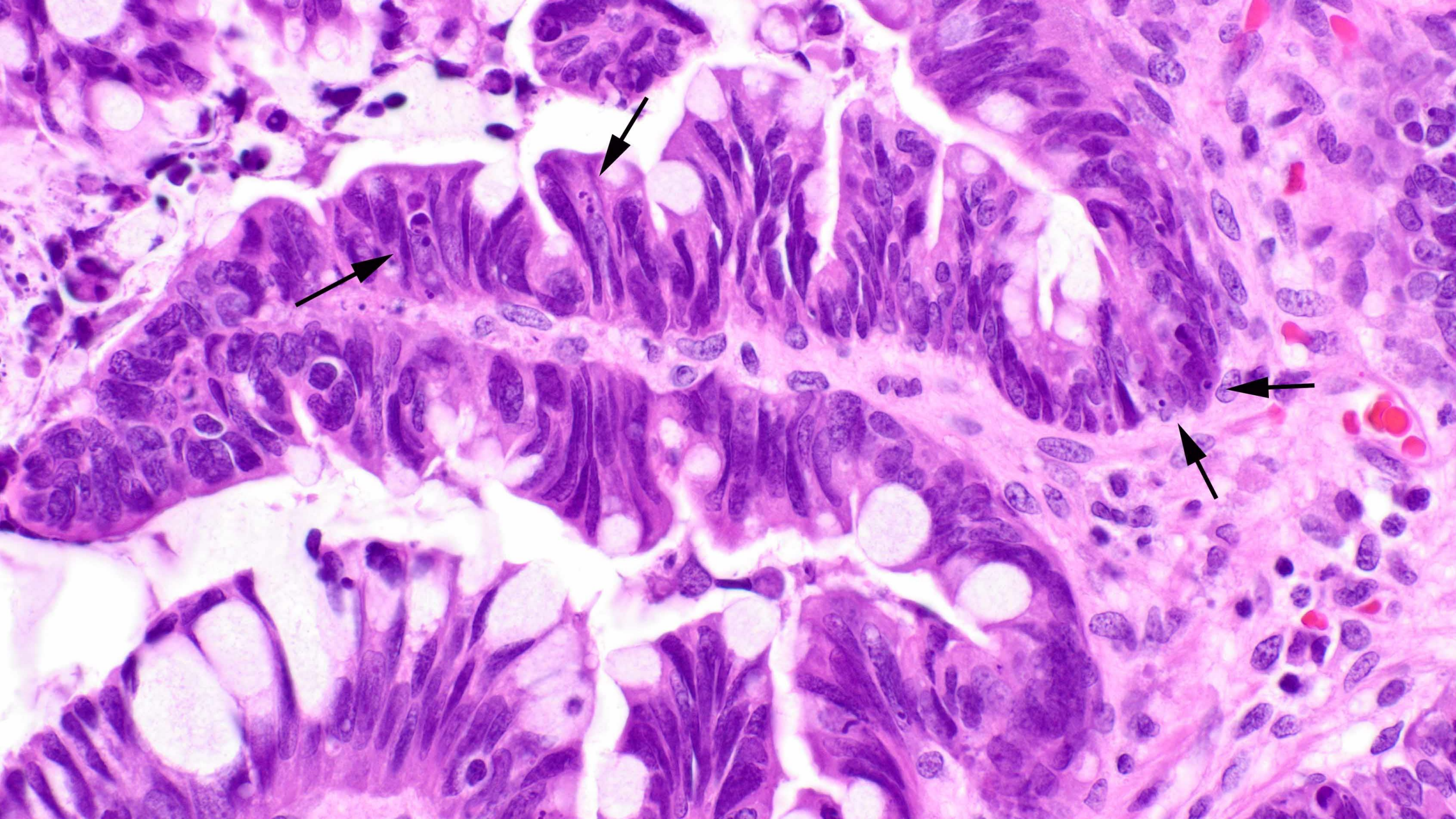
Voltaggio L, McCluggage WG, Iding JS, Martin B, Longacre TA, Ronnett BM. A novel group of HPV-related adenocarcinomas of the lower anogenital tract (vagina, vulva, and anorectum) in women and men resembling HPV-related endocervical adenocarcinomas. Mod Pathol. 2020 May;33(5):944-952. PMID: 31857682.

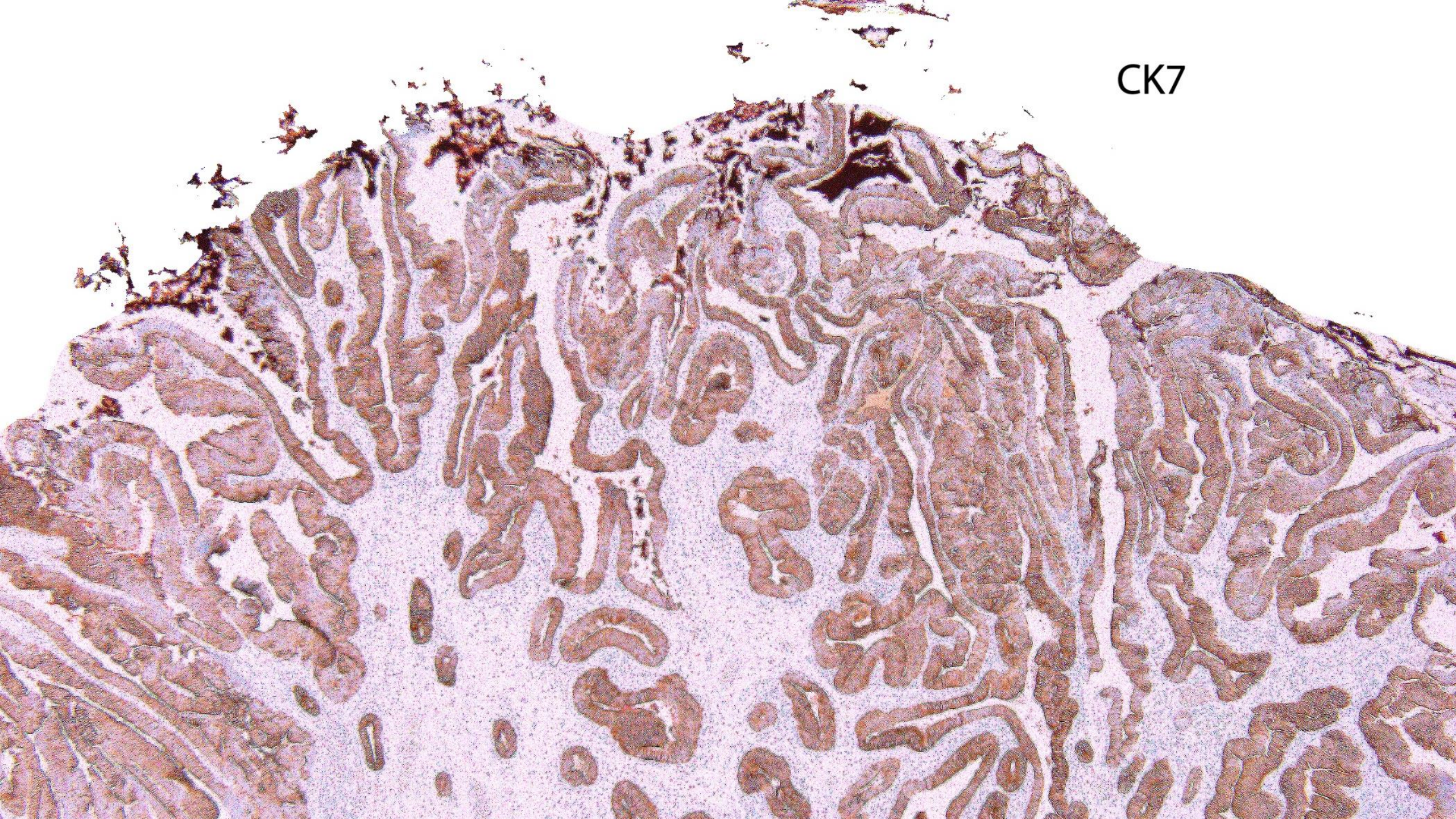
Brigitte M. Ronnett

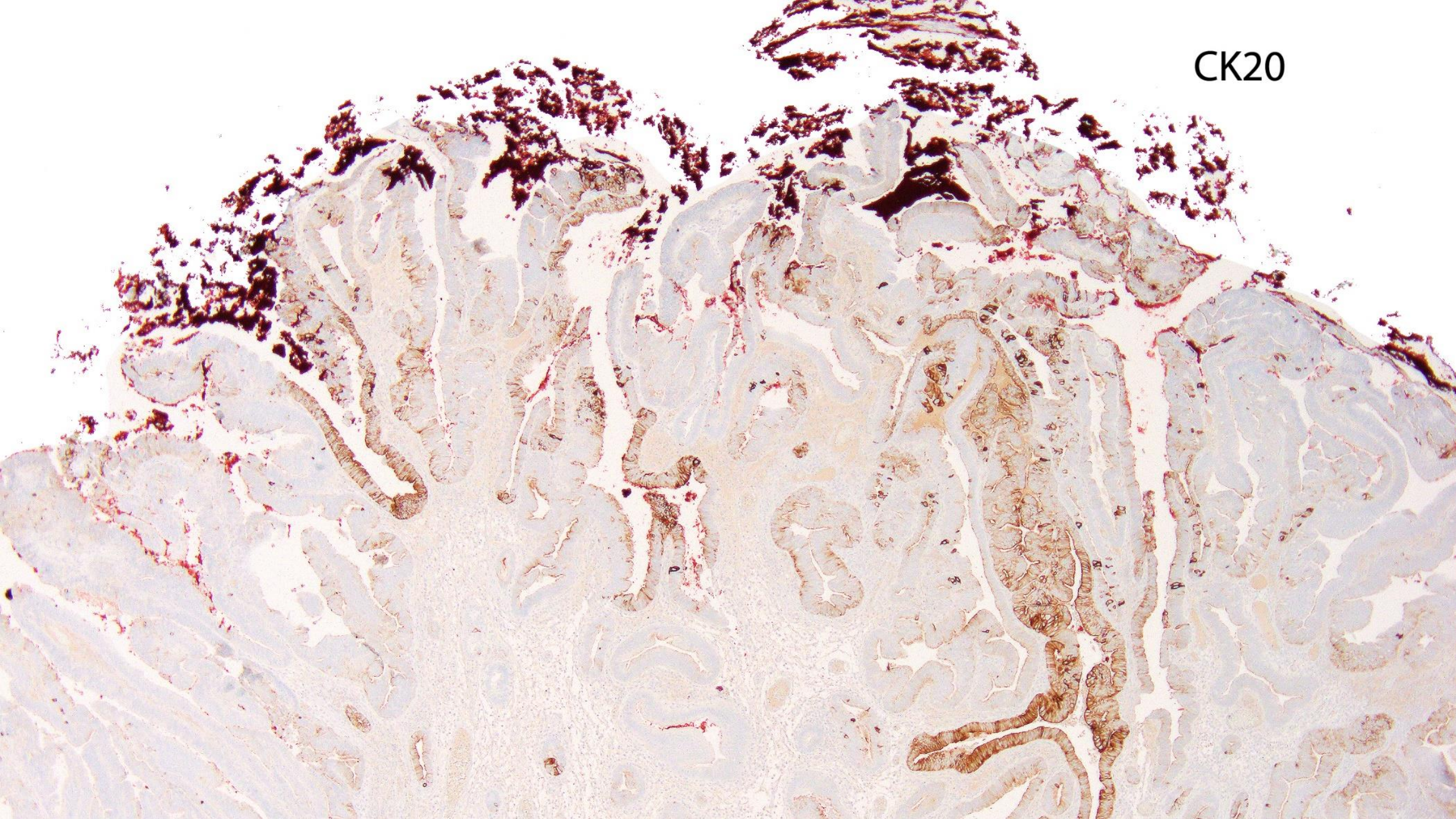

Little kiss of
adjoining
squamous
mucosa

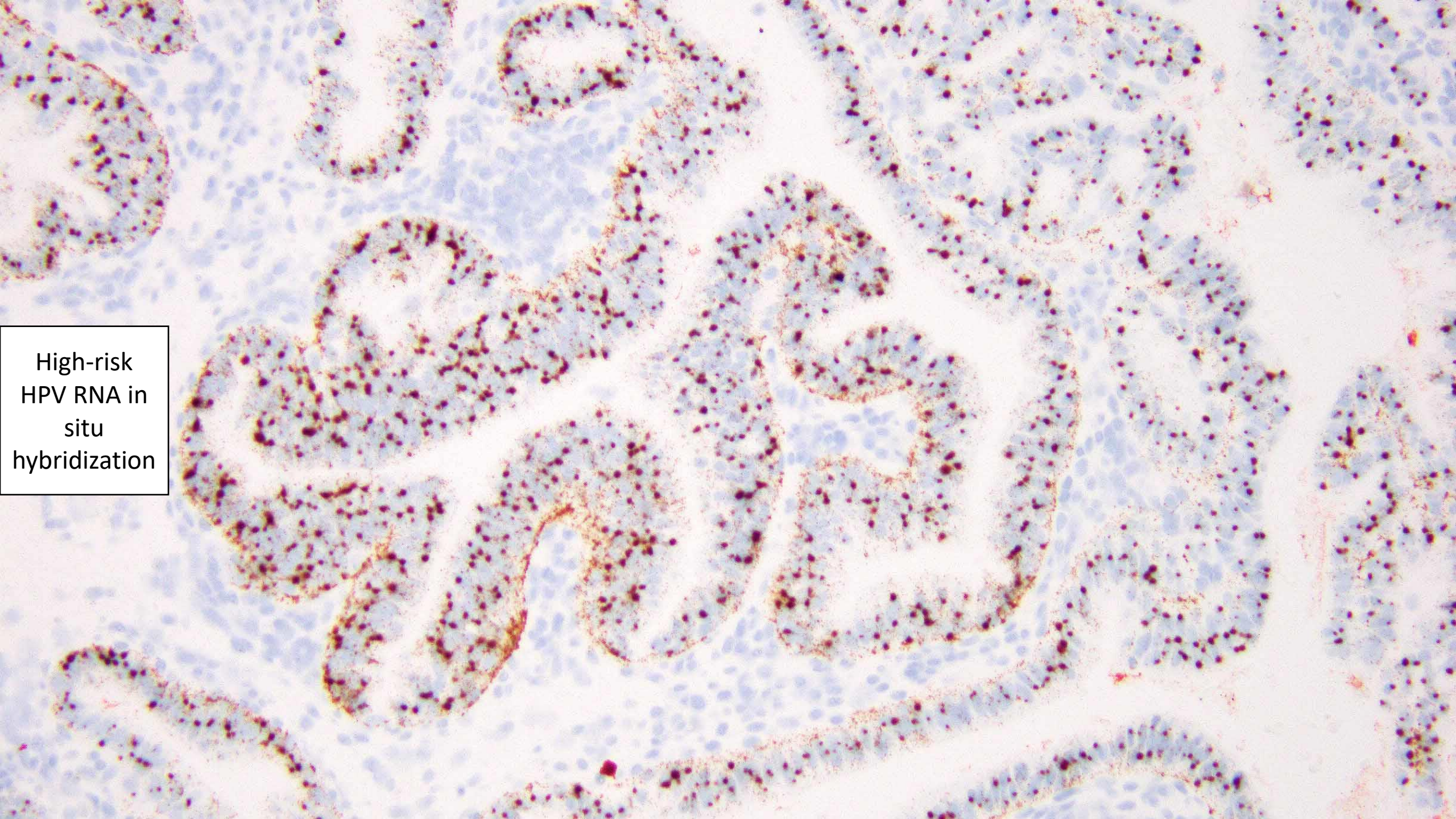




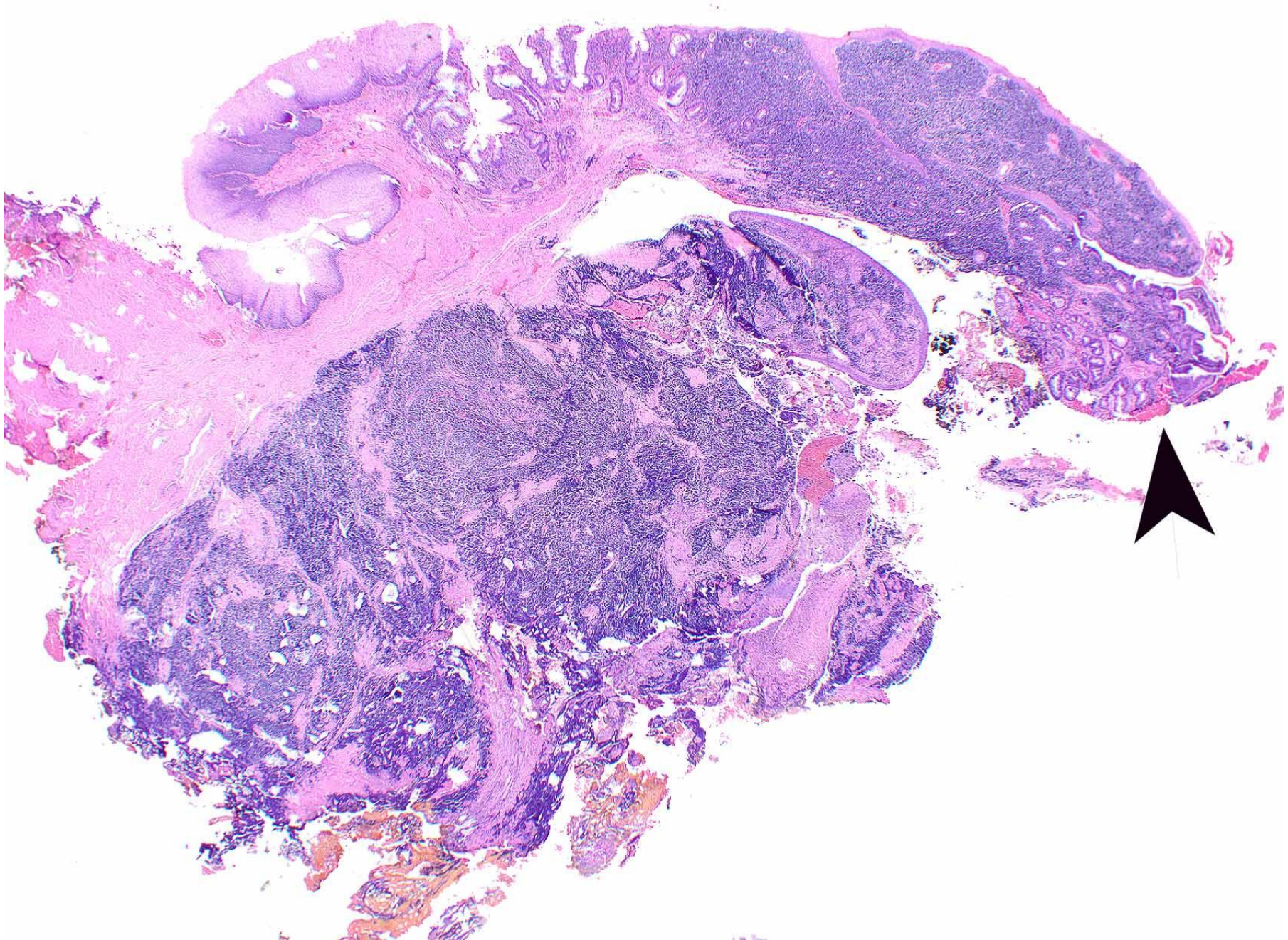


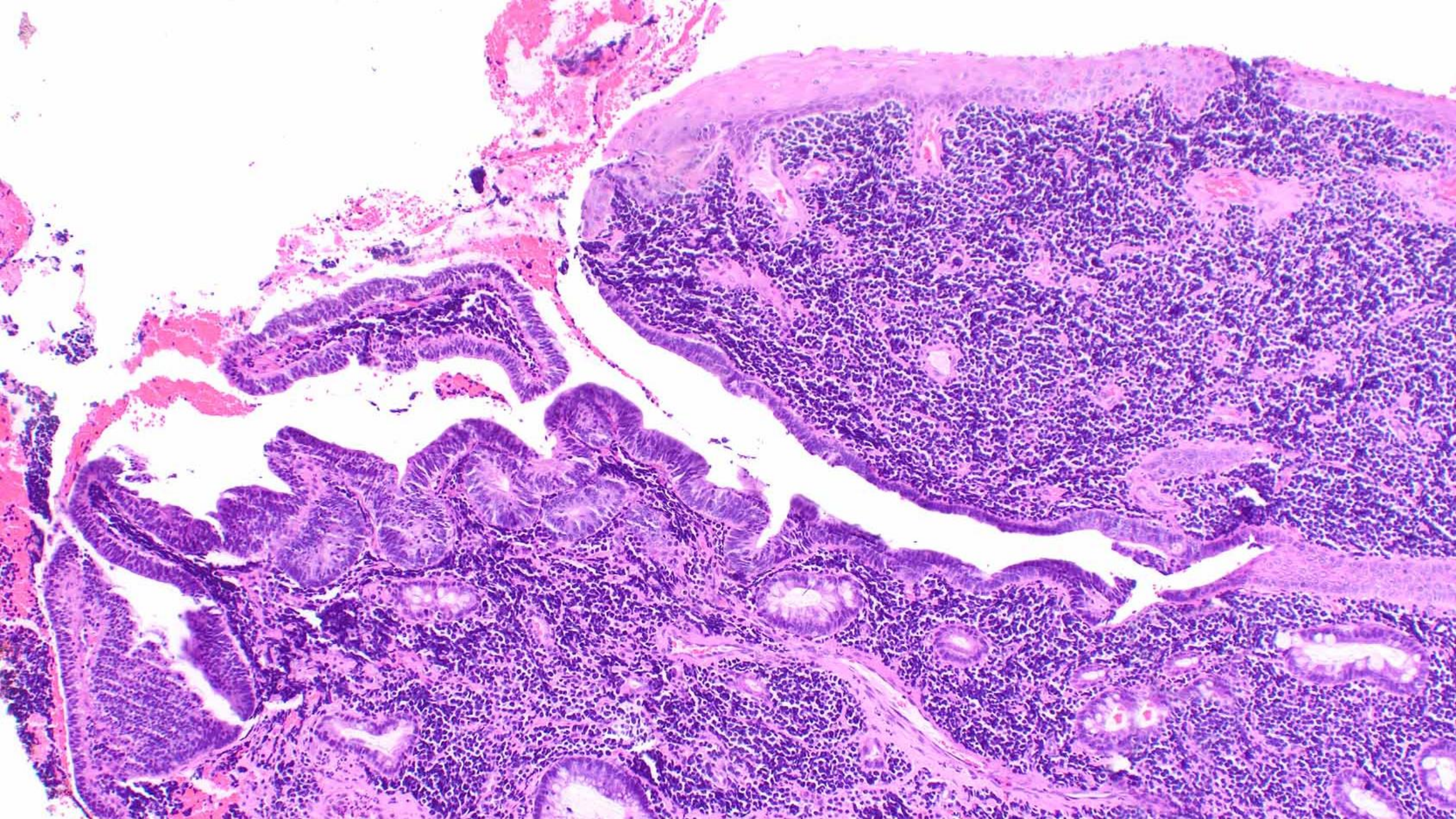

CK7

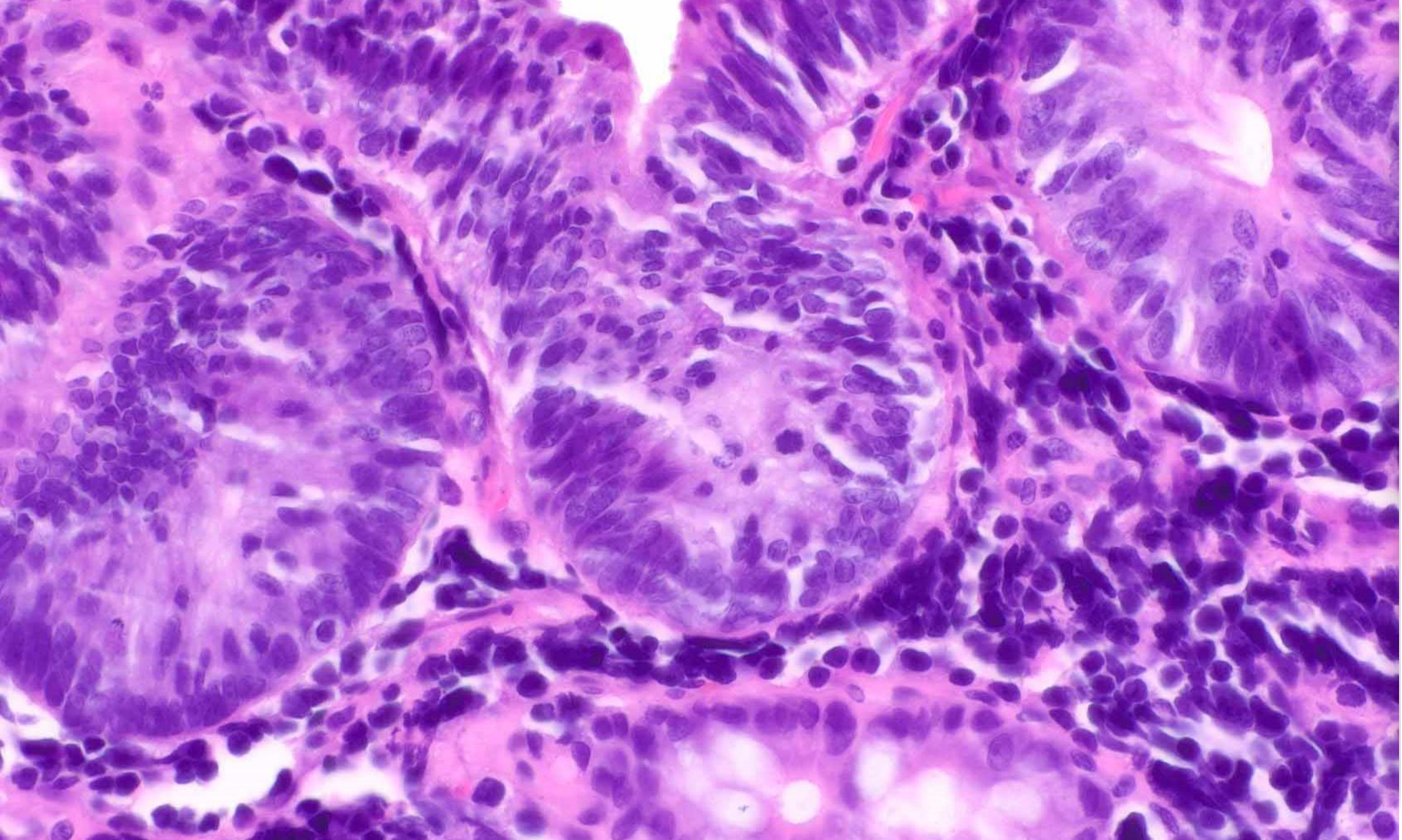

CK20


High-risk
HPV RNA in
situ
hybridization

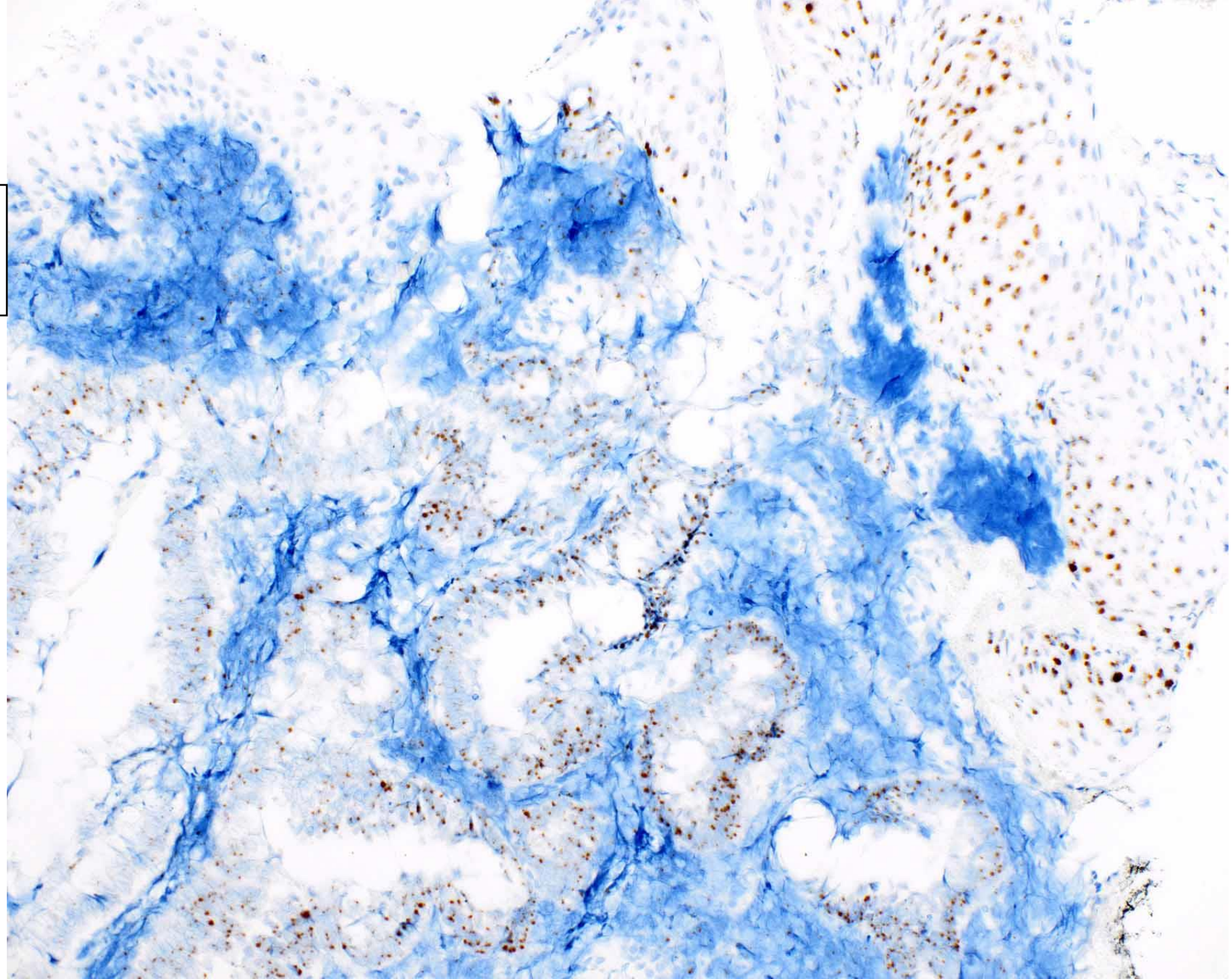
Small cell carcinoma associated with an anal columnar precursor







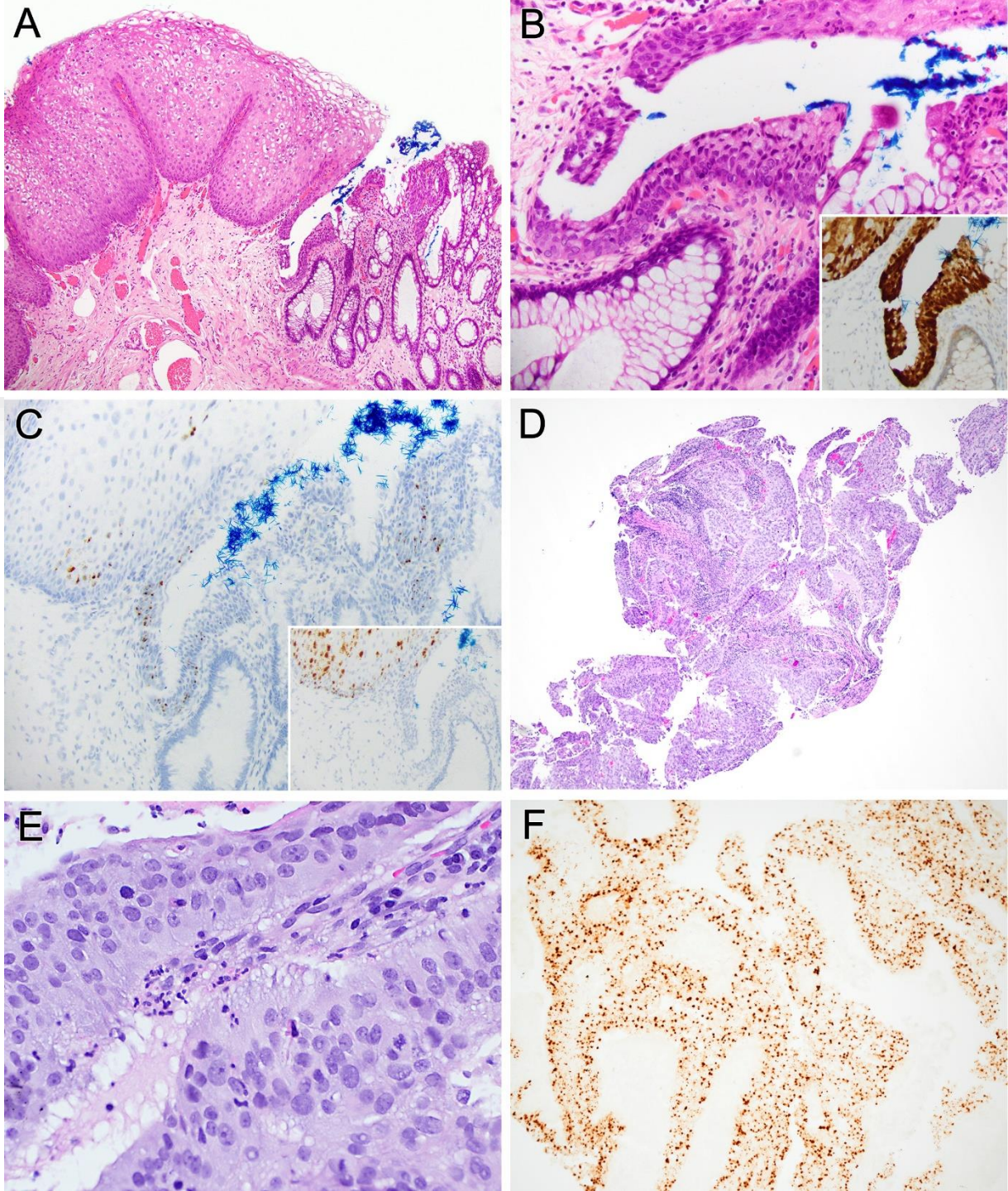
High-risk HPV RNA in situ hybridization



…And it gets stranger and stranger – plenty of cervix things can be found in the anus

- Stratified mucinous intraepithelial lesion (SMILE).*
- Adenoid basal carcinoma.

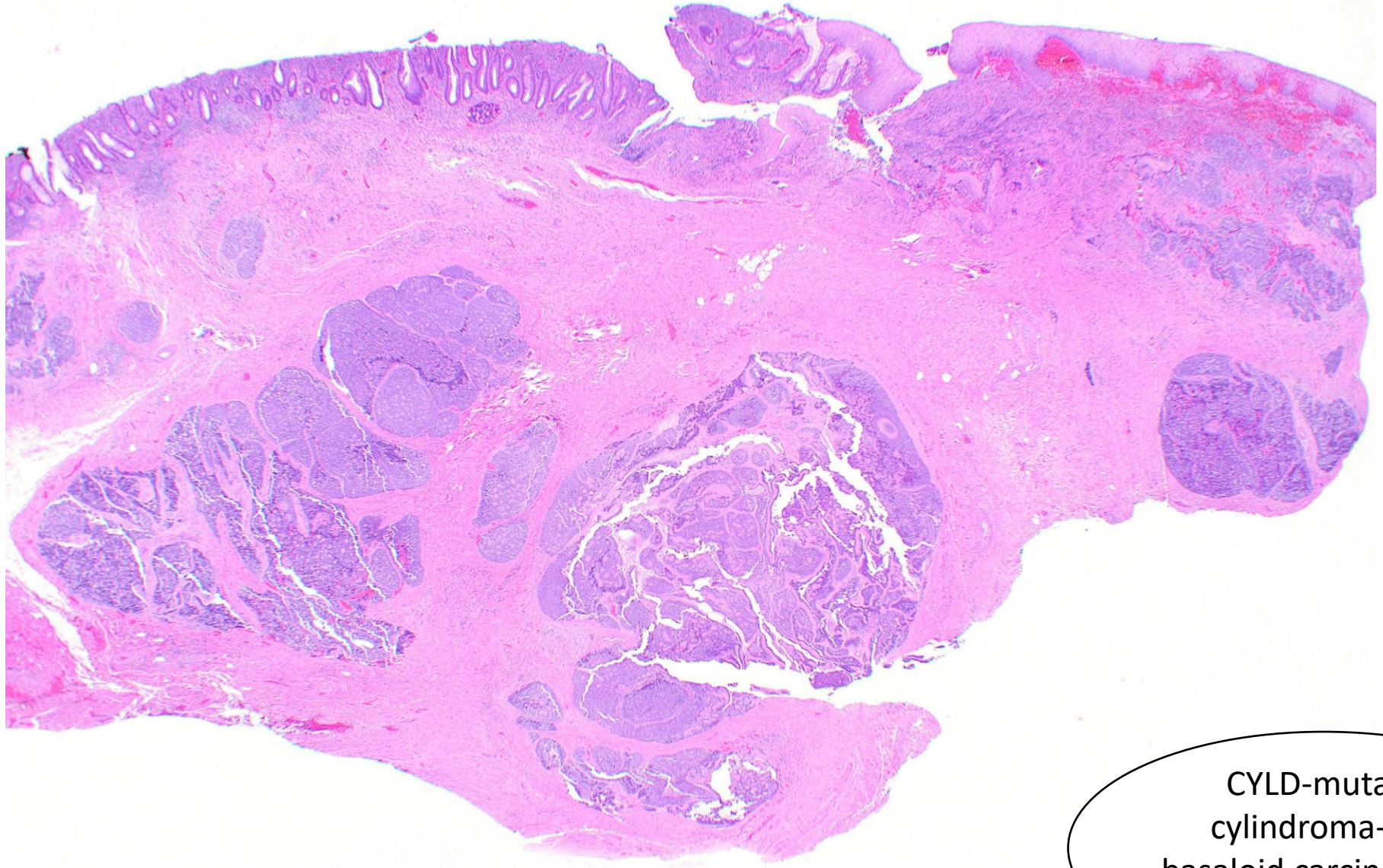
*Sappenfield R, Camacho-Cordovez F, Larman T, Xing D, Montgomery EA, Ronnett BM, Voltaggio L. Stratified Mucin-producing Lesions of the Anus: Insights into an Emerging Histologic Type of HPV-driven Anal Neoplasia. Am J Surg Pathol. 2024 Sep 23. doi: Epub ahead of print. PMID: 39308041.



CYLD-mutant Cylindroma-like Basaloid Carcinoma of the Anus

- *CYLD* mutations, seen in cases of familial and sporadic cutaneous cylindroma, are found in about 10-15% of anal carcinomas
- Anal carcinomas with *CYLD* mutations are enriched for younger patients, women, and near-universal infection with HR HPV, mainly HPV16
- Basaloid neoplastic cells surrounded by a thick basement membrane arranged in a jigsaw pattern and displaying hyaline globular inclusions
- *CYLD* mutations have been identified in about 20% of head and neck carcinomas -associated with cylindroma-like histologic features

Reference; Williams EA, Montesion M, Sharaf R, Corines J, Patel PJ, Gillespie BJ, et al. CYLD-mutant cylindroma-like basaloid carcinoma of the anus: a genetically and morphologically distinct class of HPV-related anal carcinoma. Mod Pathol. 2020 -12;33(12):2614-25.



CYLD-mutant cylindroma-like basaloid carcinoma of the anus

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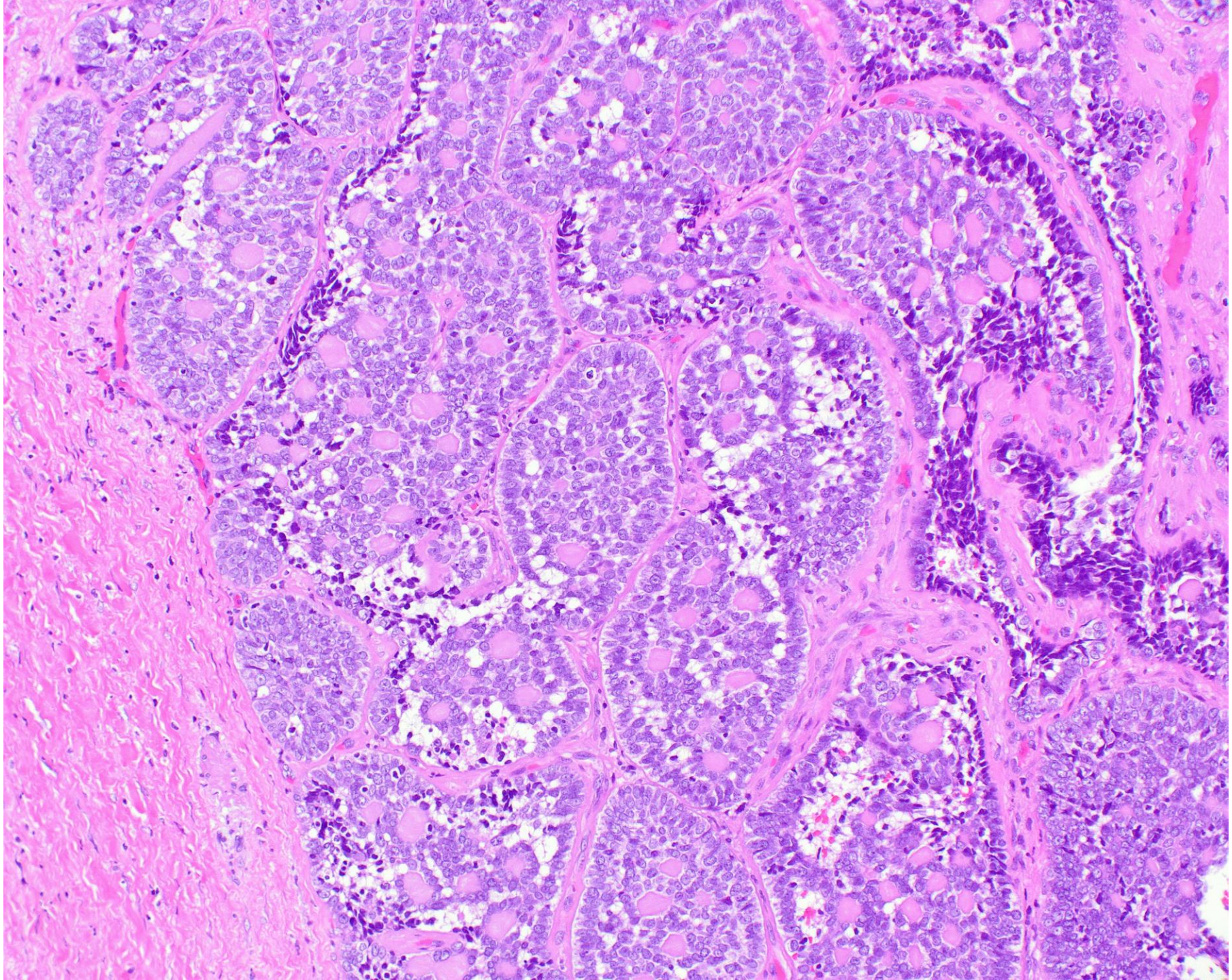
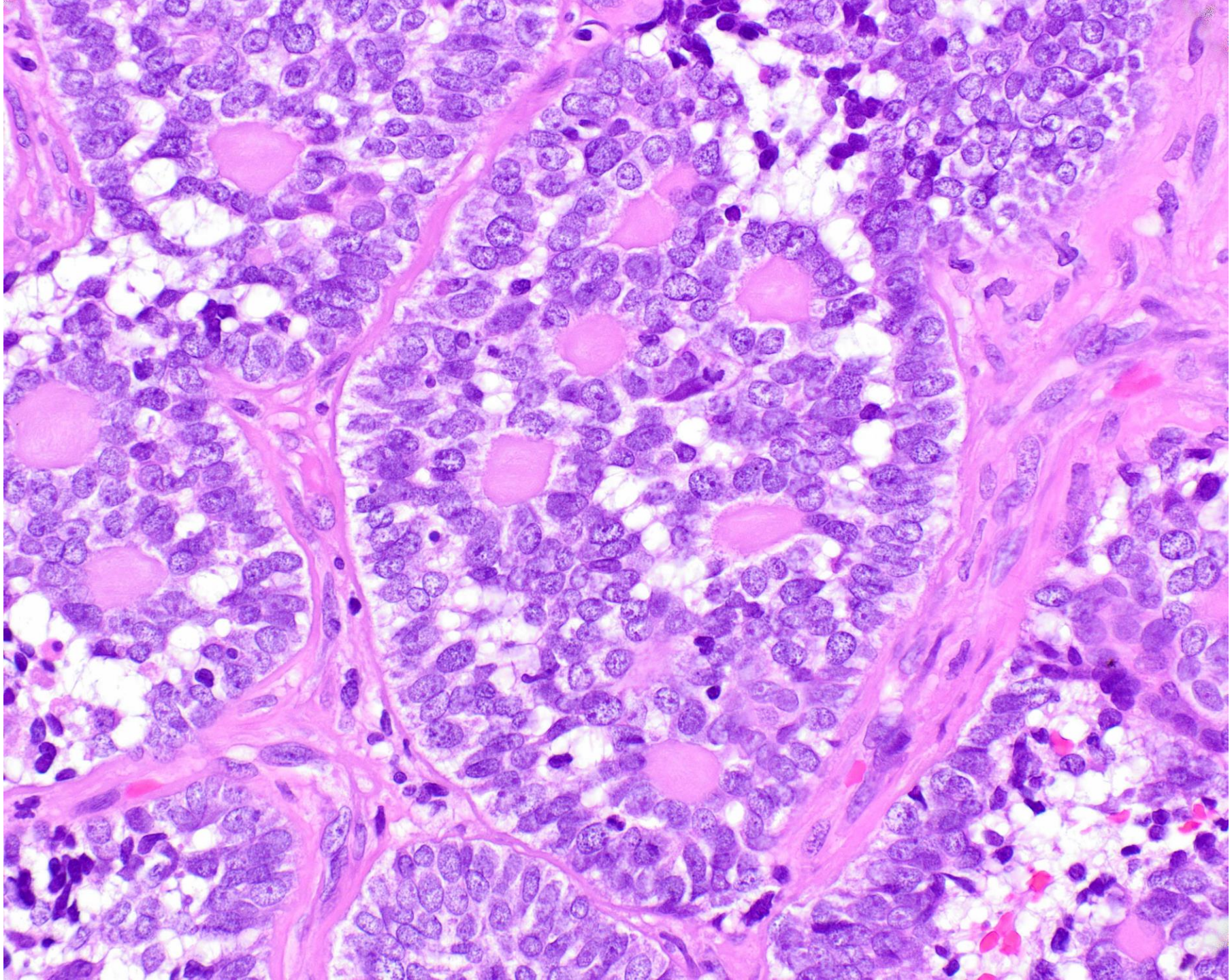
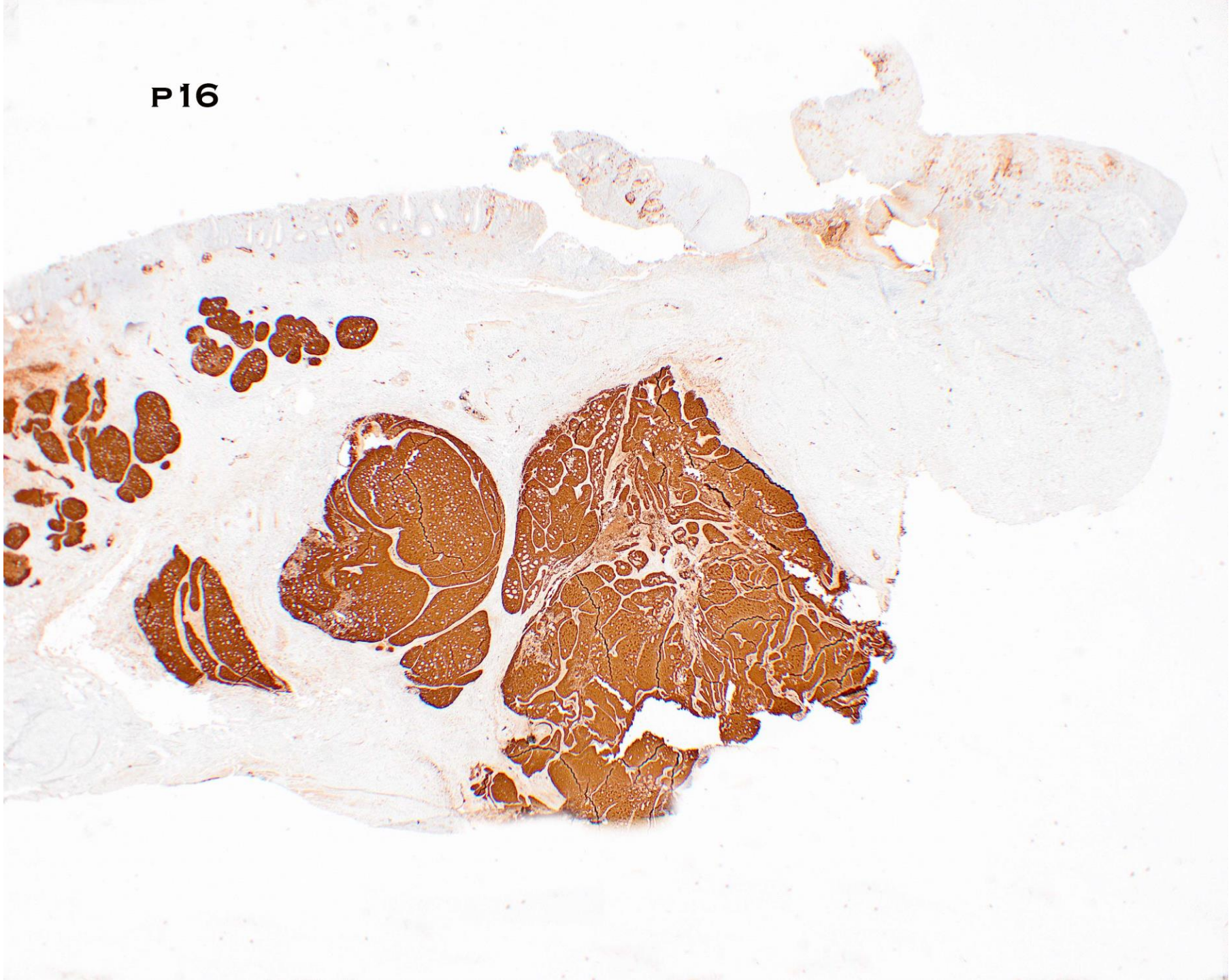


CYLD-mutant cylindroma-like basaloid carcinoma of the anus





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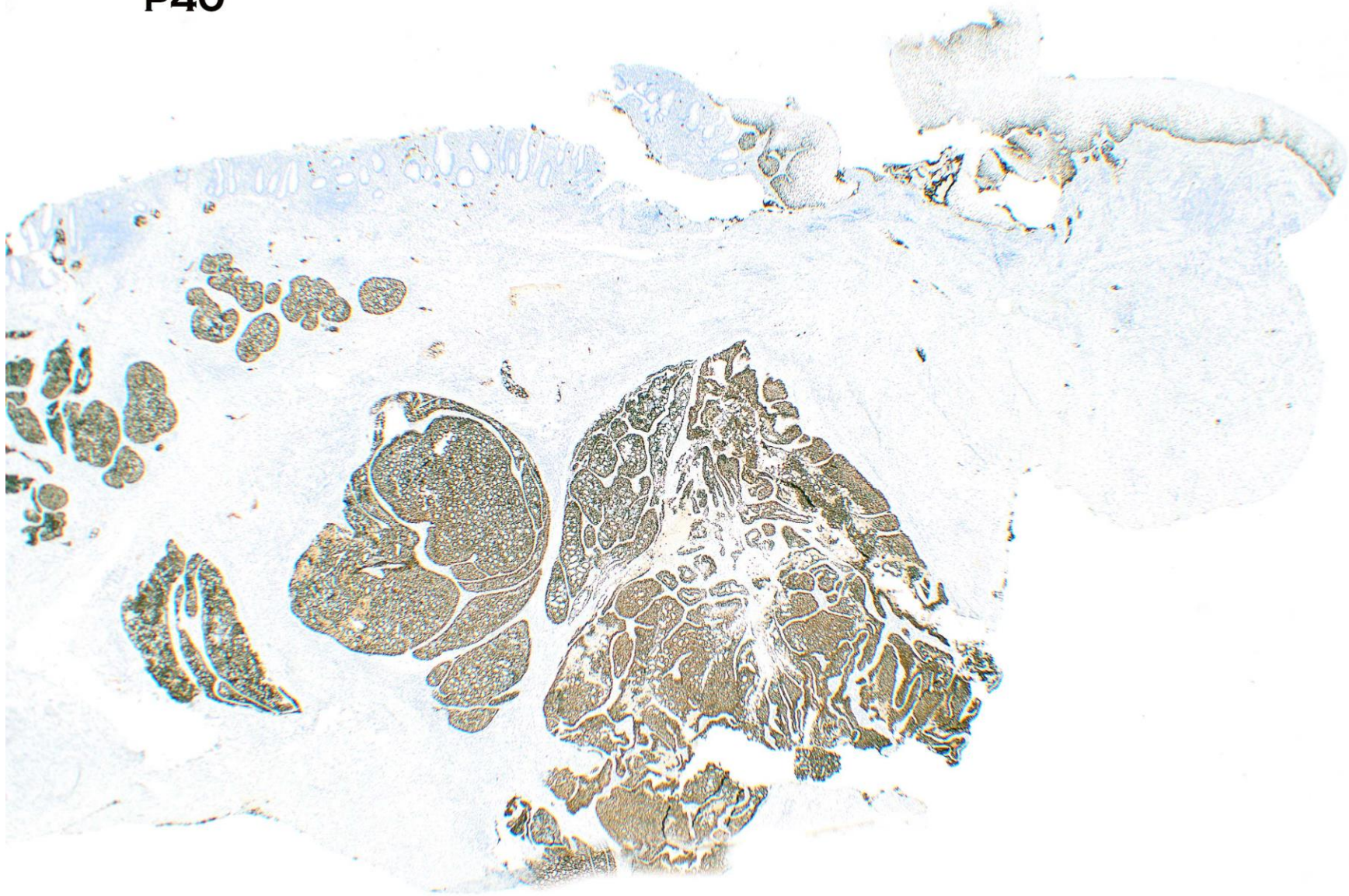
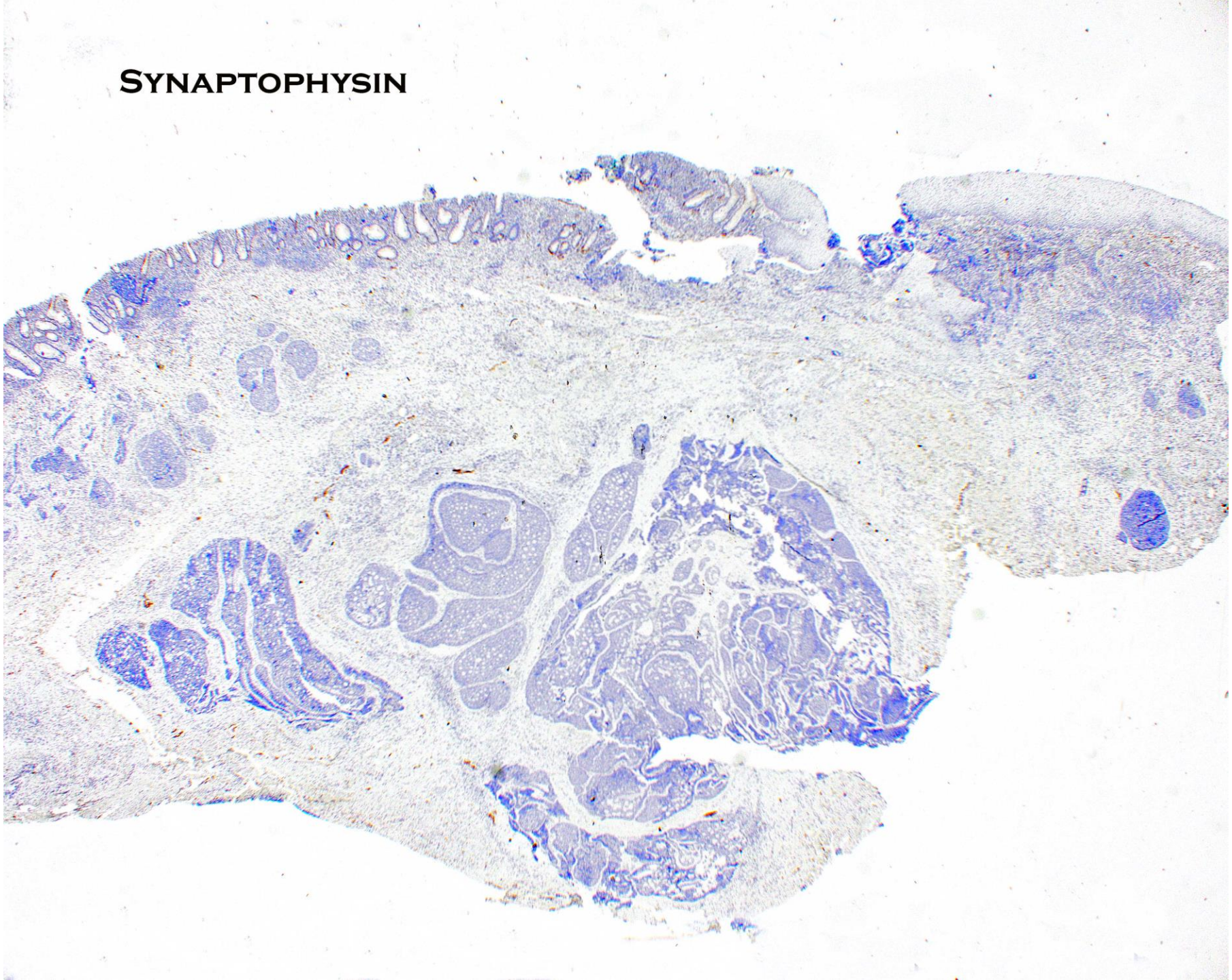


CYLD-mutant cylindroma-like basaloid carcinoma of the anus



Summary

- We have discussed tips for addressing reactive versus dysplastic lesions in the esophagus and stomach
- We have discussed an interesting squamous carcinoma precursor and a pattern of intra-epithelial spread
- We have discussed the ability of metastases to the small bowel to mimic *in situ* lesions
- We have commented on classification and treatment of gastric and colorectal dysplasia
- We have seen some newly recognized anal lesions

Thank you