

RODGER C. HAGGITT MEMORIAL
LECTURE: The Frontiers of Dysplasia in
the GI Tract

Elizabeth Montgomery, MD

Some Morphology Frontiers of Dysplasia in the GI Tract

Not much molecular or cutting edge science

Rodger Haggitt was an
amazing beloved man

He taught many of us the bread and butter of GI pathology before his
tragic death in 2000

Invitations for named talks mean one of two things

- You are really amazing

- You are getting old

Objectives

- To make a few points about squamous dysplasia of the esophagus
- To make a few points about esophageal columnar dysplasia and gastric dysplasia
- To avoid the small bowel as much as possible since everything is colonization by metastatic malignant neoplasms
- To comment on colitis-associated dysplasia
- To save the anus for LAST – actually to save the anus FROM LAST.

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) – not well-established as a precursor but provocative
- 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.



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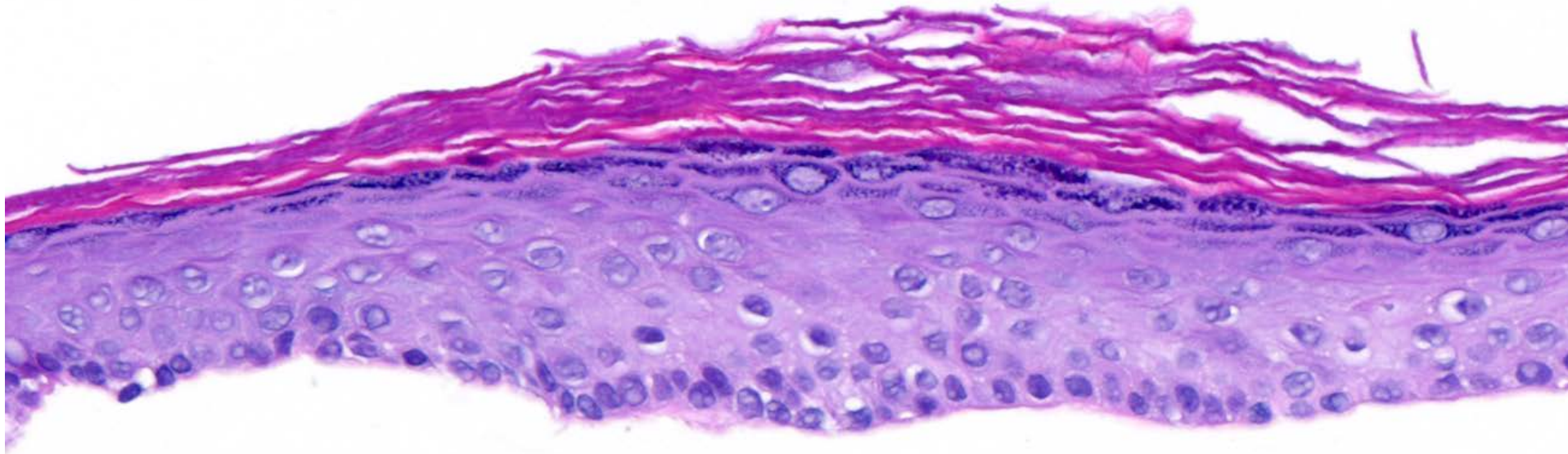
Epidermoid Metaplasia

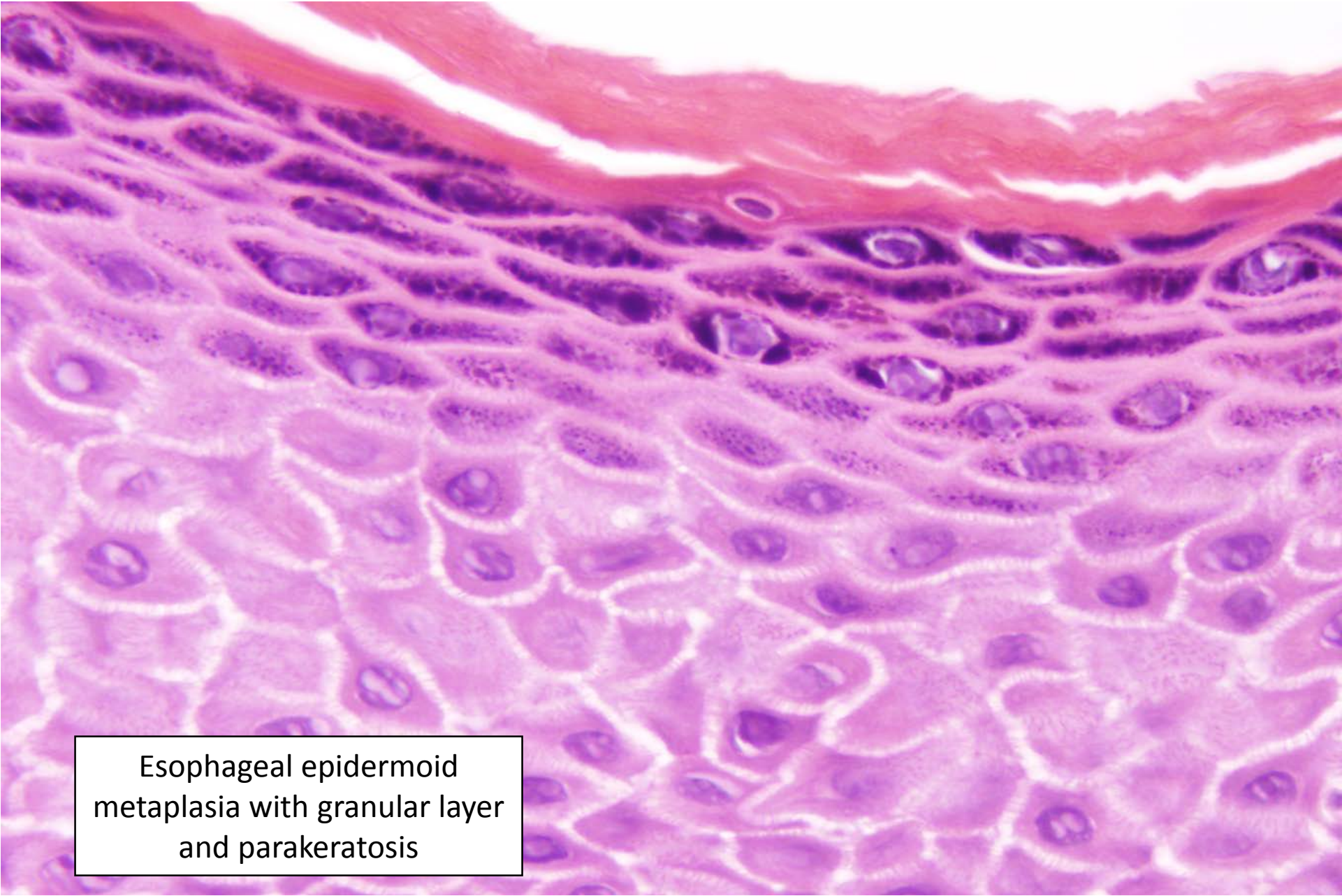
- Plaques of white, thickened mucosa, or red areas which are typically more prominent toward the distal third of the esophagus.
- Biopsies show epithelial hyperplasia and hyperkeratosis and a granular layer just like skin.

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 parakeratosis – presents as a plaque to the endoscopist





Esophageal epidermoid metaplasia with granular layer and parakeratosis

Epidermoid metaplasia
and mass – Courtesy of
Dr. Christina Arnold

Sex: Age:

/20/2013

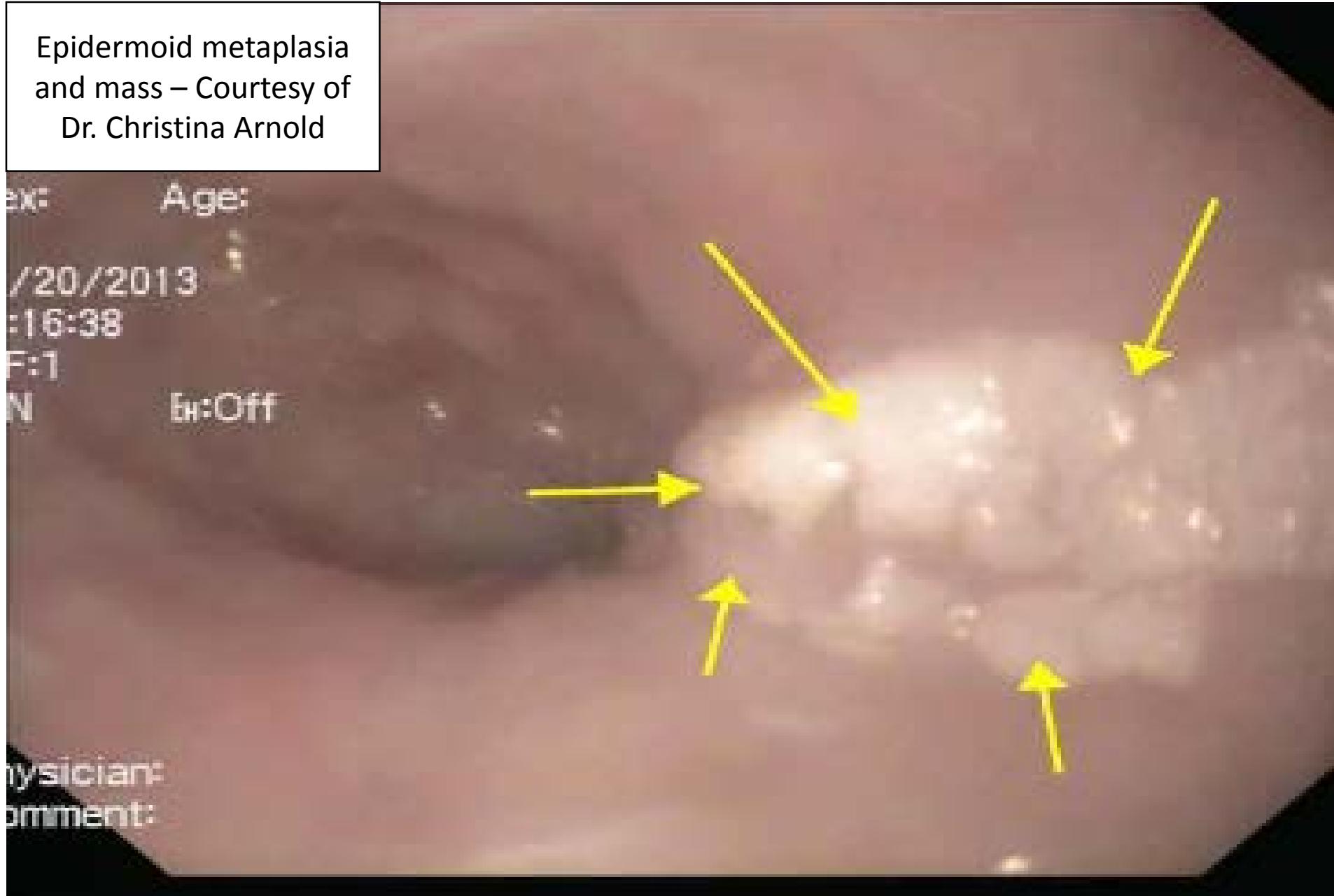
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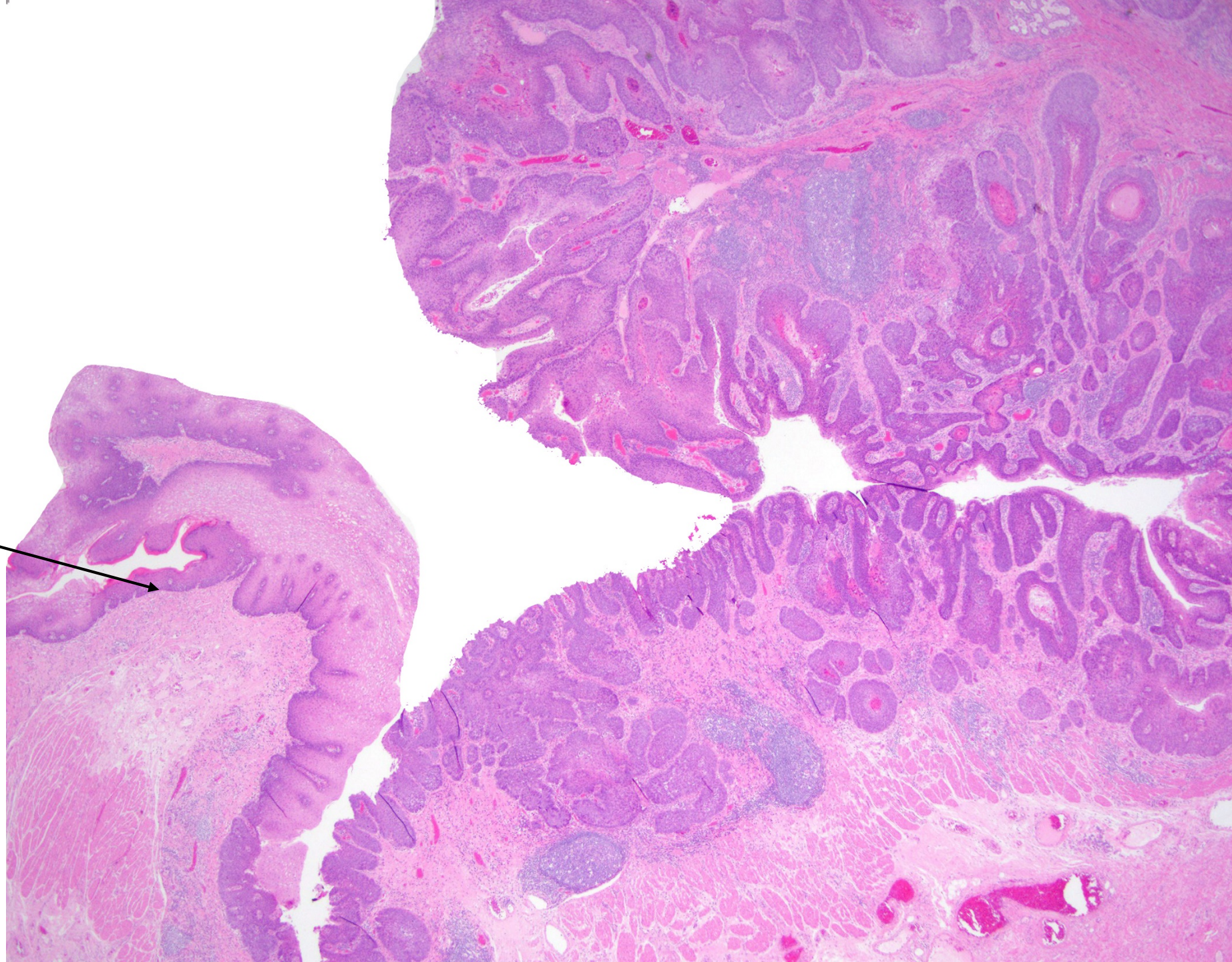
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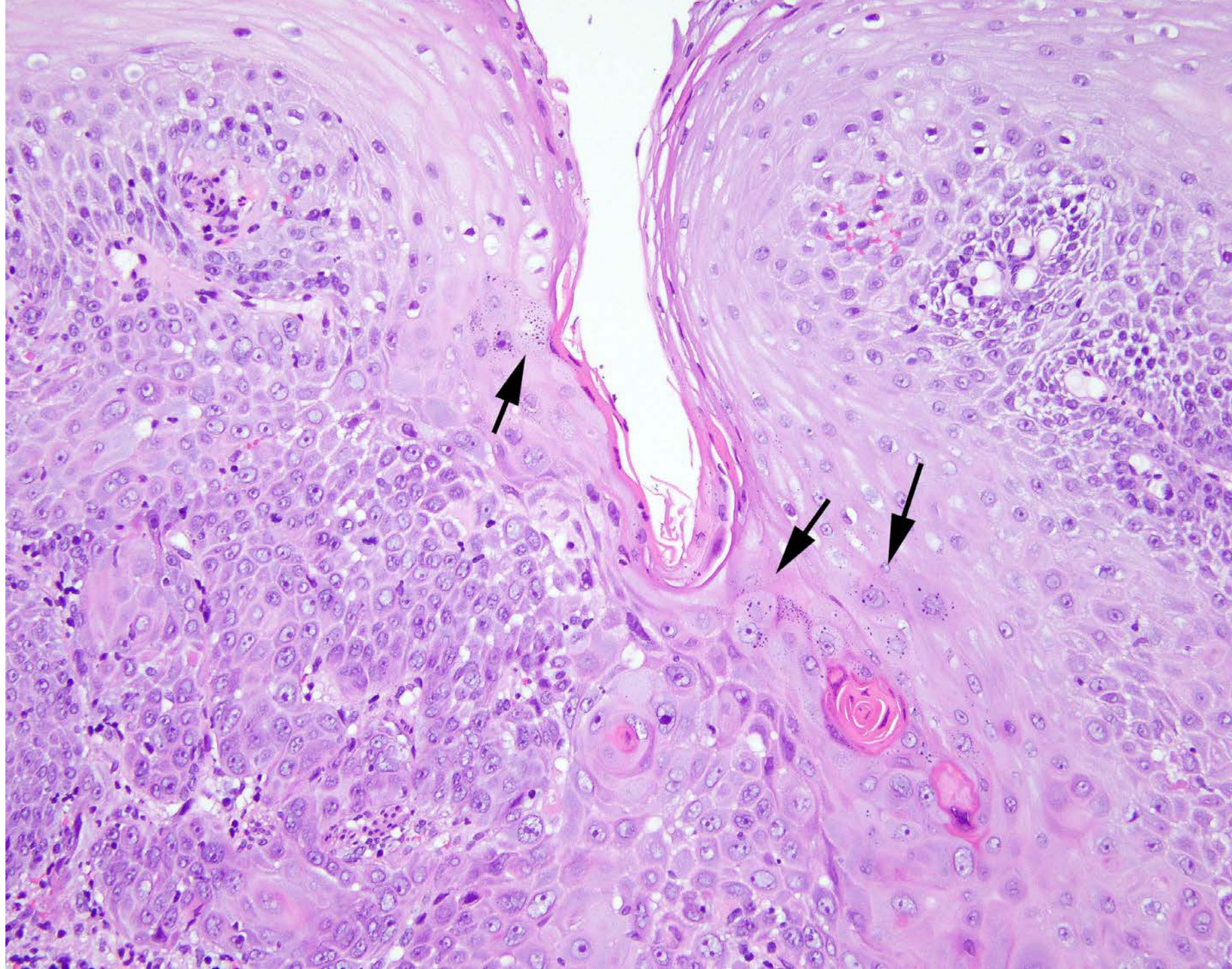
Physician:

Comment:

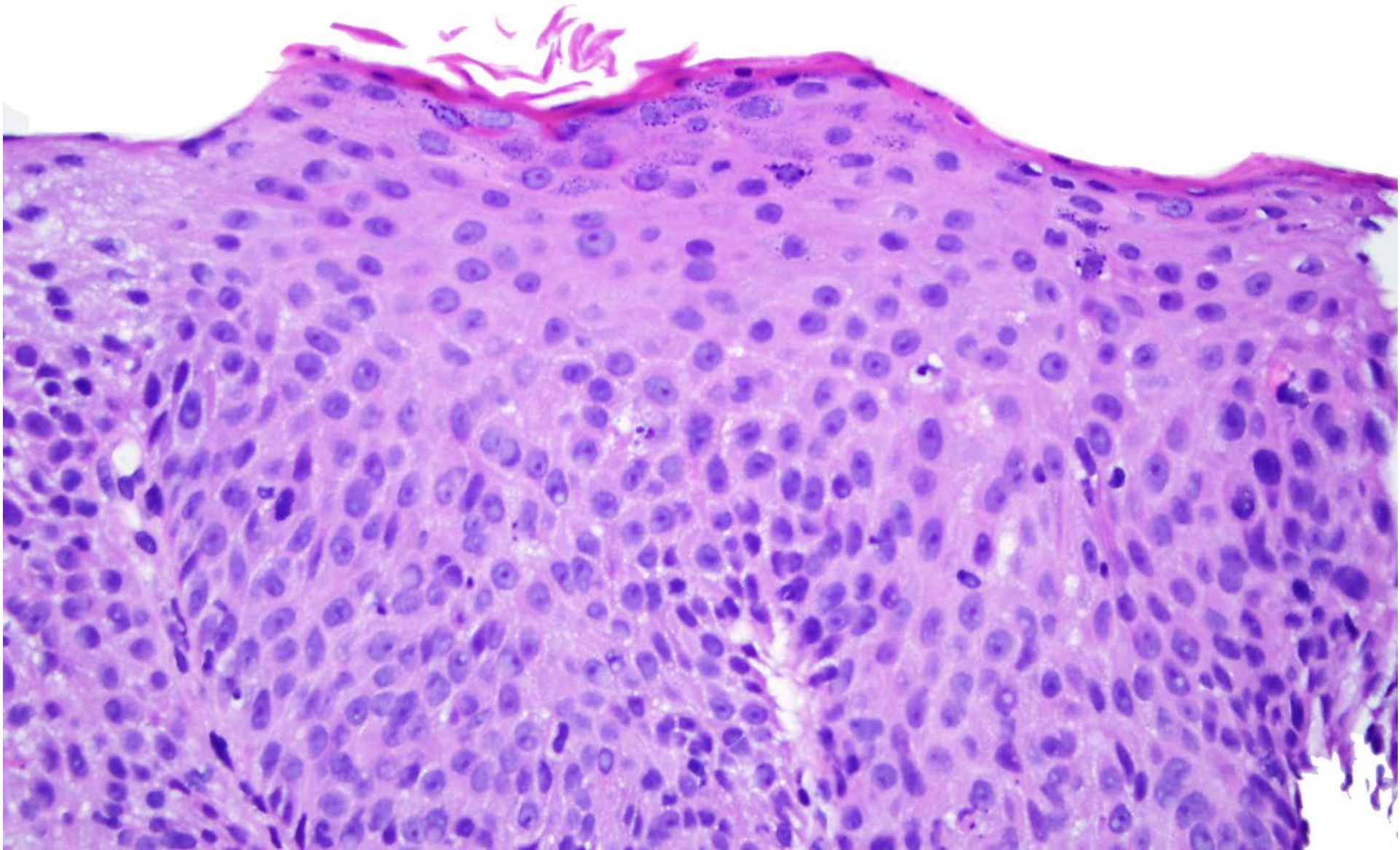


Epidermoid metaplasia
– Courtesy
of C. Arnold





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.

Epidermoid metaplasia seems to be at play in the larynx as well!

- **Abstract #:** 1226

Abstract Title: Epidermoid/Orthokeratotic Metaplasia of the Larynx: Toward a Unifying Concept for Pre-Dysplastic Lesions of the Upper Aerodigestive Tract

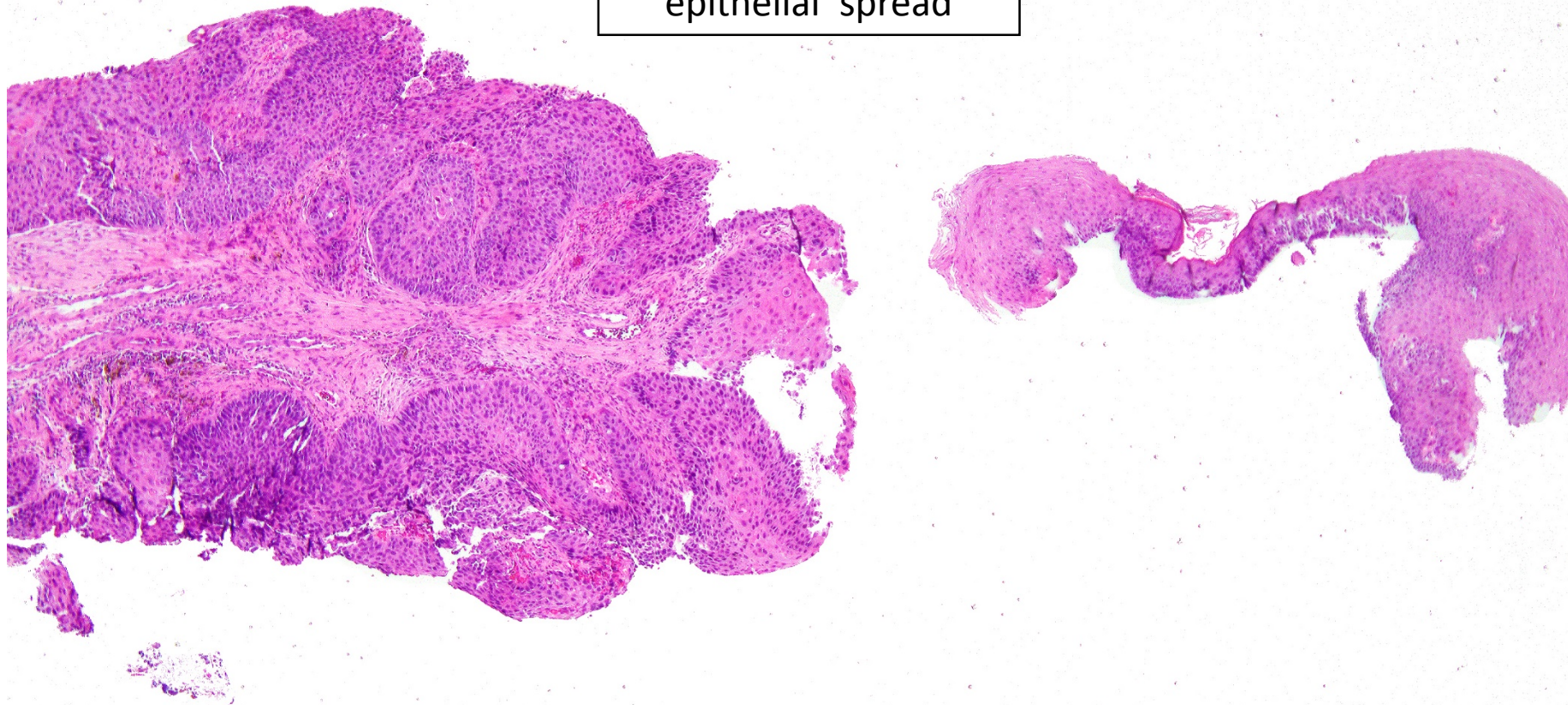
Platform Presentation: Platform - Monday AM - Head and Neck Pathology on Monday, March 02, 2020 from 8:00 AM - 12:00 PM at the Los Angeles Convention Center in LACC 402 AB*

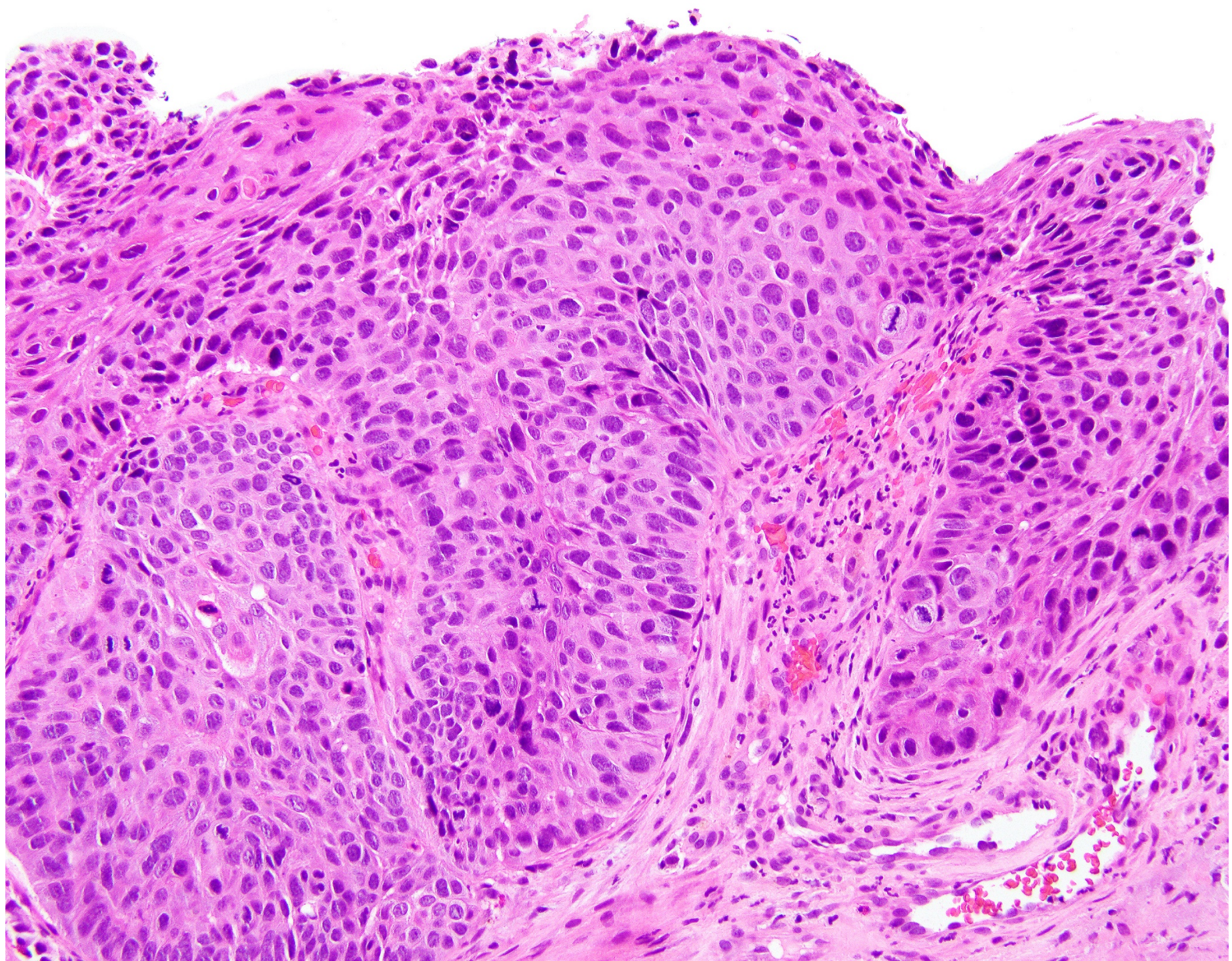
Presentation Time: 11:00 AM - 11:15 AM

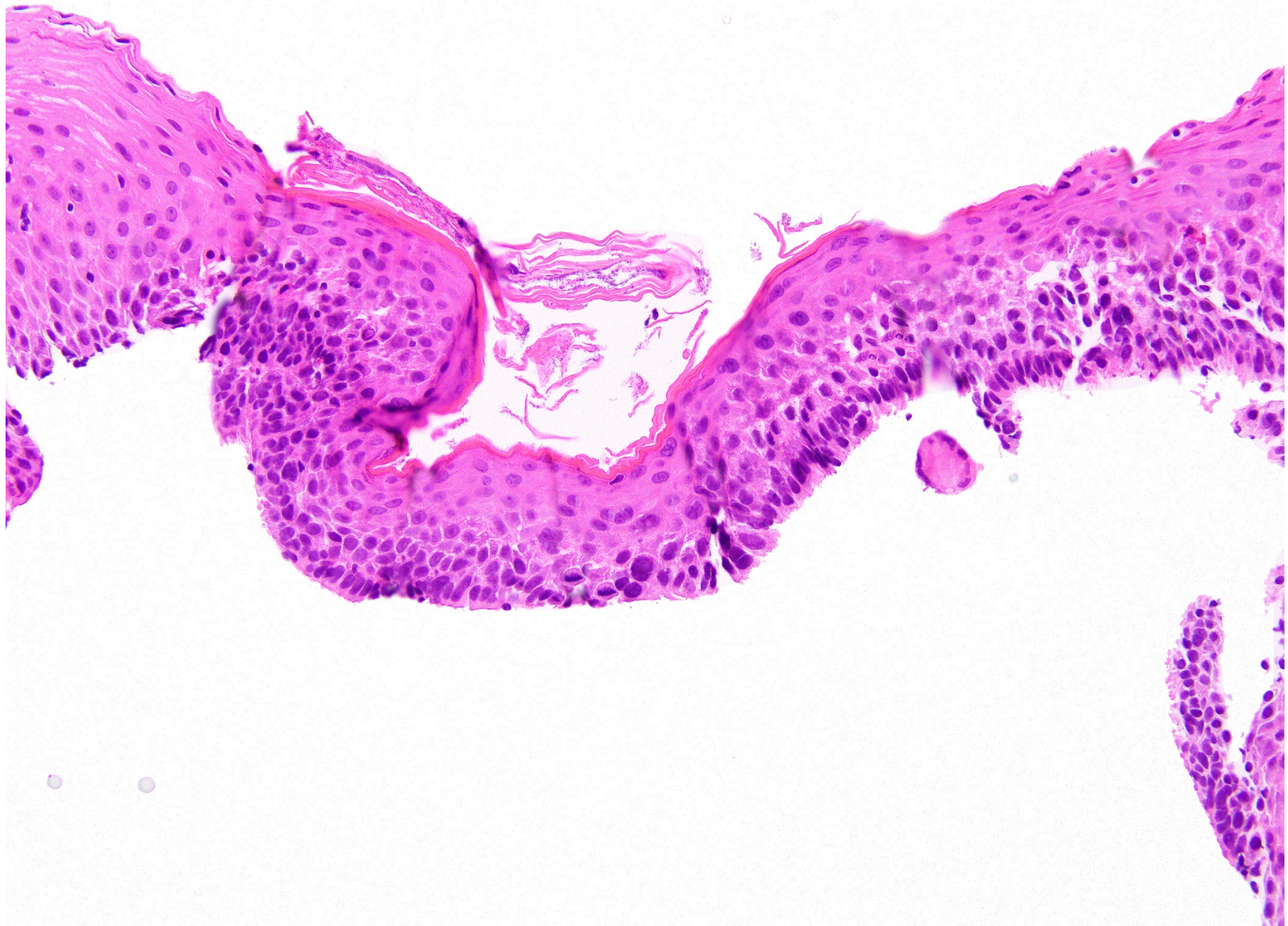
*Session rooms are subject to change. Please check the final schedule in February 2020 for confirmation.

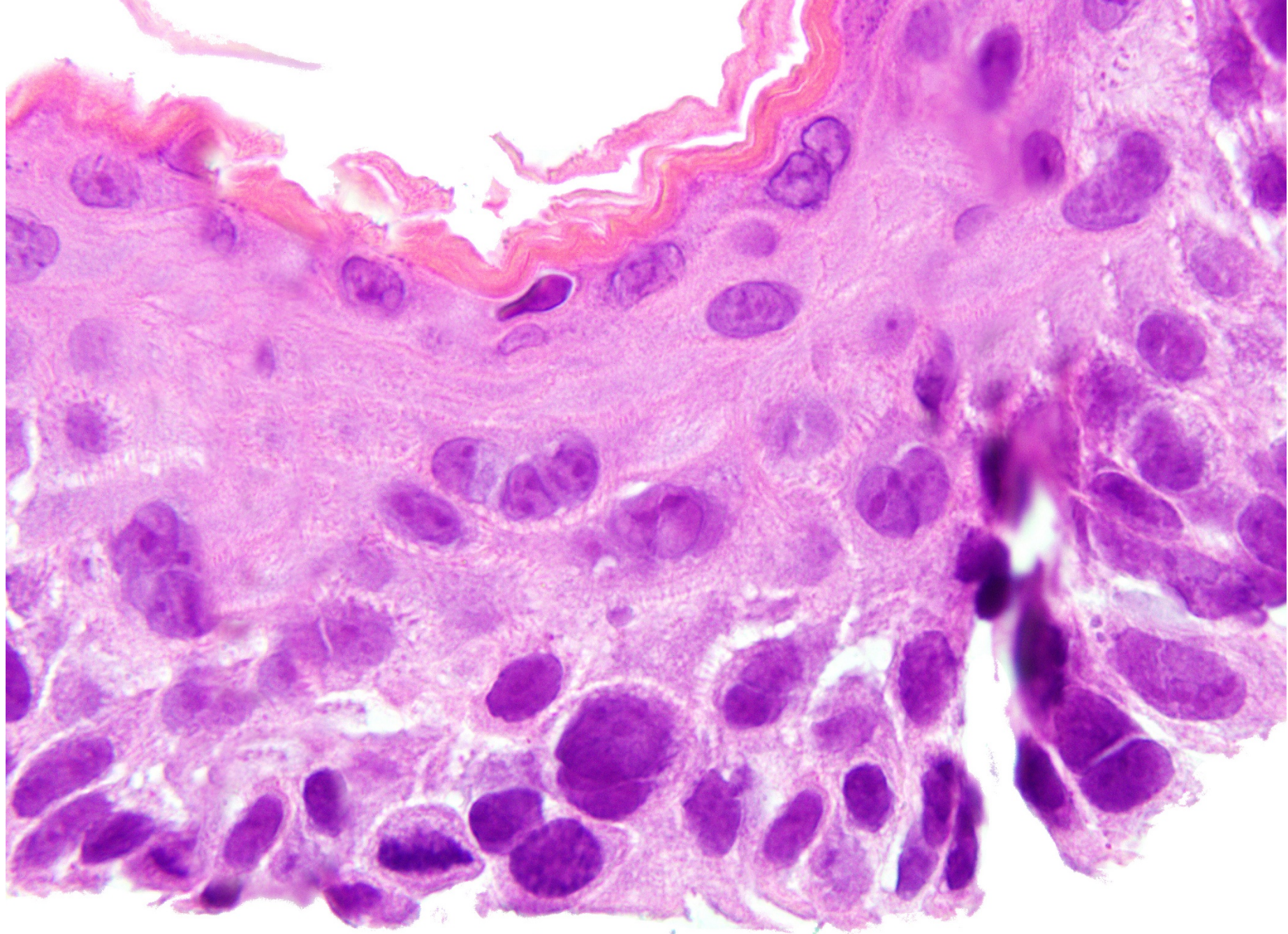
- **Presenting Author:** Danielle Hutchings
- **Senior Author:** Lisa Rooper

Squamous cell carcinoma – intra-epithelial spread





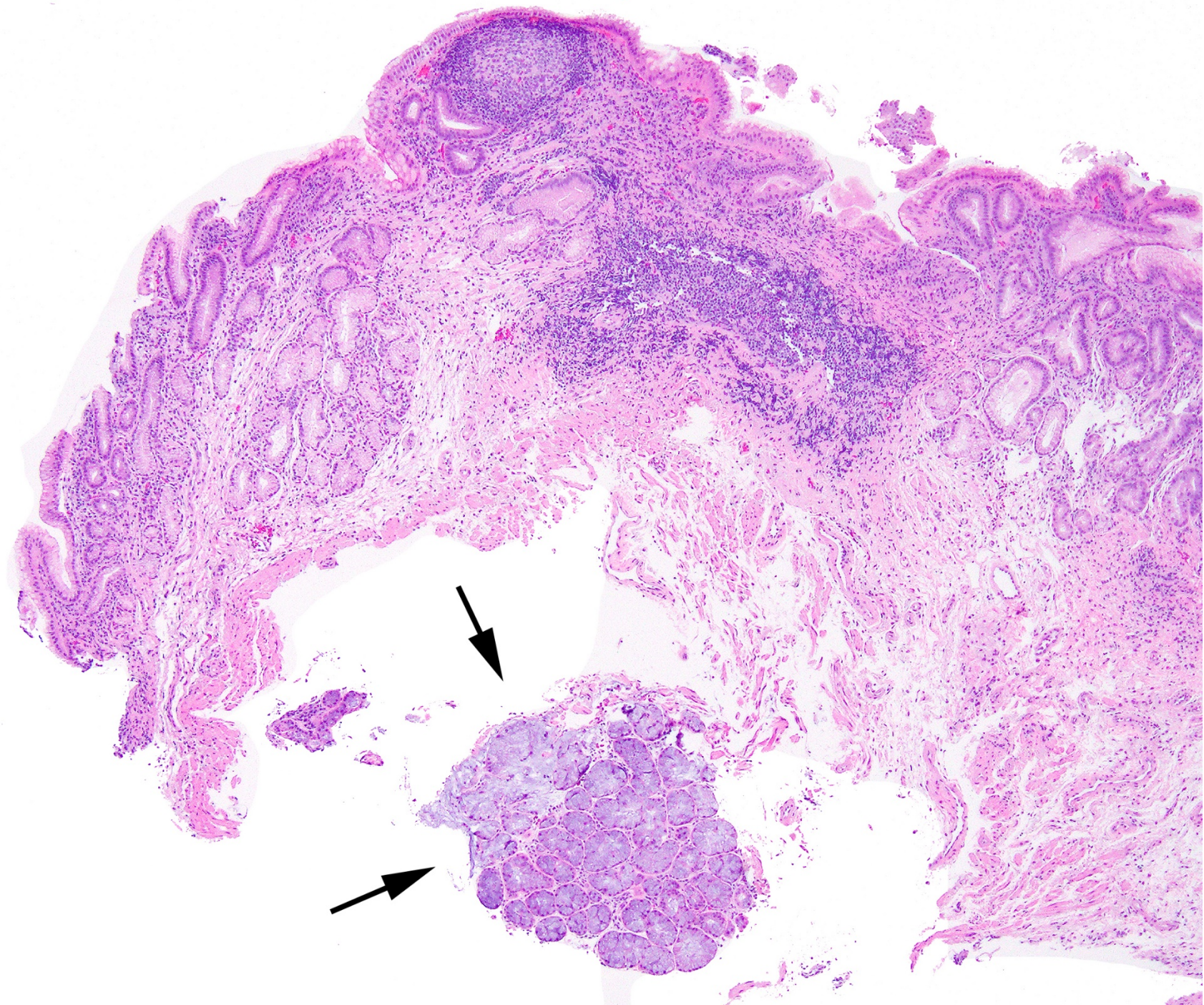




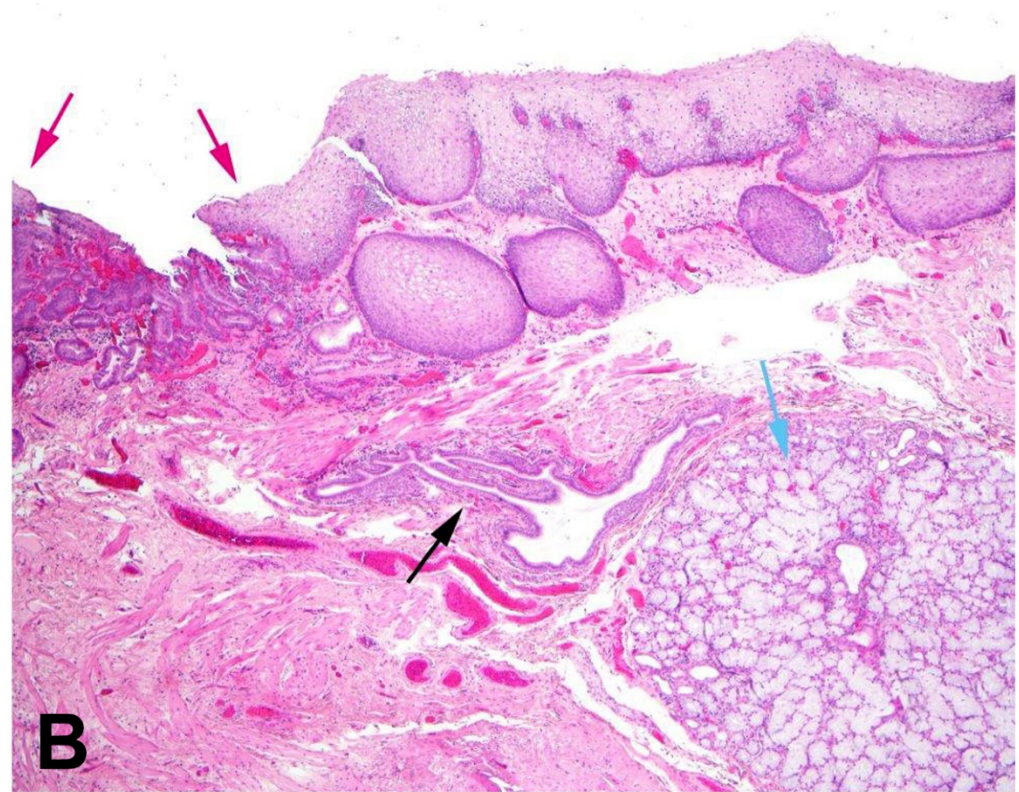
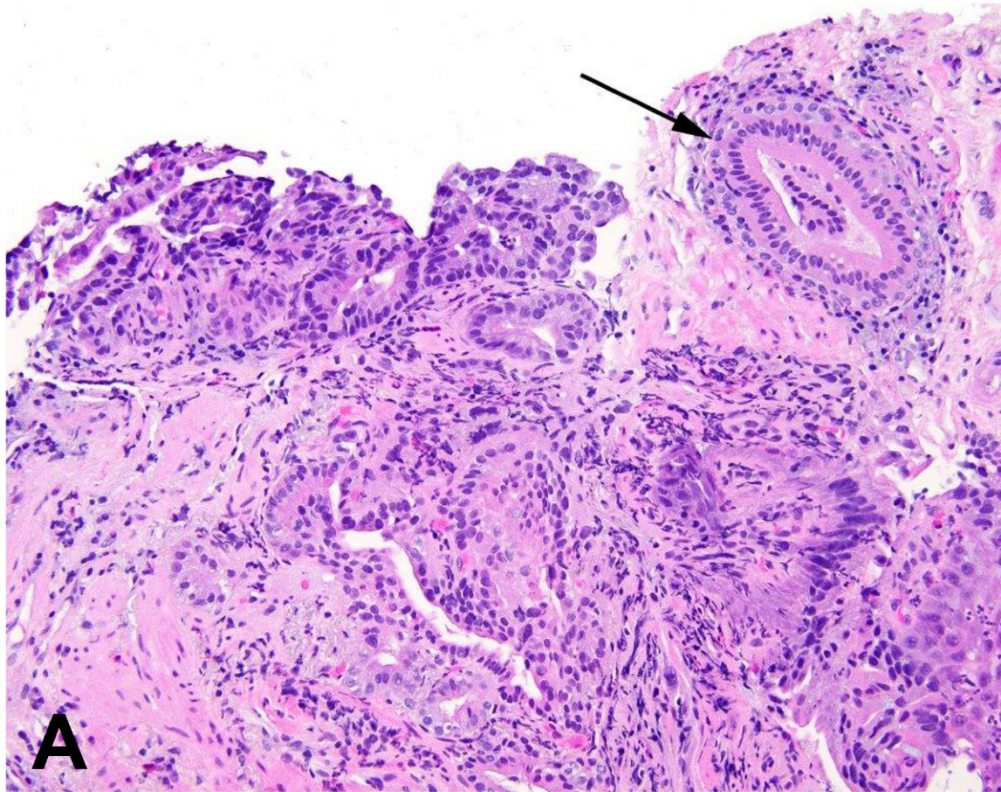
Columnar esophagus and stomach

FAQ: What are some histologic clues that a sample showing columnar epithelium has been taken from the tubular esophagus when the information has not been provided.

- Finding squamous epithelium is a terrific clue that a sample is from the GEJ but does not prove that a sample of columnar epithelium included in the biopsy is from the tubular esophagus itself.
- On the other hand, finding esophageal ducts or submucosal glands proves that a sample is from the tubular esophagus
- Srivastava A, Odze RD, Lauwers GY, Redston M, Antonioli DA, Glickman JN. Morphologic features are useful in distinguishing Barrett esophagus from carditis with intestinal metaplasia. *Am J Surg Pathol*. 2007;31(11):1733-1741.



Esophageal ducts are indicated with black arrows; squamous epithelium with red arrows



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, Ragnath 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, Gerson LB, American College of G. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. *Am J Gastroenterol*. 2016;111(1):30-50; quiz 51.

Sample Reports and Notes Using ACG Criteria

- **Situation A – Biopsy Labeled “Esophagus”:** Barrett’s esophagus, negative for dysplasia. See note.
- **Note:** The above diagnosis of Barrett esophagus is made due to presence of goblet cells (intestinal metaplasia) with the assumption that the biopsies were obtained from columnar mucosa in the distal esophagus. In addition, the 2016 American College of Gastroenterology (ACG) guidelines advocate that the mucosal irregularity must extend at least 1 cm above the top of the gastric folds.
- *Reference: Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol. 2016 Jan;111(1):30-50*

Sample Reports and Notes Using ACG Criteria

- **Situation B – Biopsy Labeled “Gastro-esophageal Junction”:** Cardiac mucosa with intestinal metaplasia. See note.
- **Note:** This biopsy shows gastric-type mucosa with scattered goblet cells. The diagnosis in this case depends on the location of this biopsy. If the metaplasia is in the tubular esophagus and a mucosal irregularity is noted that extends at least 1 cm above the top of the gastric folds, the findings are consistent with Barrett’s esophagus. If the GEJ and SCJ are coincident the findings are diagnostic of intestinal metaplasia of the gastric cardia
- *Reference: Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol. 2016 Jan;111(1):30-50*

FAQ: Why do some observers want to eliminate the requirement for goblet cells for a diagnosis of Barrett's esophagus?

- Some studies suggest that most esophageal adenocarcinomas that are detected arise in the absence of intestinal metaplasia. In one of them, for example, the authors evaluated endoscopic mucosal resection samples and found adjoining intestinal metaplasia in less than half of the samples with early cancer – the authors made no attempts to learn if goblet cells were detected on prior or separate samples.
- It is known that the likelihood of finding goblet cells is a function of both the length of the Barrett's esophagus segment and the rigor of the biopsy protocol – taking biopsies according to guidelines increases the likelihood of finding them

Aida J, Vieth M, Shepherd NA, et al. Is carcinoma in columnar-lined esophagus always located adjacent to intestinal metaplasia?: a histopathologic assessment. *Am J Surg Pathol*. 2015;39(2):188-196.

Chandrasoma PT, Der R, Ma Y, Peters J, Demeester T. Histologic classification of patients based on mapping biopsies of the gastroesophageal junction. *Am J Surg Pathol*. 2003;27(7):929-936.

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

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.

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: Finding which structure in an esophageal biopsy confirms that the sample is truly from the tubular esophagus?

Answer

C. Esophageal ducts.

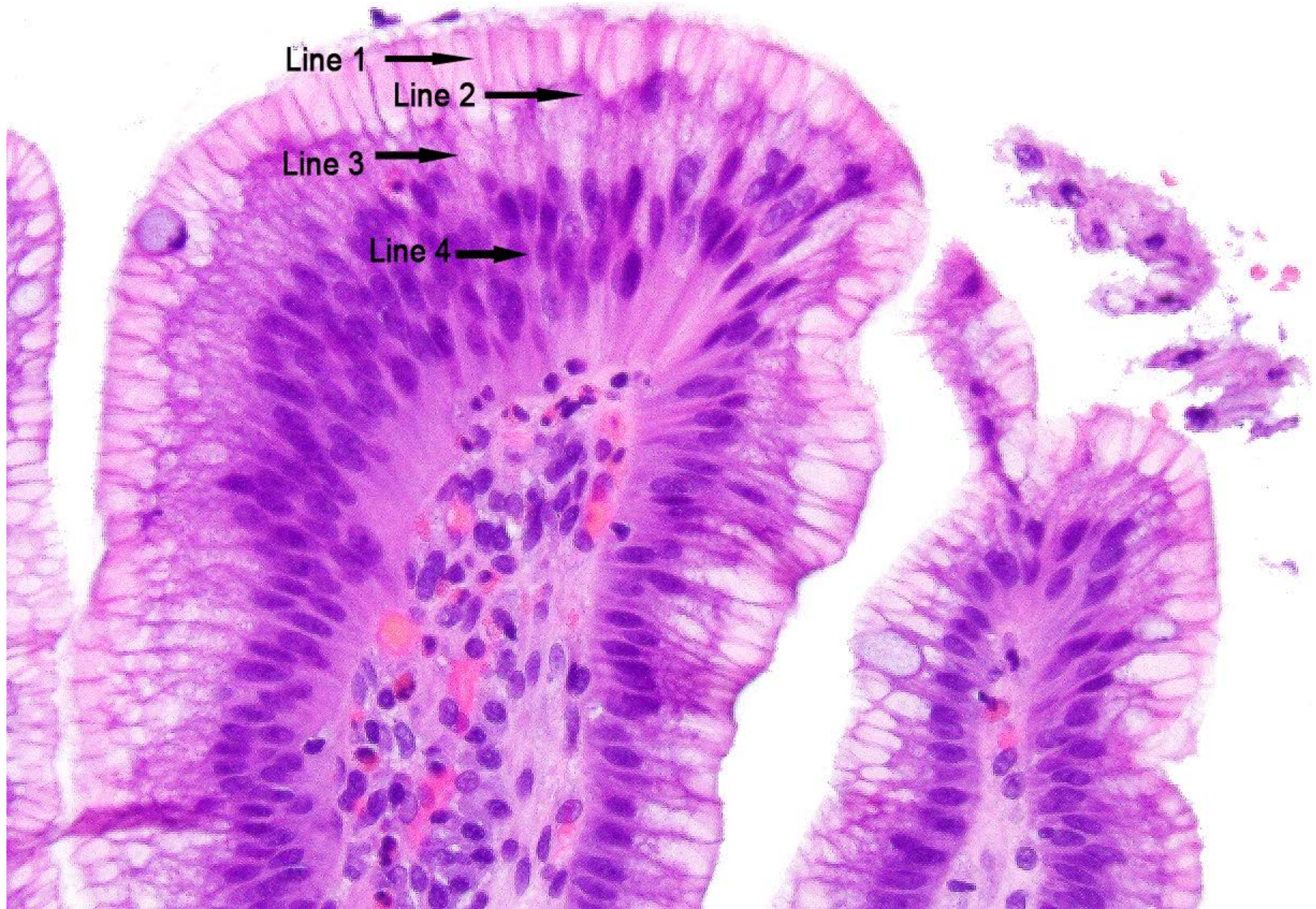
Squamous epithelium can be found at the gastroesophageal junction and goblet cells can be found in the esophagus or stomach. Esophageal ducts are unique to the esophagus.

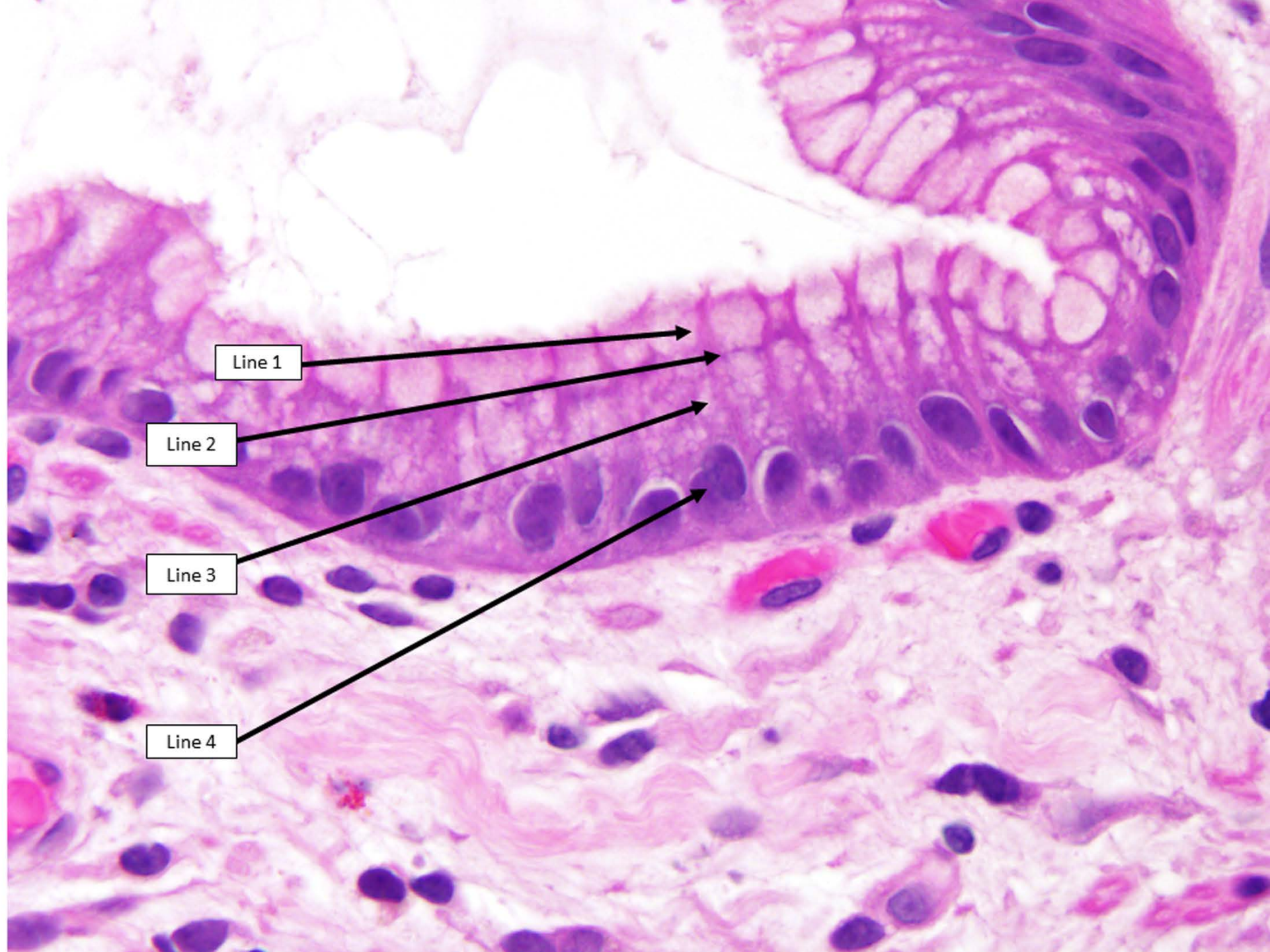
Ref; Srivastava A, Odze RD, Lauwers GY, Redston M, Antonioli DA, Glickman JN. Morphologic features are useful in distinguishing Barrett esophagus from carditis with intestinal metaplasia. *Am J Surg Pathol.* 2007;31(11):1733-1741.

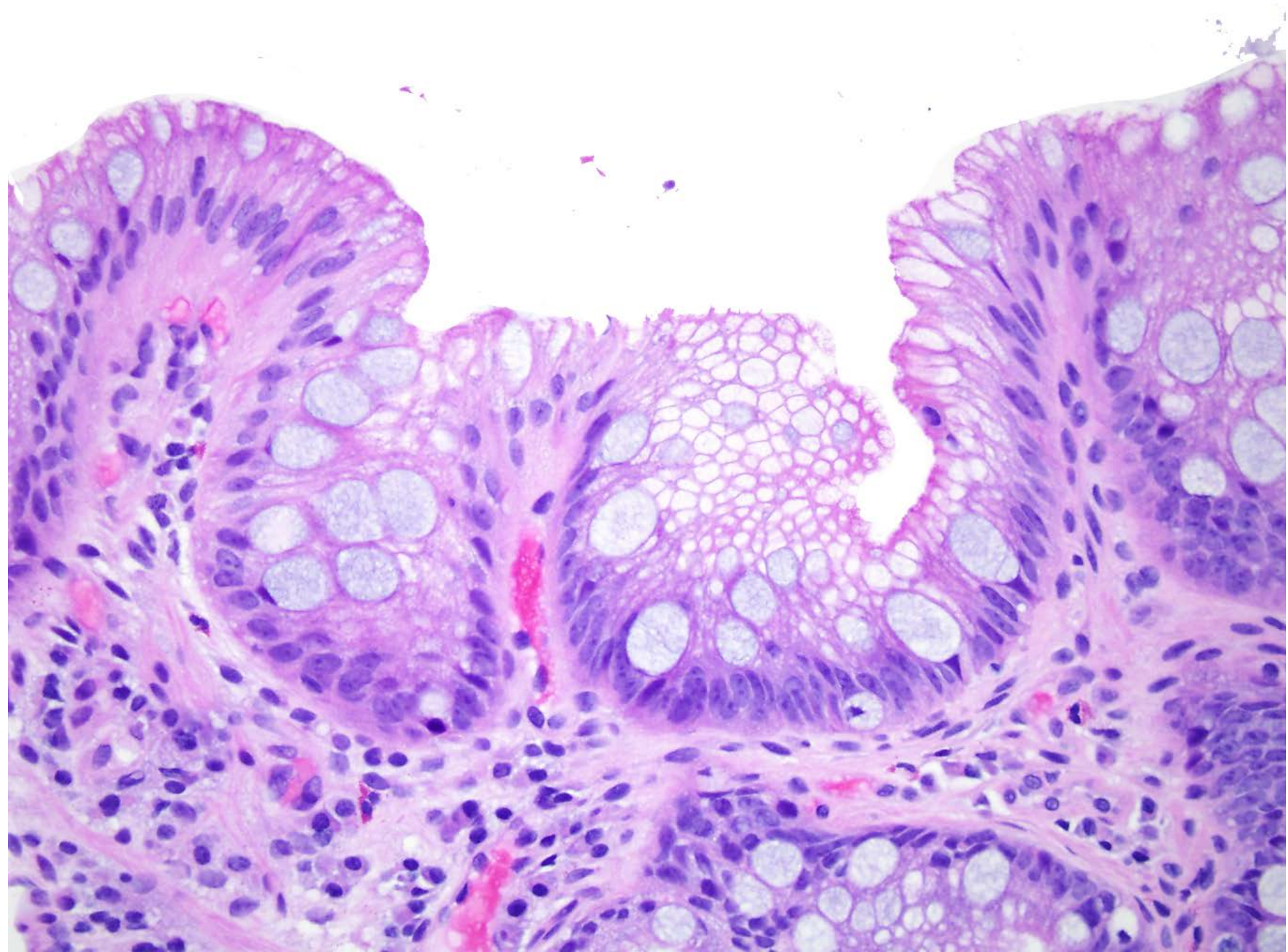
Avoiding overdiagnosis of
dysplasia

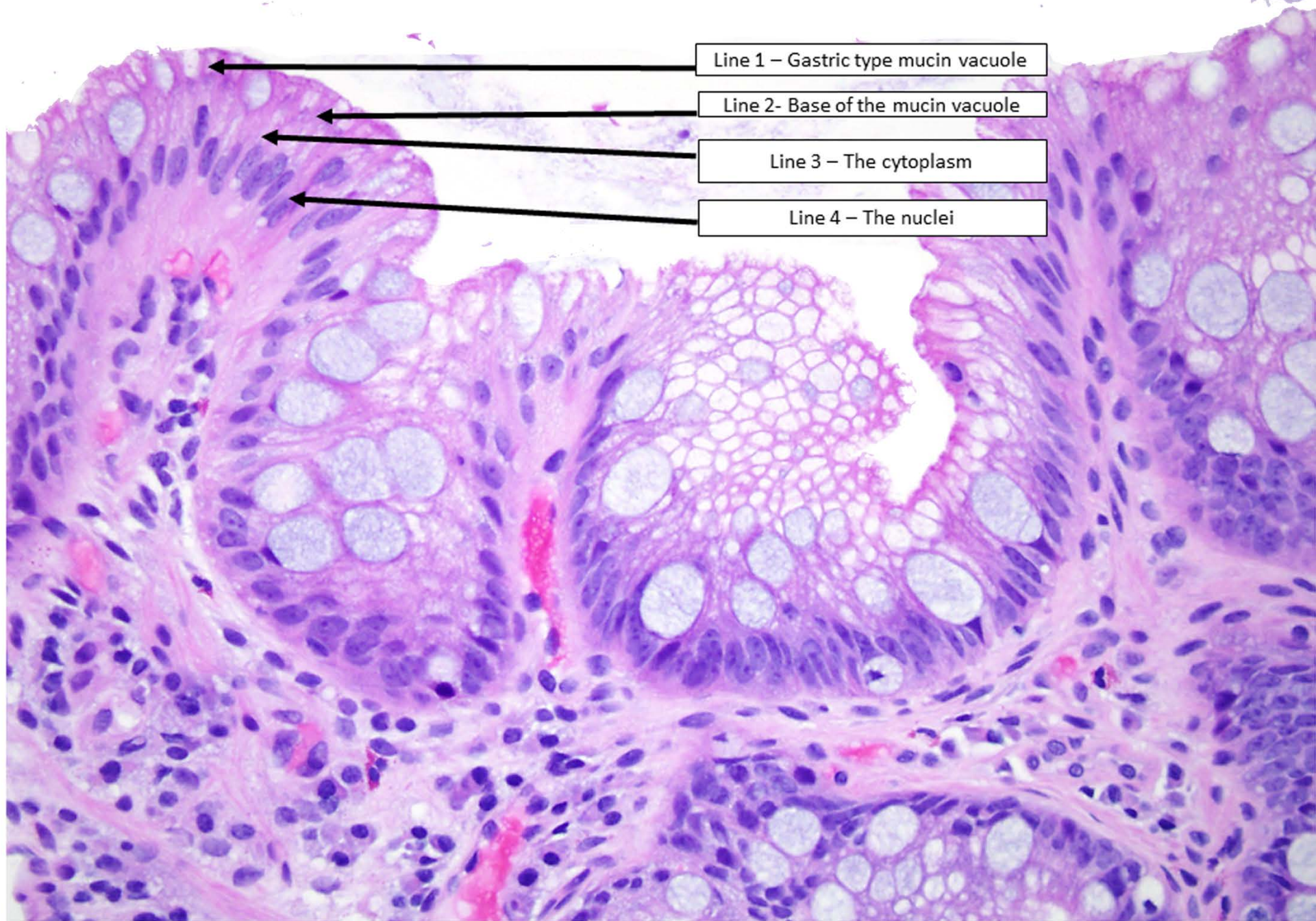
A fantastic clue

- 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







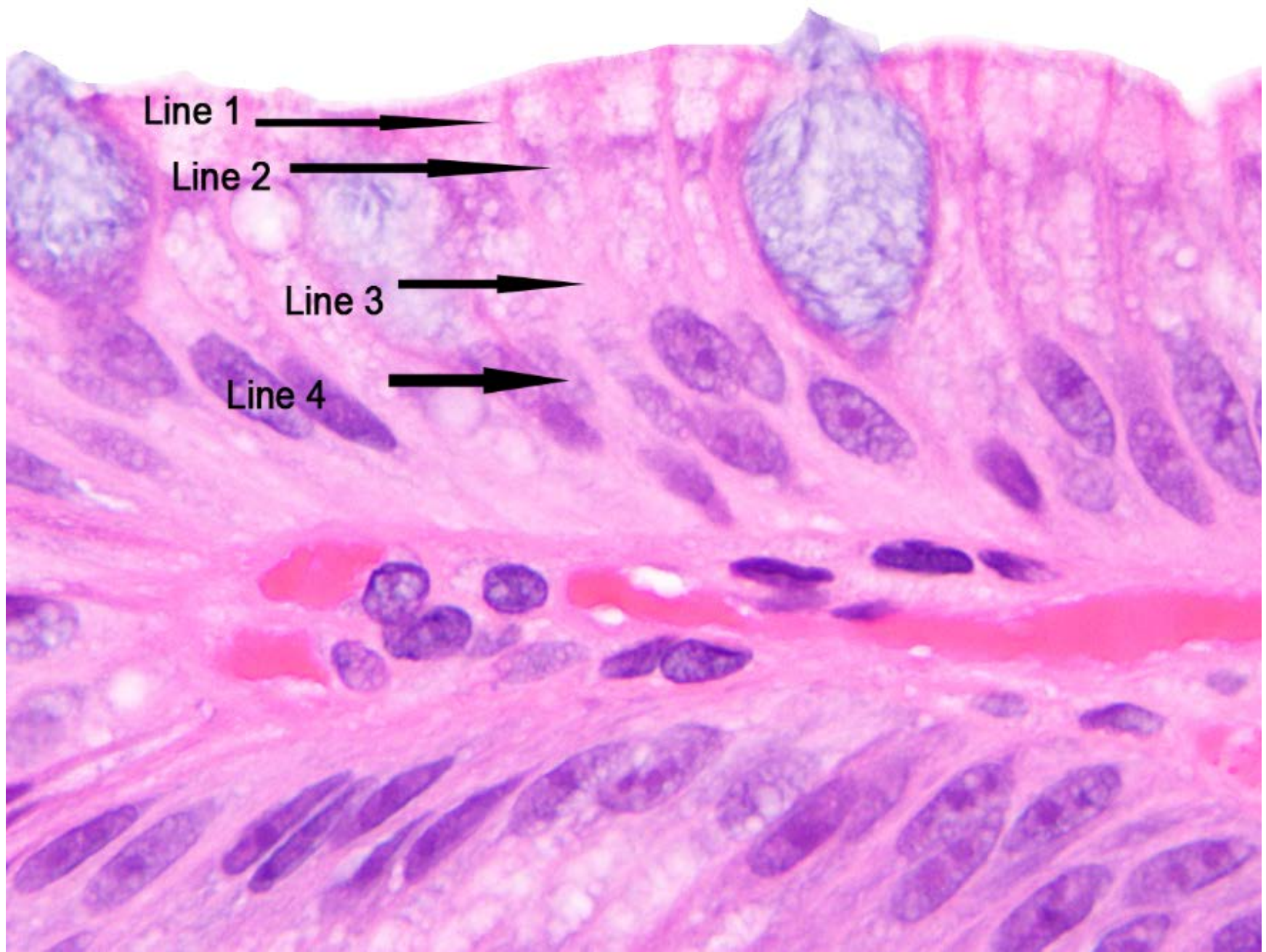


Line 1 – Gastric type mucin vacuole

Line 2- Base of the mucin vacuole

Line 3 – The cytoplasm

Line 4 – The nuclei



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

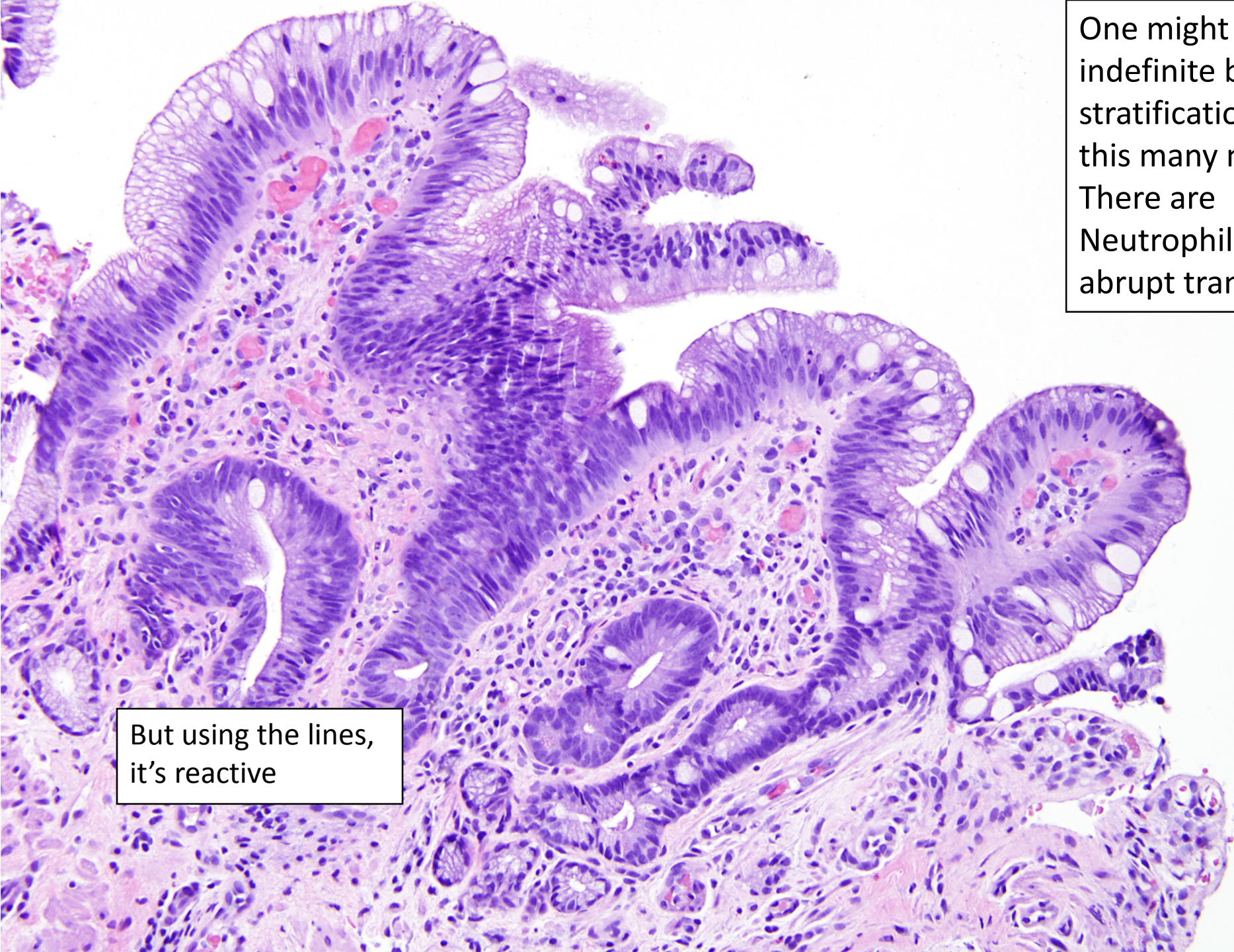
But.....

- 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.

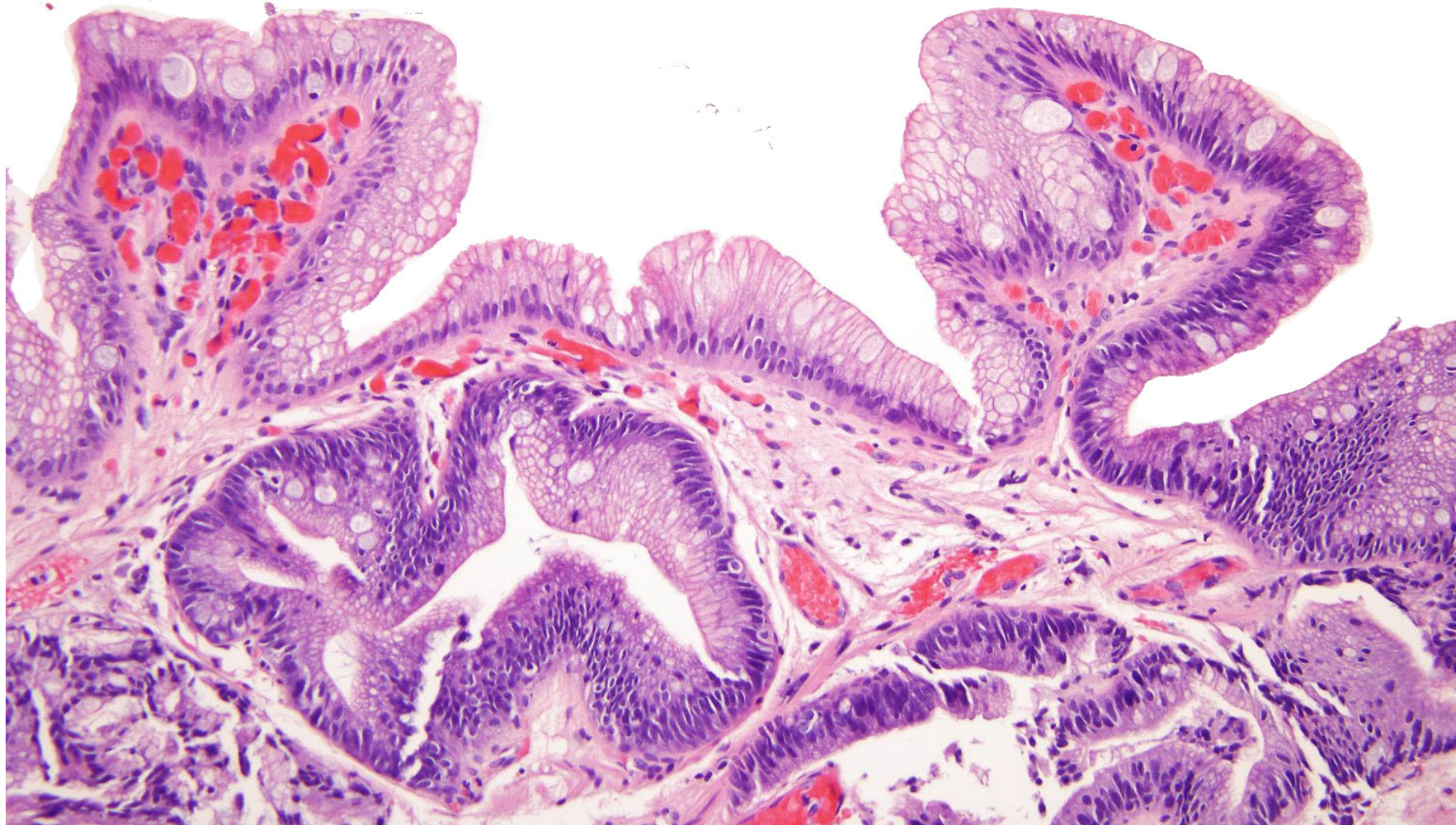
BE, Indefinite for Dysplasia

- 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**

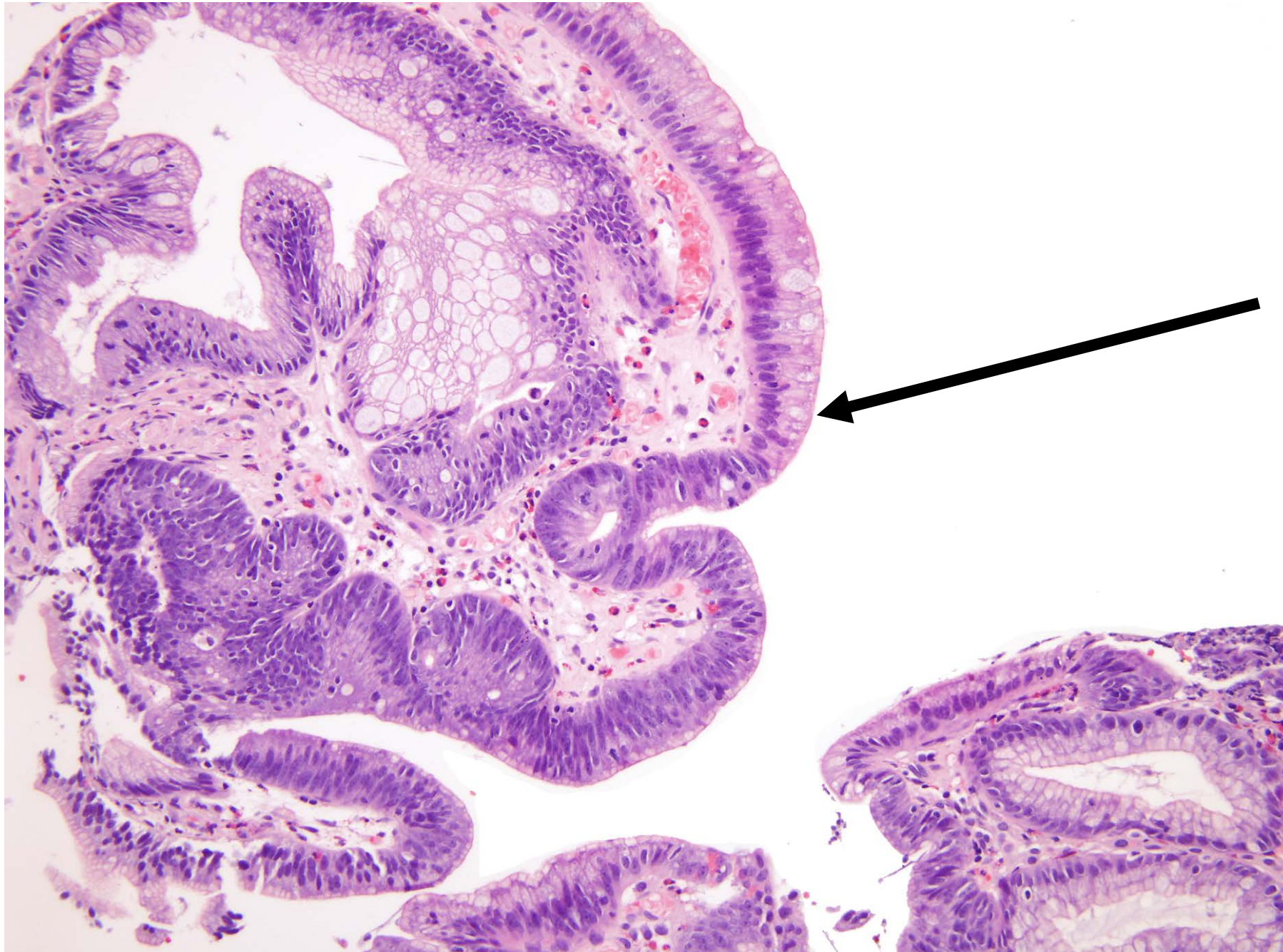


One might call indefinite because of stratification (we did this many many times). There are Neutrophils and no abrupt transition

But using the lines, it's reactive



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

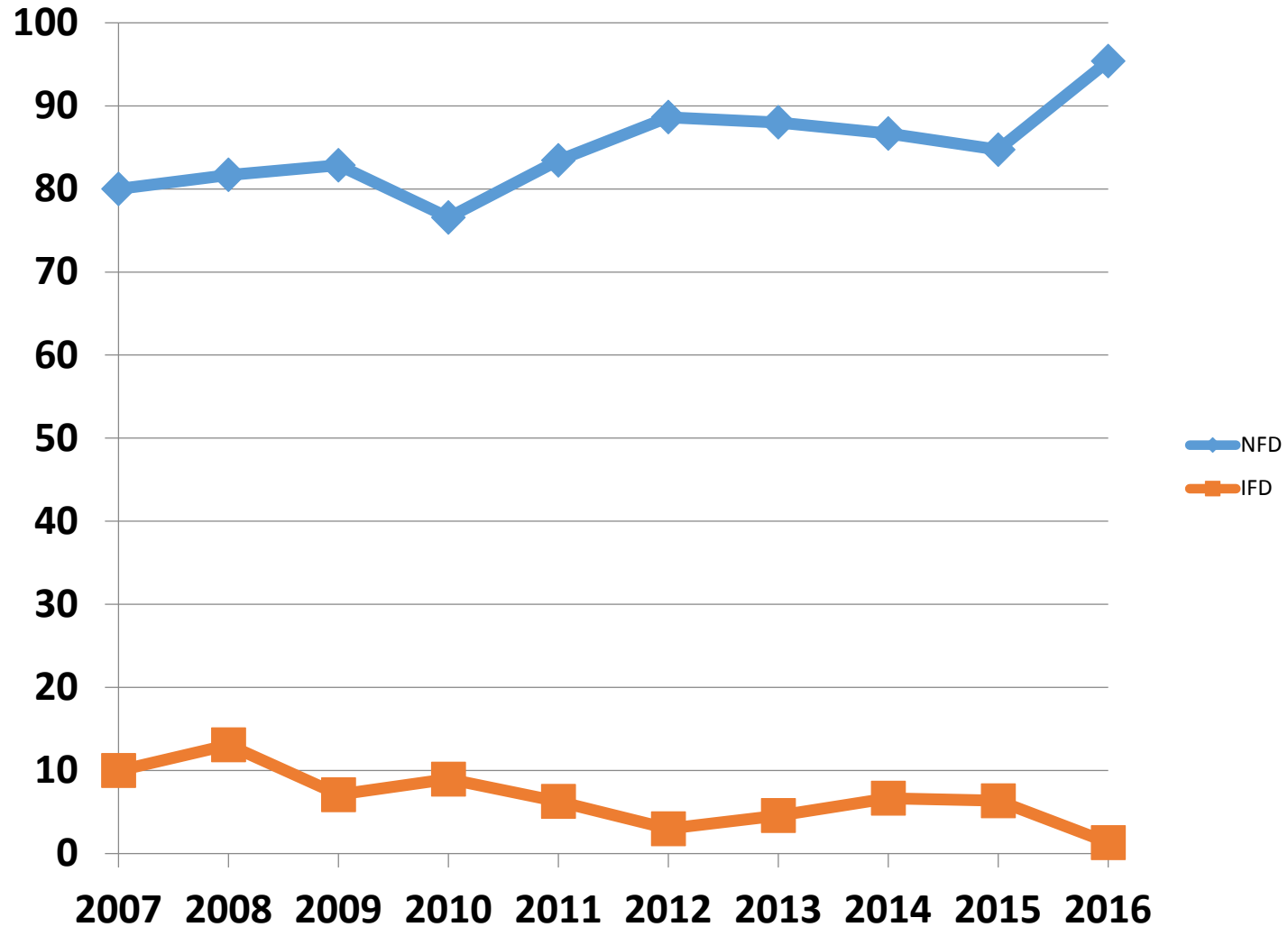


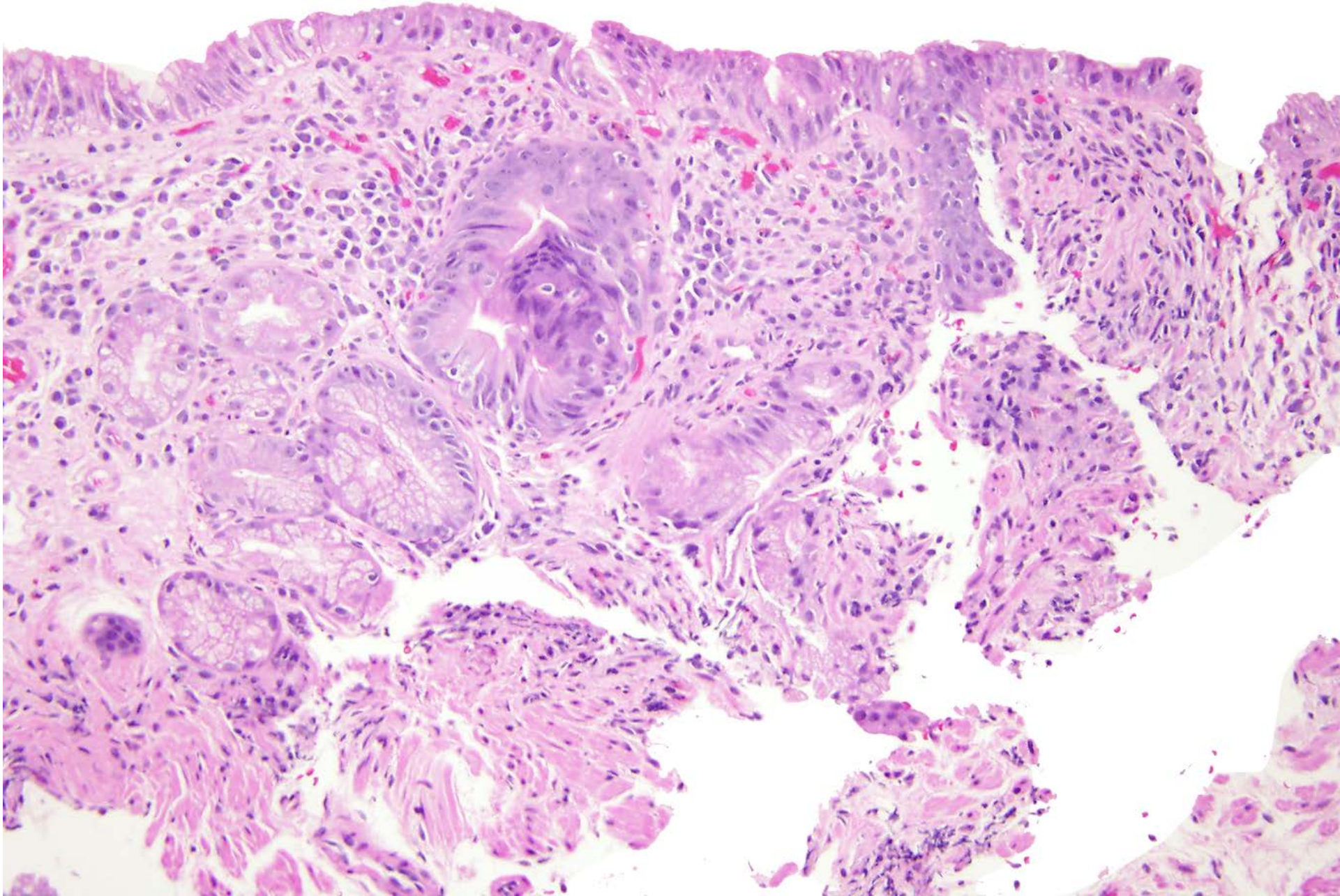
Dysplasia - Sharp demarcation of zone of abnormal nuclei

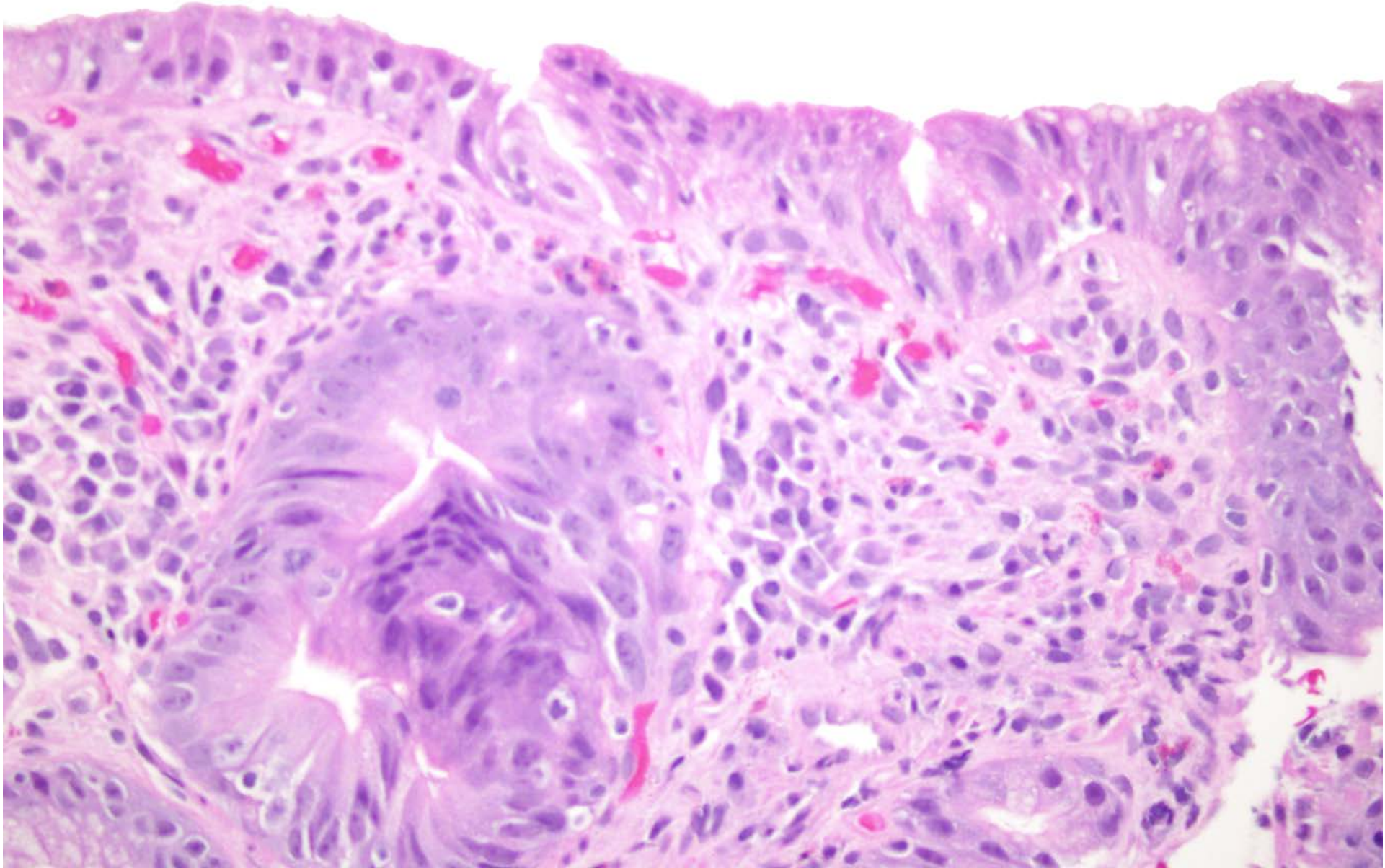
Our dirty laundry

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





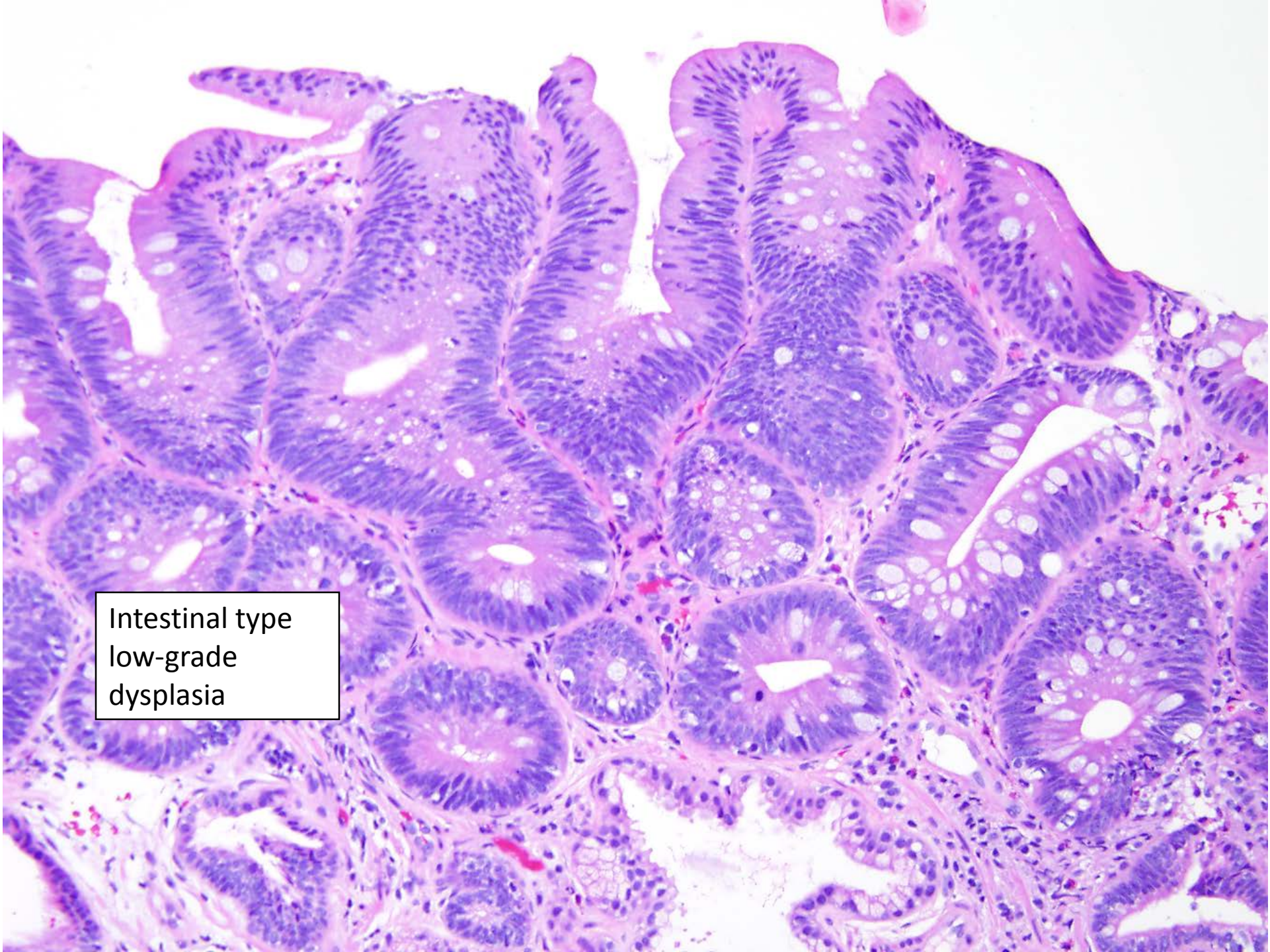


Ideally: Quality Assurance in A Typical Pathology Practice

- <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.

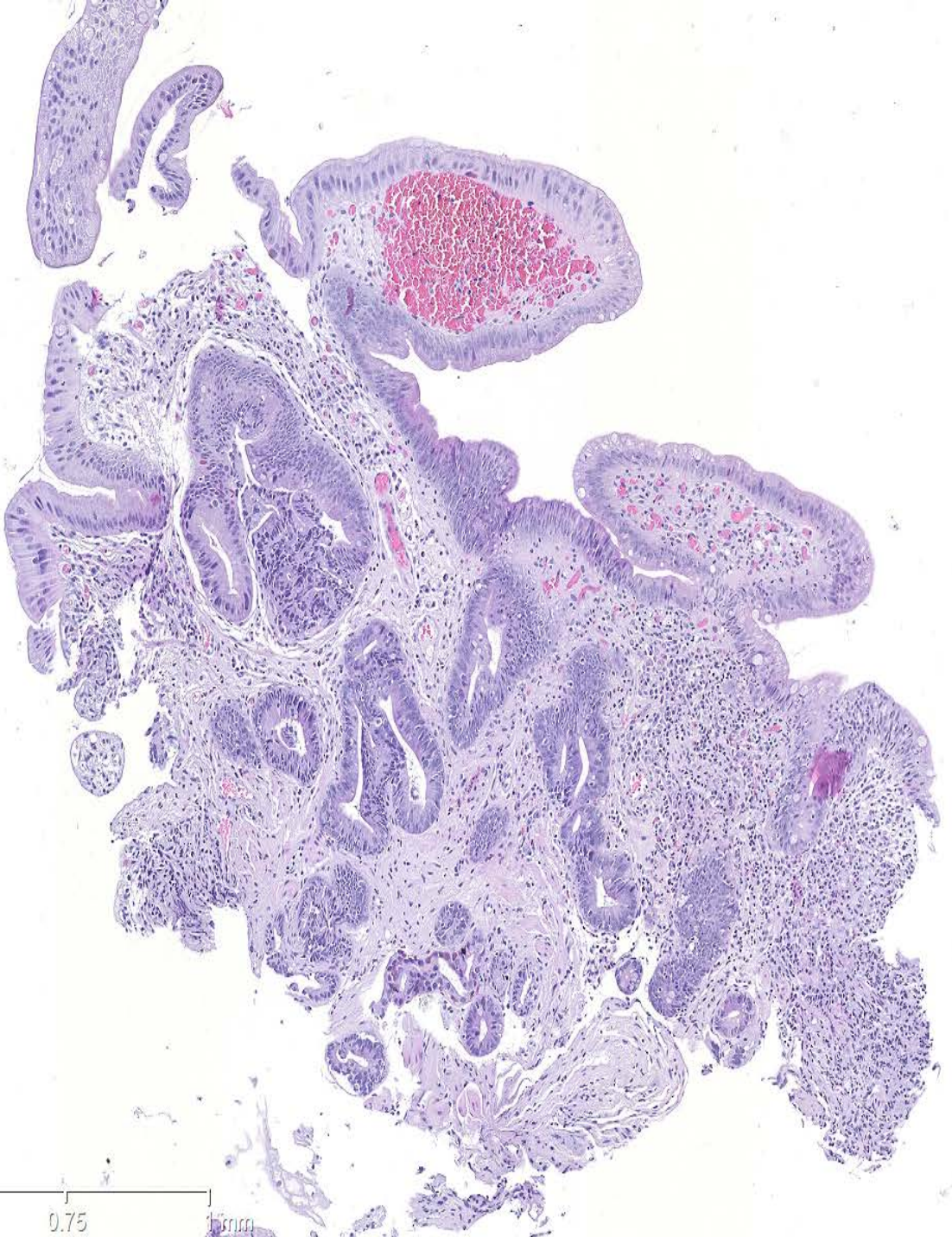
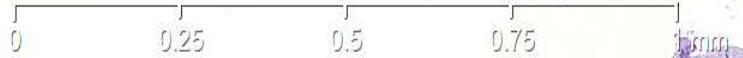
Additionally

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

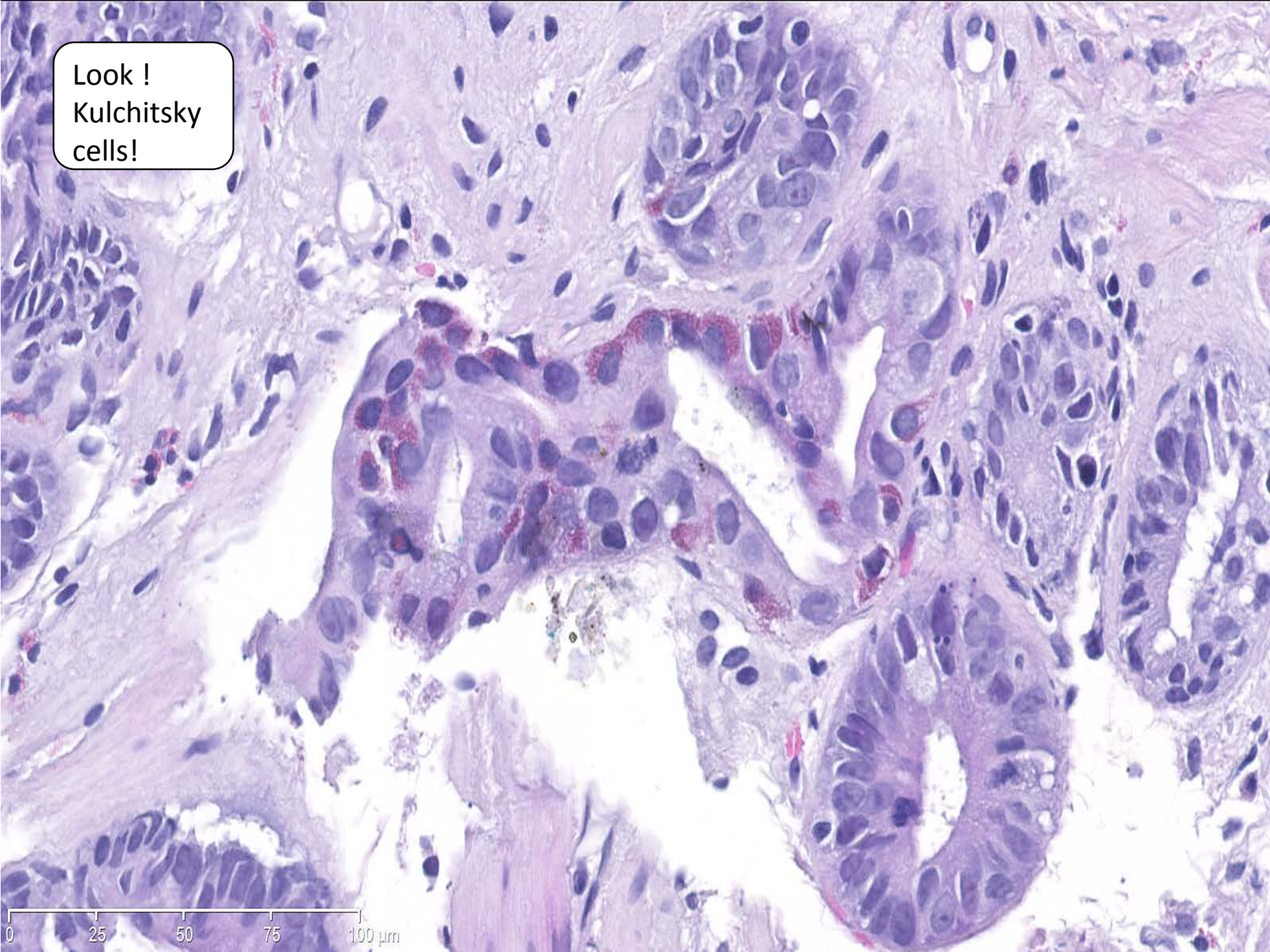


Intestinal type
low-grade
dysplasia

Intestinal
type HGD

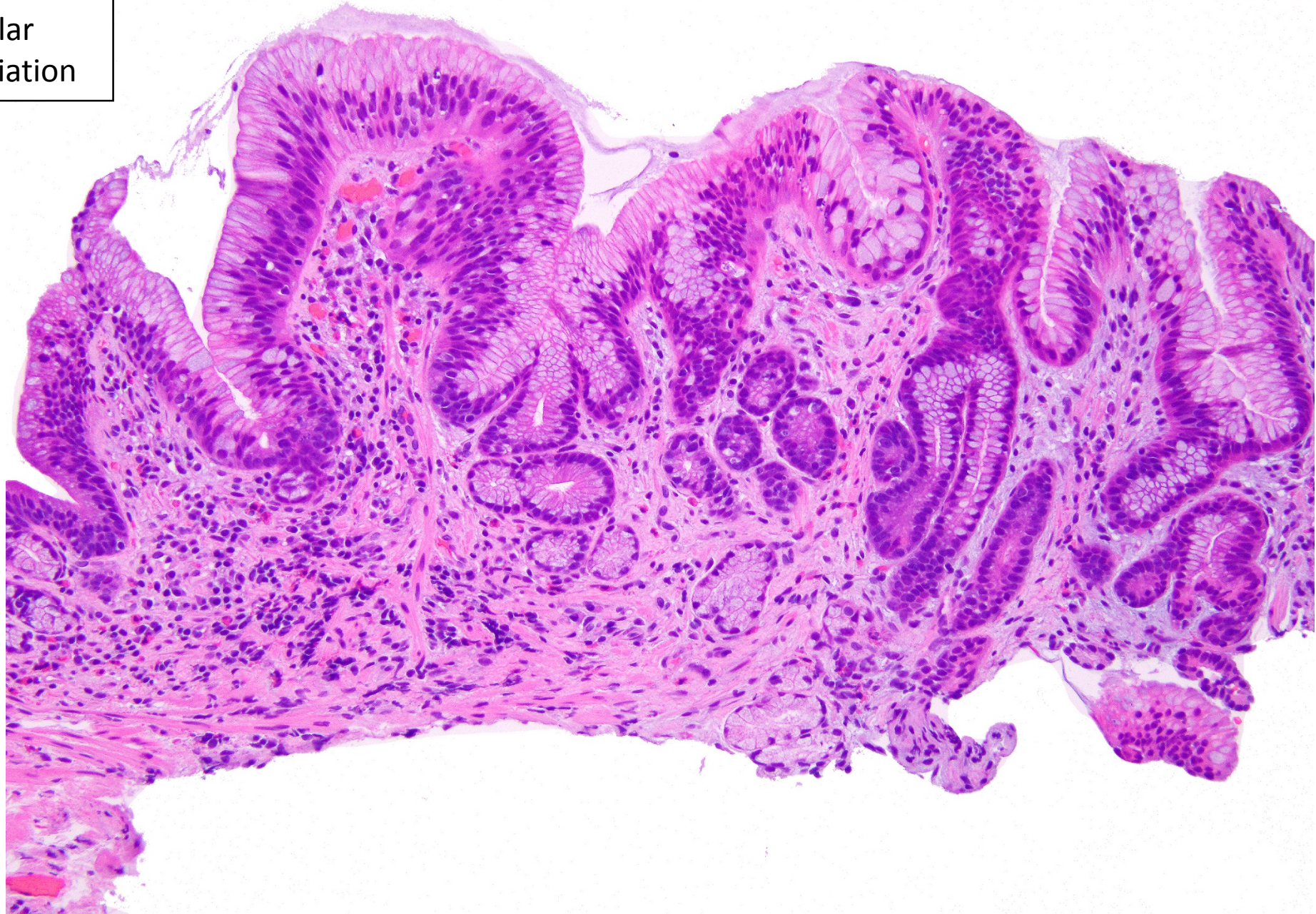


Look !
Kulchitsky
cells!

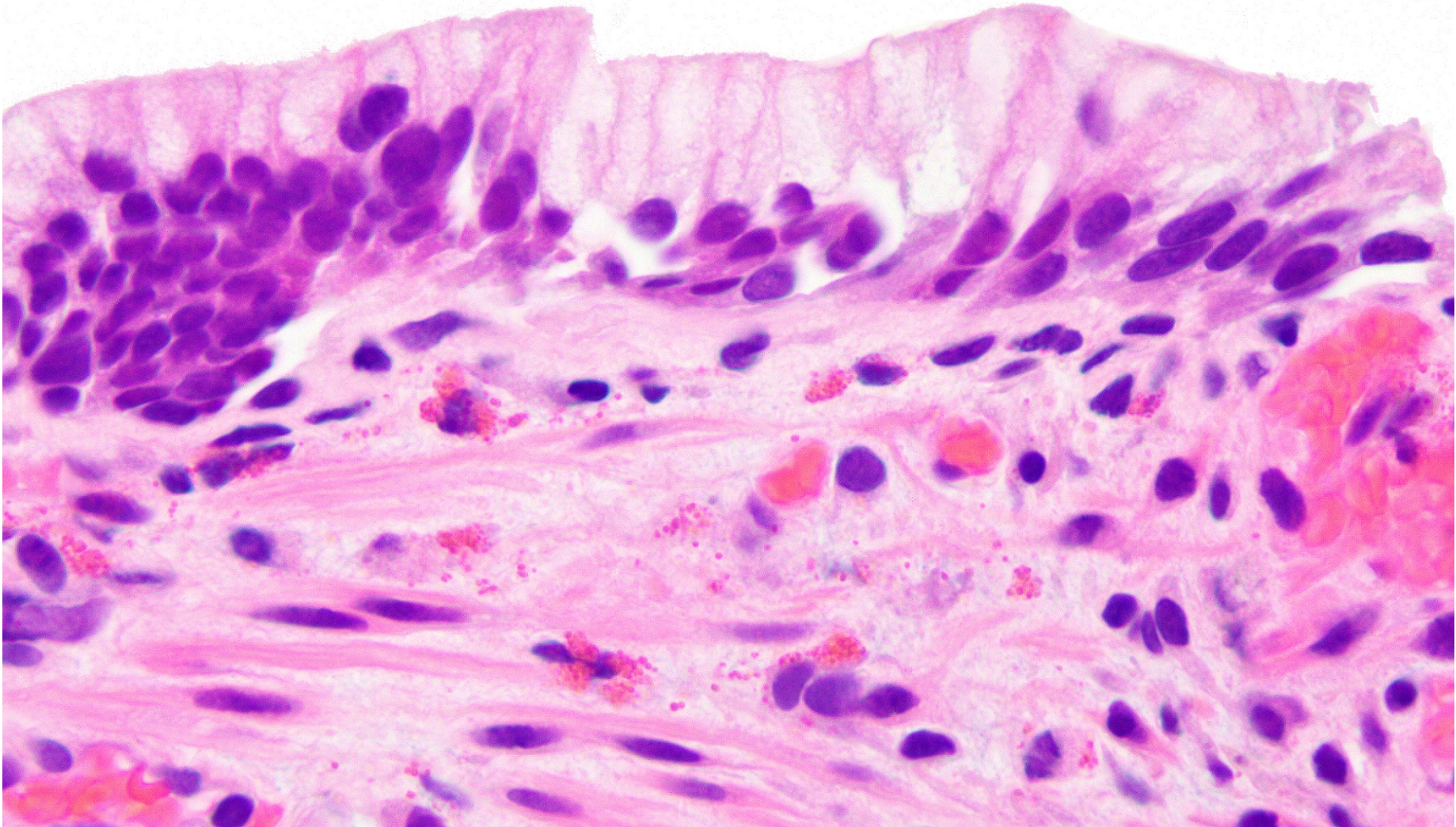


0 25 50 75 100 μm

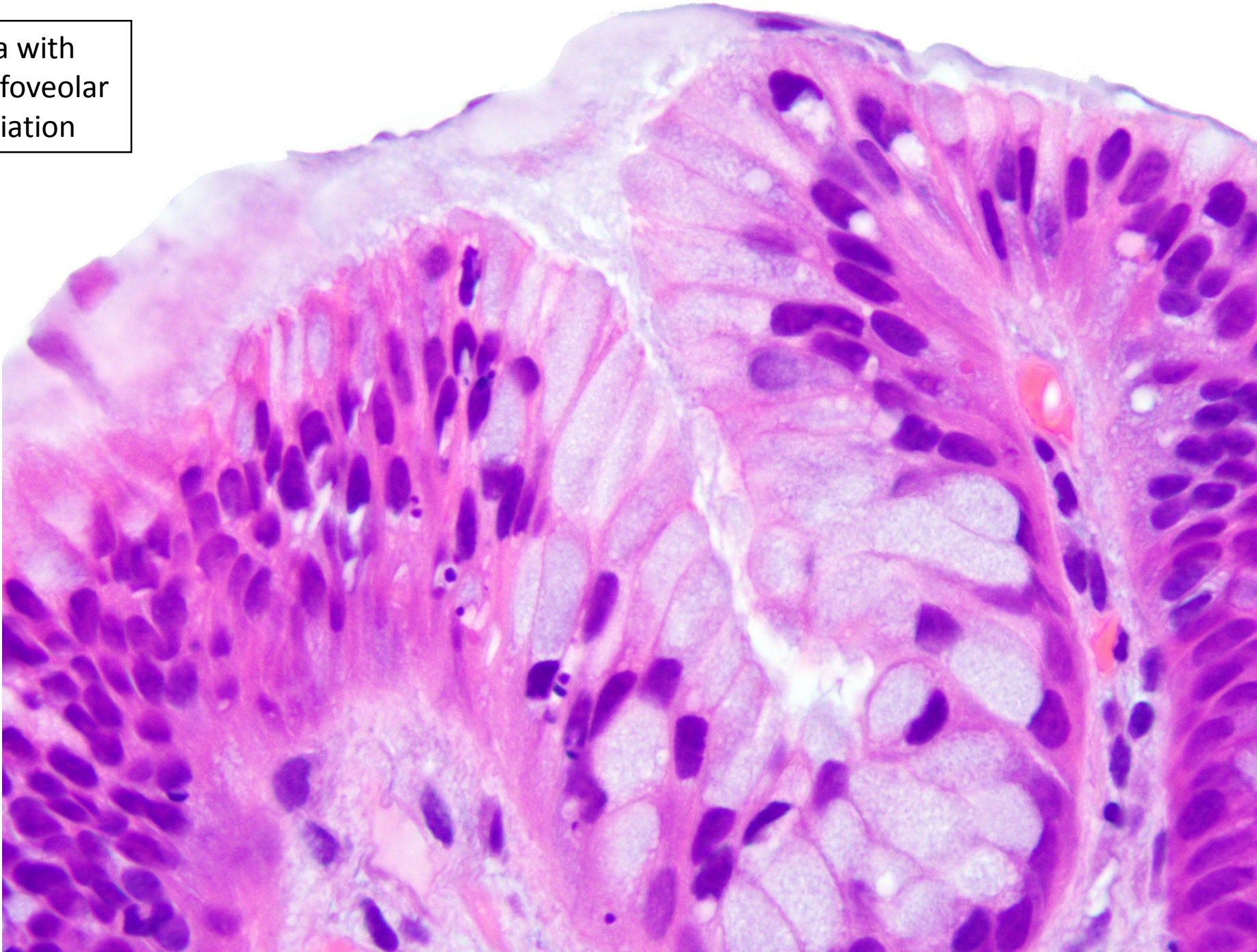
Dysplasia with
prominent
foveolar
differentiation



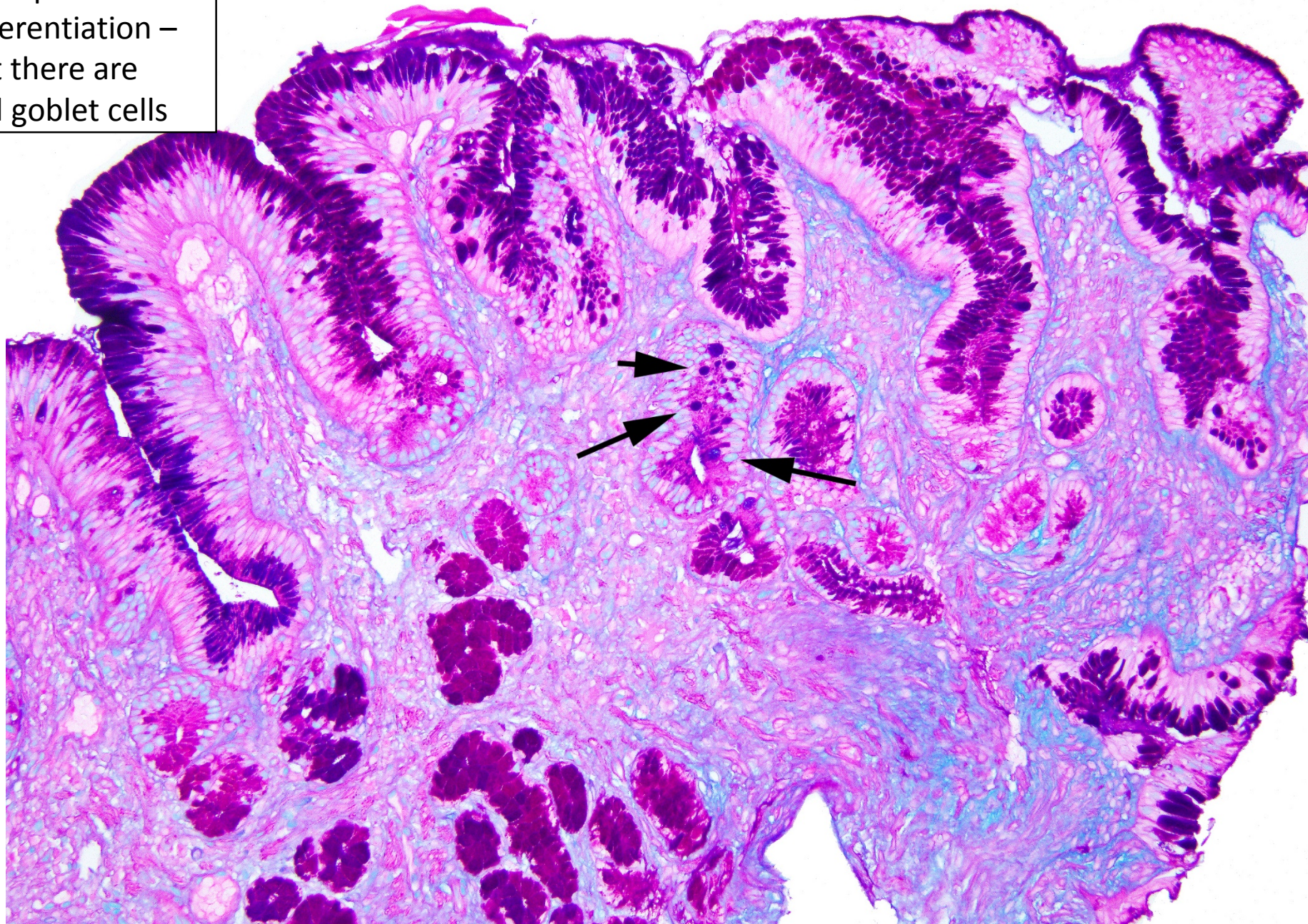
Dysplasia with
prominent foveolar
differentiation

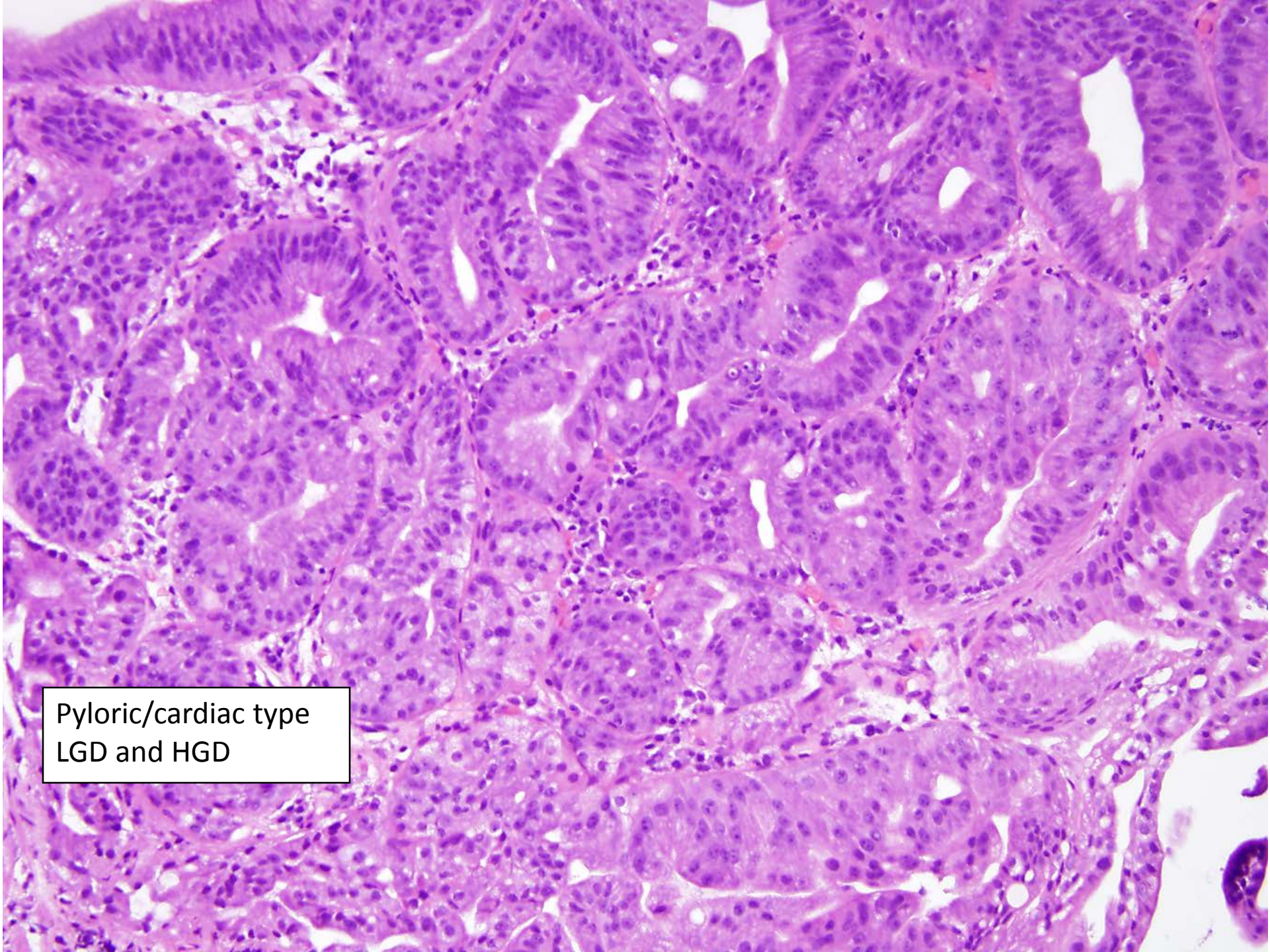


Dysplasia with prominent foveolar differentiation

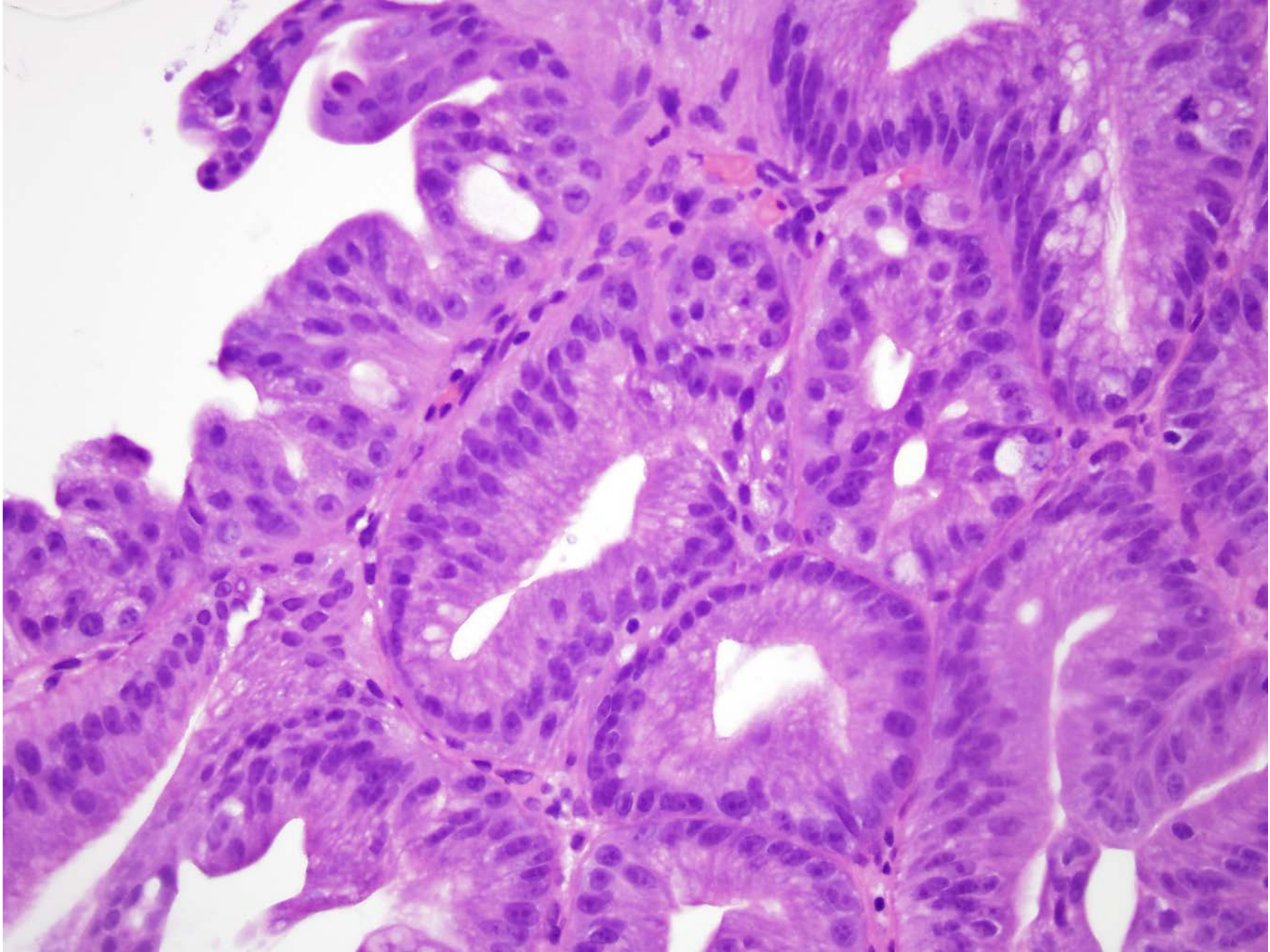


Dysplasia with prominent
foveolar differentiation –
Note that there are
background goblet cells





Pyloric/cardiac type
LGD and HGD

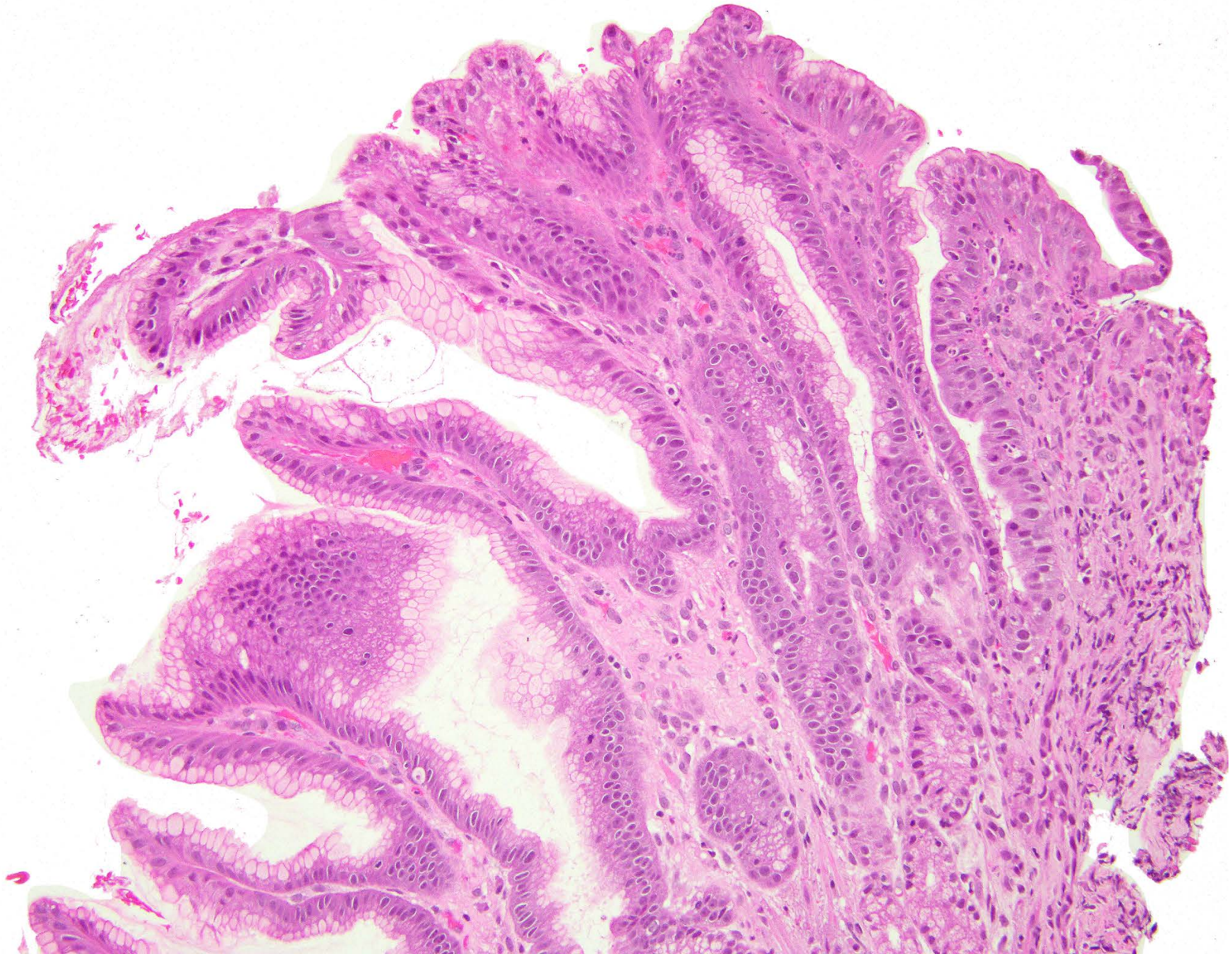


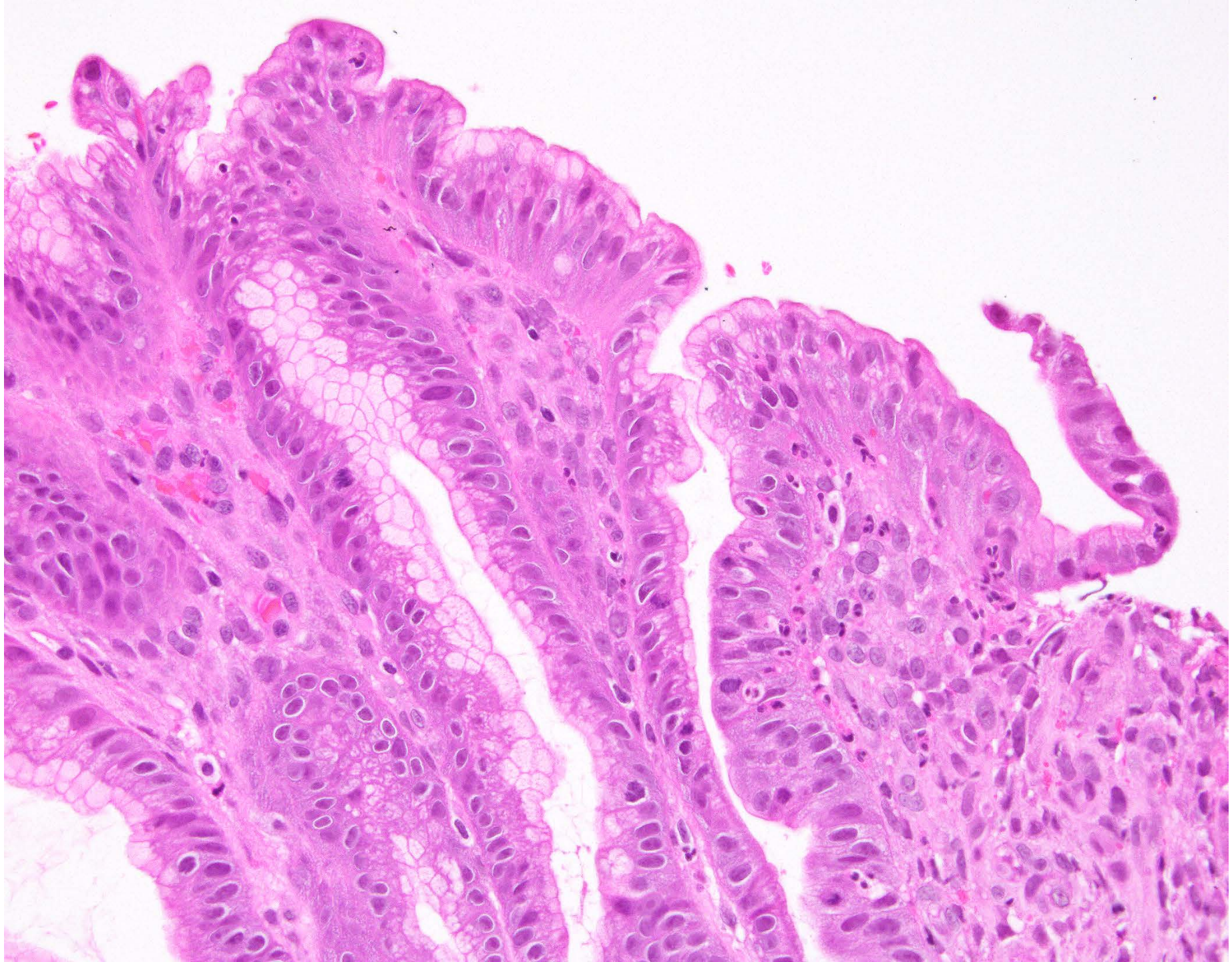
A few comments on stomach

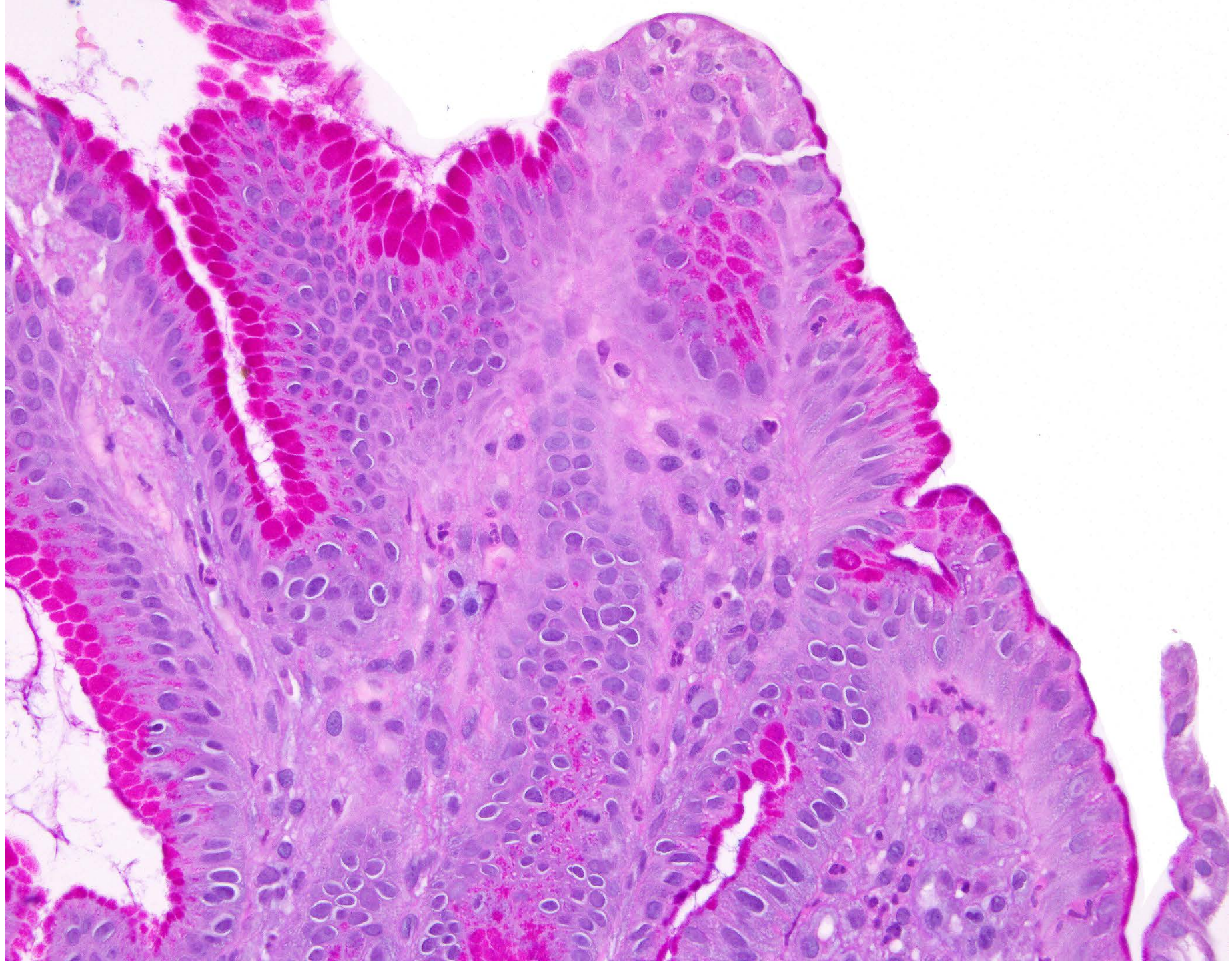
Can we use “the lines” for gastric biopsies?

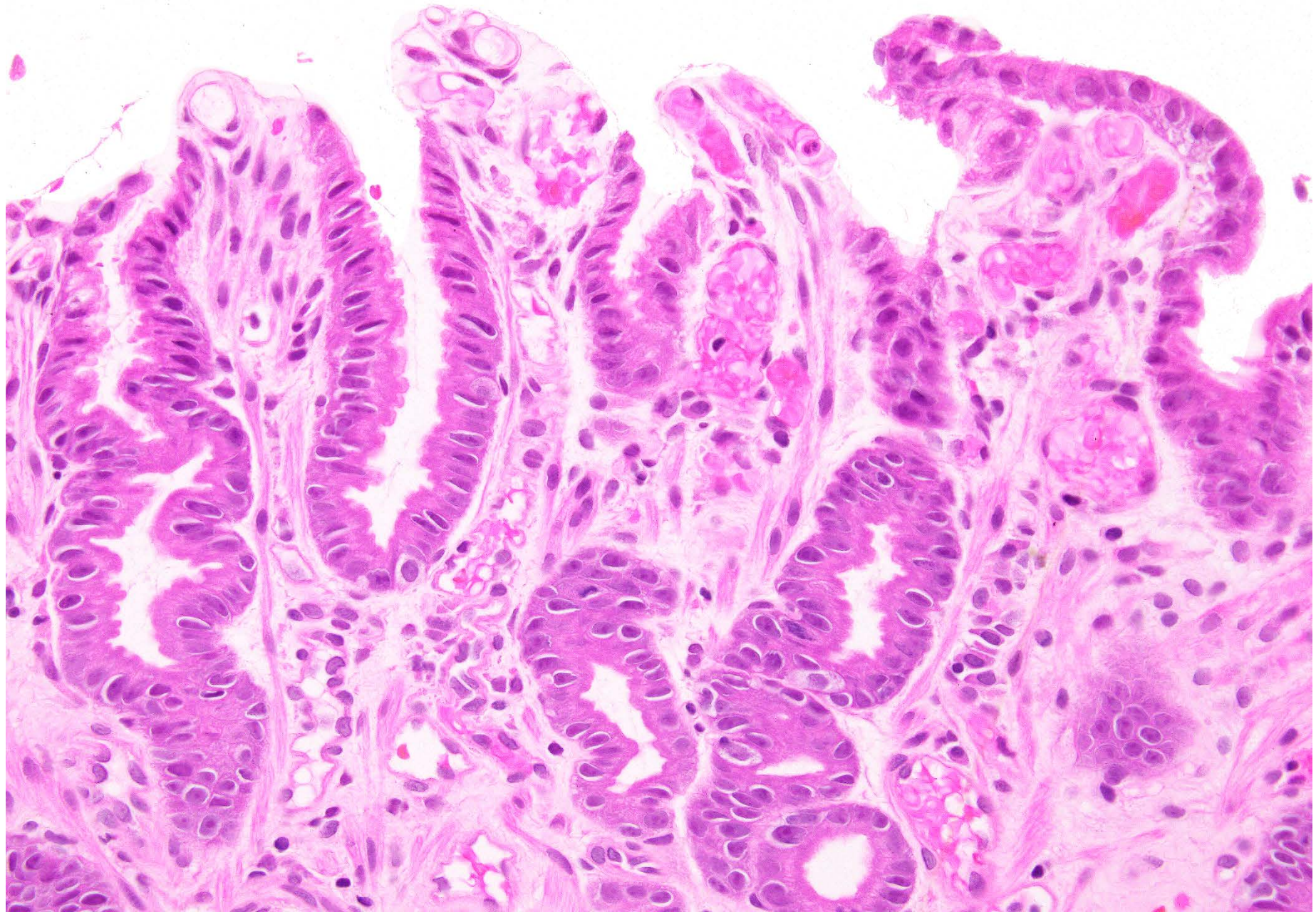
- Not as nicely as in the esophagus but in general – YES!
- **Abstract #:** 1399
Abstract Title: Assessment of Surface Cell Polarity (the “Four Lines”) Distinguishes Gastric Dysplasia from Reactive Gastropathy: A Comprehensive 2 Institution 5-Year (2008-2012) Histologic and Clinical Review
Poster Board #: 131
Presentation Details: Poster Session on Tuesday, March 03, 2020 from 1:00 PM - 4:30 PM at the Los Angeles Convention Center in West Exhibit Hall A

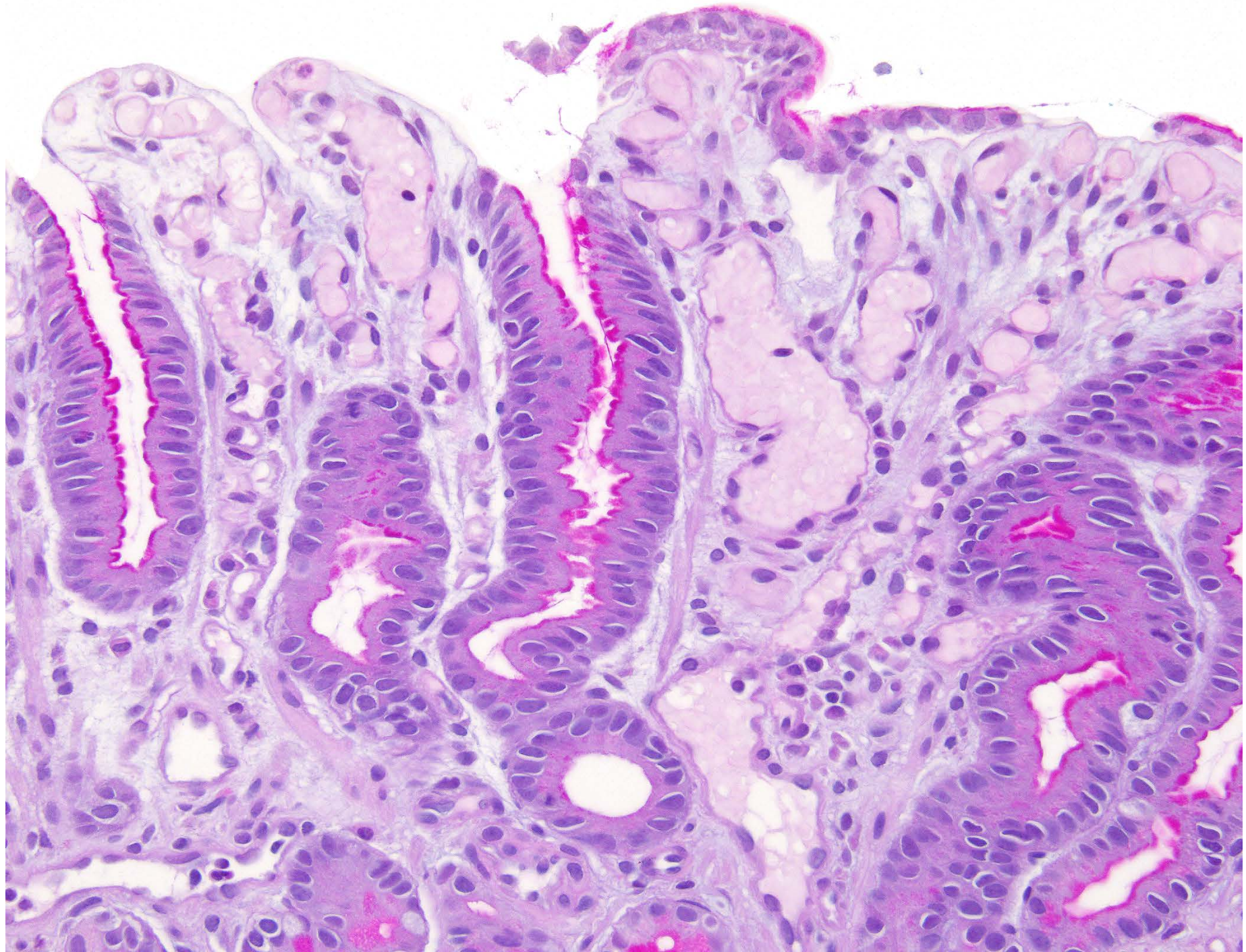
Presenting Author: Kevin Waters

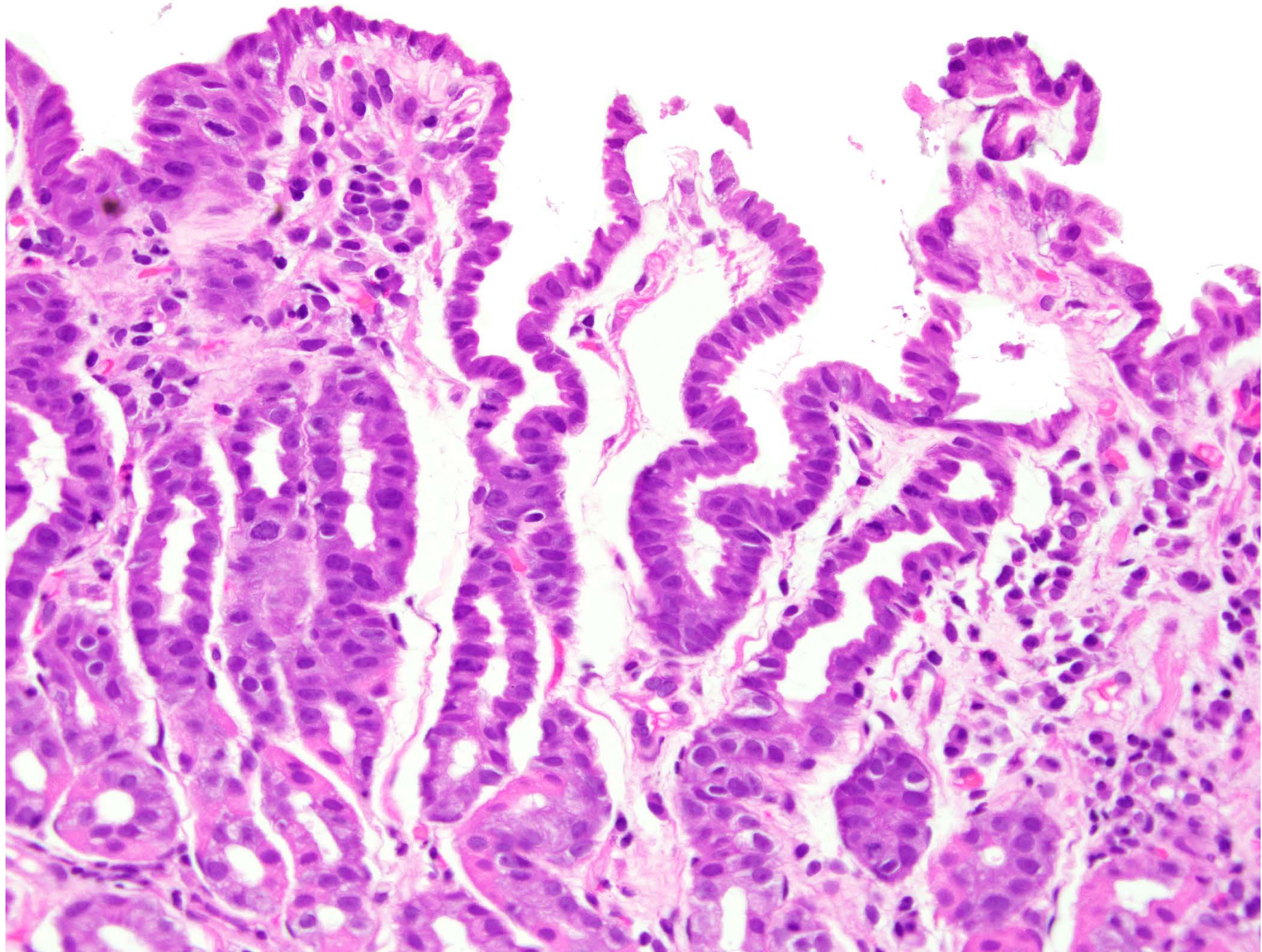


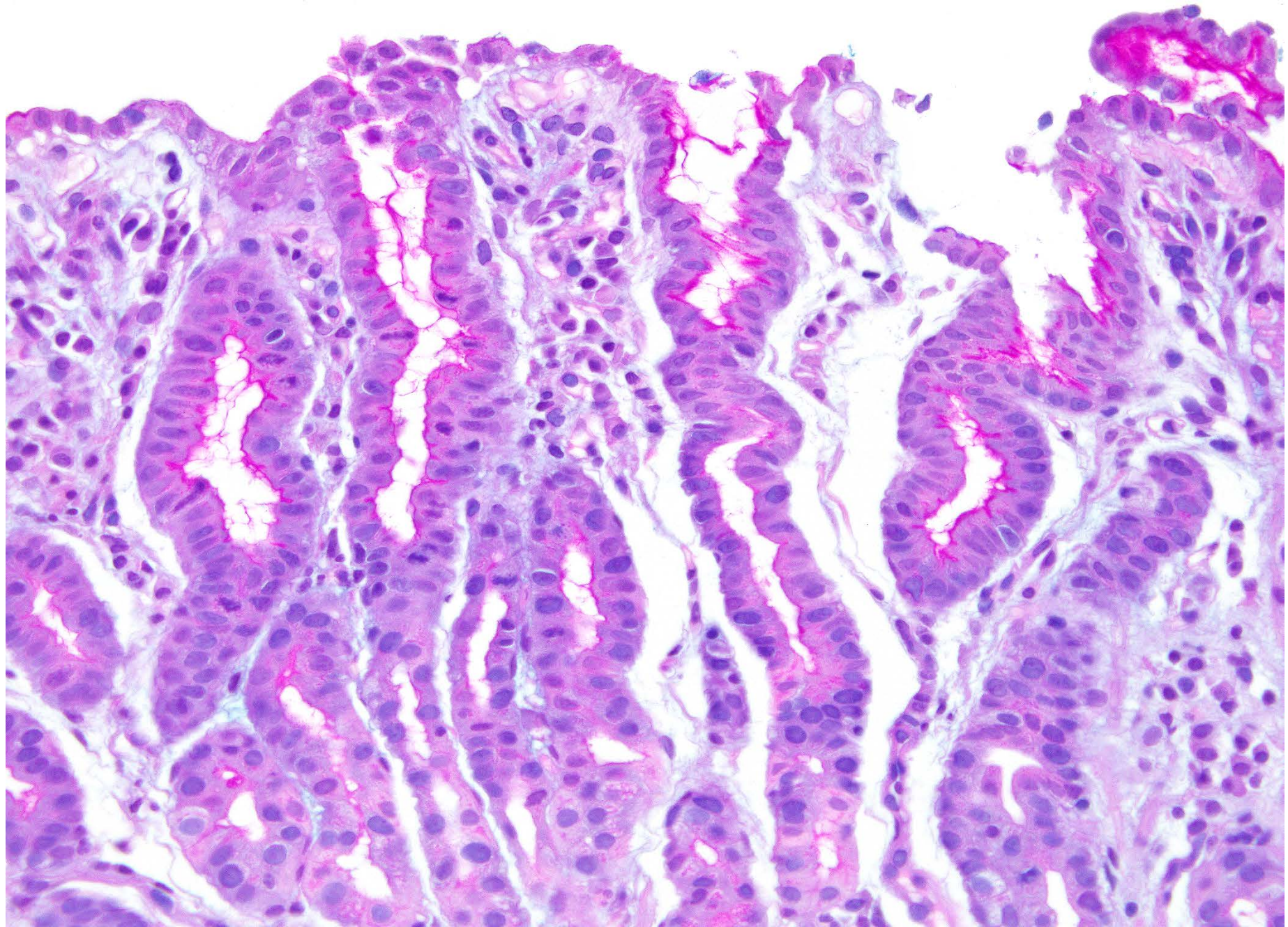












Gastric adenomas and dysplasias

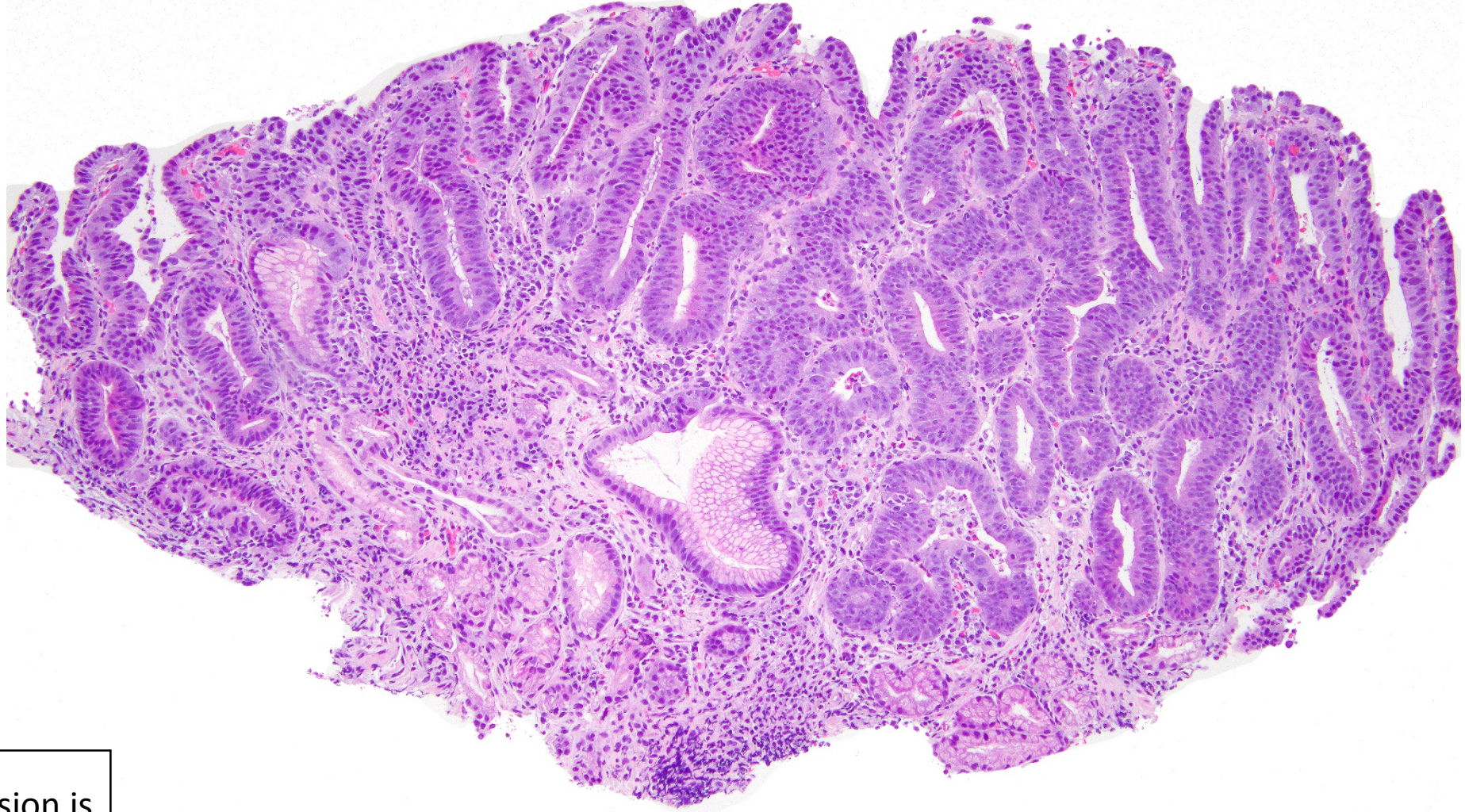
Gastric Adenomas in a Western Population

- 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

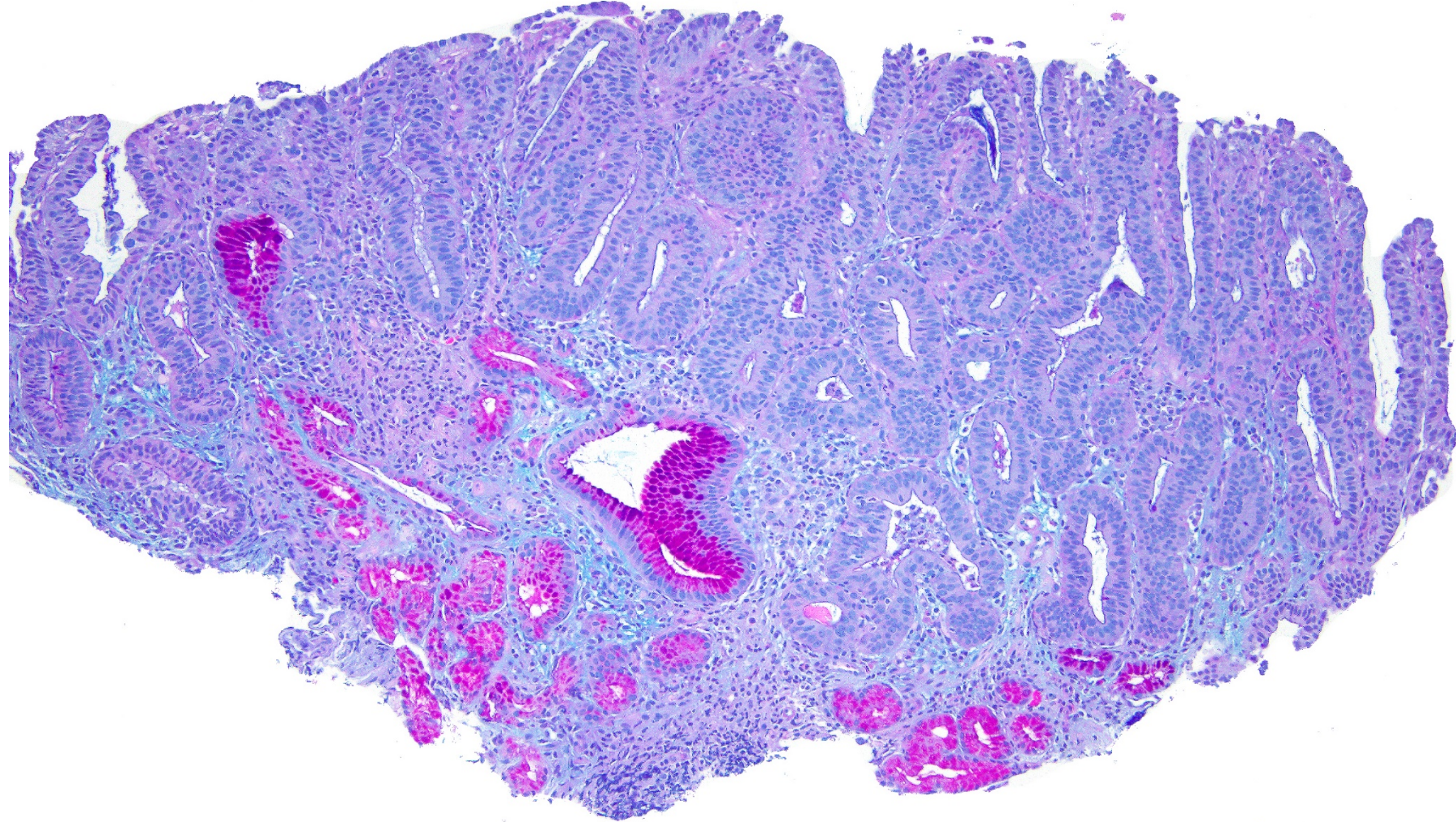
- So if a polyp with pyloric gland differentiation is found in a patient with autoimmune gastritis it is a “lesion” and the same polyp in a patient with familial adenomatous polyposis and no gastritis is an adenoma?
- So if a polyp with intestinal differentiation is found in a patient with autoimmune gastritis it is a “lesion” 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.



This lesion is
a polyp

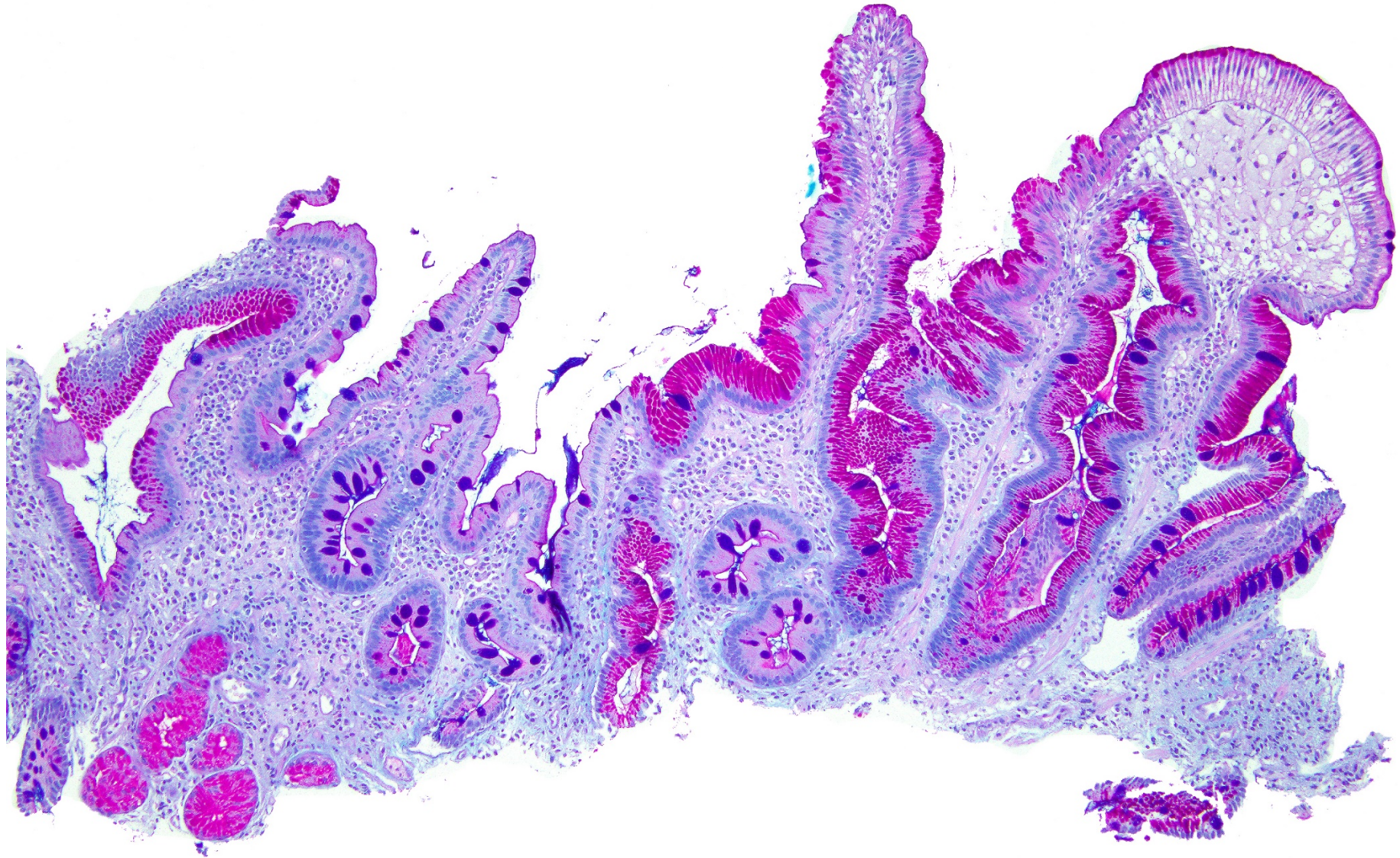
PAS/AB



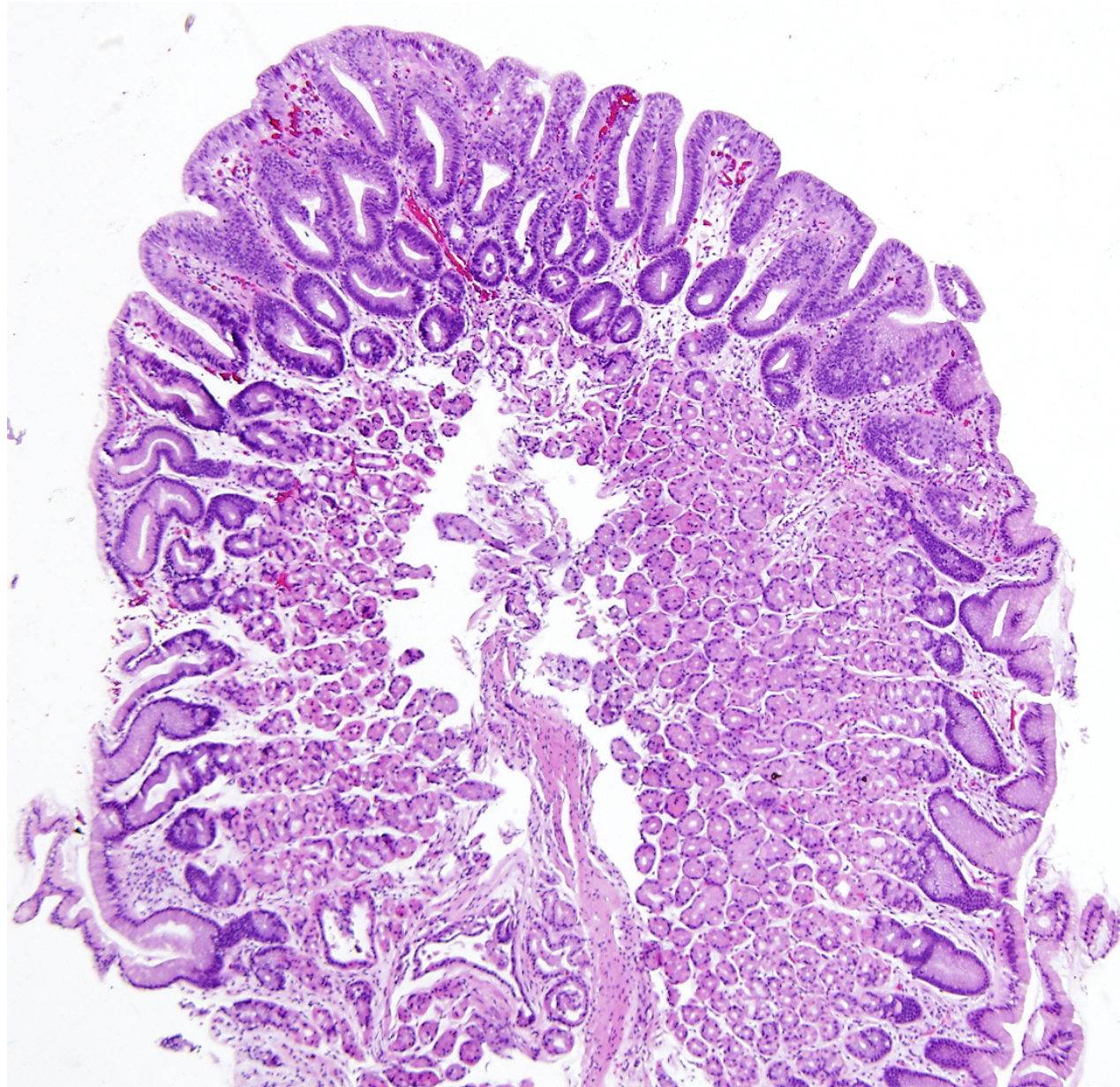


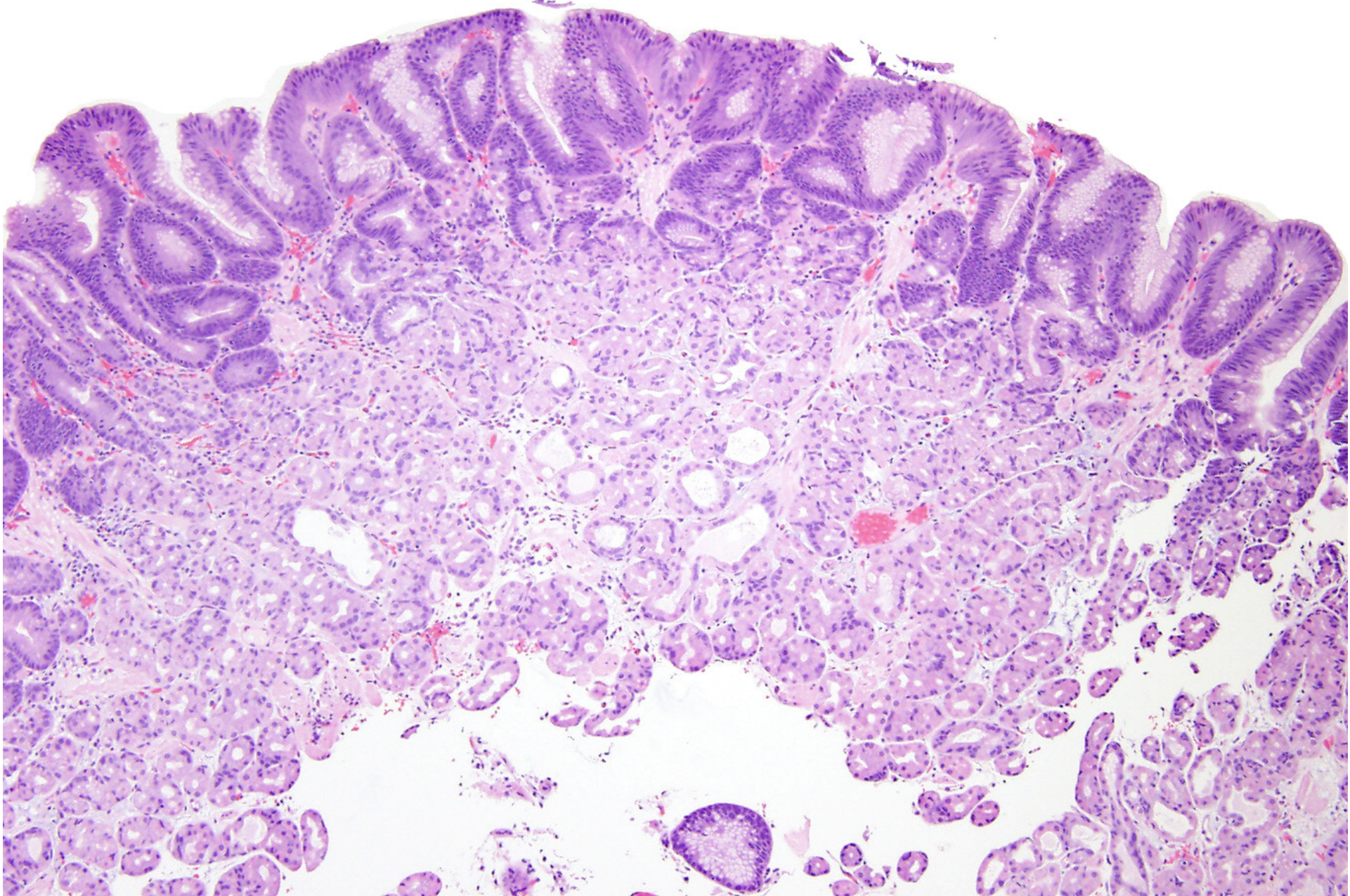
This is the flat mucosa associated with the prior polyp

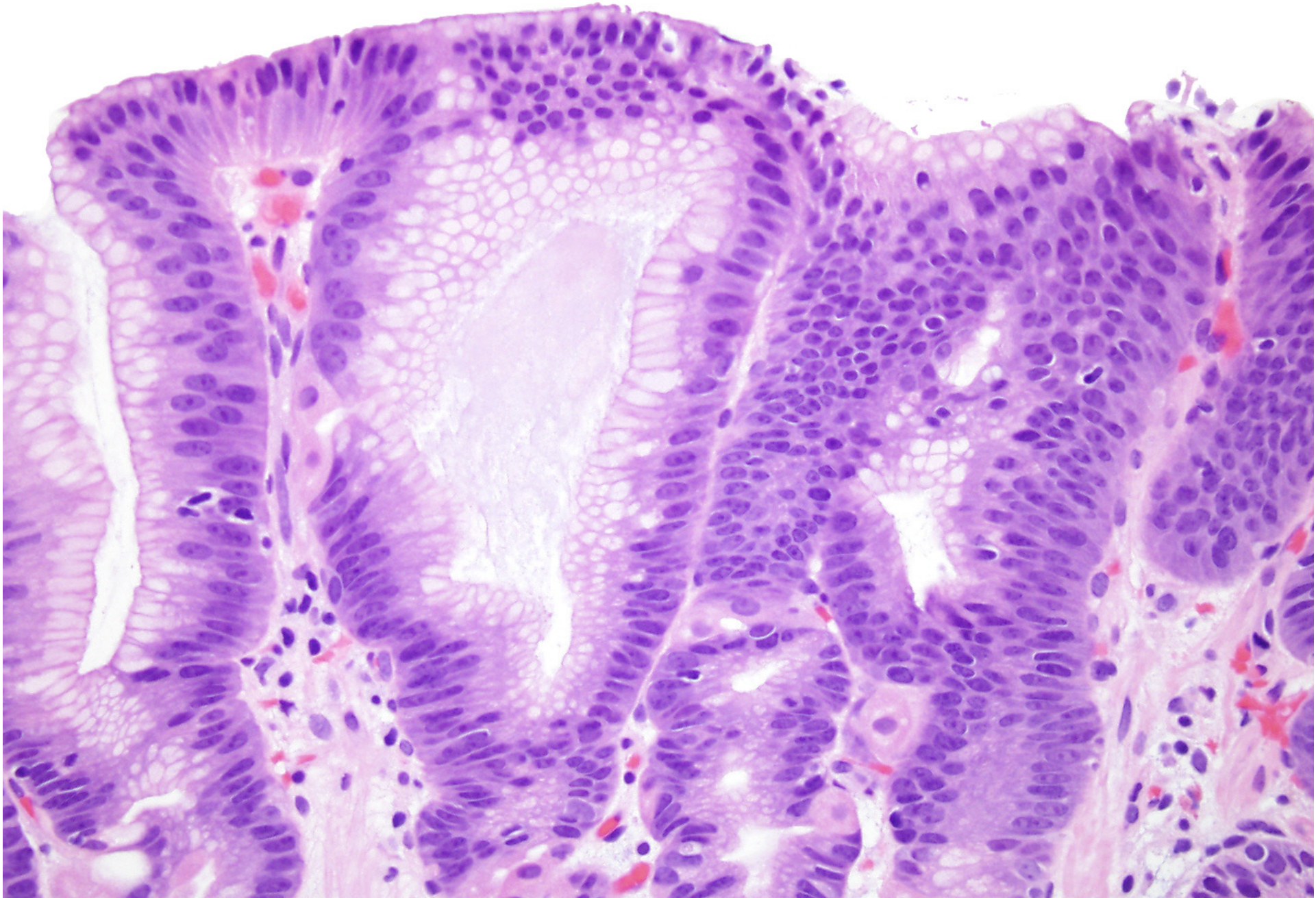
PAS/AB

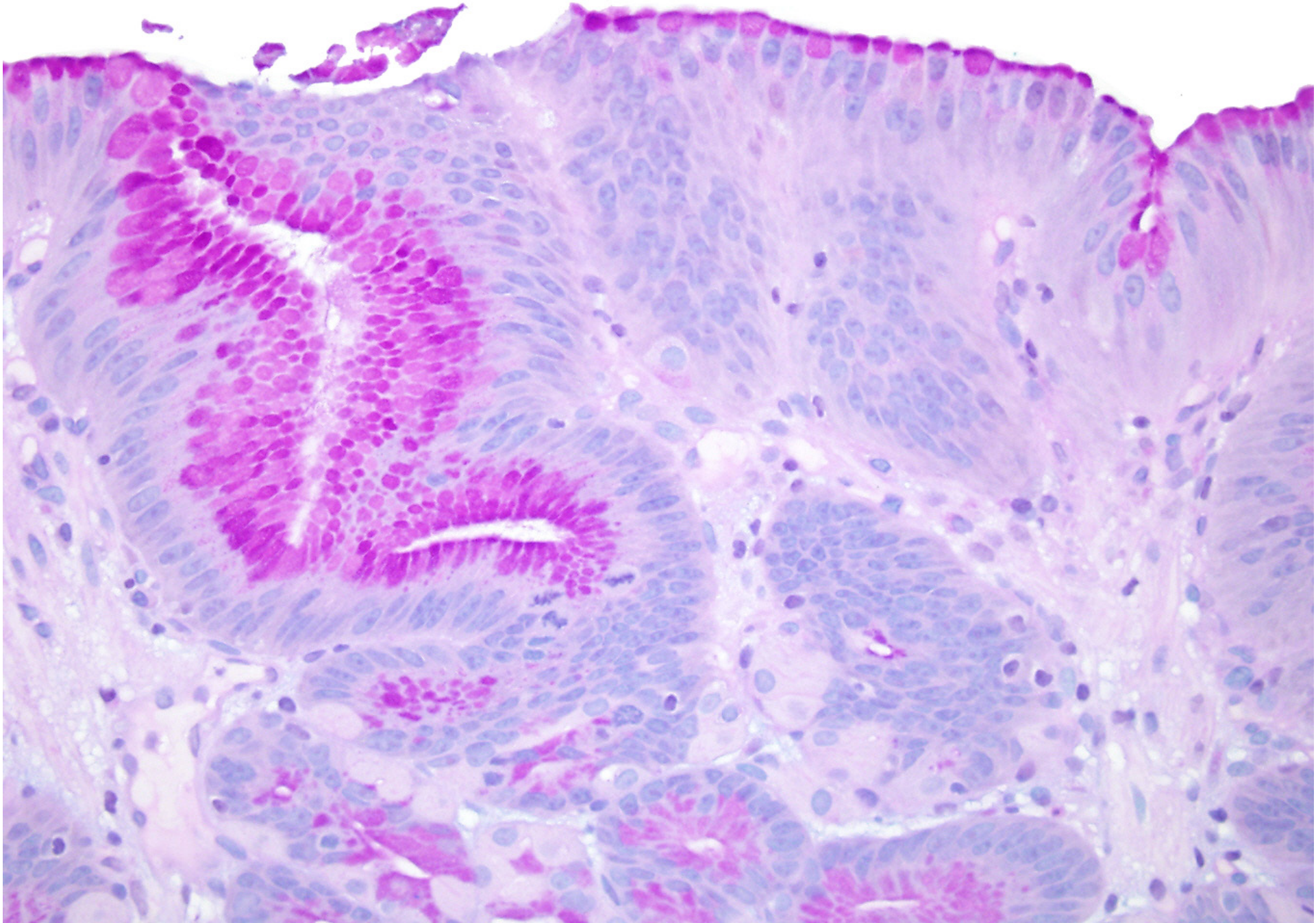


Gastric adenoma,
gastric foveolar type –
pristine background
mucosa, NO intestinal
metaplasia anywhere.
The cells have apical
neutral mucin
In Many ways
equivalent to
colorectal adenomas





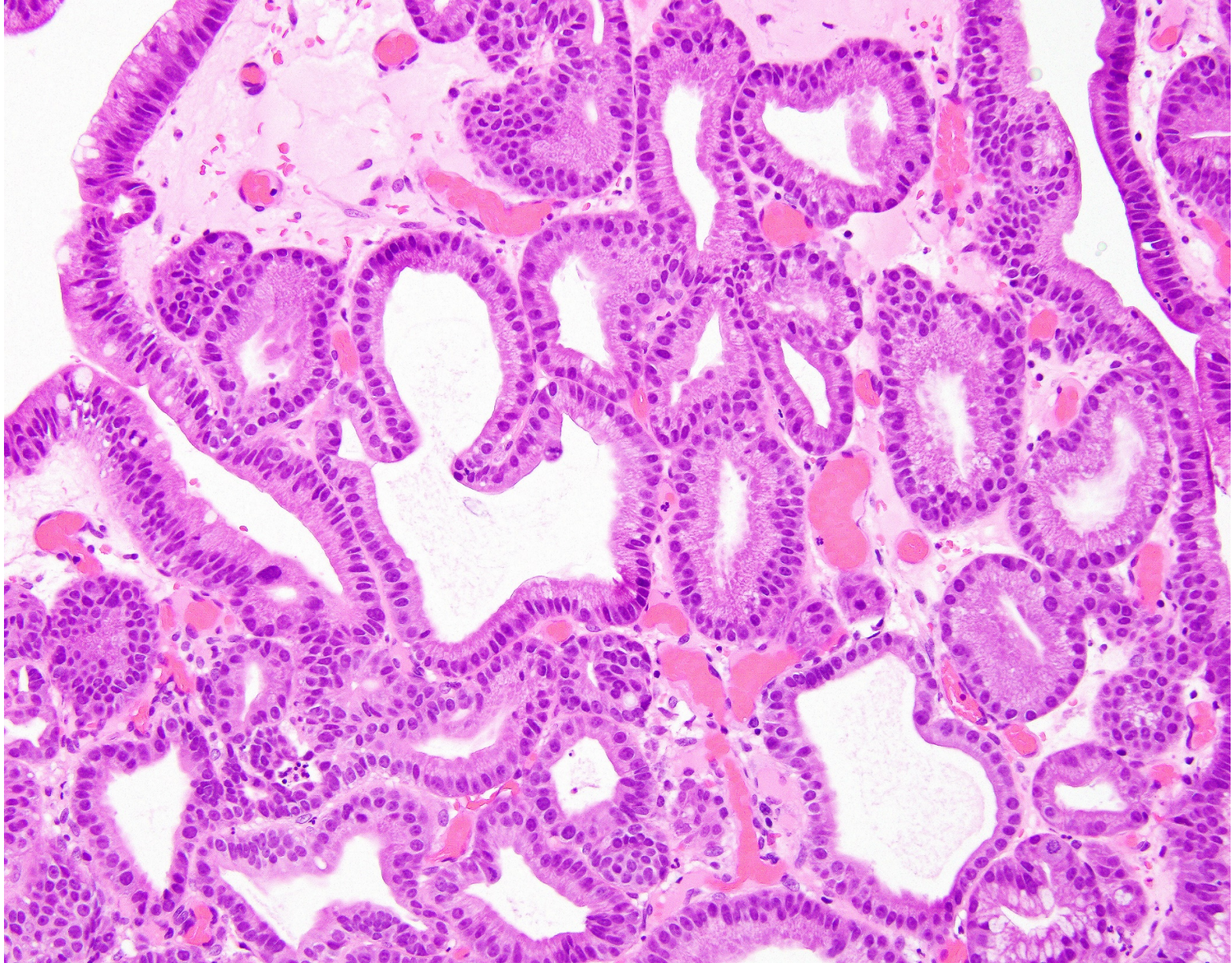


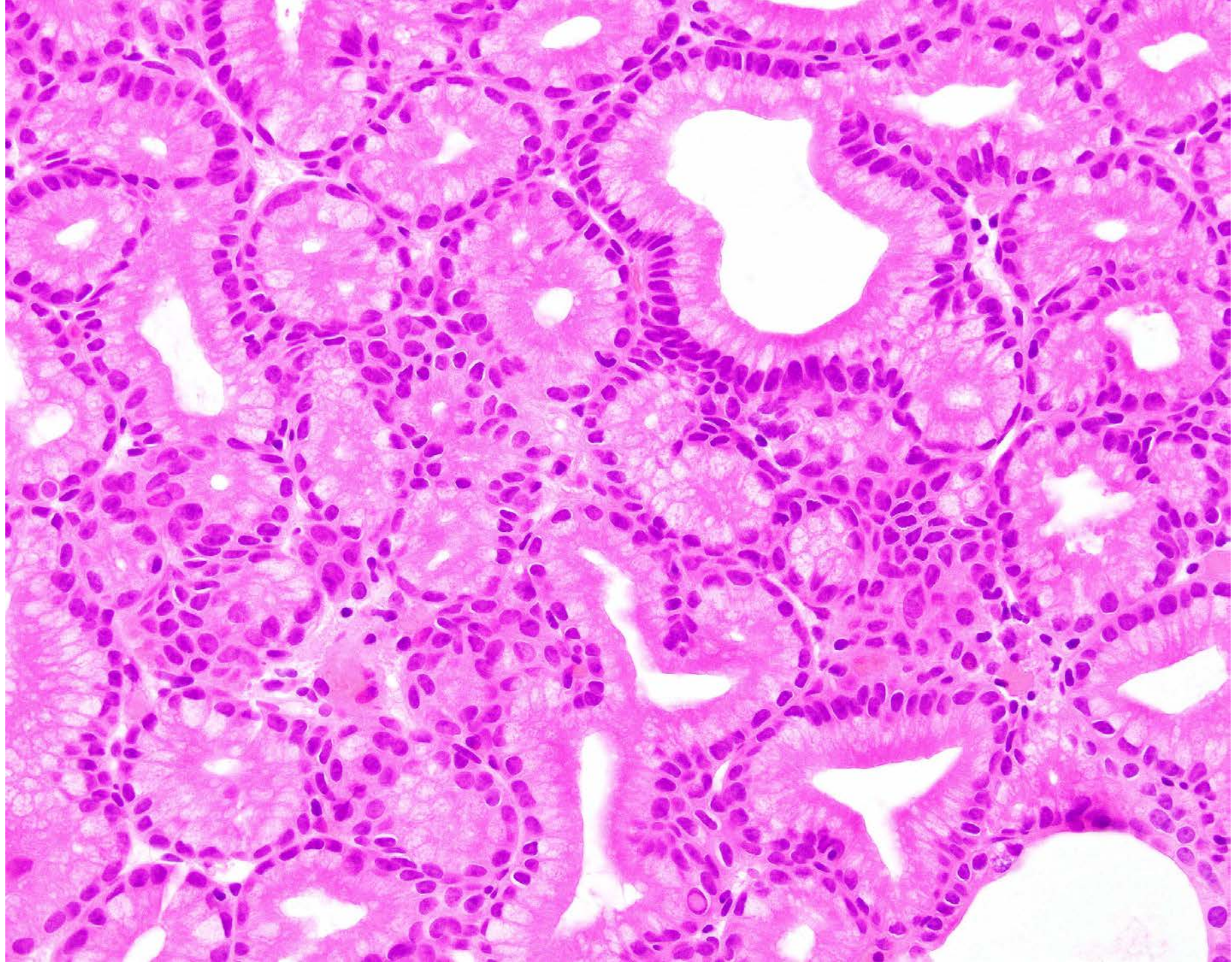


Pyloric Gland Adenoma – Defining series, Vieth et al. - [Virchows Arch.](#) 2003 Apr;442(4):317-21

- 2.7% of all gastric polyps
- Adults (73+/-12.8 years),
- **Women (75%).**
- **In stomach, mostly in body (64%), often found in patients with autoimmune gastritis (36%).**
- Some showed transition to adenocarcinoma

- Now known to have *GNAS** mutations, both sporadic and syndromic examples (familial adenomatous polyposis), which they share with oxyntic gland adenoma/chief cell adenoma.
- *guanine nucleotide-binding protein (G protein), alpha subunit”





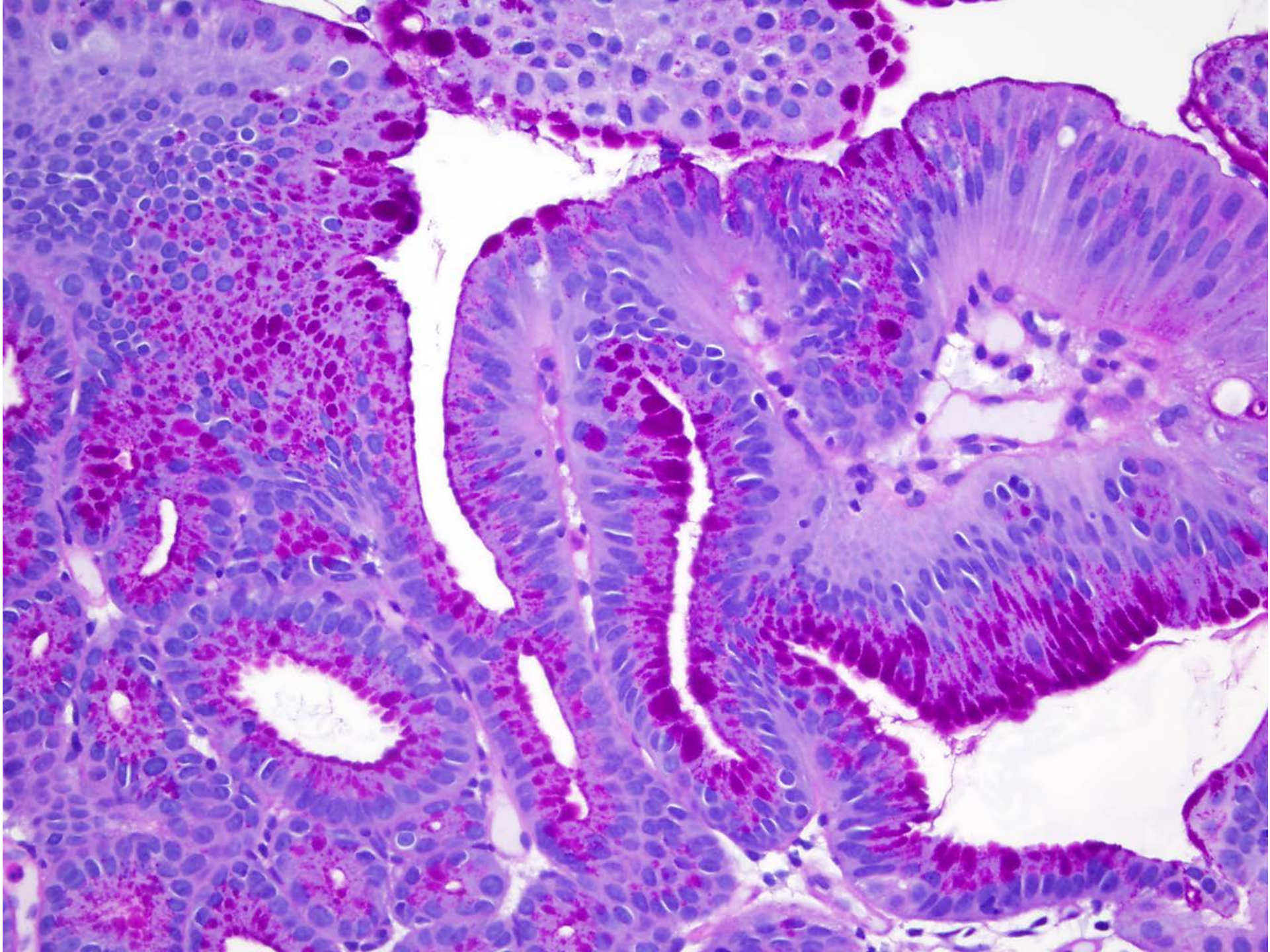


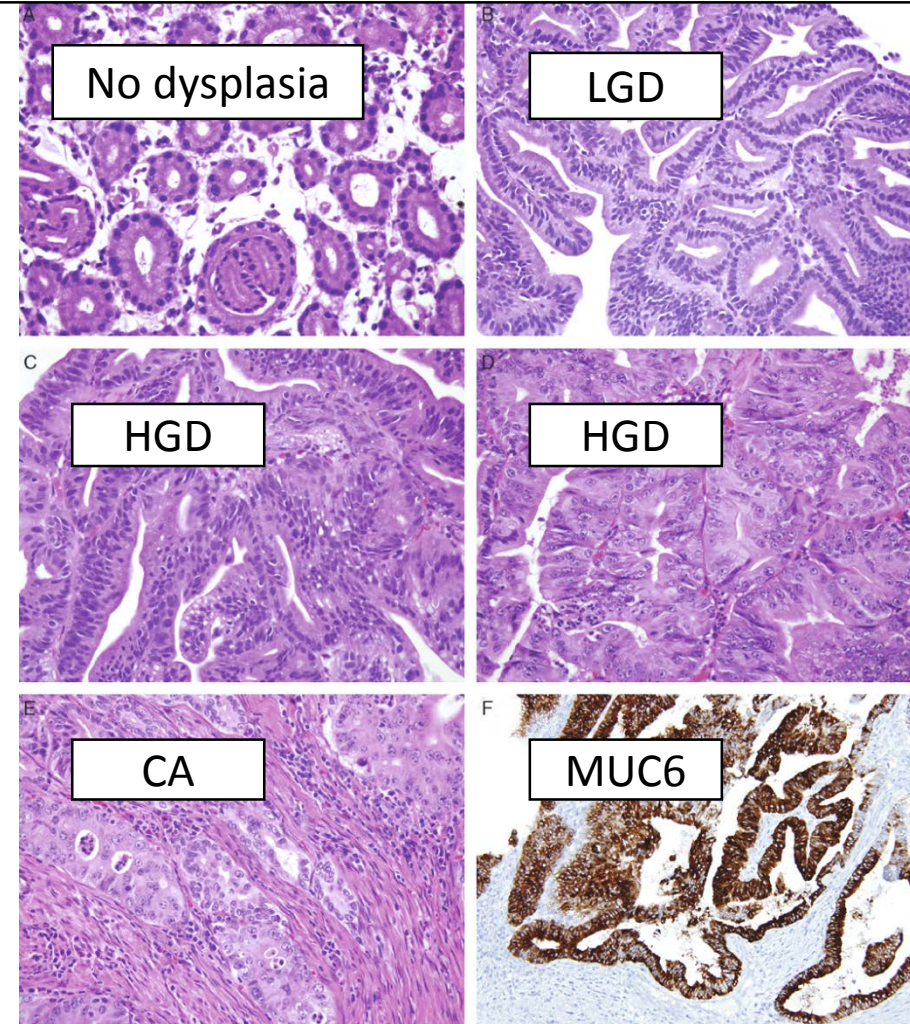
Image from Chen et al, Am J Surg Pathol 2009;33:186–193

Pyloric Gland Adenoma

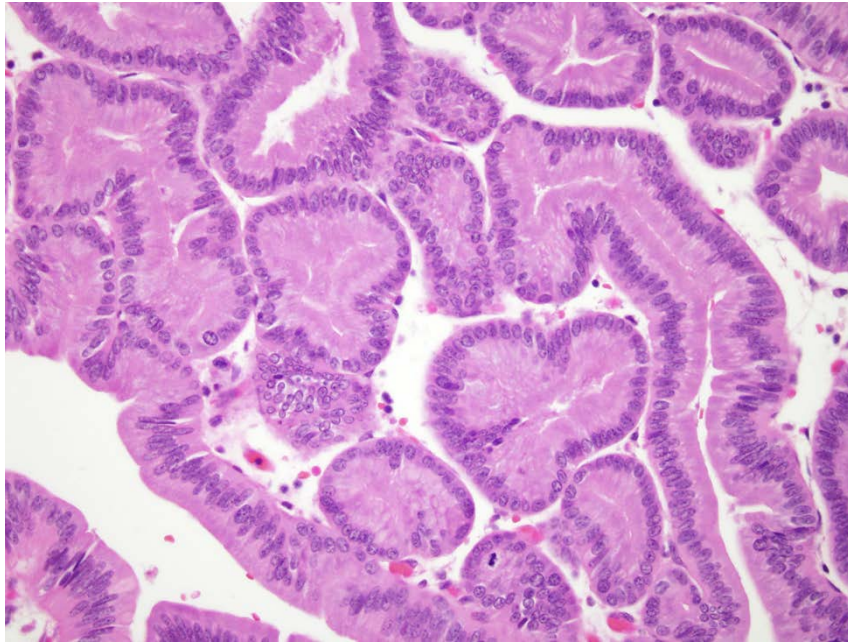
Early study suggested having a “no dysplasia” category (upper left); Am J Surg Pathol 2009;33:186–193

More recent suggestion to “lump” the “no dysplasia” and “low grade” into low grade dysplasia (Histopathology 2018; 72 (6): 1007-1014)

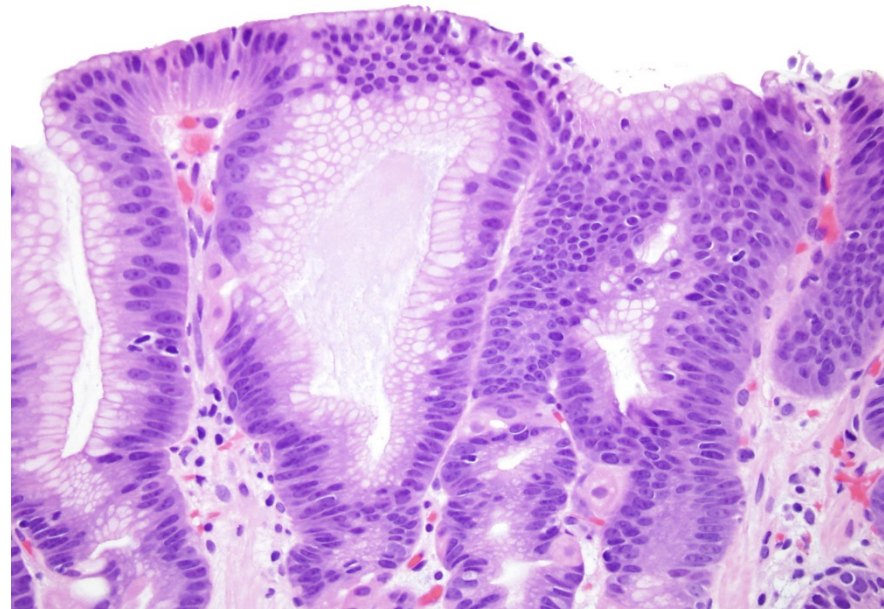
No need to report low grade dysplasia but do report high grade dysplasia



Pyloric Gland Adenoma

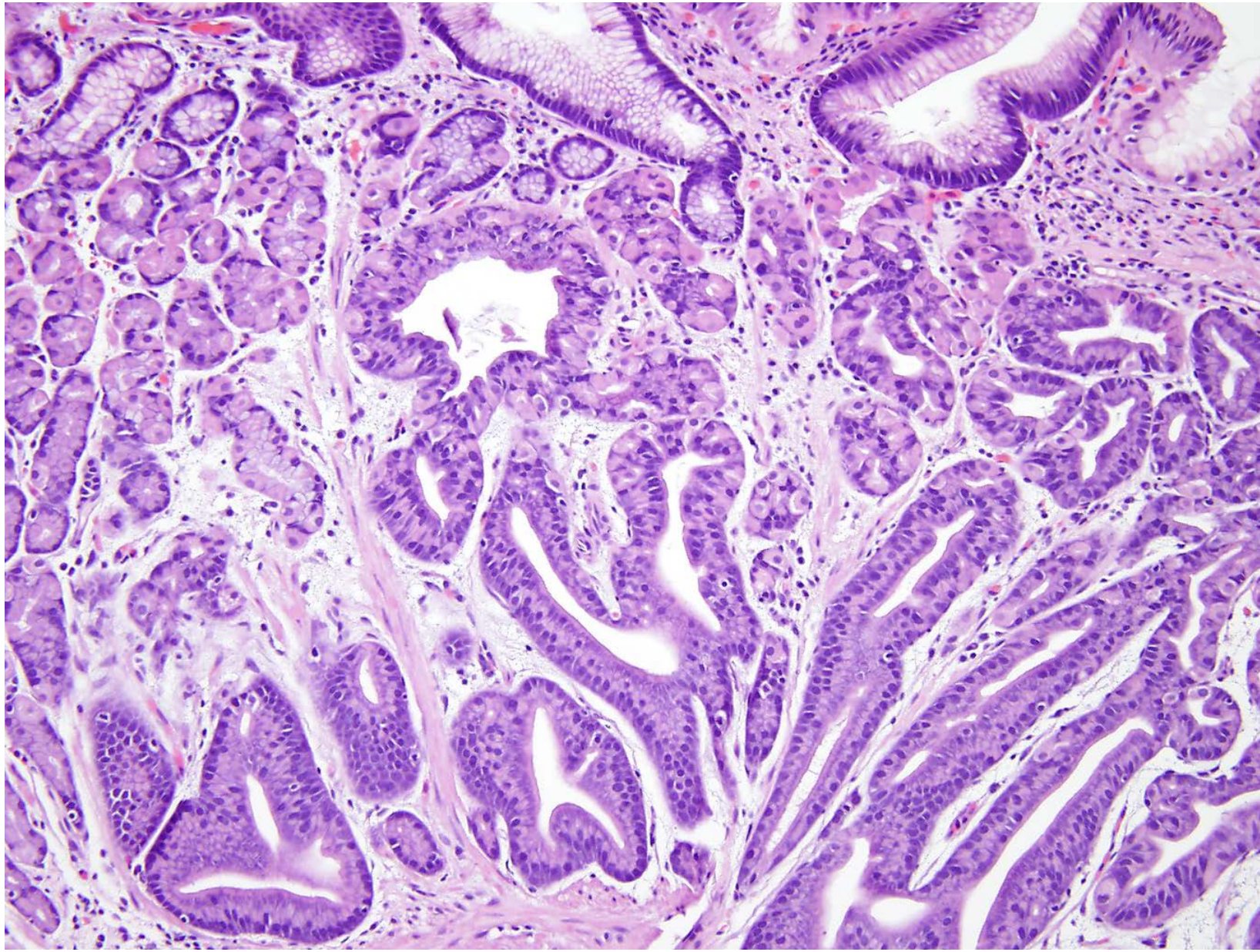


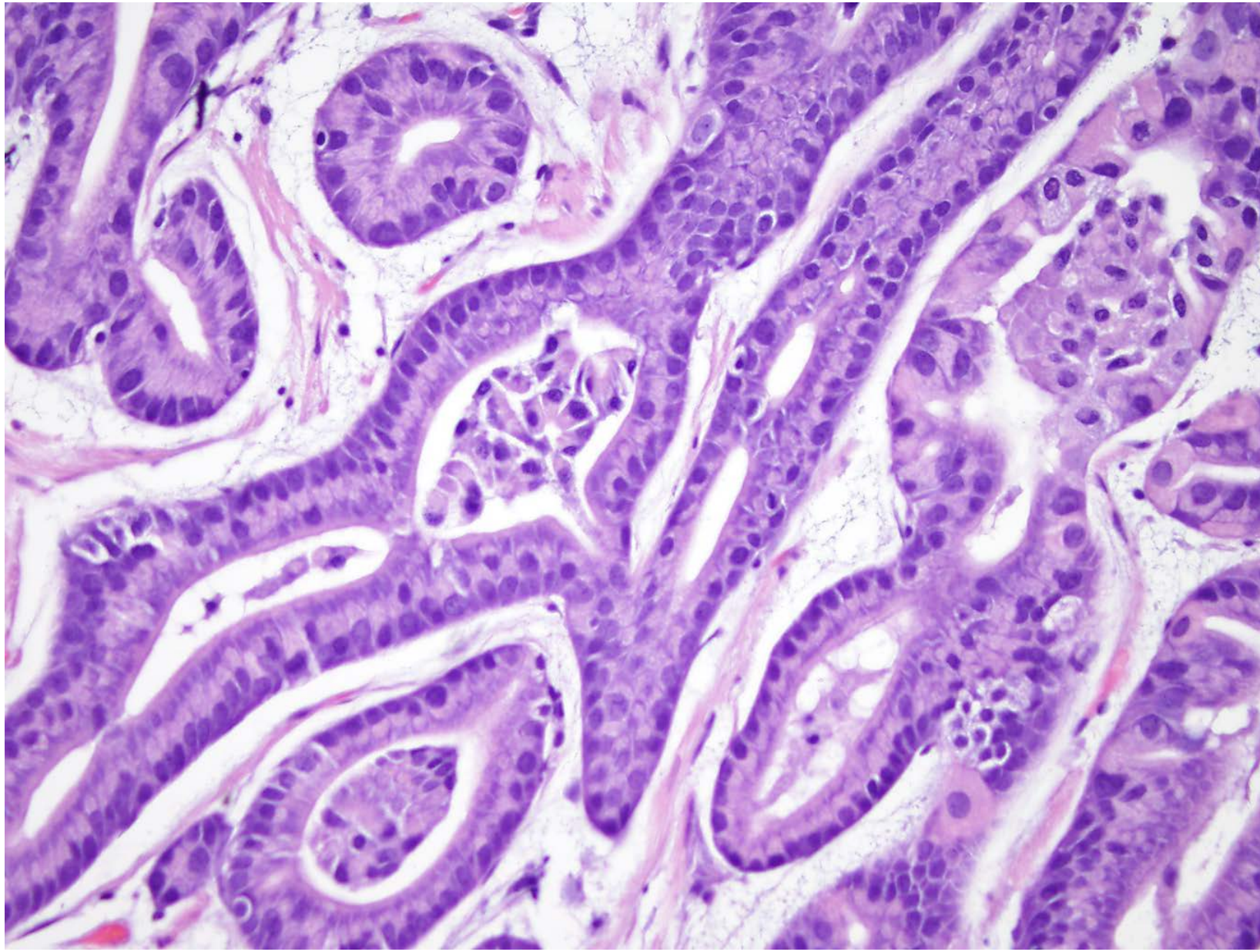
Gastric Foveolar Adenoma



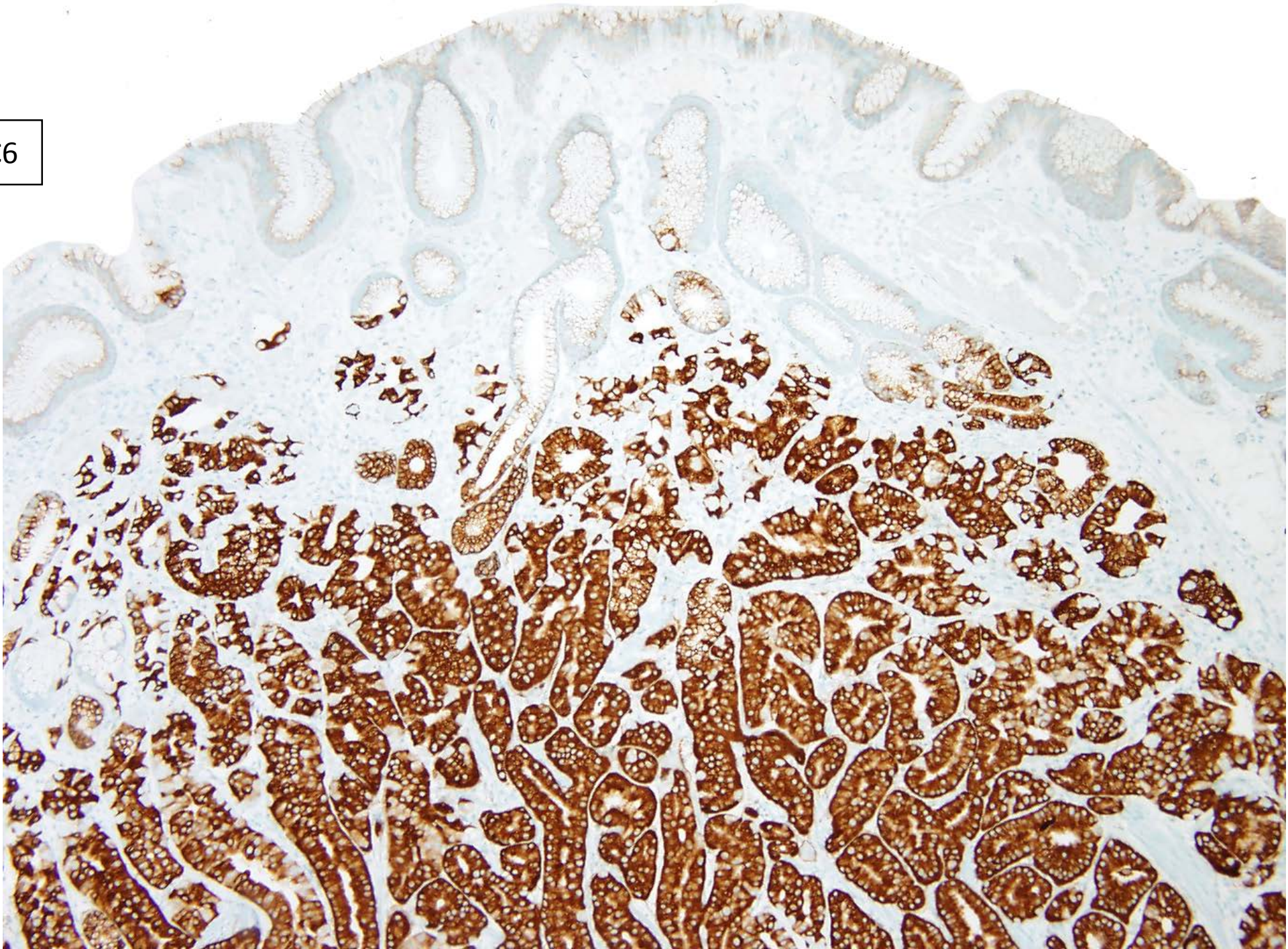
Oxyntic Gland/Chief Cell Adenoma

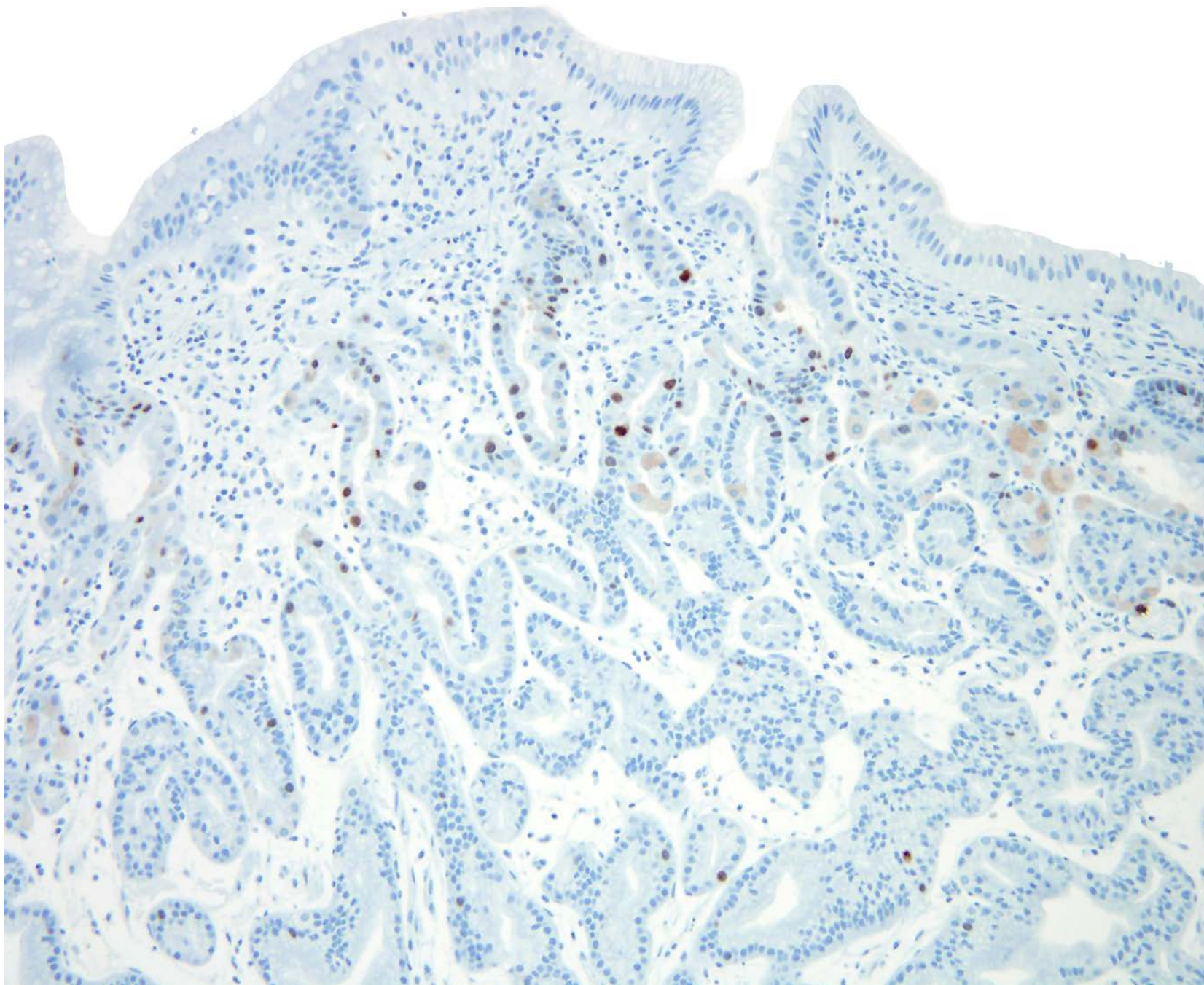
- Rare
- Same lesions have been termed “gastric adenocarcinoma of fundic type”, despite benign follow-up in all cases reported to date.
- Have *GNAS* mutations
- Limited numbers of cases reported to date so they are either benign of very low-grade/unlikely to kill patients
- Ueyama H, Yao T, Nakashima Y, Hirakawa K, Oshiro Y, Hirahashi M, Iwashita A, Watanabe S. Gastric adenocarcinoma of fundic gland type (chief cell predominant type): proposal for a new entity of gastric adenocarcinoma. *Am J Surg Pathol*. 2010 May;34(5):609-19.
- Singhi AD, Lazenby AJ, Montgomery EA. Gastric adenocarcinoma with chief cell differentiation: a proposal for reclassification as oxyntic gland polyp/adenoma. *Am J Surg Pathol*. 2012 Jul;36(7):1030-5.



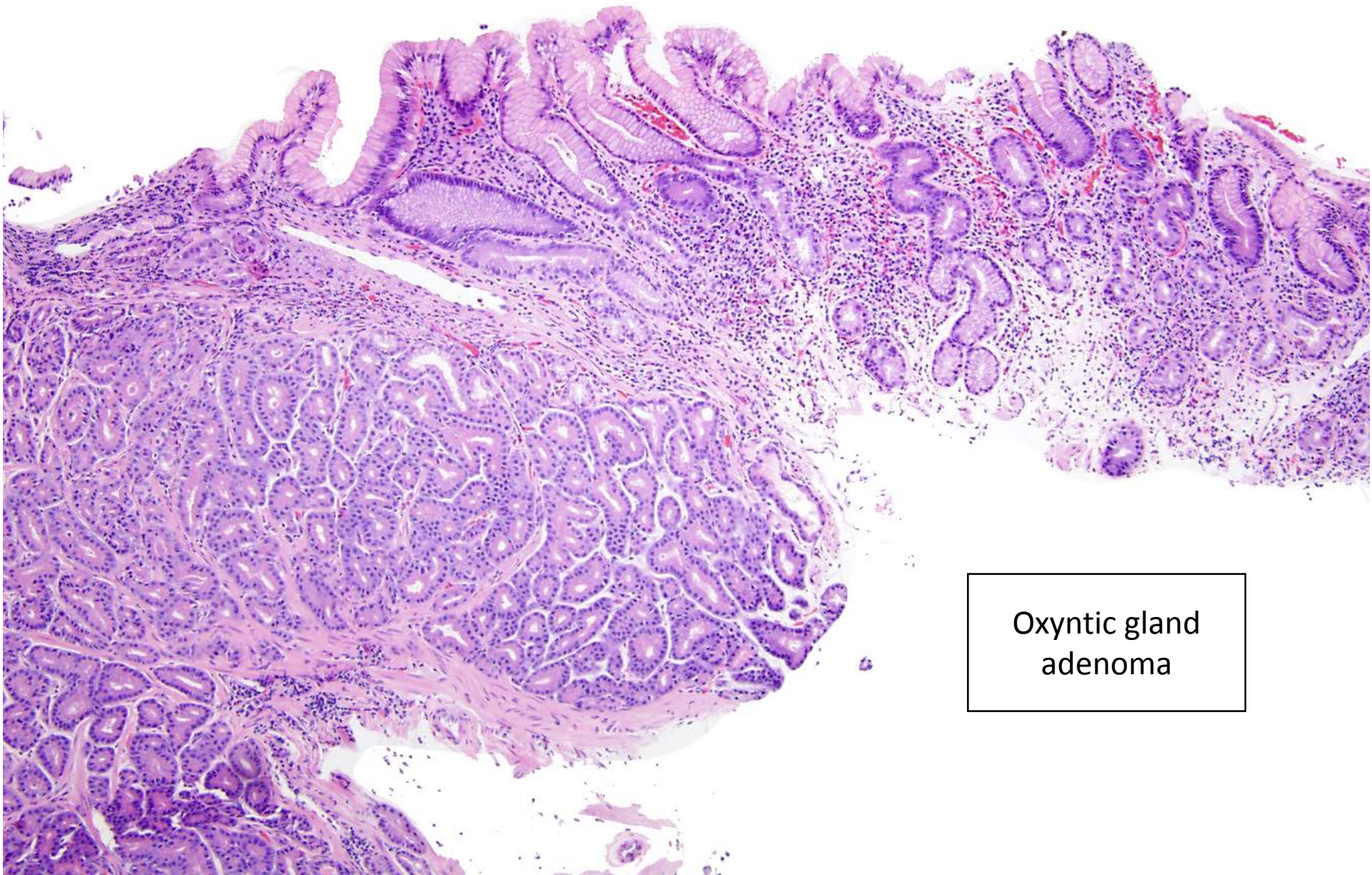


MUC6

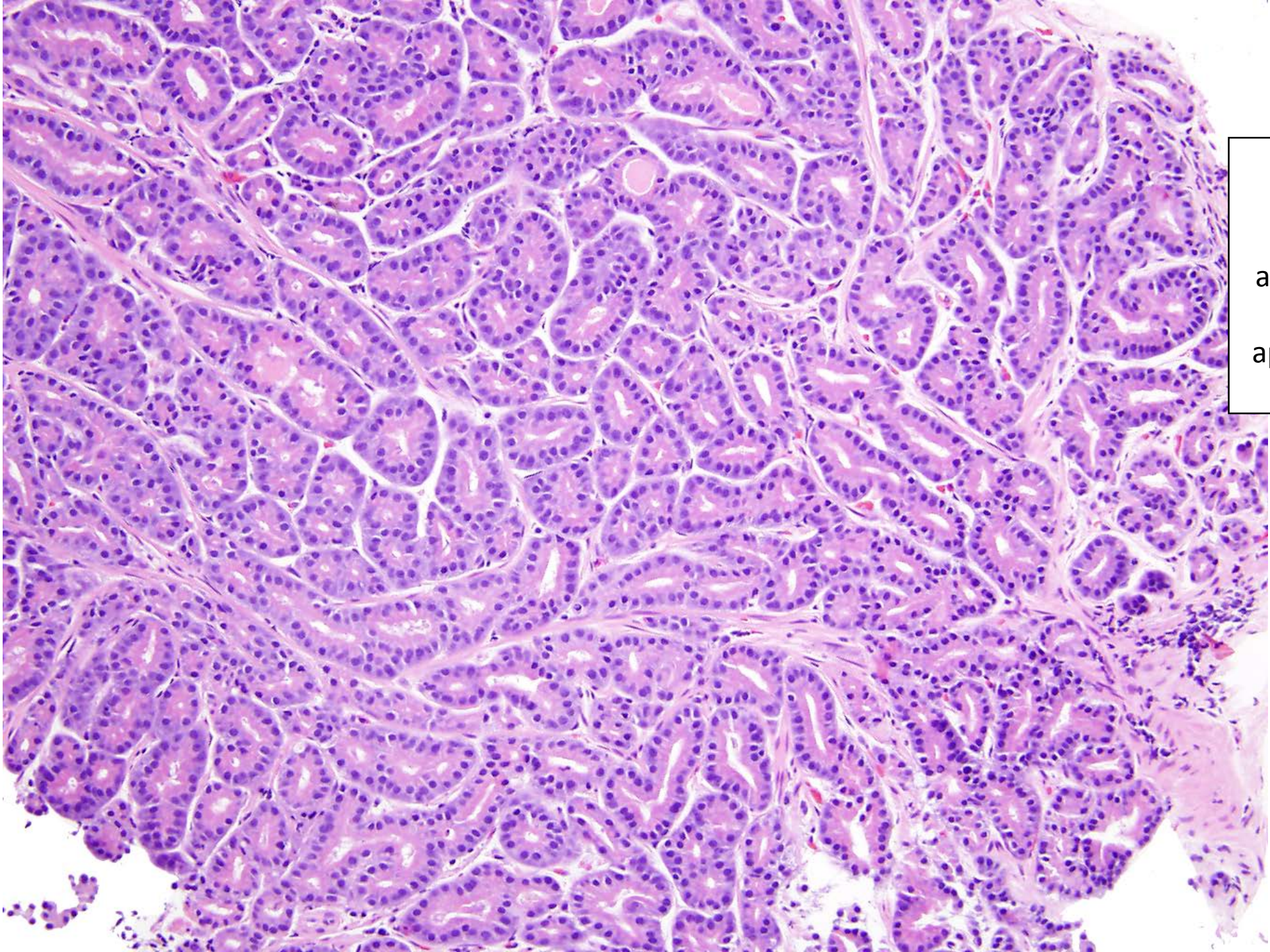




Oxyntic gland adenoma, Ki-67 – only stains the gastric mucosa proliferative compartment over the lesion

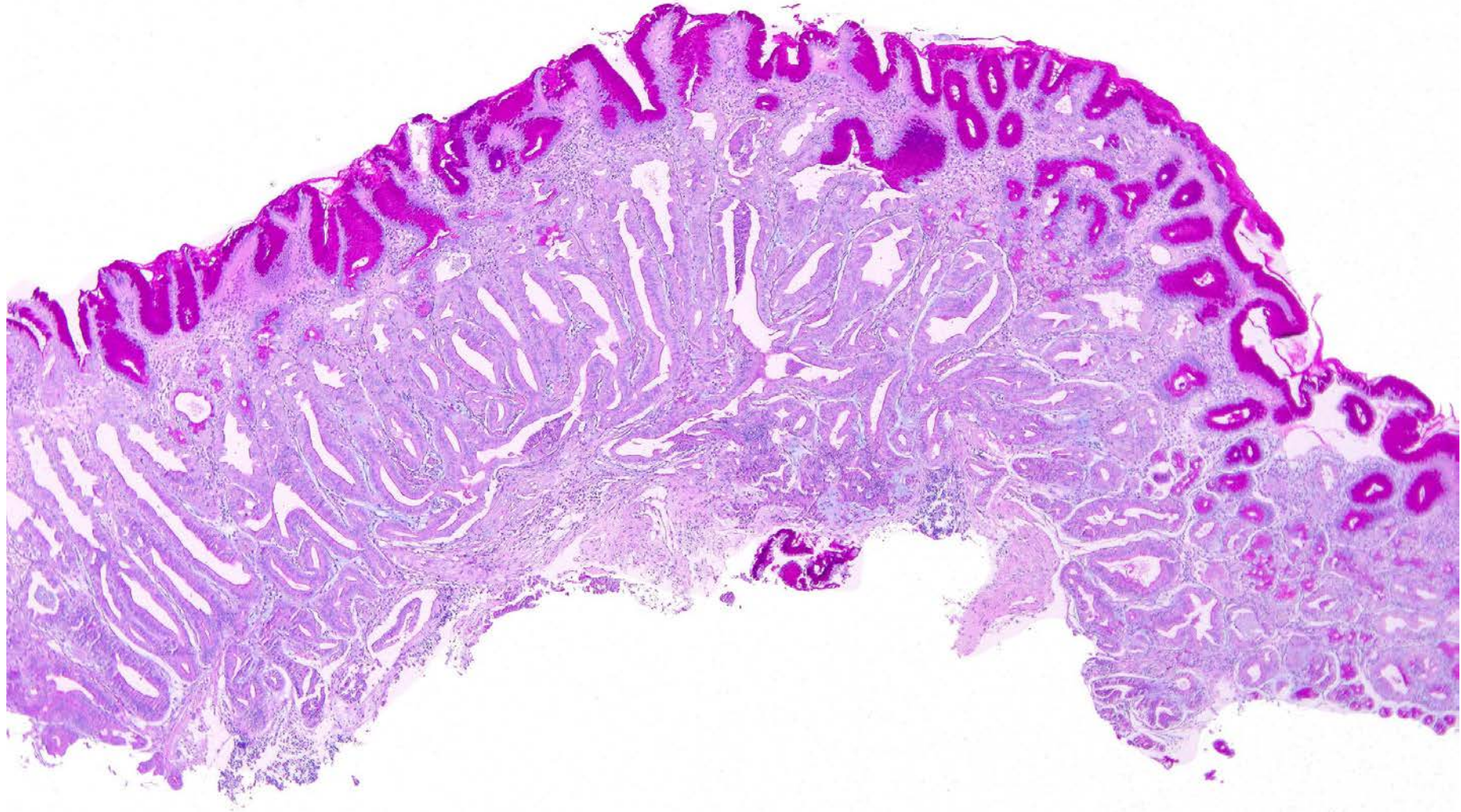


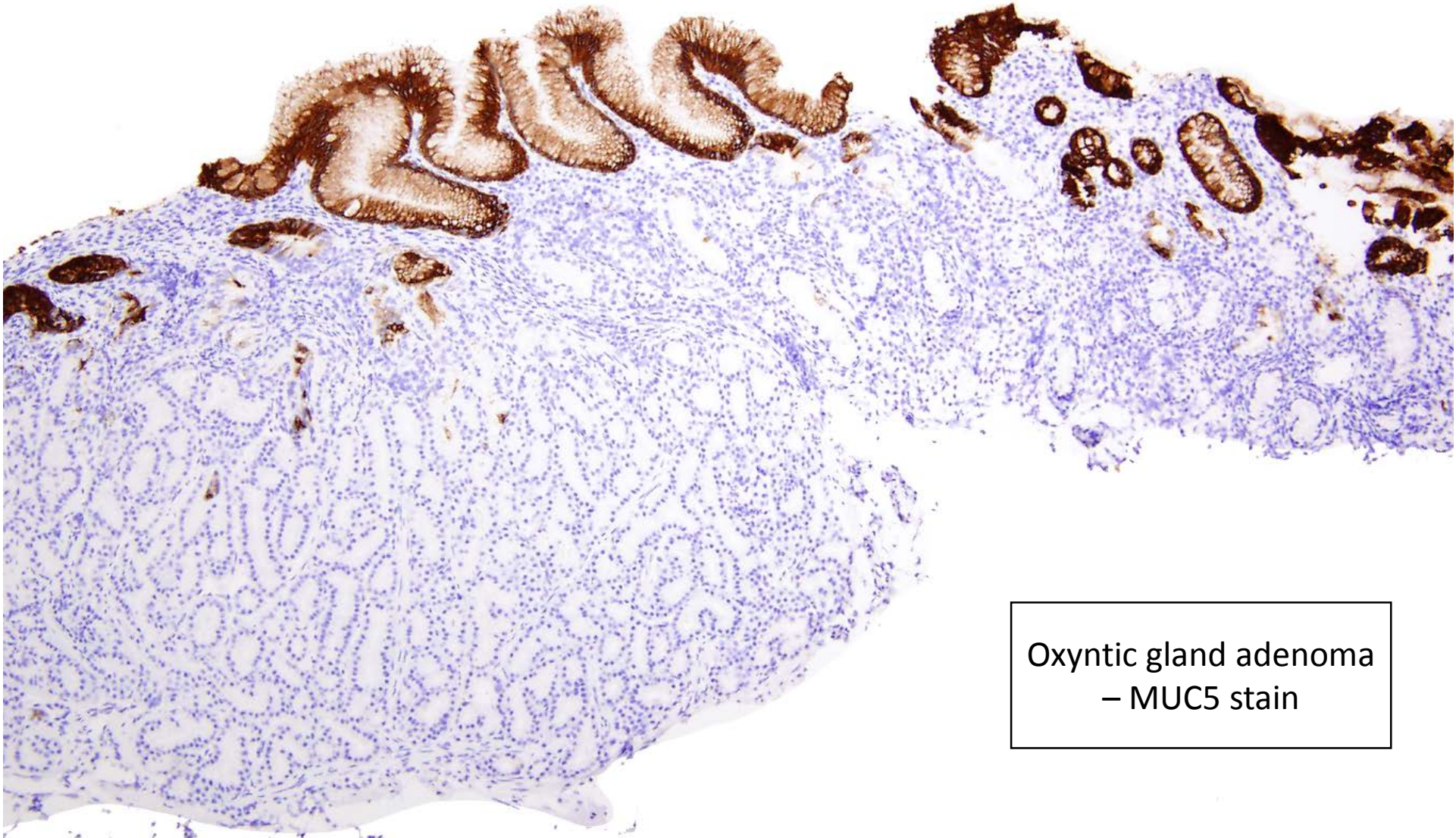
Oxyntic gland
adenoma



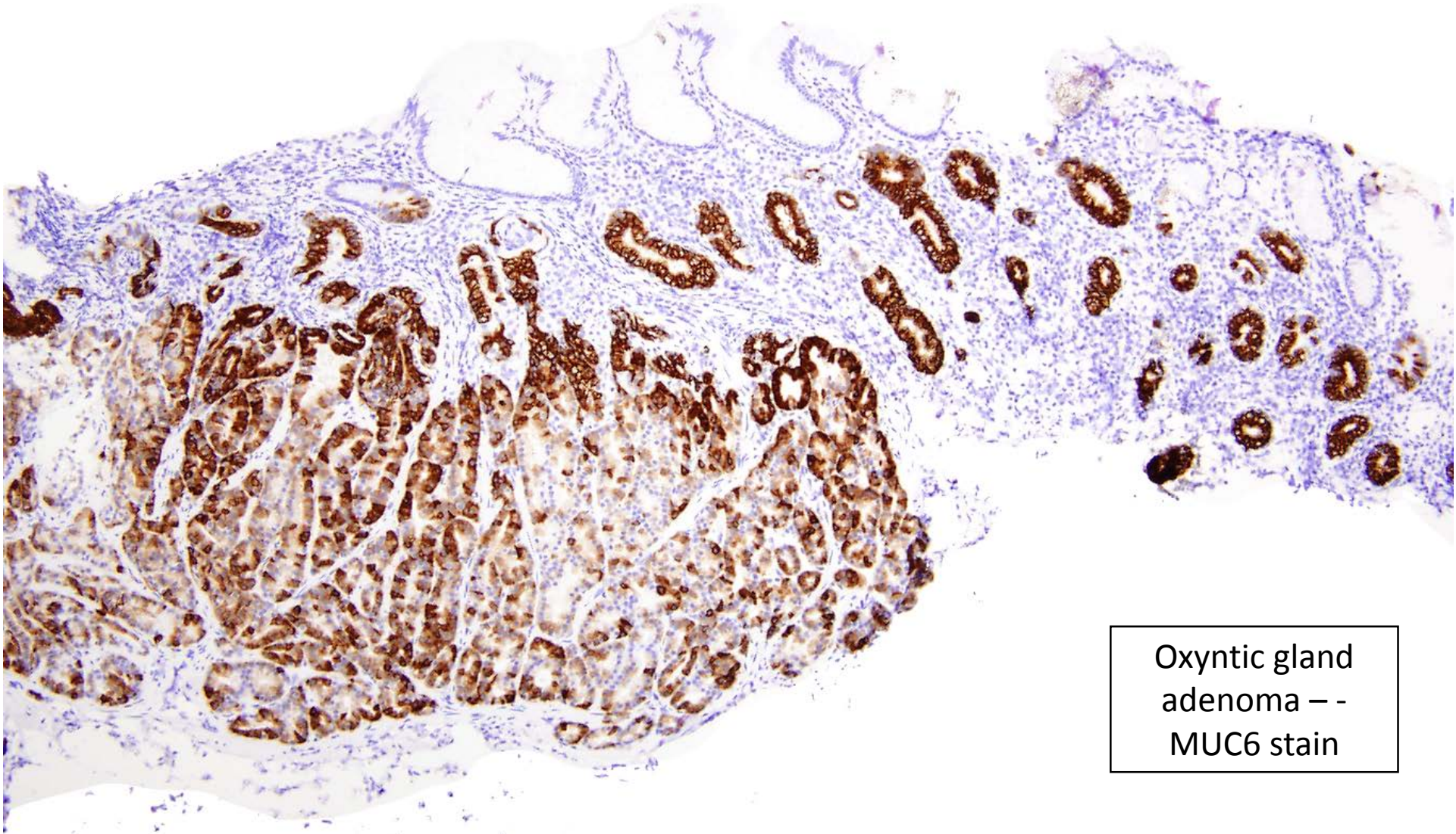
Oxyntic gland adenoma – Chief cell appearance

PAS/AB stain

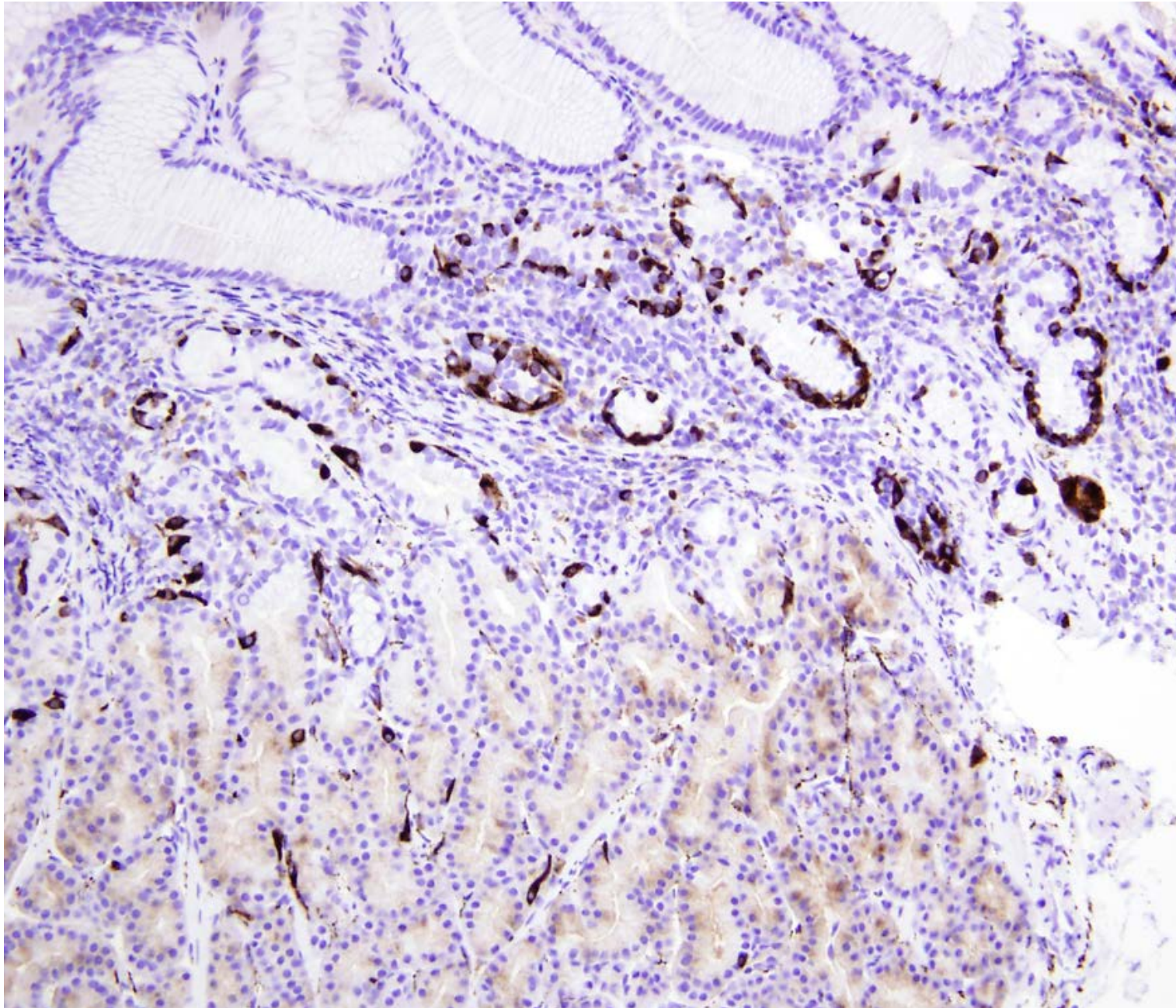




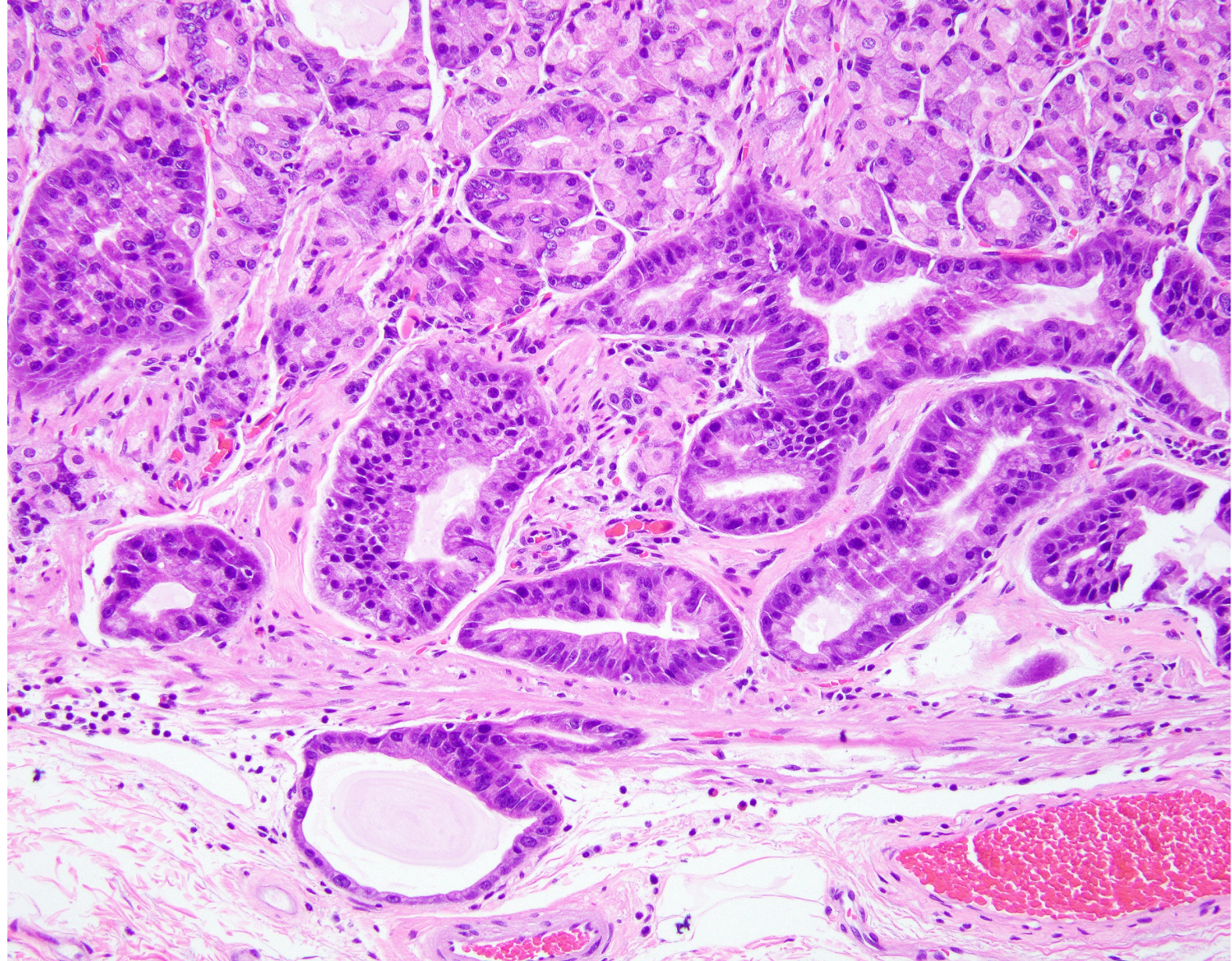
Oxyntic gland adenoma
– MUC5 stain

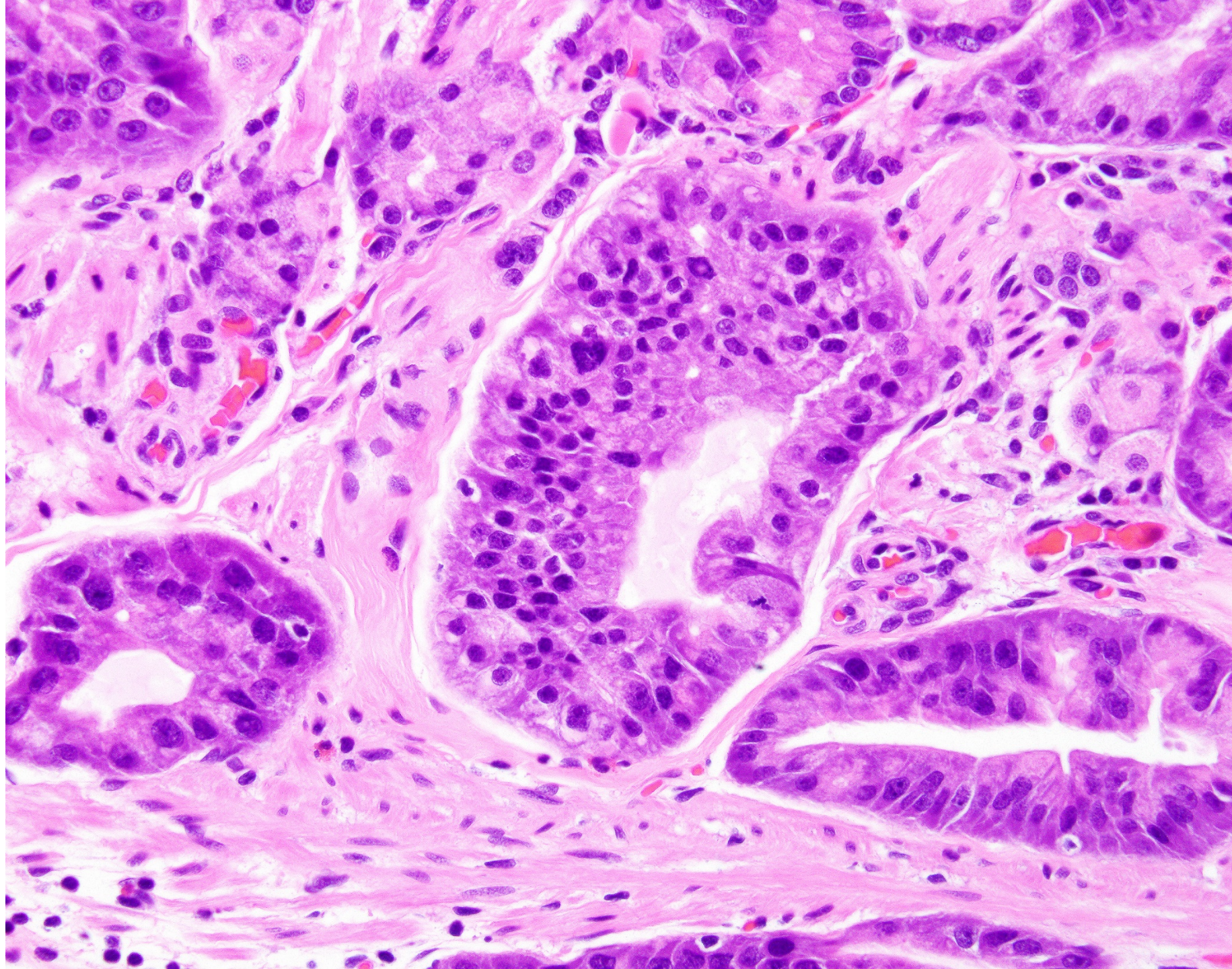


Oxyntic gland
adenoma --
MUC6 stain



Oxyntic gland
adenoma – Pitfall
alert – weak
synaptophysin
staining

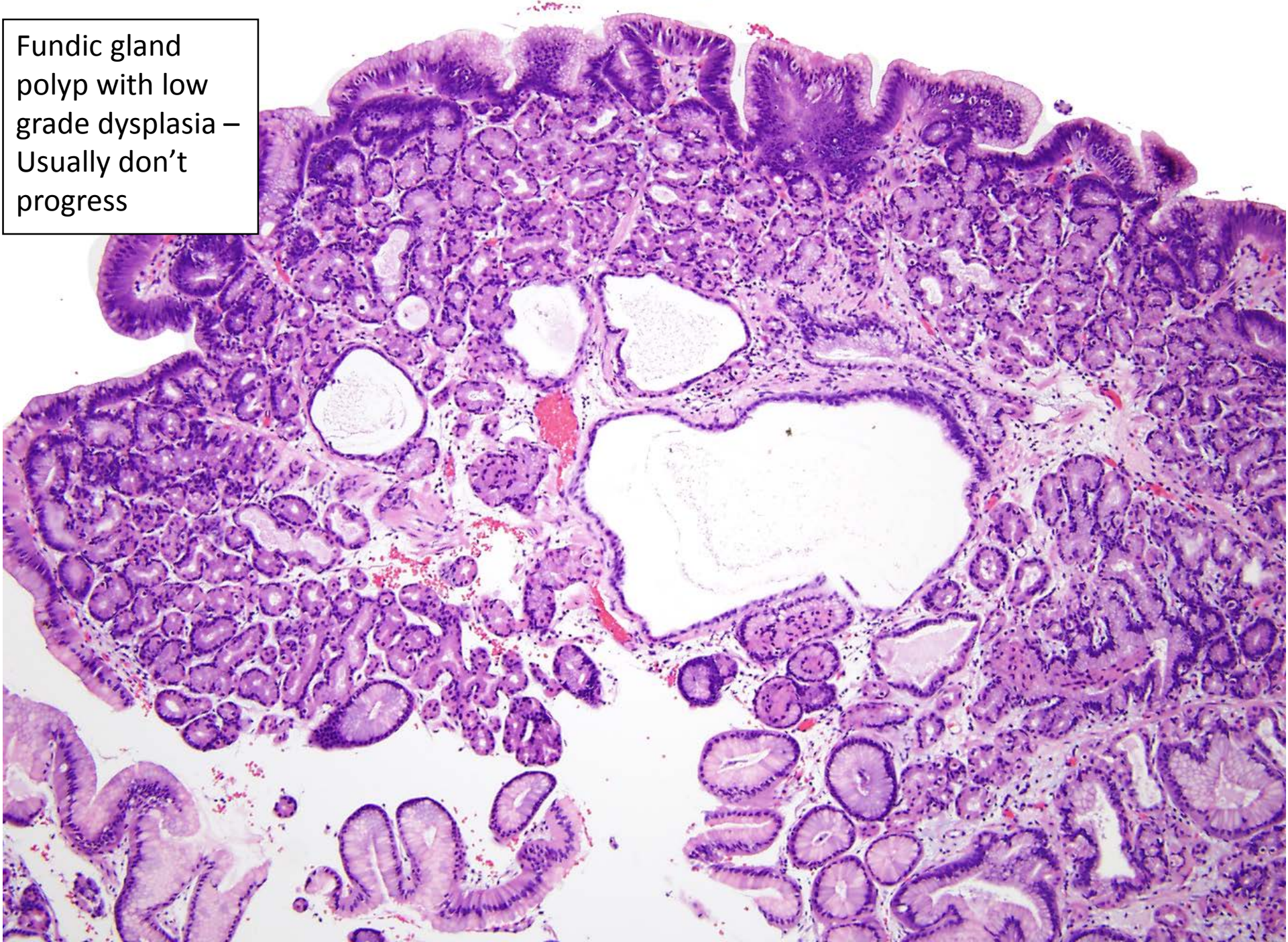




Gastric Polyps in Patients with Familial Adenomatous Polyposis

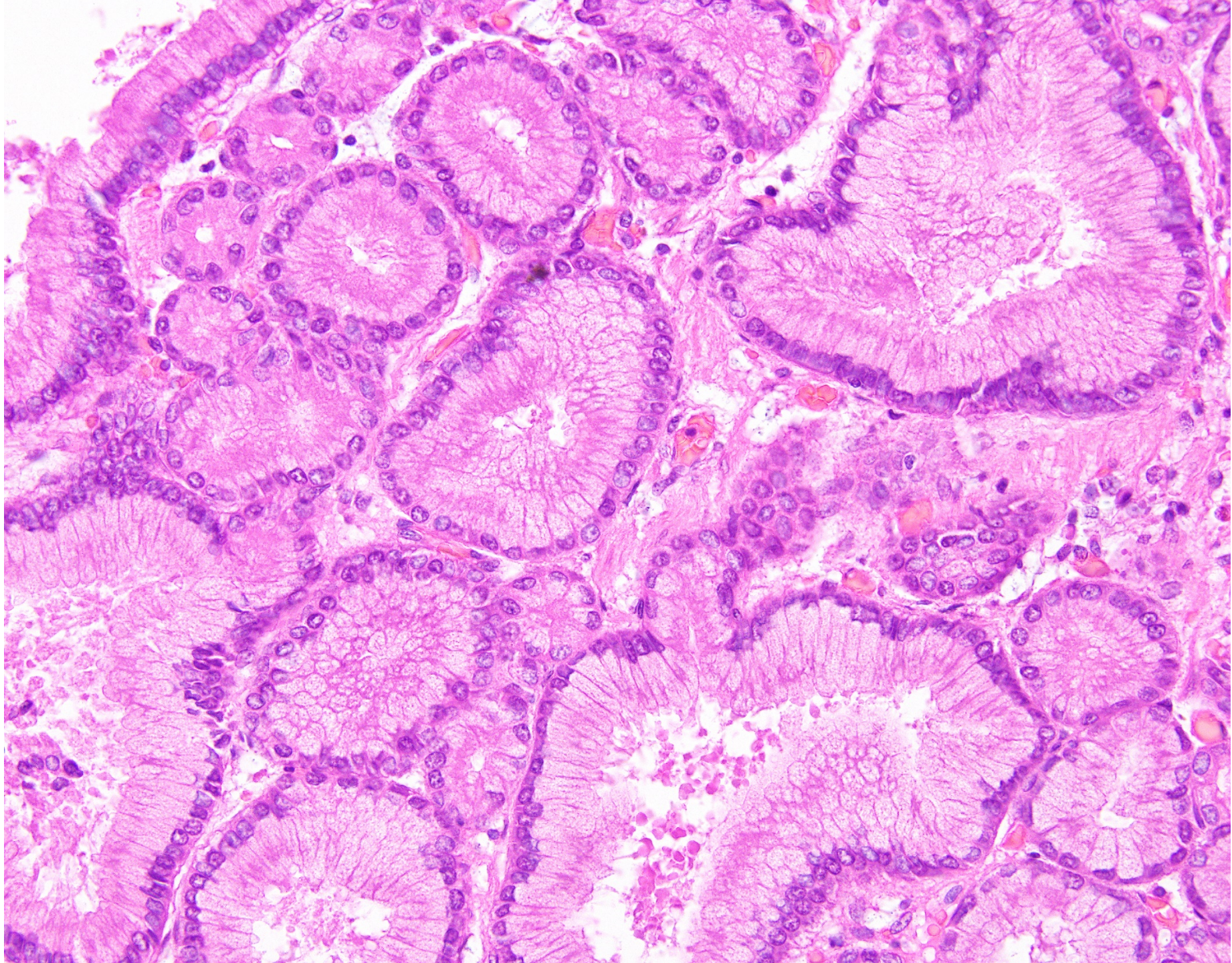
- Fundic gland polyps occur in up to 100% of FAP patients
 - Tend to be multiple and small in diameter
 - Generally considered benign, although dysplasias can occur
 - 0.5% lifetime risk of stomach cancer
- Most FAP patients will have a fundic gland polyp by age 20

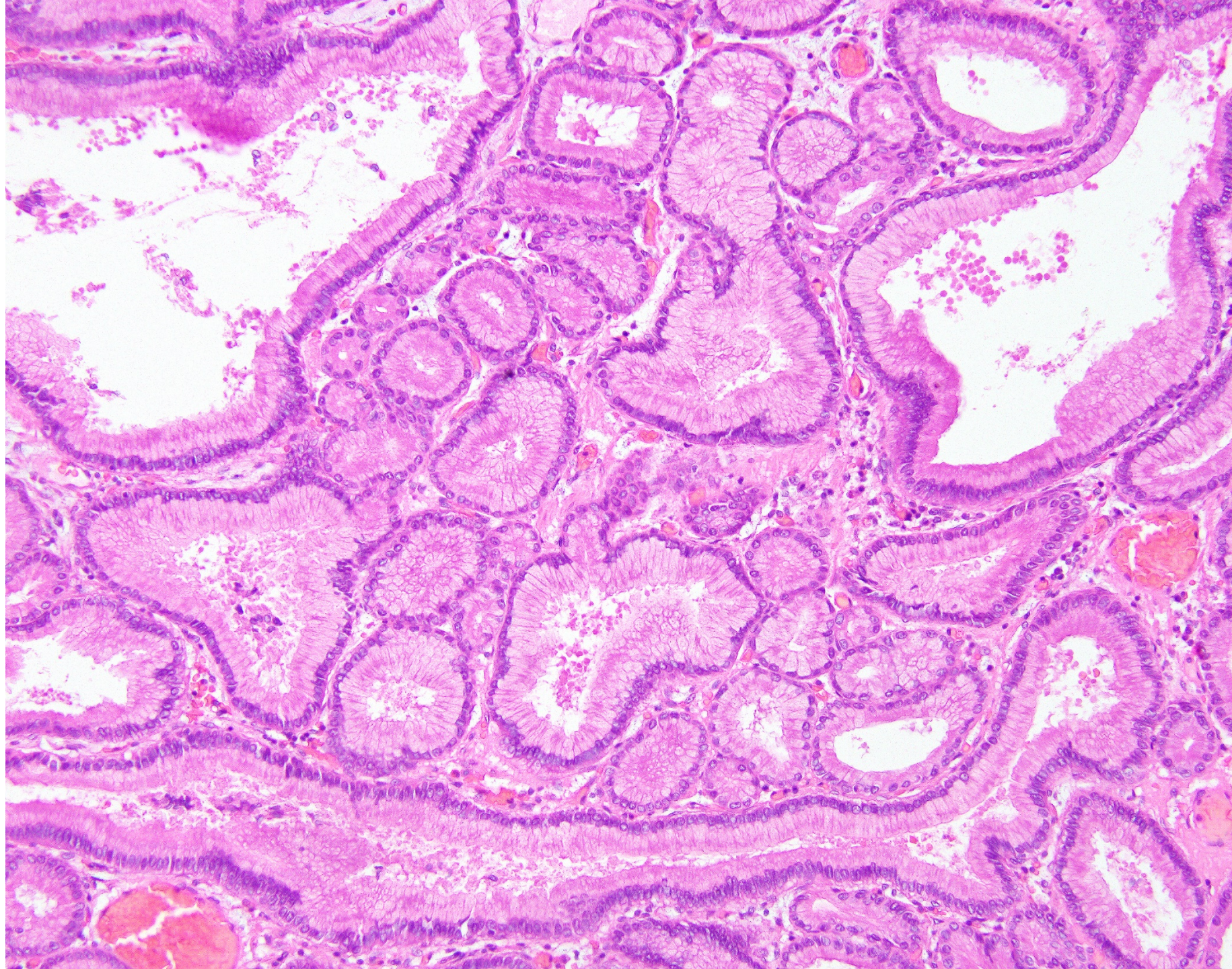
Fundic gland
polyp with low
grade dysplasia –
Usually don't
progress



Syndromic Pyloric Gland Adenoma

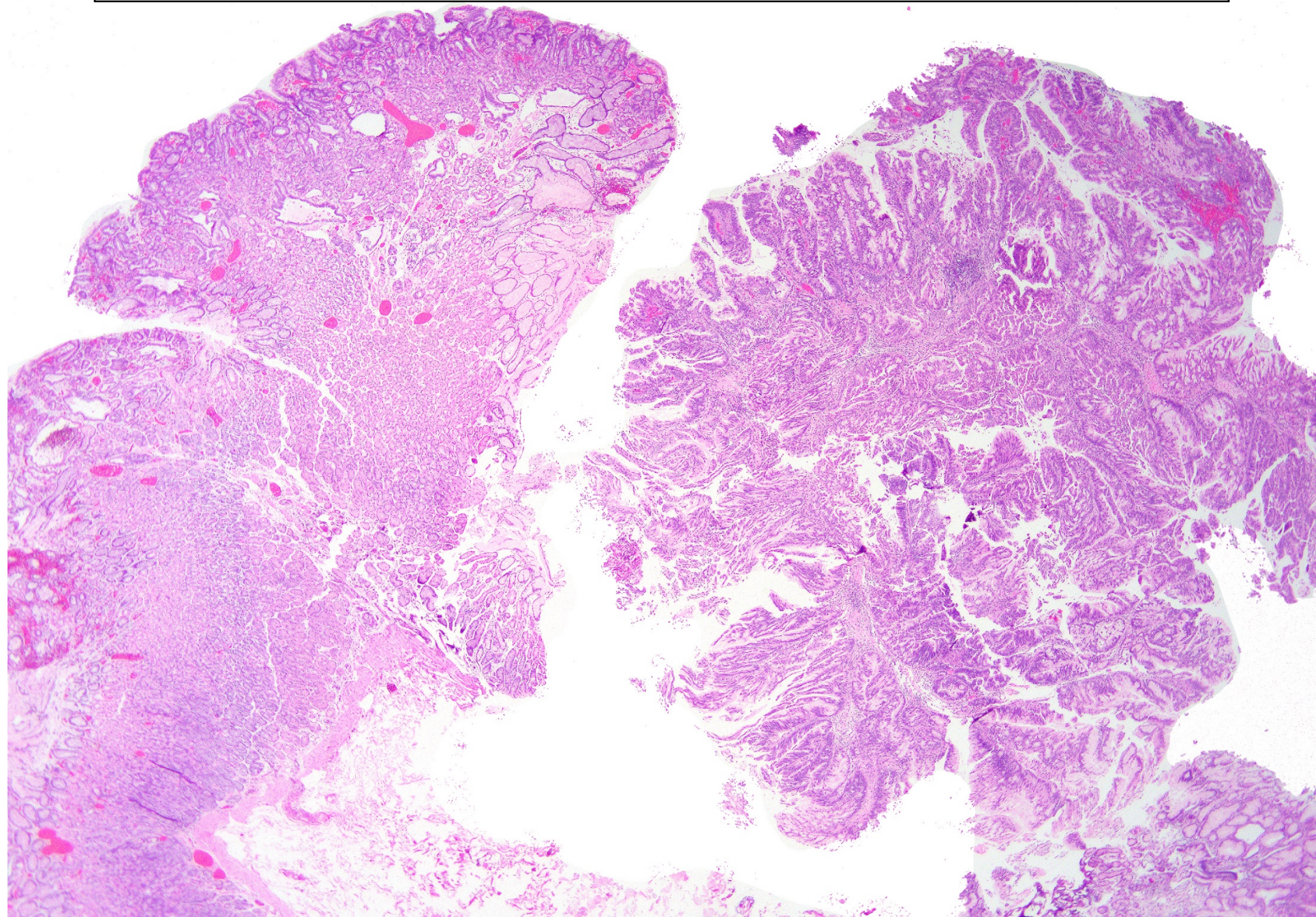
- In patients with familial adenomatous polyposis (normal background mucosa seen; US population); have *GNAS* mutations like those associated with autoimmune gastritis
- We have seen polyps that look like PGA in patients with McCune Albright syndrome (fibrous dysplasia, endocrine lesions, café au lait spots, pancreatitis, GI polyps, *GNAS* mutations)
- Wood LD, Noë M, Hackeng W, Brosens LA, Bhajjee F, Debeljak M, Yu J, Suenaga M, Singhi AD, Zaheer A, Boyce A, Robinson C, Eshleman JR, Goggins MG, Hruban RH, Collins MT, Lennon AM, Montgomery EA. Patients with McCune-Albright syndrome have a broad spectrum of abnormalities in the gastrointestinal tract and pancreas. *Virchows Arch*. 2017 Apr;470(4):391-400. PubMed PMID: 28188442
- 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



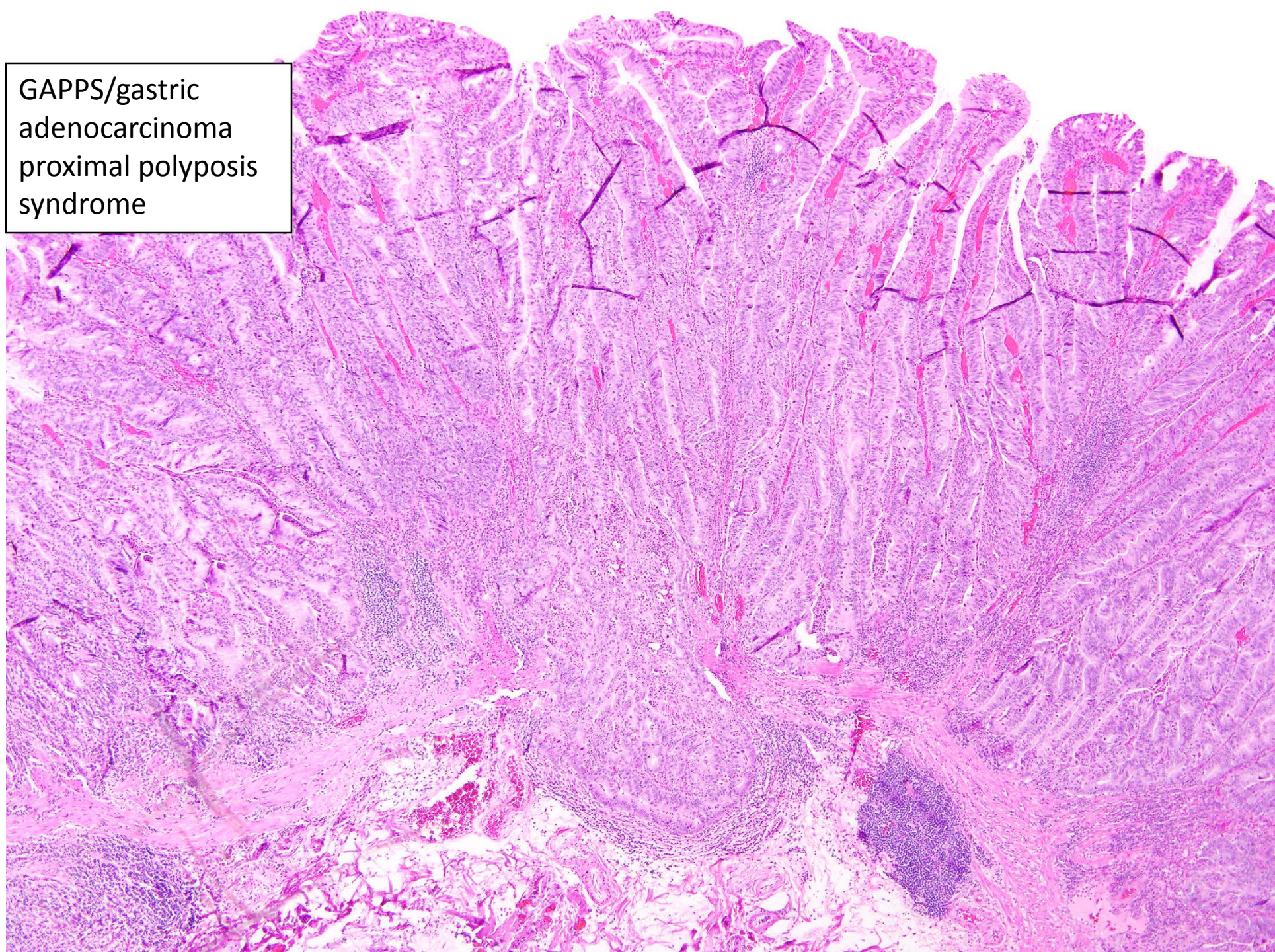


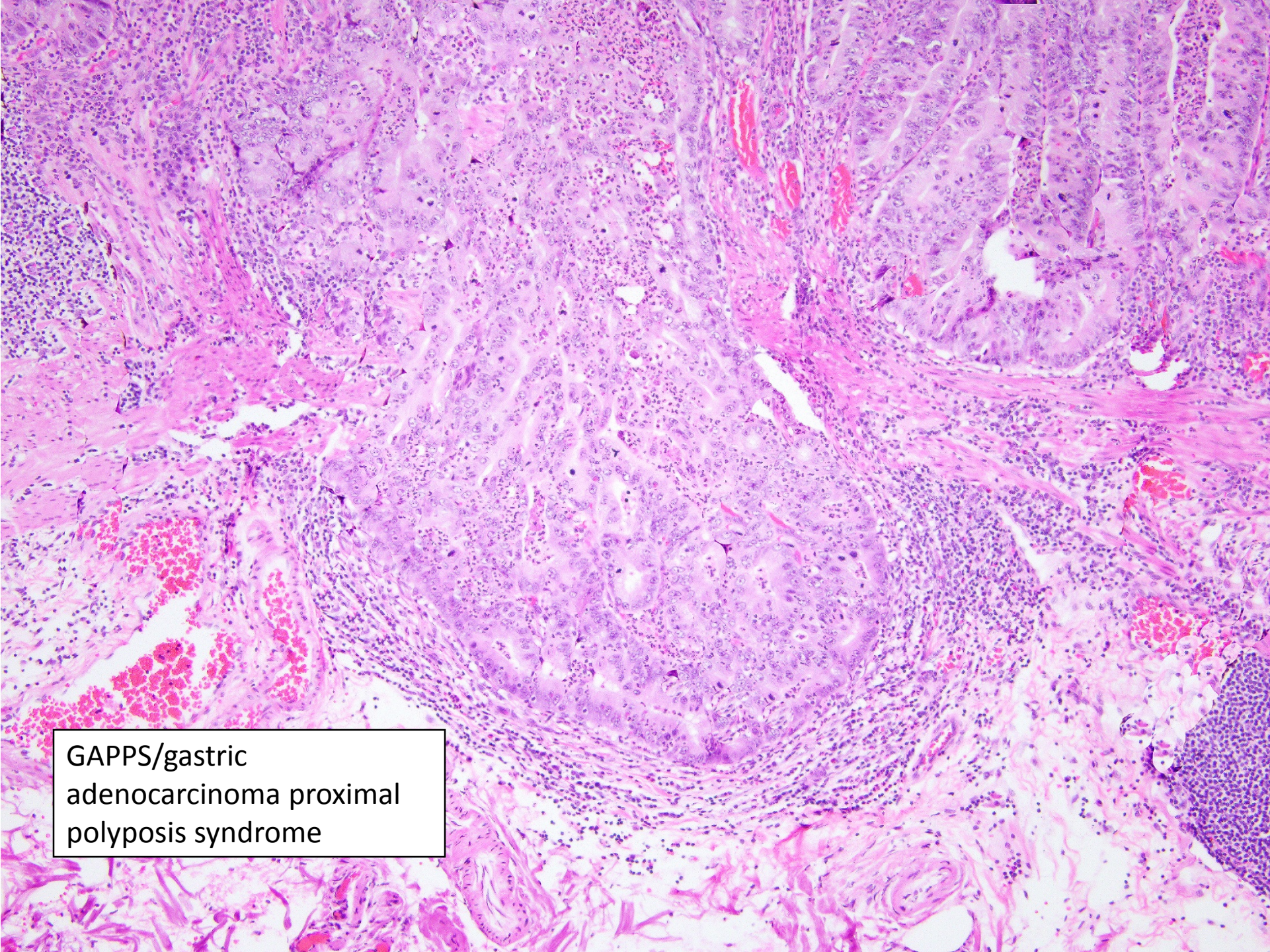
Li J, Woods SL, Healey S, Beesley J, Chen X, Lee JS, Sivakumaran H, Wayte N, Nones K, Waterfall JJ, Pearson J, Patch AM, Senz J, Ferreira MA, Kaurah P, Mackenzie R, Heravi-Moussavi A, Hansford S, Lannagan TRM, Spurdle AB, Simpson PT, da Silva L, Lakhani SR, Clouston AD, Bettington M, Grimpen F, Busuttil RA, Di Costanzo N, Boussioutas A, Jeanjean M, Chong G, Fabre A, Olschwang S, Faulkner GJ, Bellos E, Coin L, Rioux K, Bathe OF, Wen X, Martin HC, Neklason DW, Davis SR, Walker RL, Calzone KA, Avital I, Heller T, Koh C, Pineda M, Rudloff U, Quezado M, Pichurin PN, Hulick PJ, Weissman SM, Newlin A, Rubinstein WS, Sampson JE, Hamman K, Goldgar D, Poplawski N, Phillips K, Schofield L, Armstrong J, Kiraly-Borri C, Suthers GK, Huntsman DG, Foulkes WD, Carneiro F, Lindor NM, Edwards SL, French JD, Waddell N, Meltzer PS, Worthley DL, Schrader KA, Chenevix-Trench G. **Point Mutations in Exon 1B of APC Reveal Gastric Adenocarcinoma and Proximal Polyposis of the Stomach as a Familial Adenomatous Polyposis Variant.** Am J Hum Genet. 2016 May 5;98(5):830-842. doi: 10.1016/j.ajhg.2016.03.001. Epub 2016 Apr 14. PubMed PMID: 27087319; PubMed Central PMCID: PMC4863475.

GAPPS/gastric adenocarcinoma proximal polyposis syndrome



GAPPS/gastric
adenocarcinoma
proximal polyposis
syndrome





GAPPS/gastric
adenocarcinoma proximal
polyposis syndrome

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: Which lesion is not associated with gastritis?

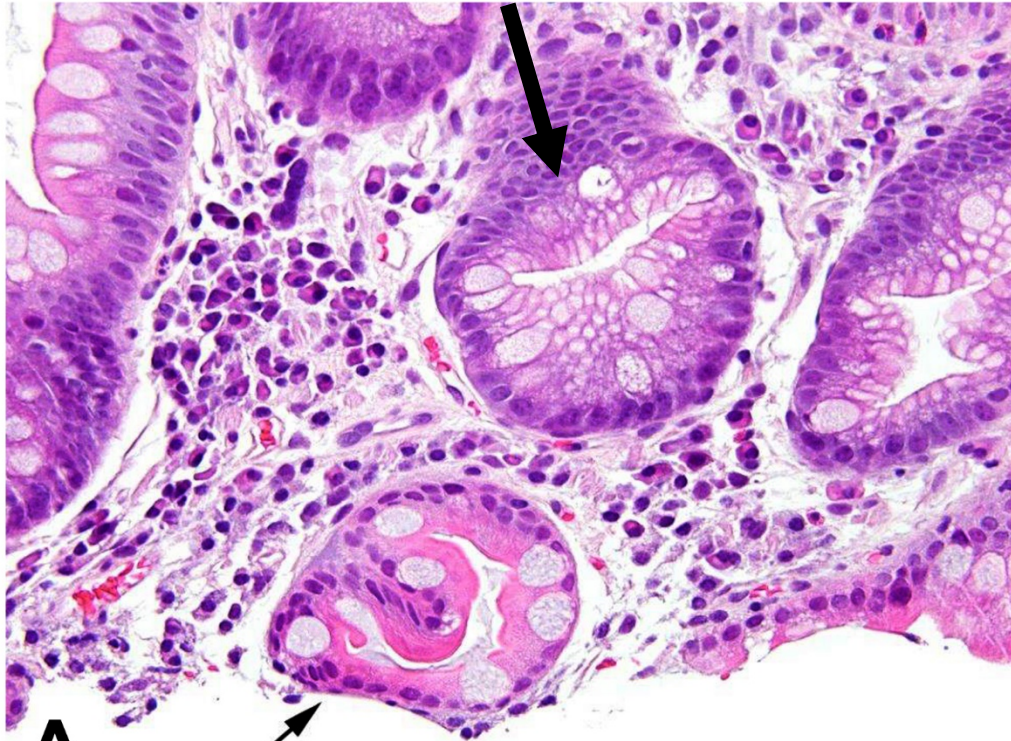
Answer A

- Fundic gland polyps arise in intact oxyntic mucosa. The others can be associated with gastritis.
- 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. PubMed PMID: 30841008.

Oh Dear, Yet Another New Demand

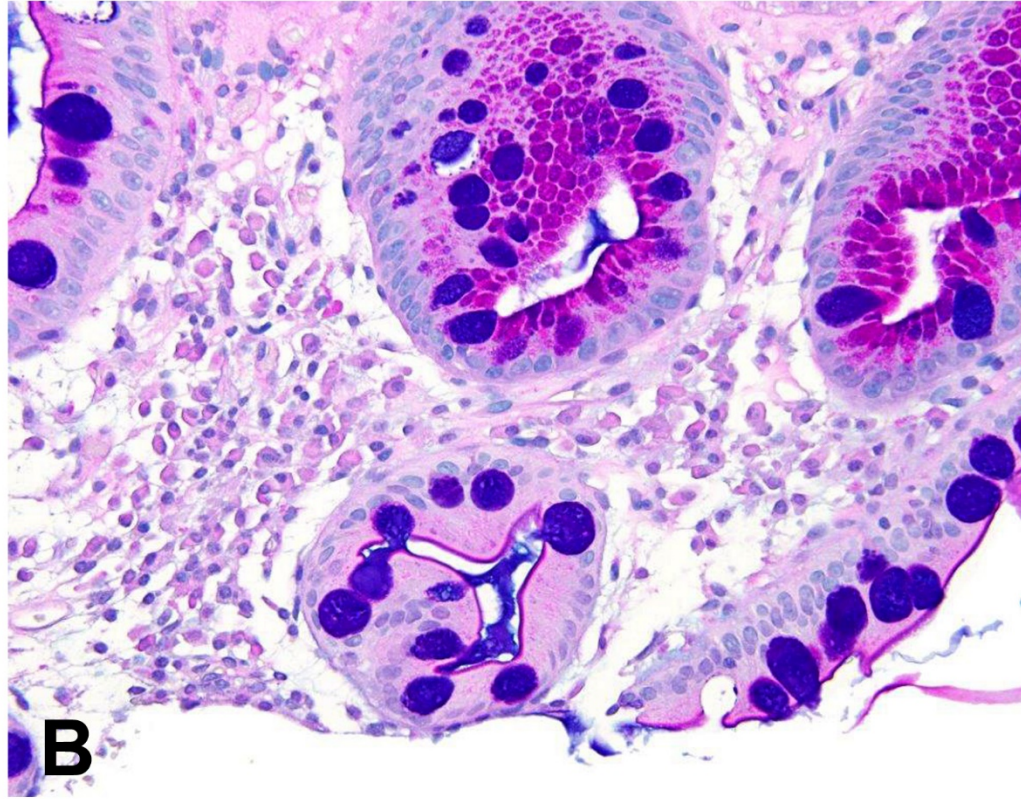
- Gupta S, Li D, El Serag HB, Davitkov P, Altayar O, Sultan S, Falck-Ytter Y, Mustafa RA. AGA Clinical Practice Guidelines on Management of Gastric Intestinal Metaplasia. *Gastroenterology*. 2020 Feb;158(3):693-702. doi: 10.1053/j.gastro.2019.12.003. Epub 2019 Dec 6. PubMed PMID: 31816298.
- Makes a fuss about incomplete IM versus complete IM
- New demands when probably overkill

Incomplete



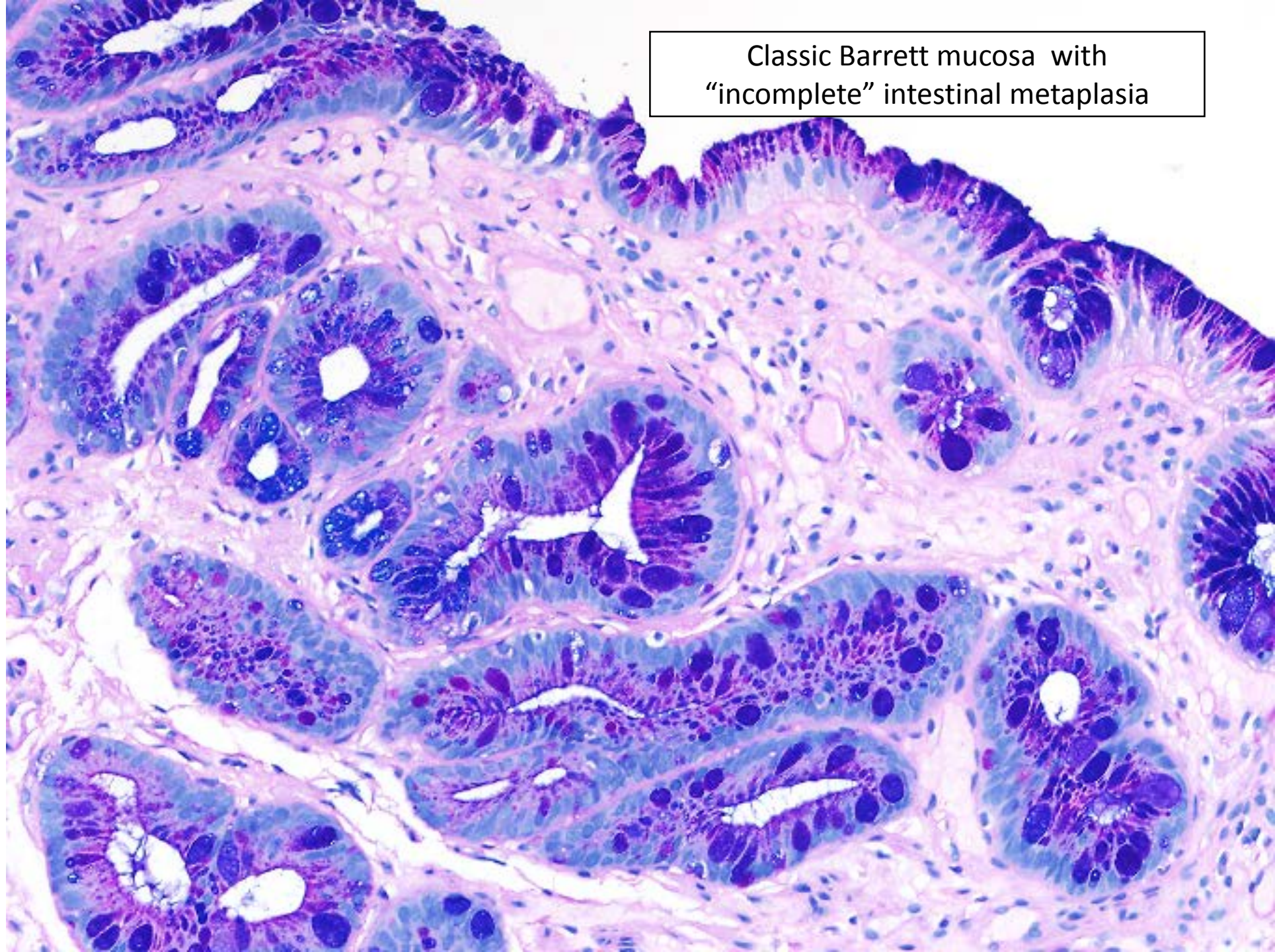
A

Complete

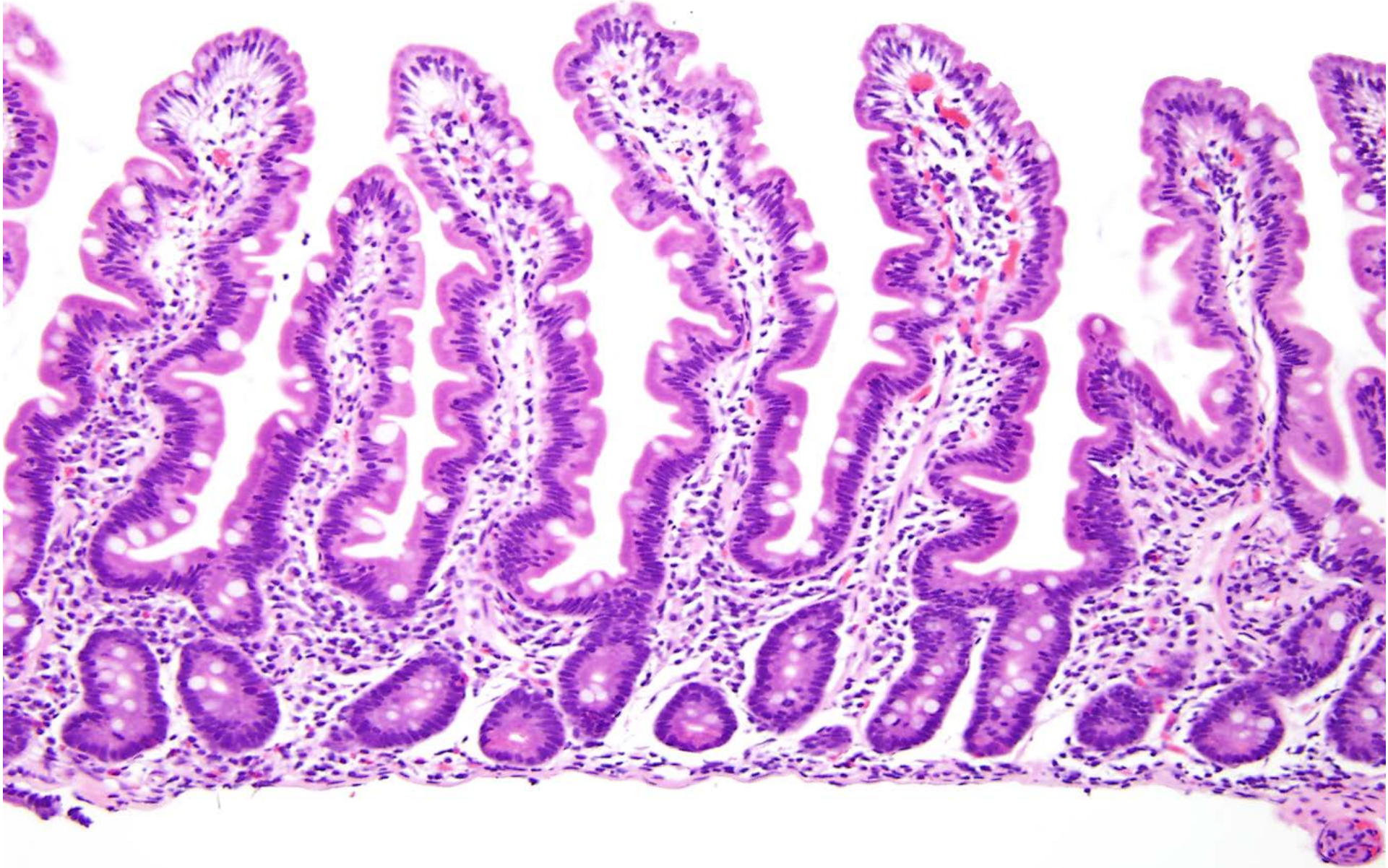


B

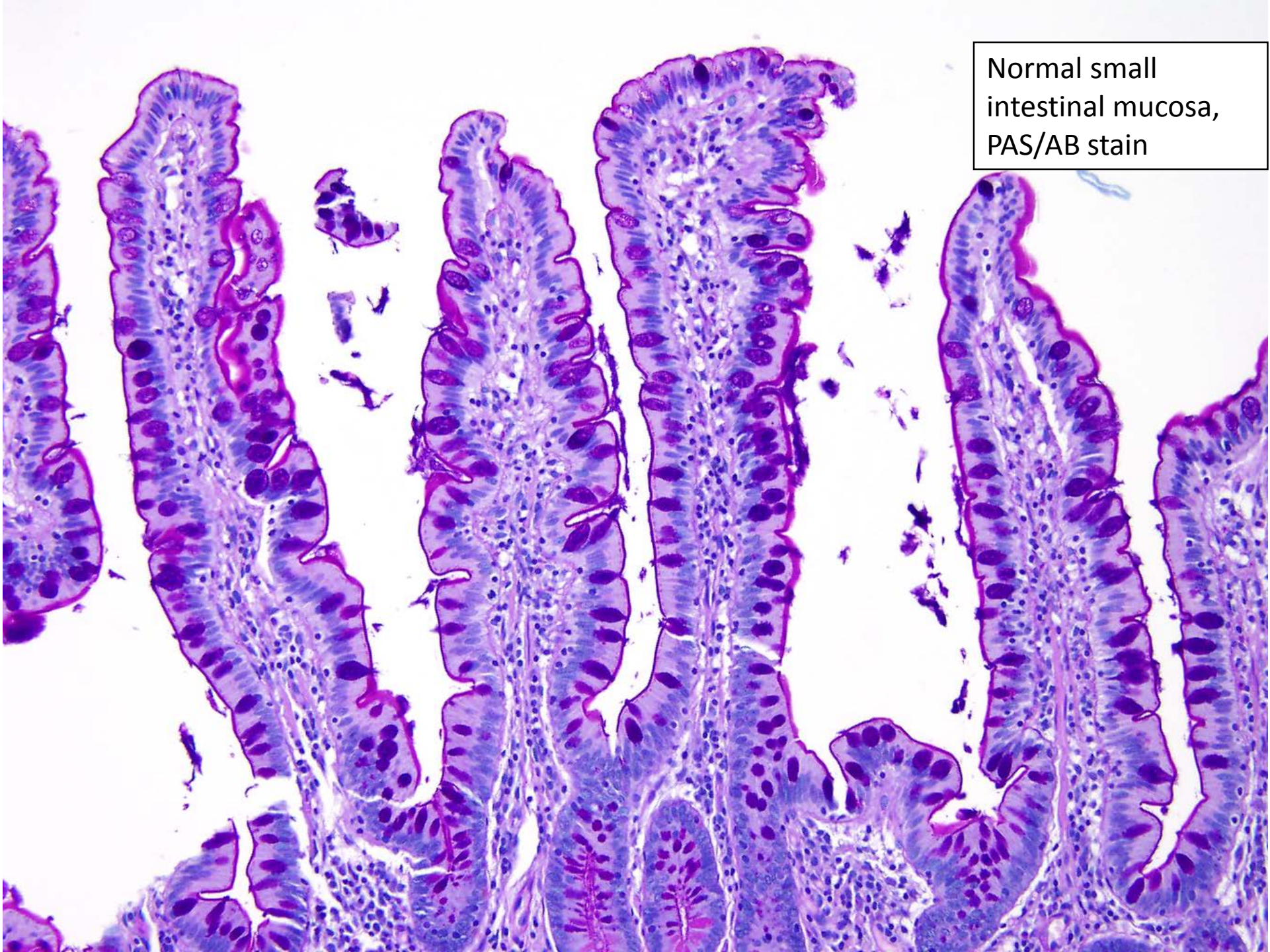
Classic Barrett mucosa with
“incomplete” intestinal metaplasia



Normal small intestinal mucosa



Normal small
intestinal mucosa,
PAS/AB stain



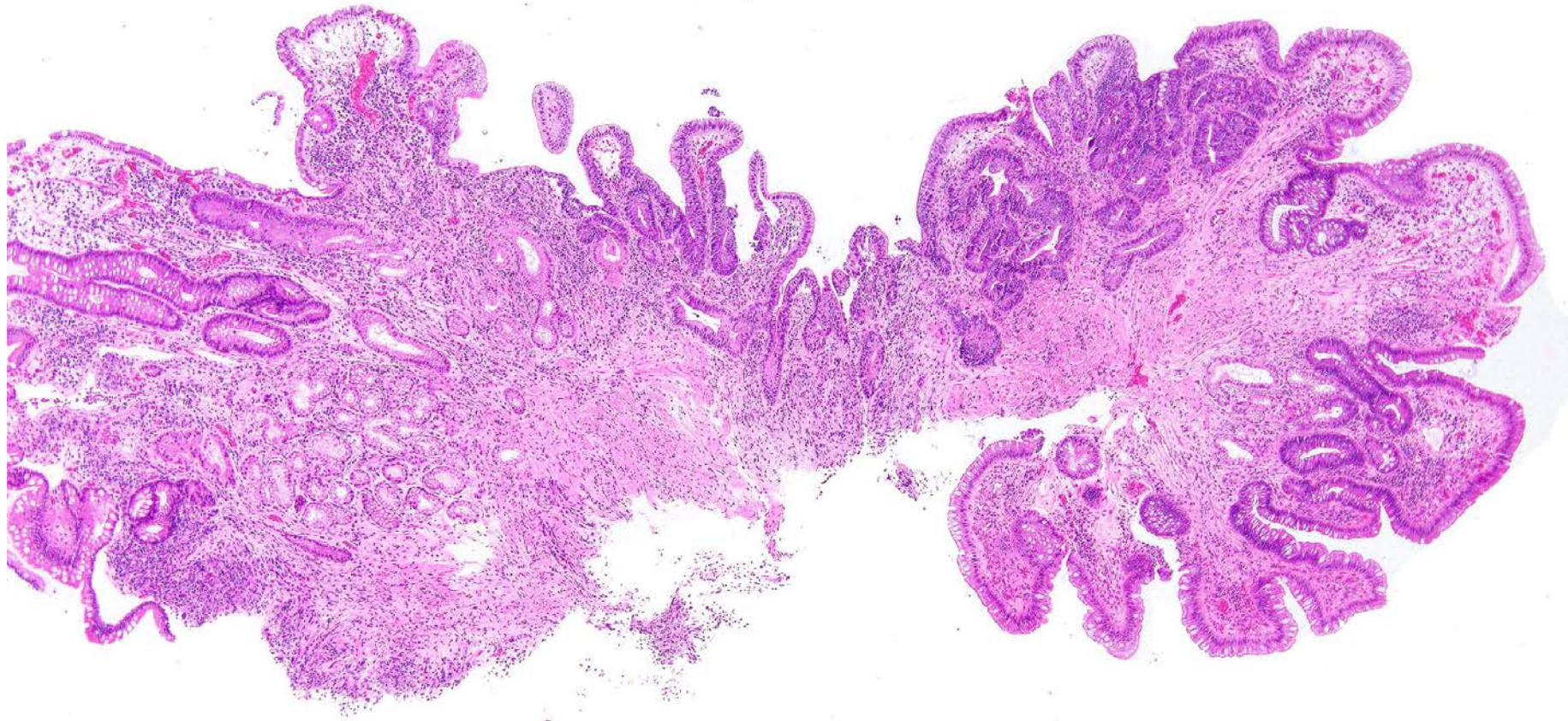


Incomplete

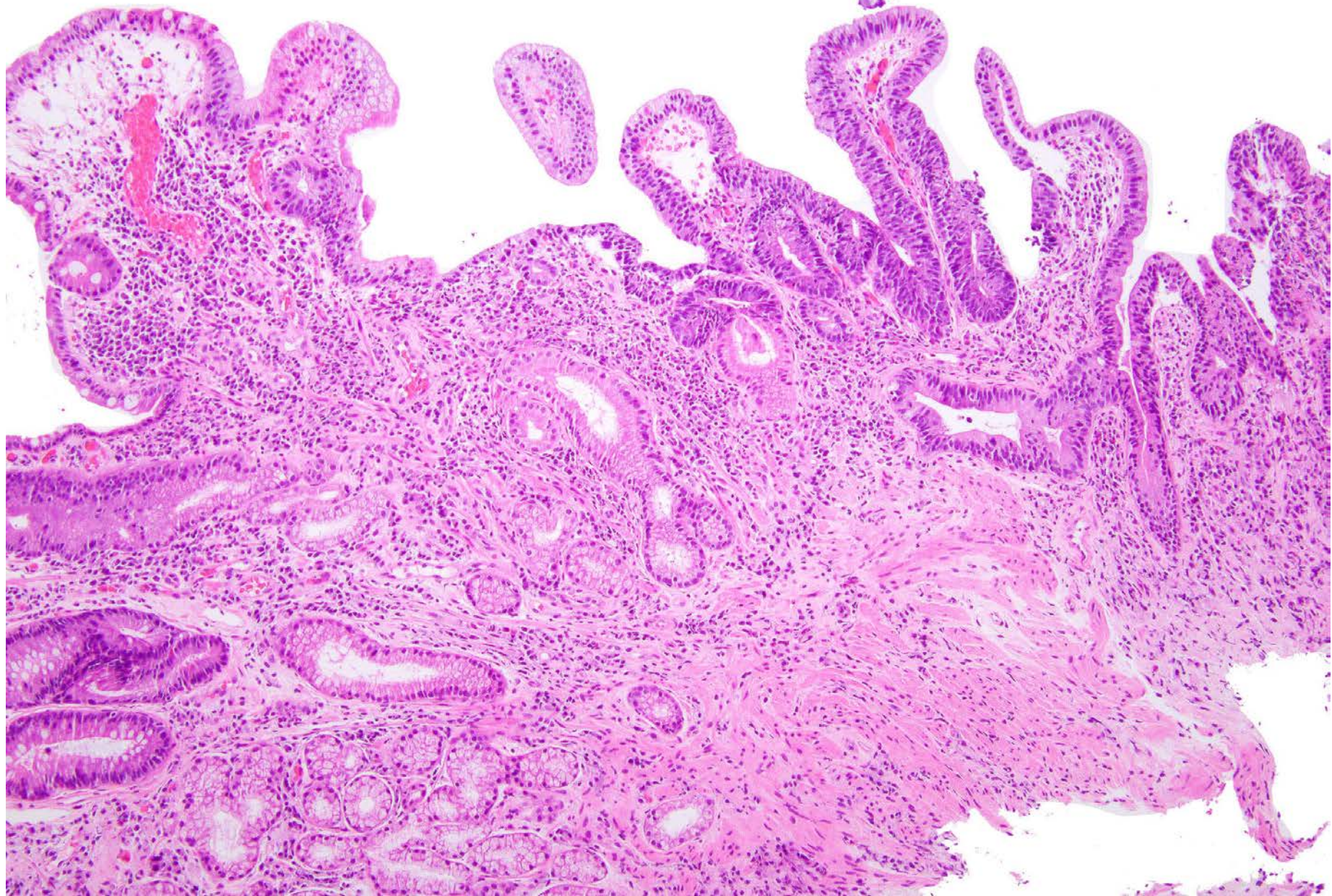
Complete

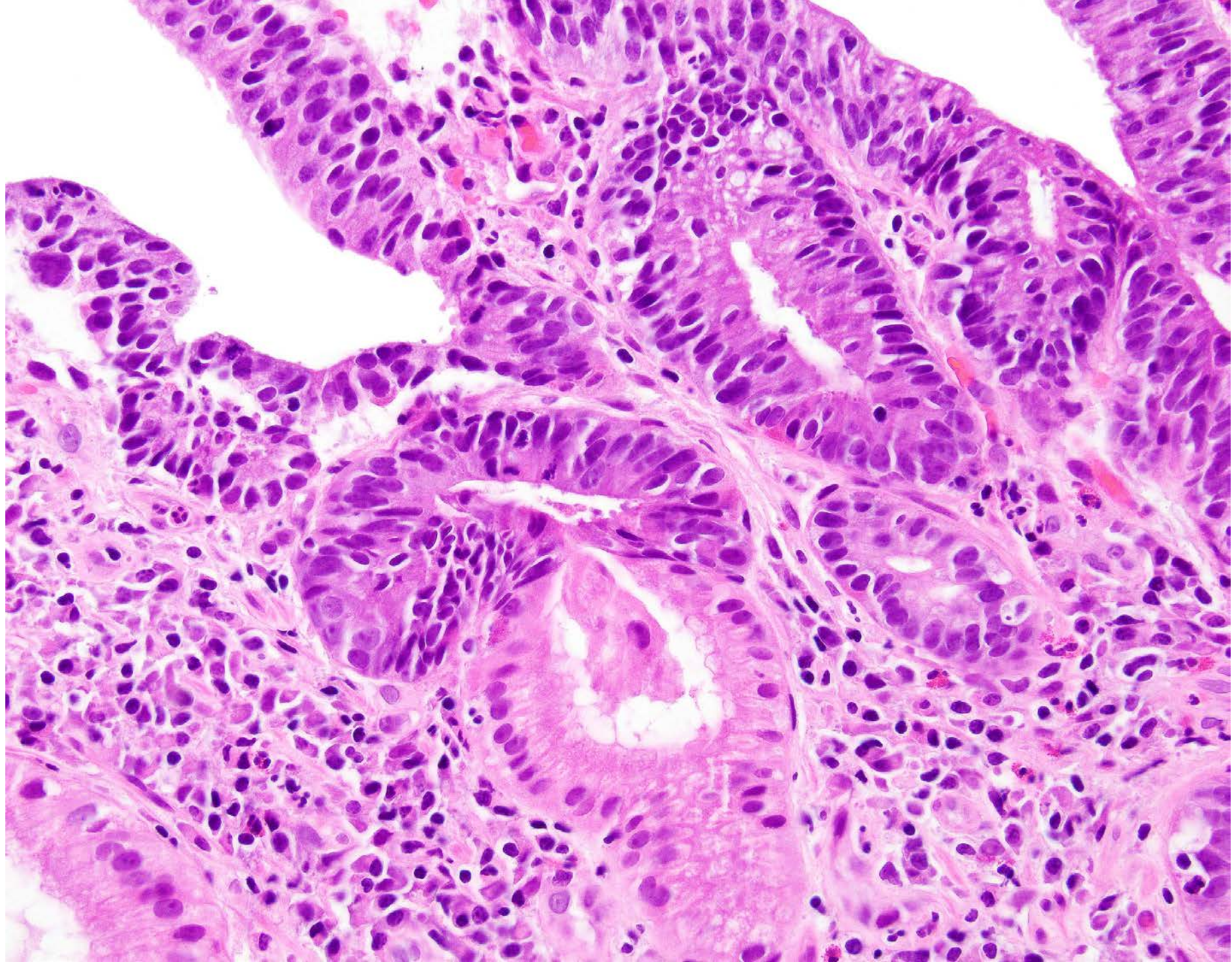
Small bowel

- 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

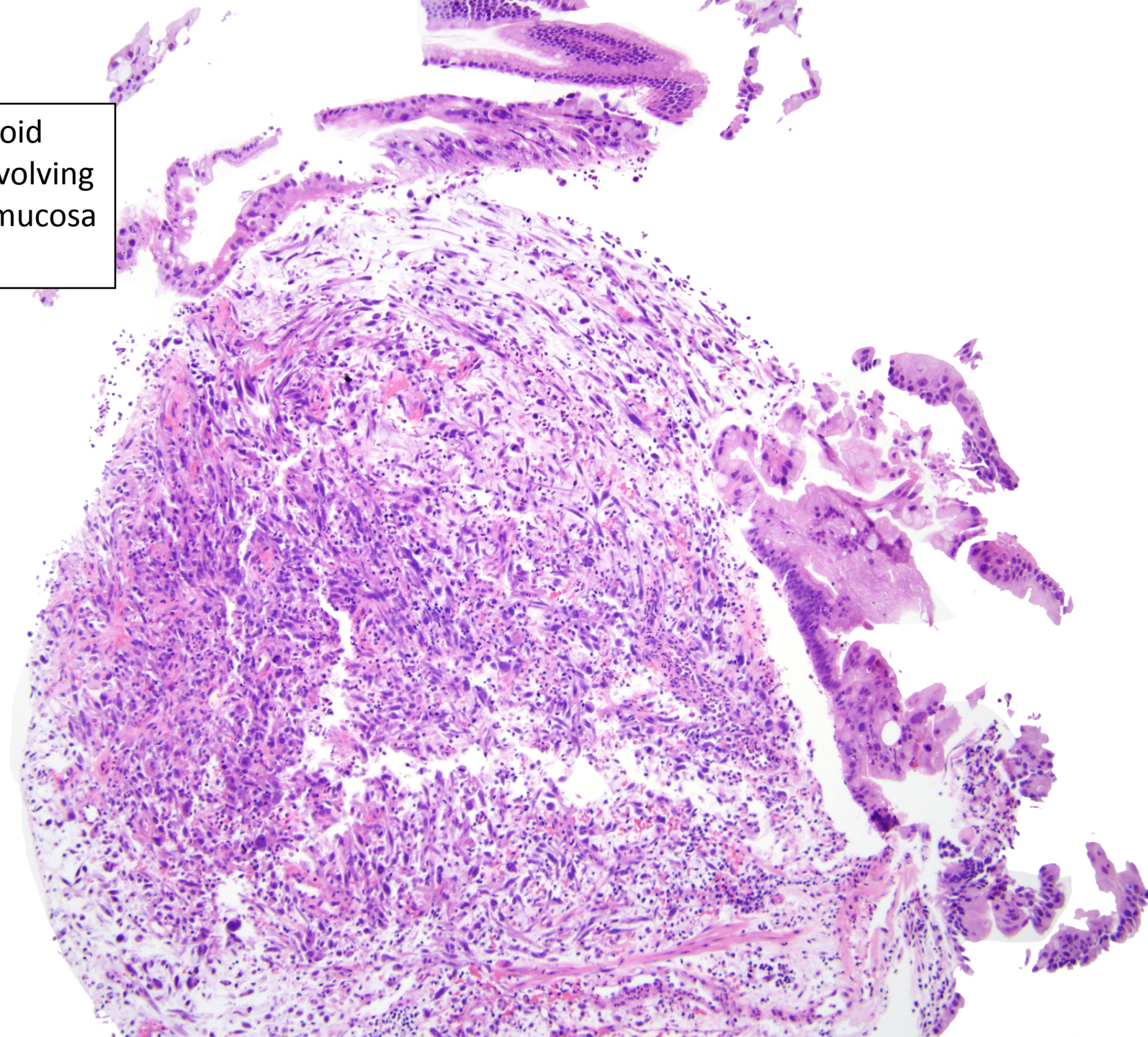




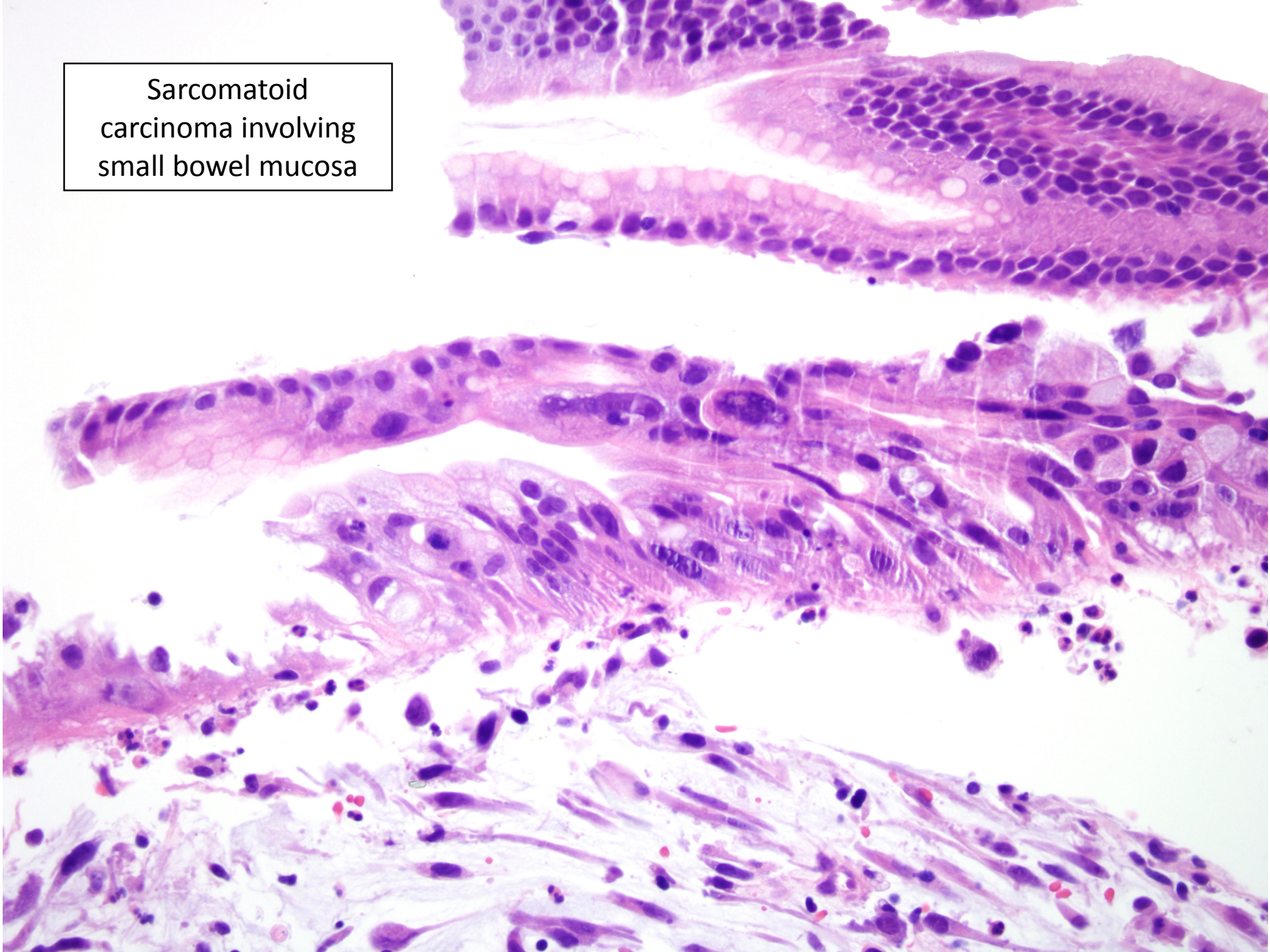
An Important Thing to Recall

- The small bowel is treacherous since its 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.

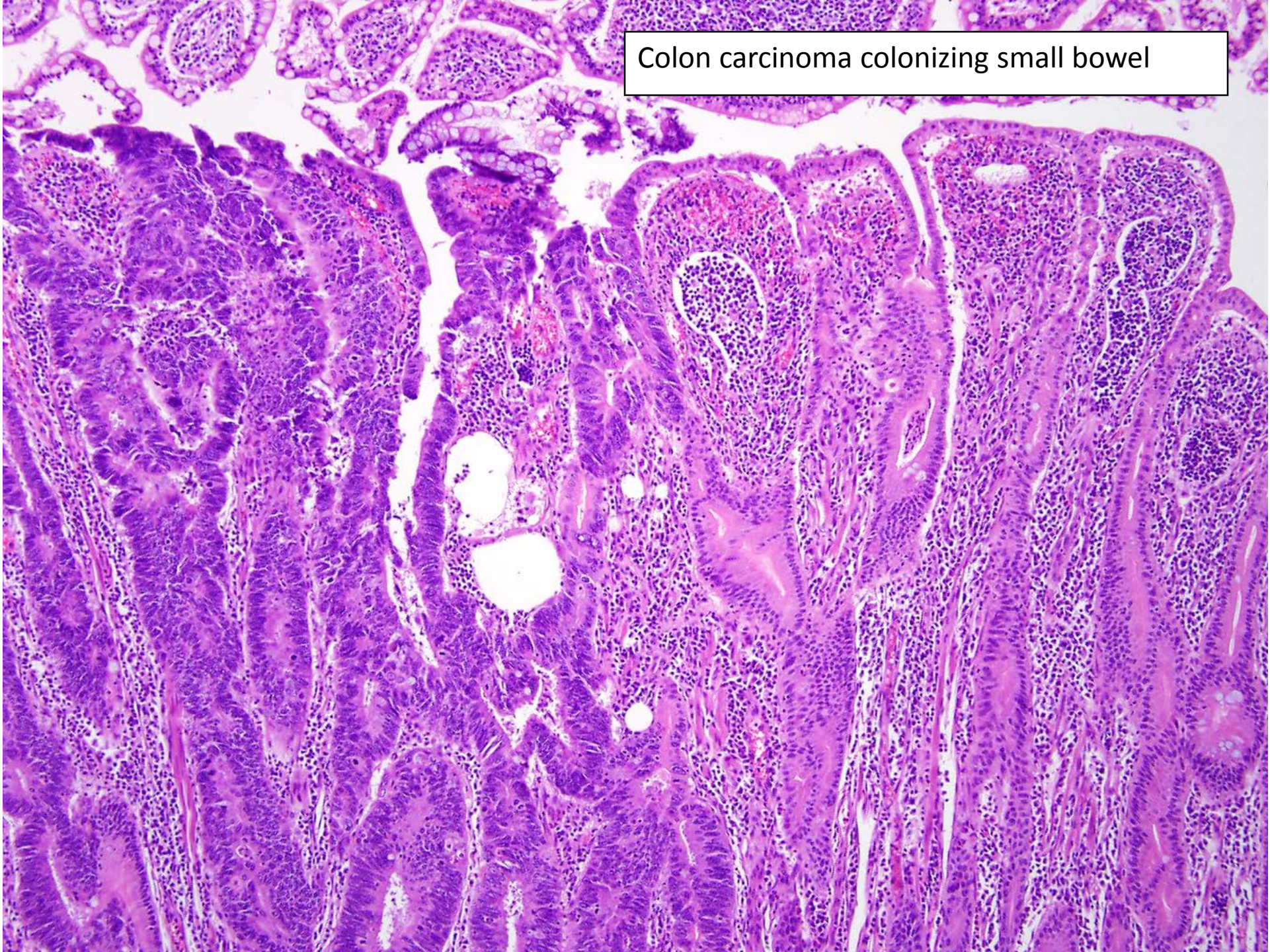
Sarcomatoid carcinoma involving small bowel mucosa



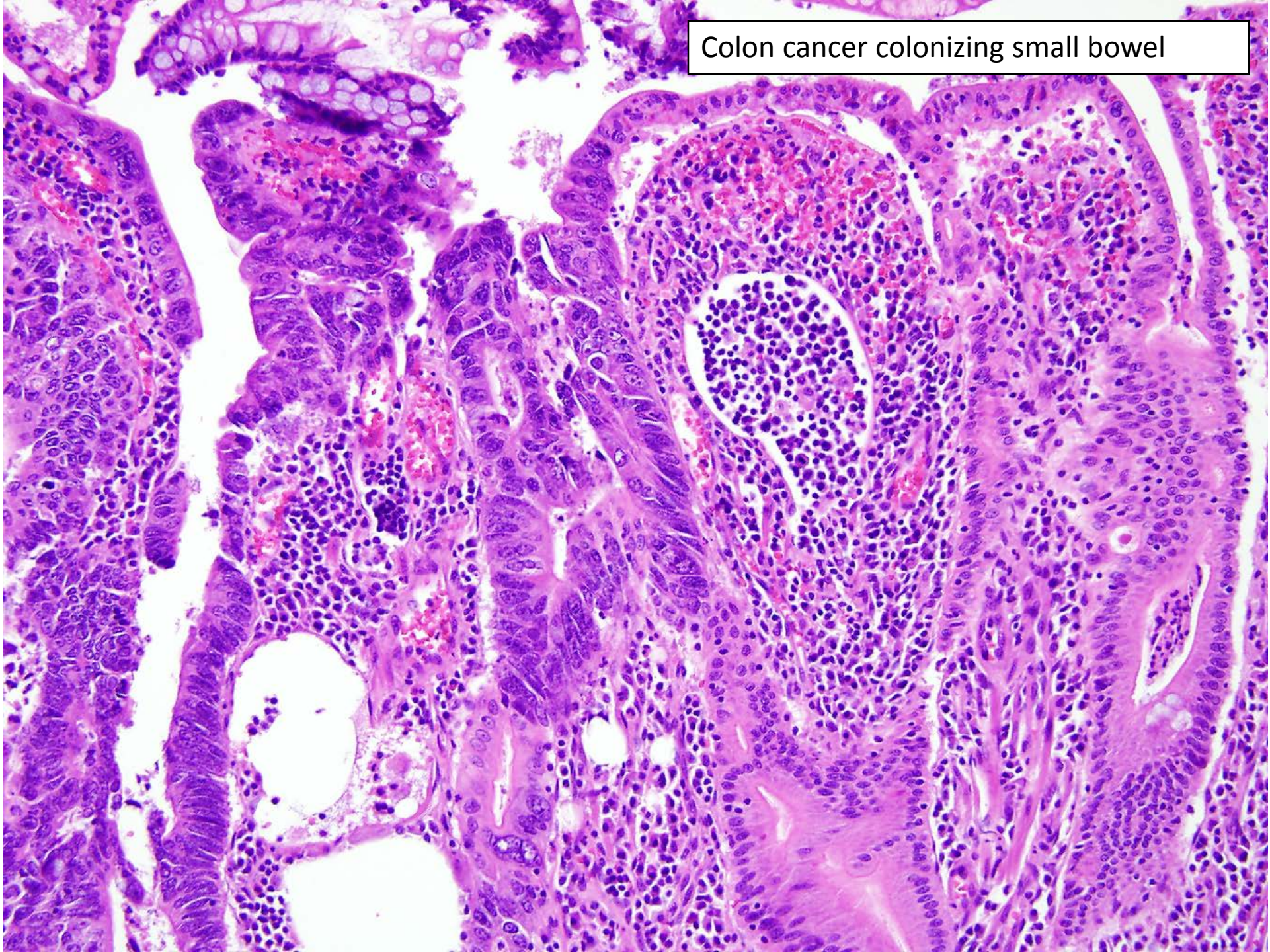
Sarcomatoid
carcinoma involving
small bowel mucosa

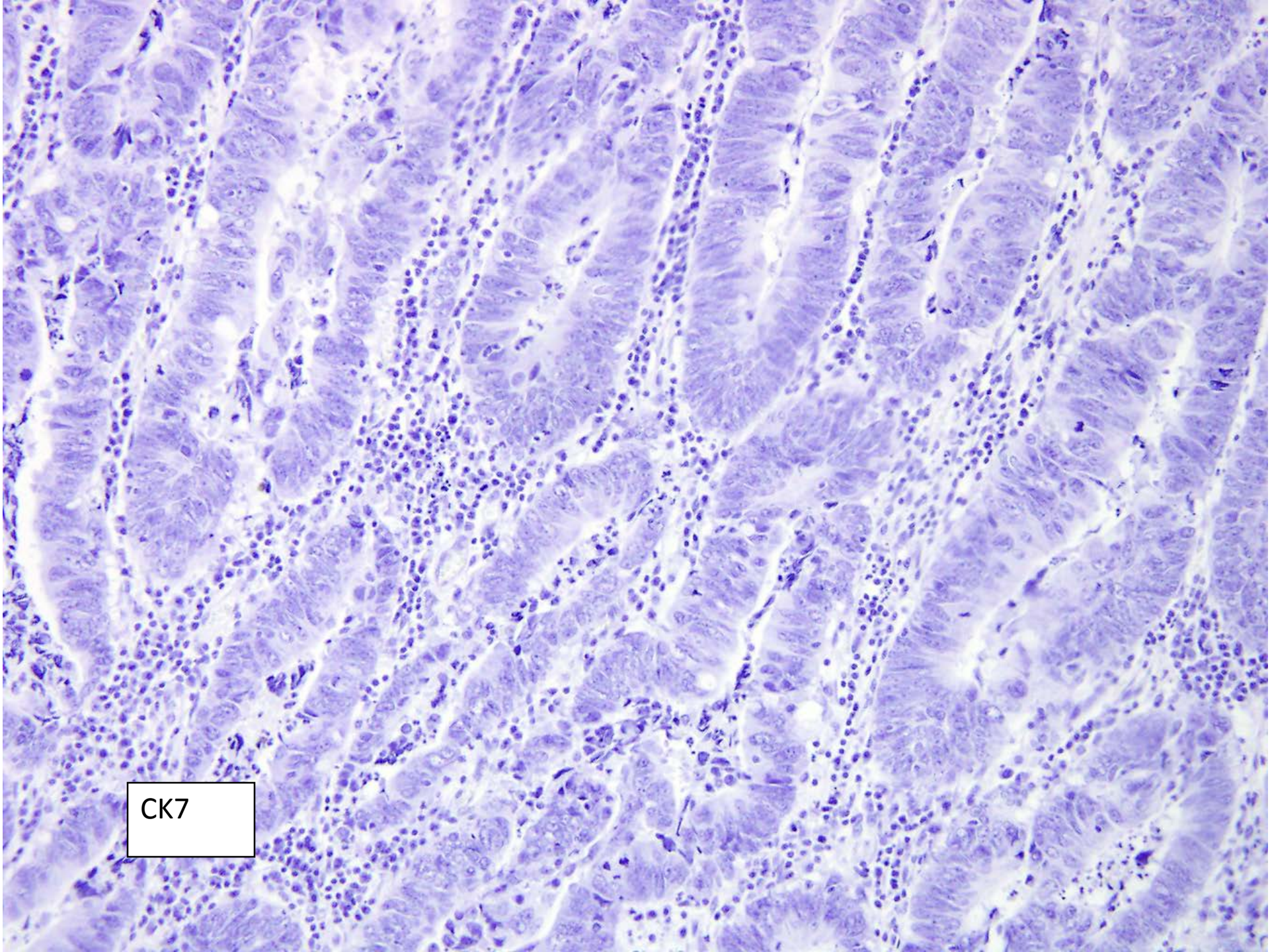


Colon carcinoma colonizing small bowel

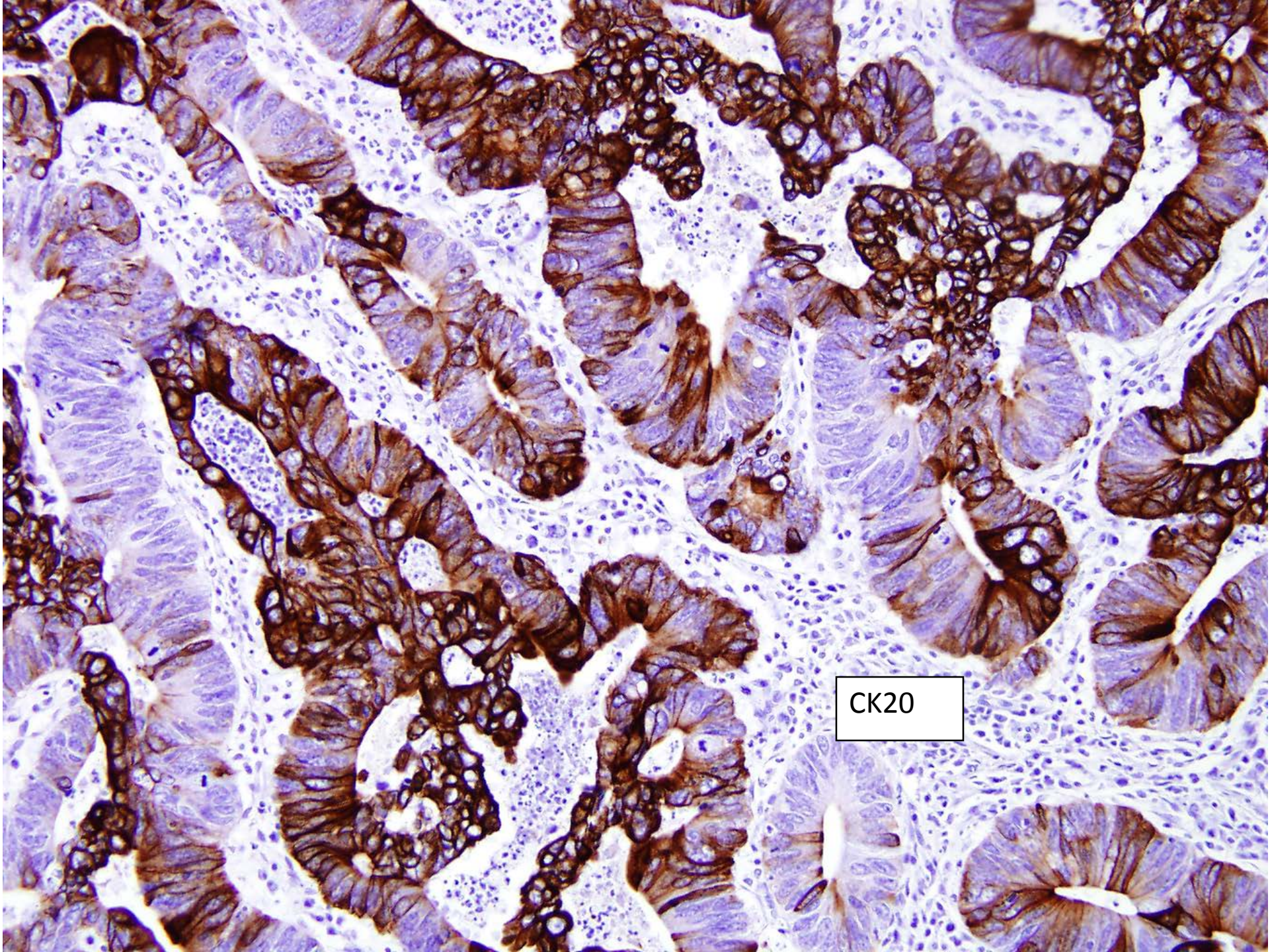


Colon cancer colonizing small bowel



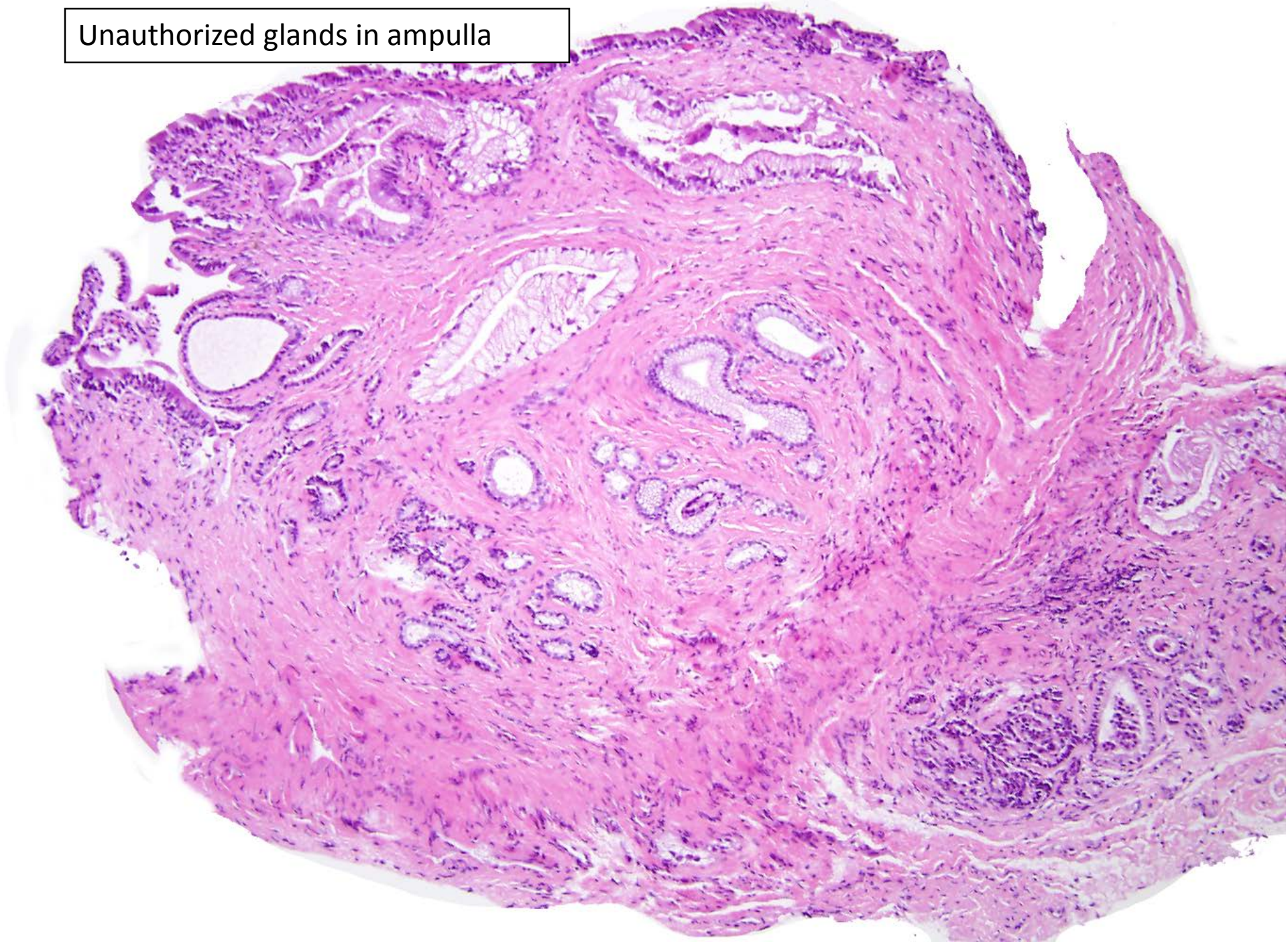


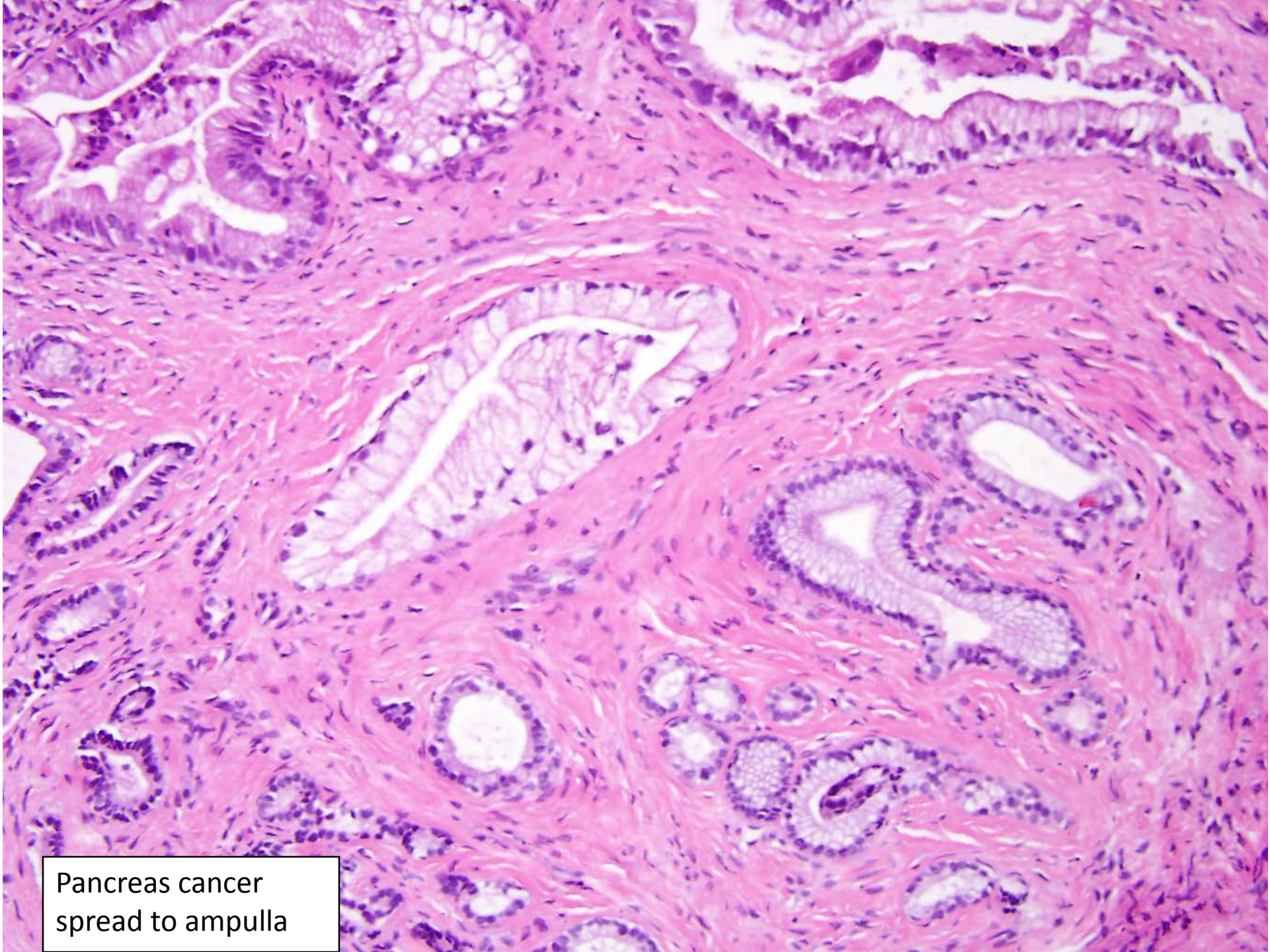
CK7



CK20

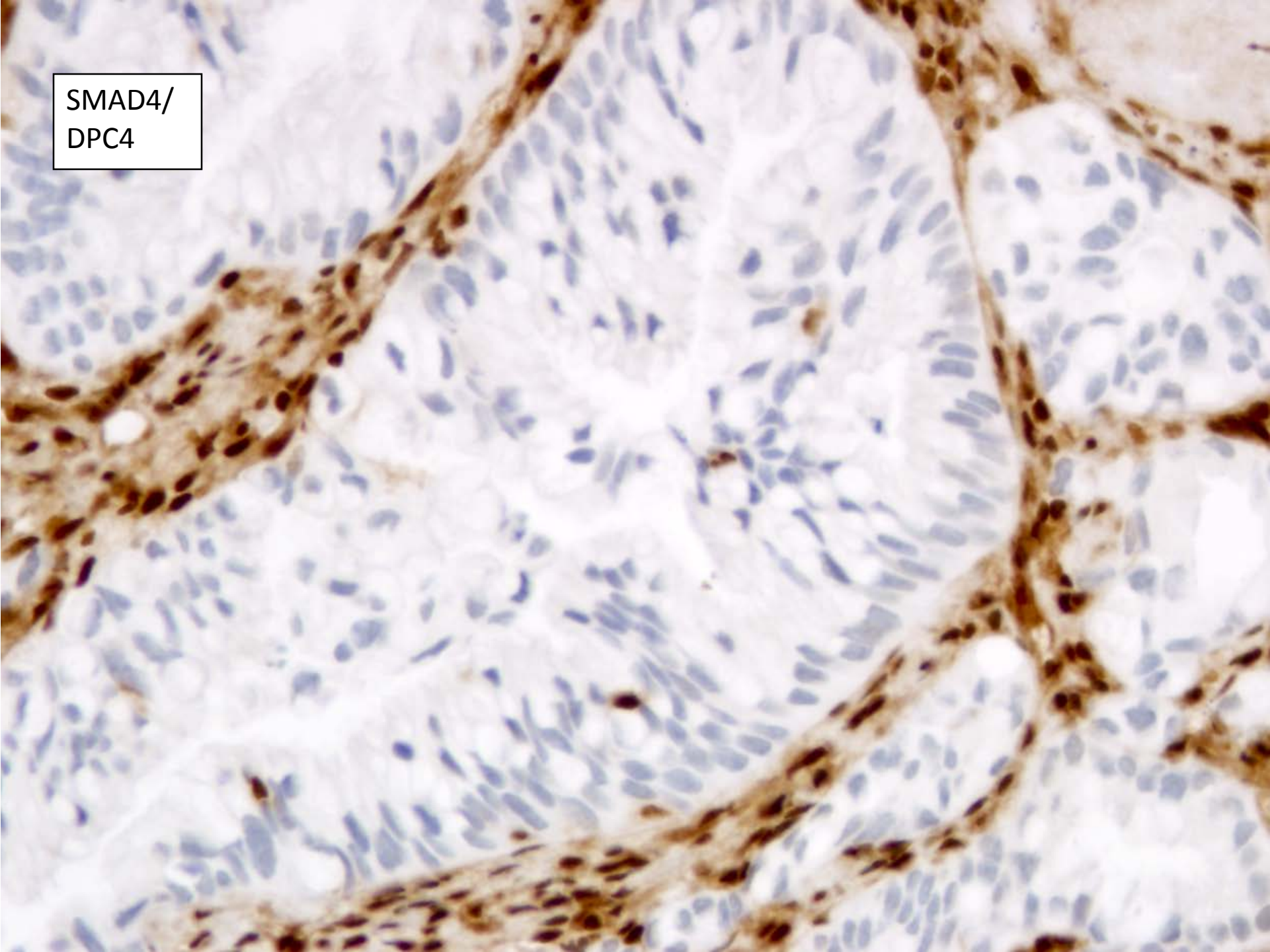
Unauthorized glands in ampulla





Pancreas cancer spread to ampulla

SMAD4/
DPC4



Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: Which stain is sometimes useful in confirming an interpretation of spread of pancreatobiliary adenocarcinoma to the small bowel?

Answer C

- There is loss of SMAD4/DPC4 nuclear staining in about 60% of pancreatobiliary carcinomas. SATB2 and a CK20+/CK7- phenotype can be great for confirming spread of colorectal carcinoma to small bowel. MUC1 is EMA!
- Ref; Wilentz RE, Su GH, Dai JL, Sparks AB, Argani P, Sohn TA, Yeo CJ, Kern SE, Hruban RH. Immunohistochemical labeling for dpc4 mirrors genetic status in pancreatic adenocarcinomas : a new marker of DPC4 inactivation. Am J Pathol. 2000 Jan;156(1):37-43. PubMed PMID: 10623651

Colon

- The big issue is of course 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.* 2019 Dec 10. doi: 10.1038/s41379-019-0419-1. [Epub ahead of print] PubMed PMID: 31822800.

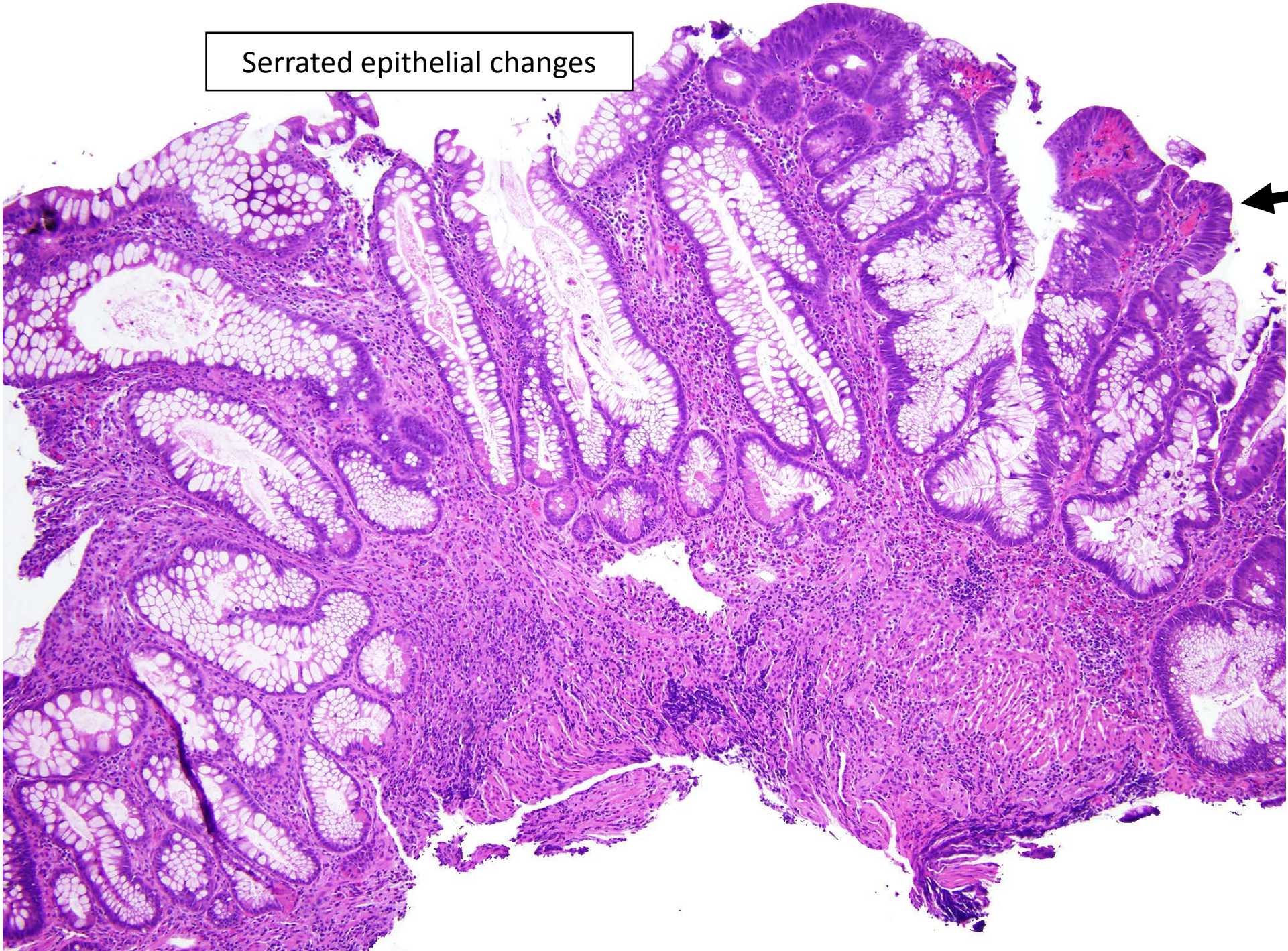
- **Colleagues also noted unusual serrated changes**

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.

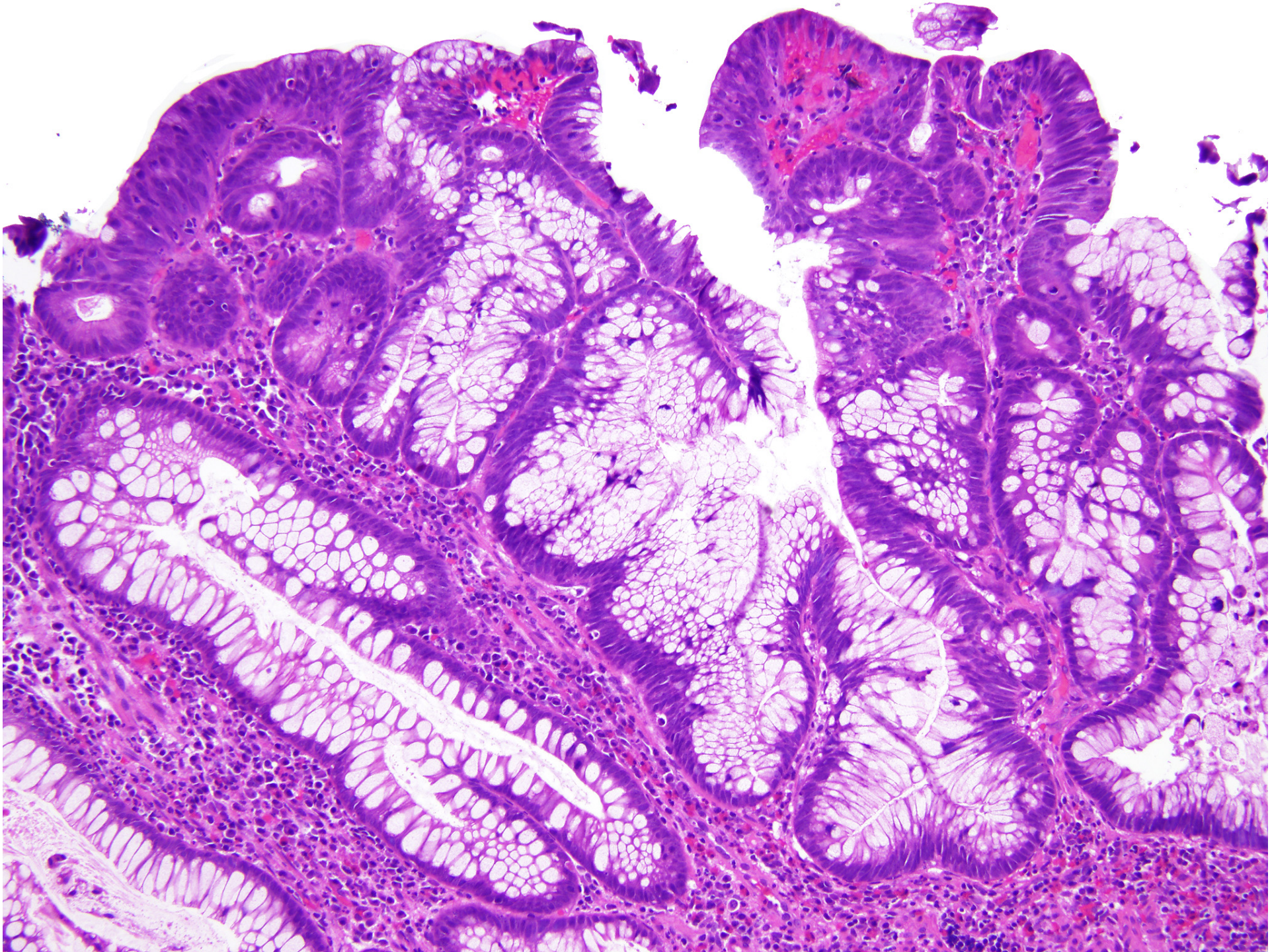
Parian A, Koh J, Limketkai BN, Eluri S, Rubin DT, Brant SR, Ha CY, Bayless TM, Giardiello F, Hart J, Montgomery E, Lazarev MG. Association between serrated epithelial changes and colorectal dysplasia in inflammatory bowel disease. *Gastrointest Endosc.* 2016 Jul;84(1):87-95. PMID: 26709112



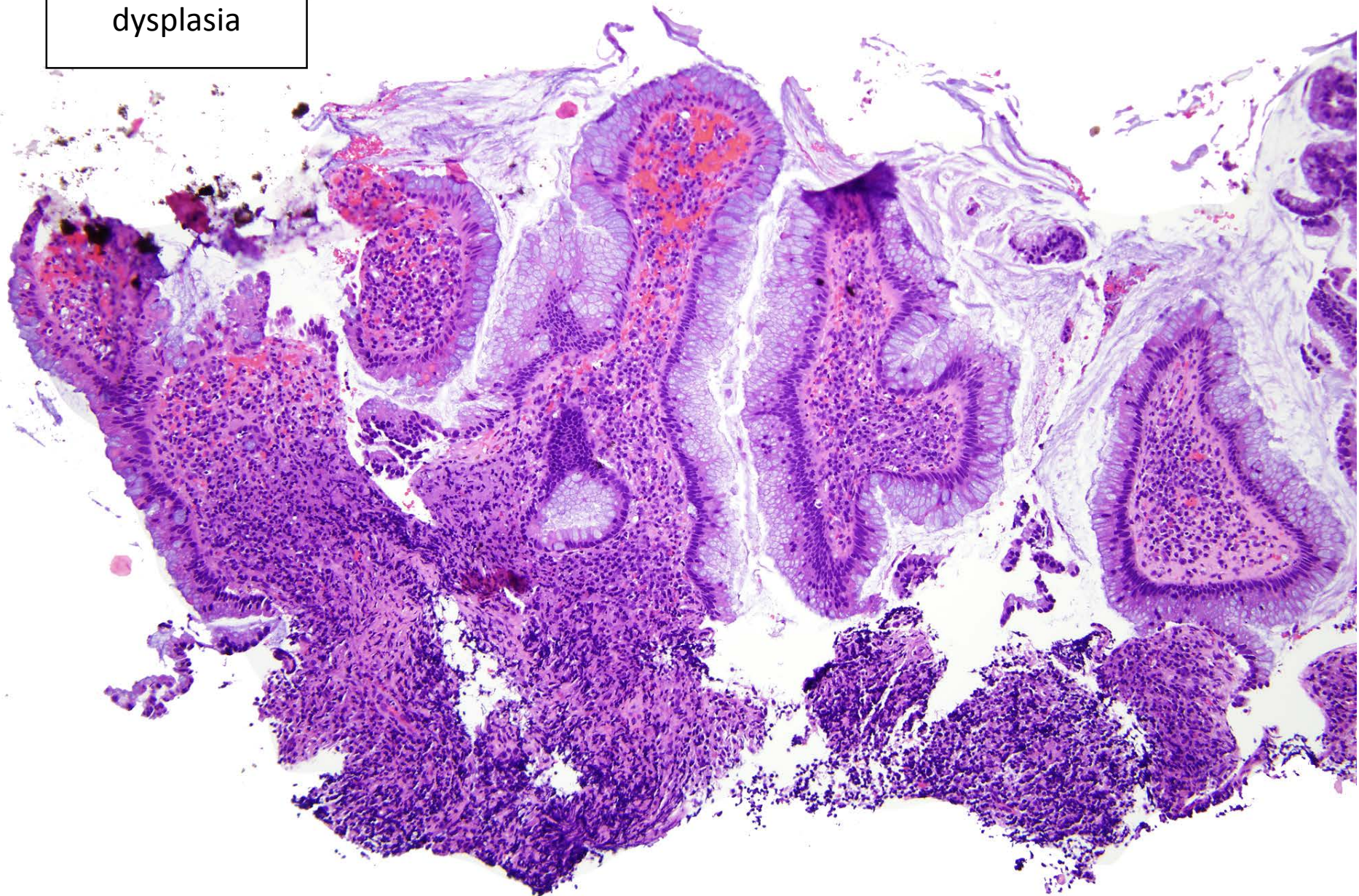
Serrated epithelial changes



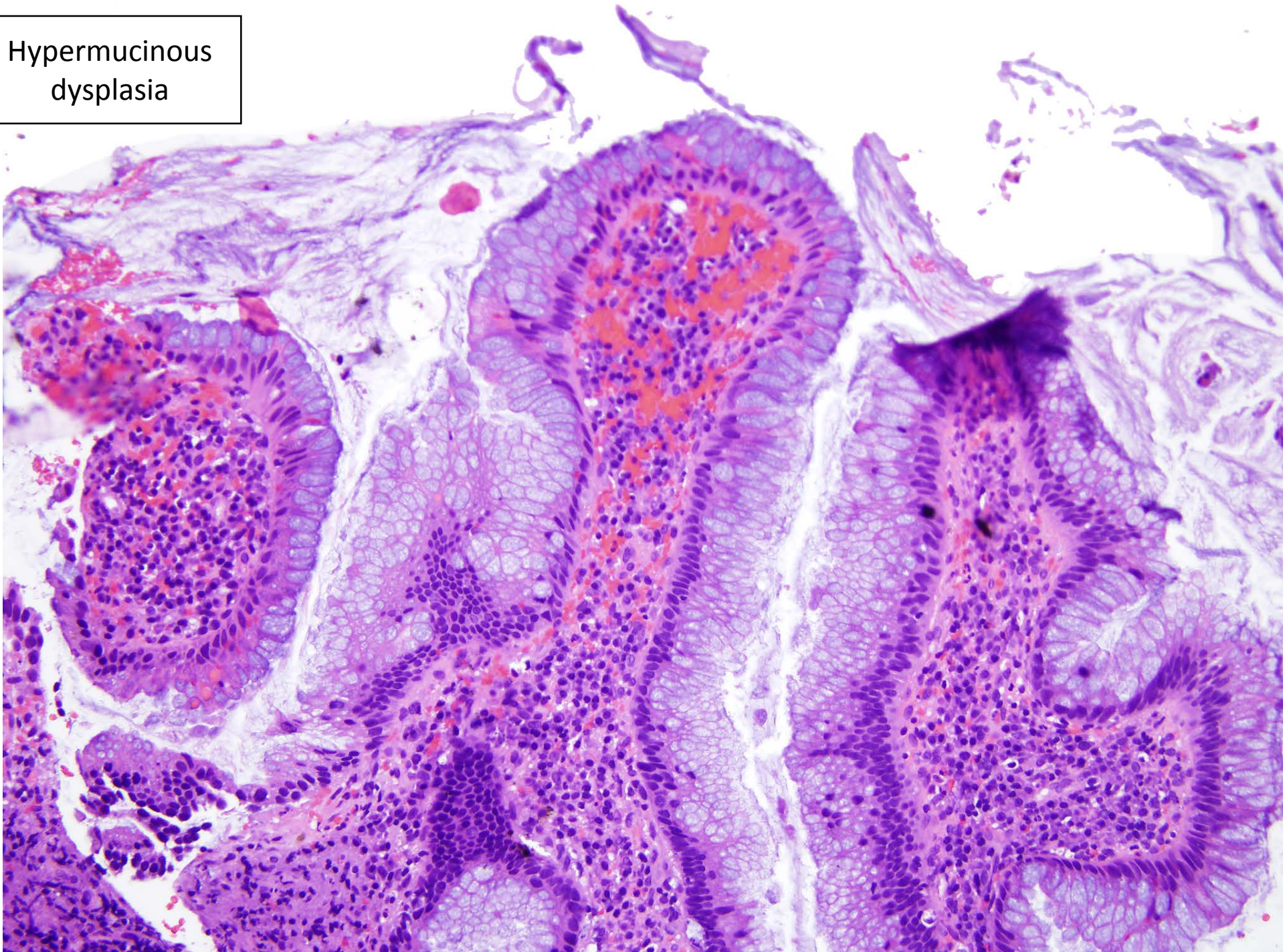
Dysplasia

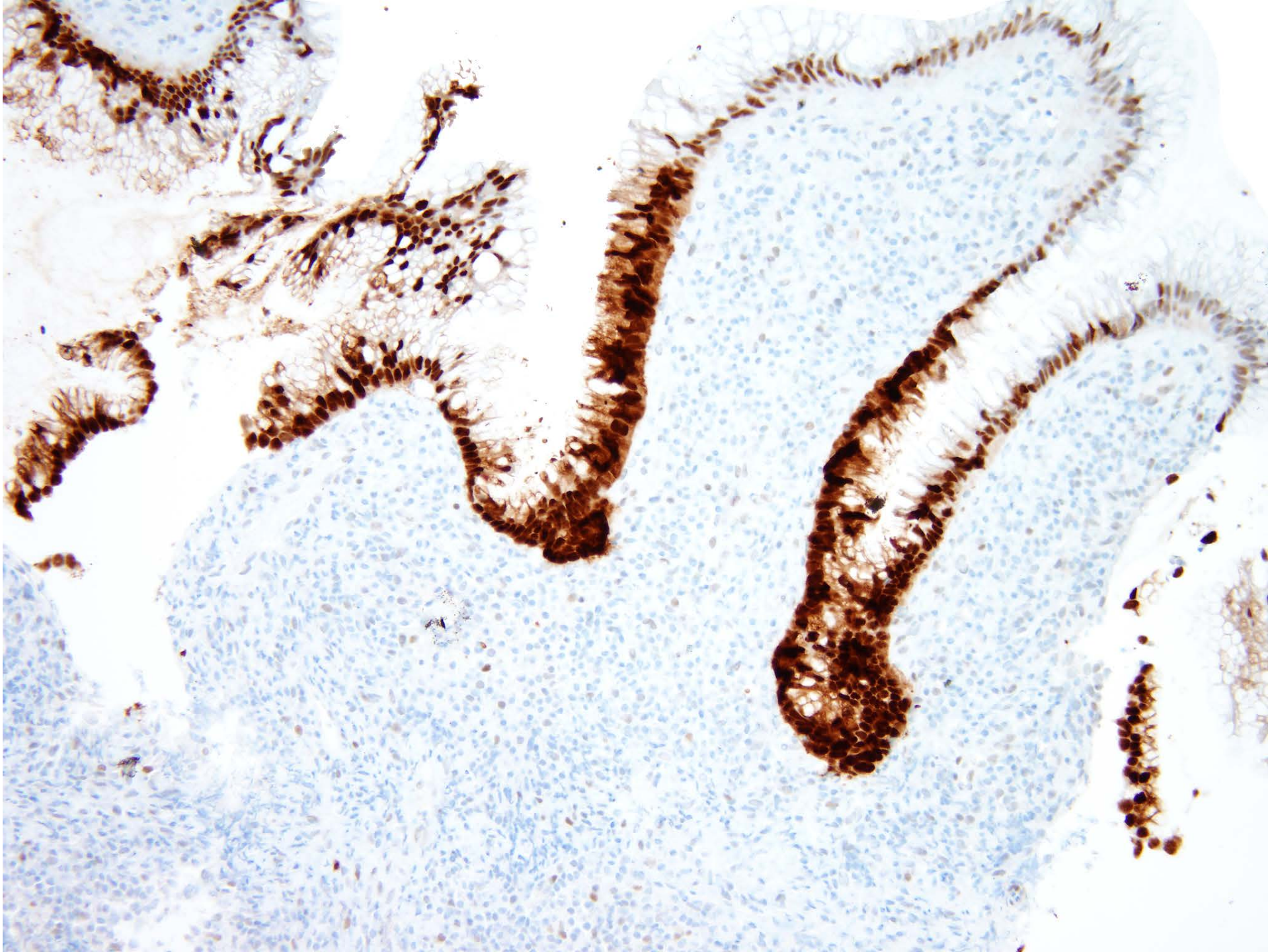


Hypermucinous
dysplasia



Hypermucinous
dysplasia





p53

Interesting data

- **Abstract #:** 1394

Abstract Title: Serrated Epithelial Change in Long-Standing Inflammatory Bowel Disease (IBD) - A Precursor Lesion Morphologically and Genetically Distinct from Sporadic Serrated Polyps Arising in IBD Patients

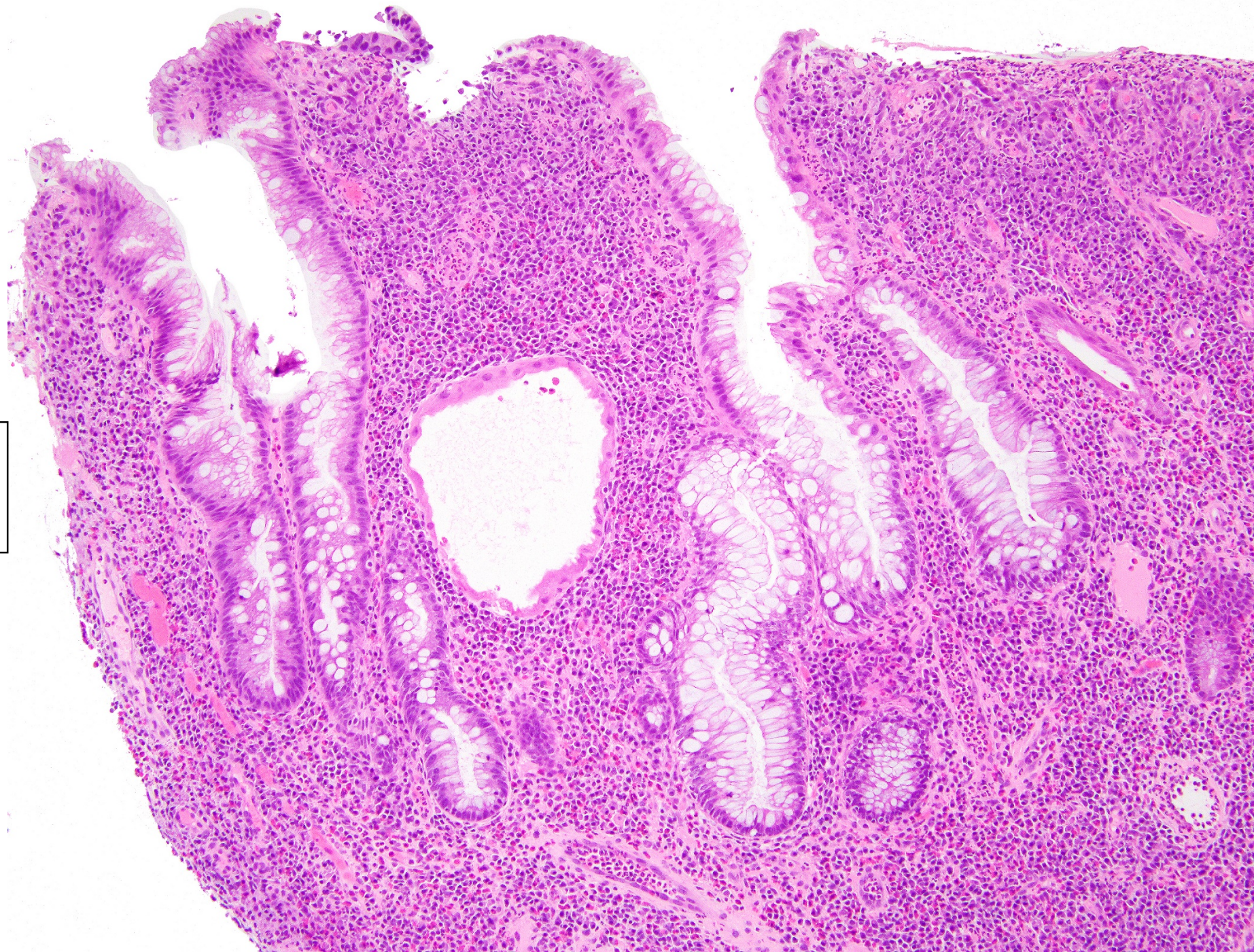
Platform Presentation: Platform - Monday AM - Gastrointestinal Pathology on Monday, March 02, 2020 from 8:00 AM - 12:00 PM at the Los Angeles Convention Center in LACC 408 A*

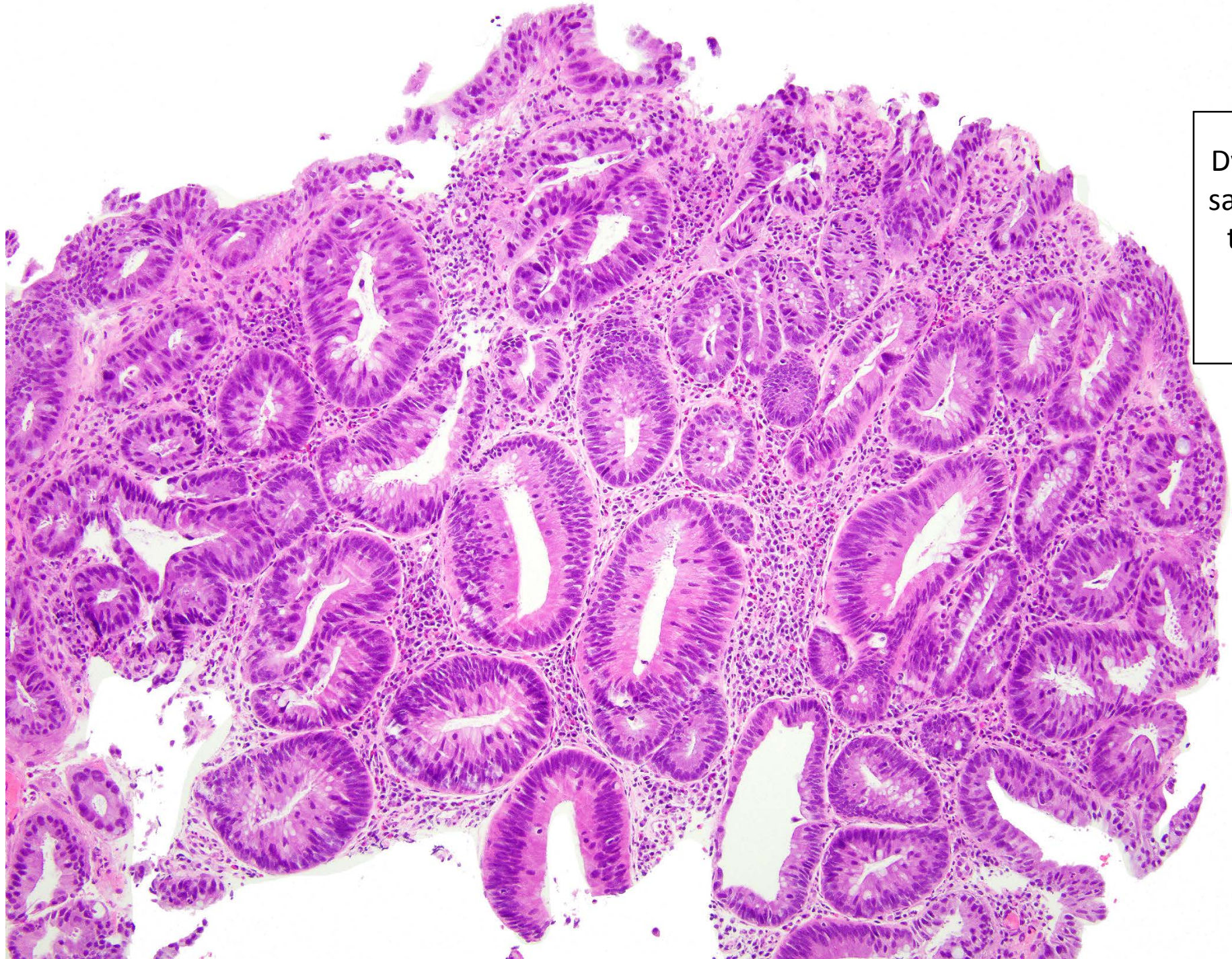
Presentation Time: 9:15 AM - 9:30 AM

*Session rooms are subject to change. Please check the final schedule in February 2020 for confirmation.

- **Presenting Author:** Aatur Singhi

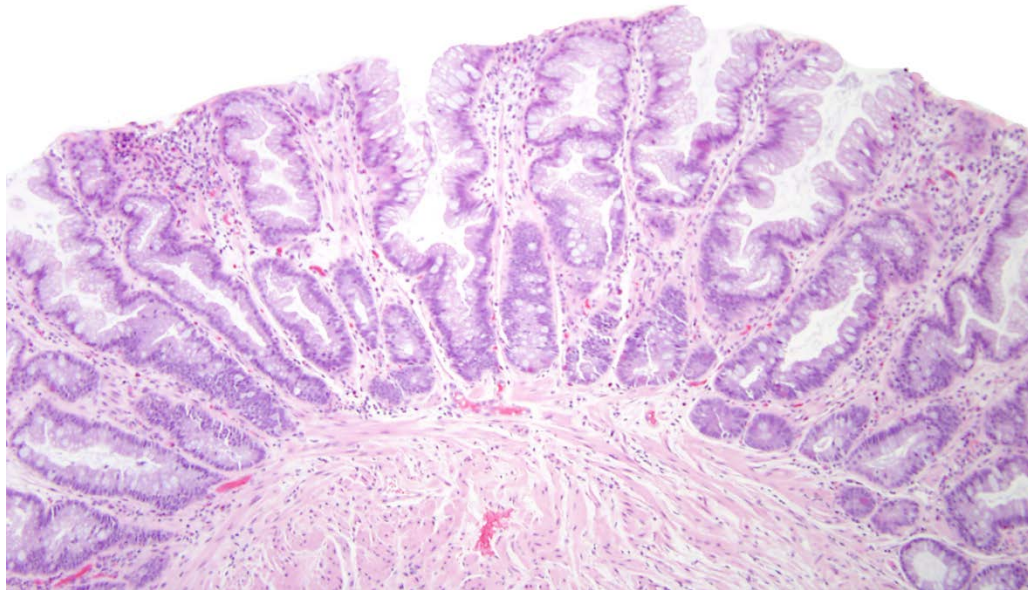
Serrated
epithelial
change



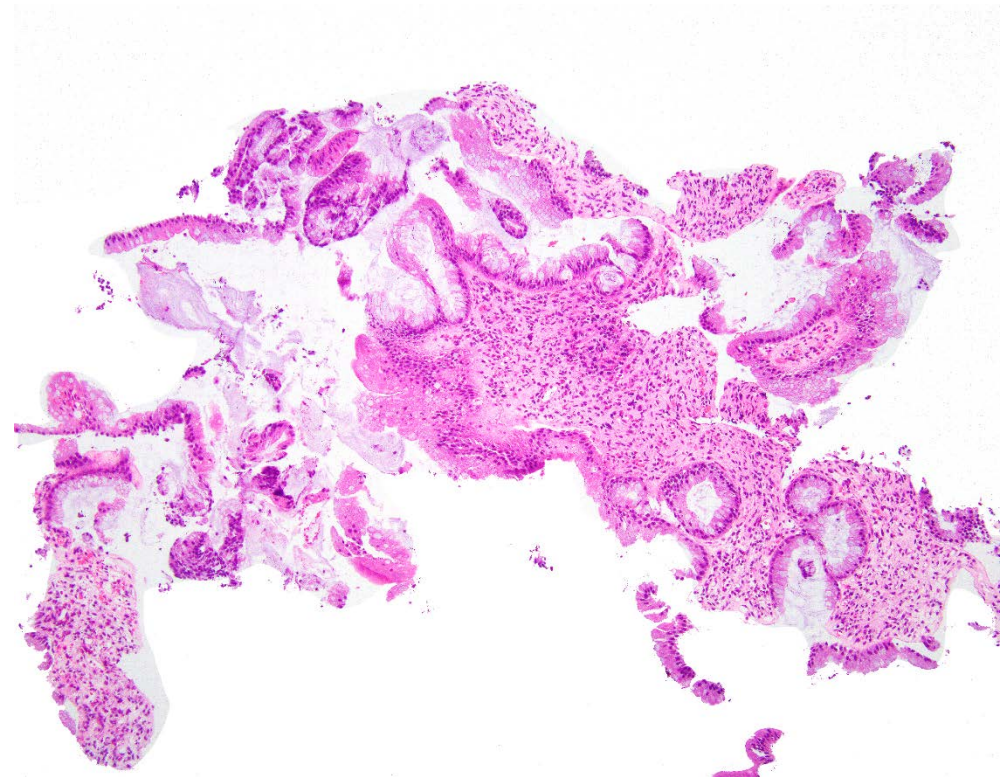


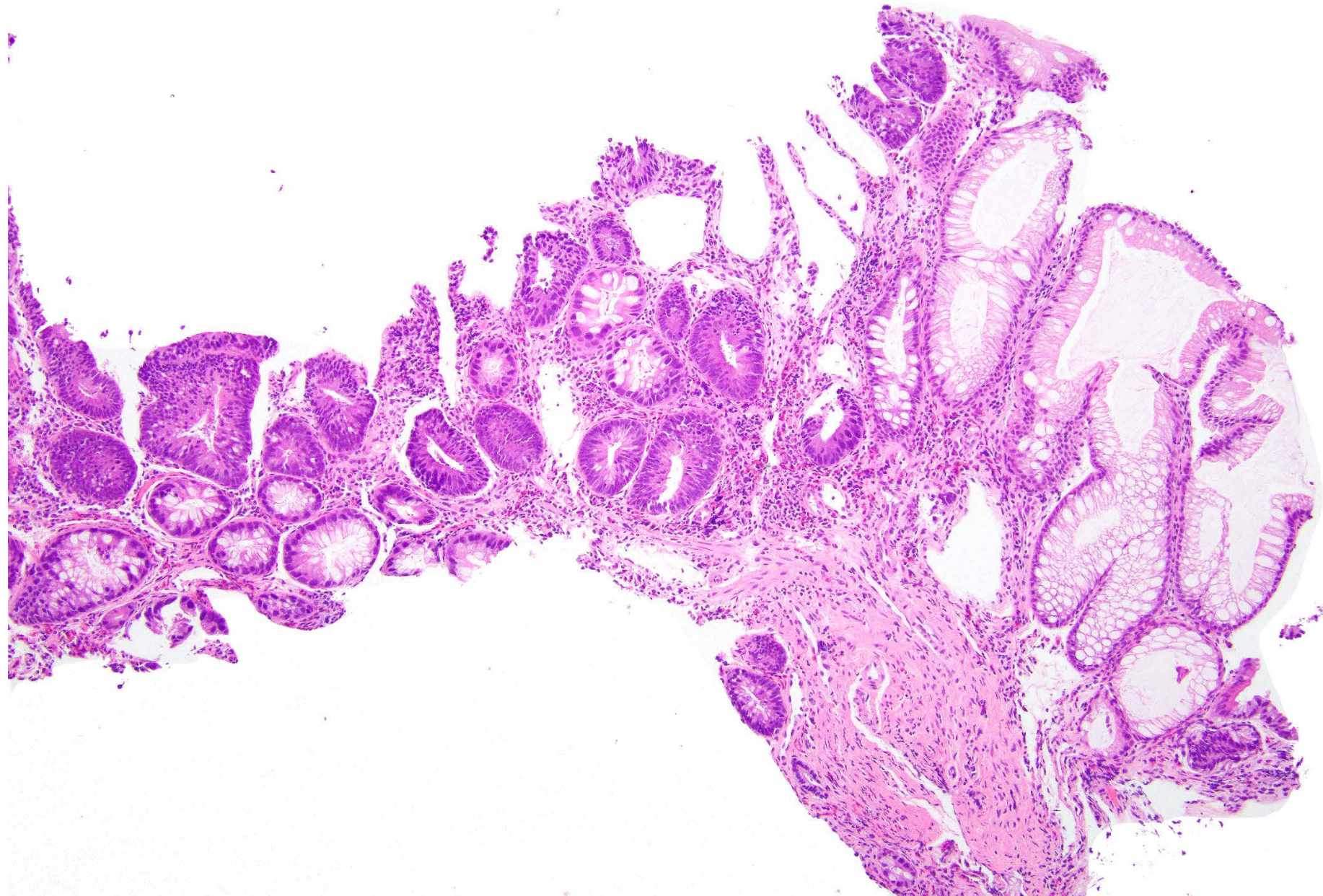
Dysplasia from
same biopsy as
the serrated
epithelial
change

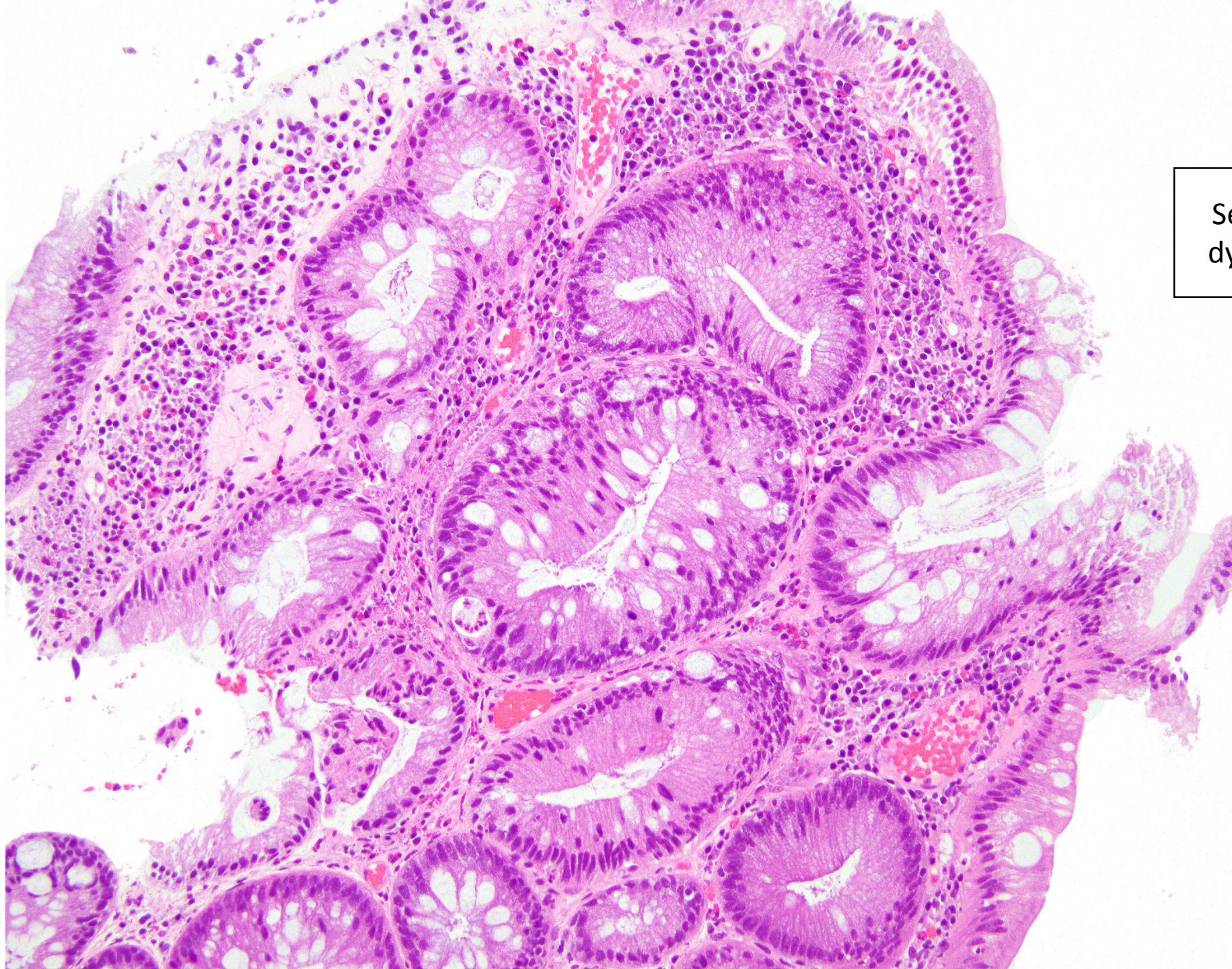
Hyperplastic polyp or sessile serrated adenoma has basically normal architecture with crypt bases landing on muscularis mucosae



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

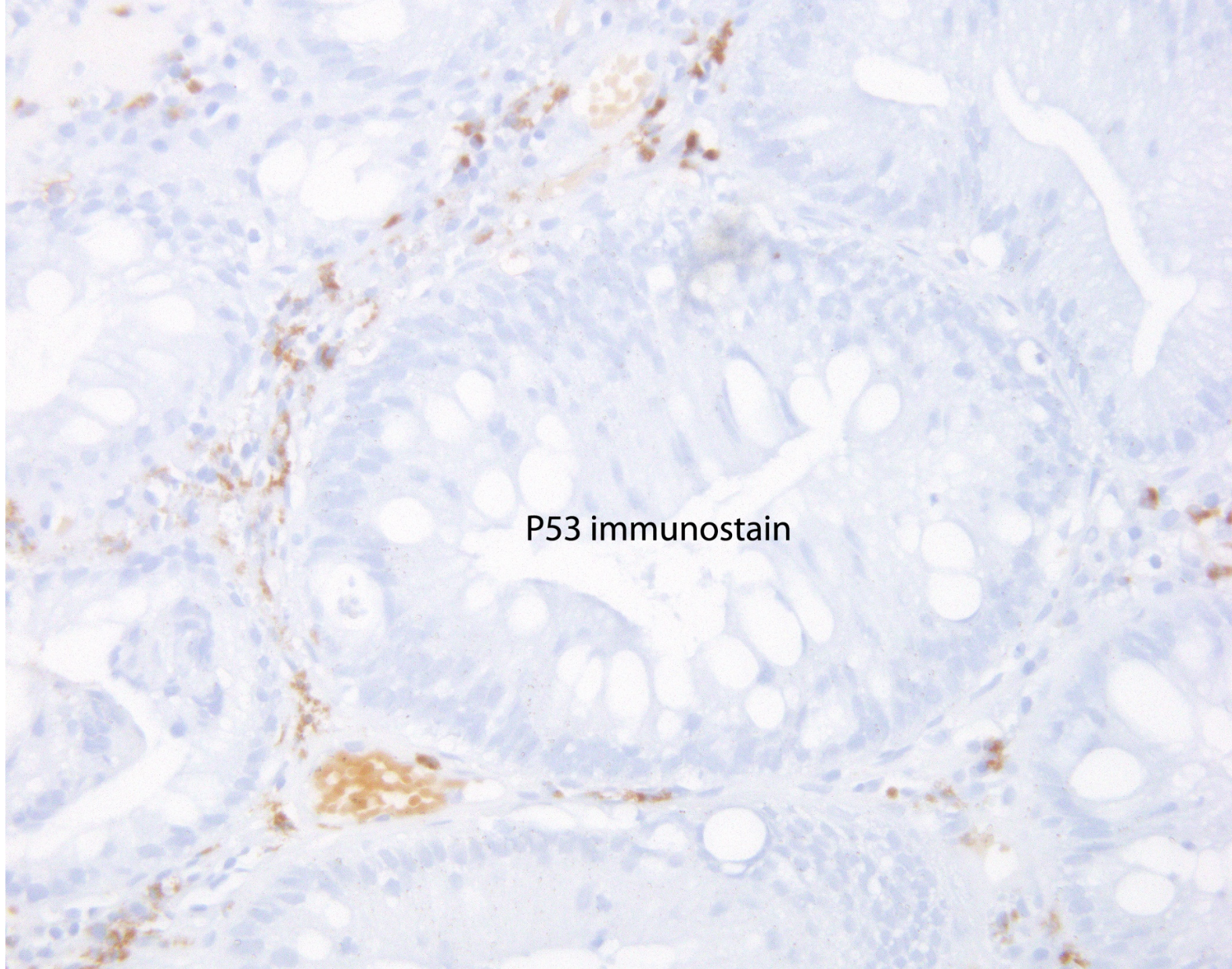






Serrated
dysplasia

Null
pattern
p53



P53 immunostain

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.

ARS Question

- Which statement is true?
- A. Patients with polypoid colitis-associated dysplasia should undergo colectomy
- B. Visible colitis-associated dysplasia can be managed endoscopically
- C. Colitis-associated dysplasia has become a major public health scourge

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: Which statement is true?

Answer B

- According to accumulated data, visible lesions of colitis-associated dysplasia can be managed endoscopically
- 1. 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. doi: 10.1053/j.gastro.2015.01.031. PubMed PMID: 25702852.
- 2: Quinn AM, Farraye FA, Naini BV, Cerda S, Coukos J, Li Y, Khor T, Odze RD. Polypectomy is adequate treatment for adenoma-like dysplastic lesions (DALMs) in Crohn's disease. *Inflamm Bowel Dis*. 2013 May;19(6):1186-93. doi: 10.1097/MIB.0b013e318280e749. PubMed PMID: 23567776.
- 3: Odze RD, Farraye FA, Hecht JL, Hornick JL. Long-term follow-up after polypectomy treatment for adenoma-like dysplastic lesions in ulcerative colitis. *Clin Gastroenterol Hepatol*. 2004 Jul;2(7):534-41. PubMed PMID: 15224277.

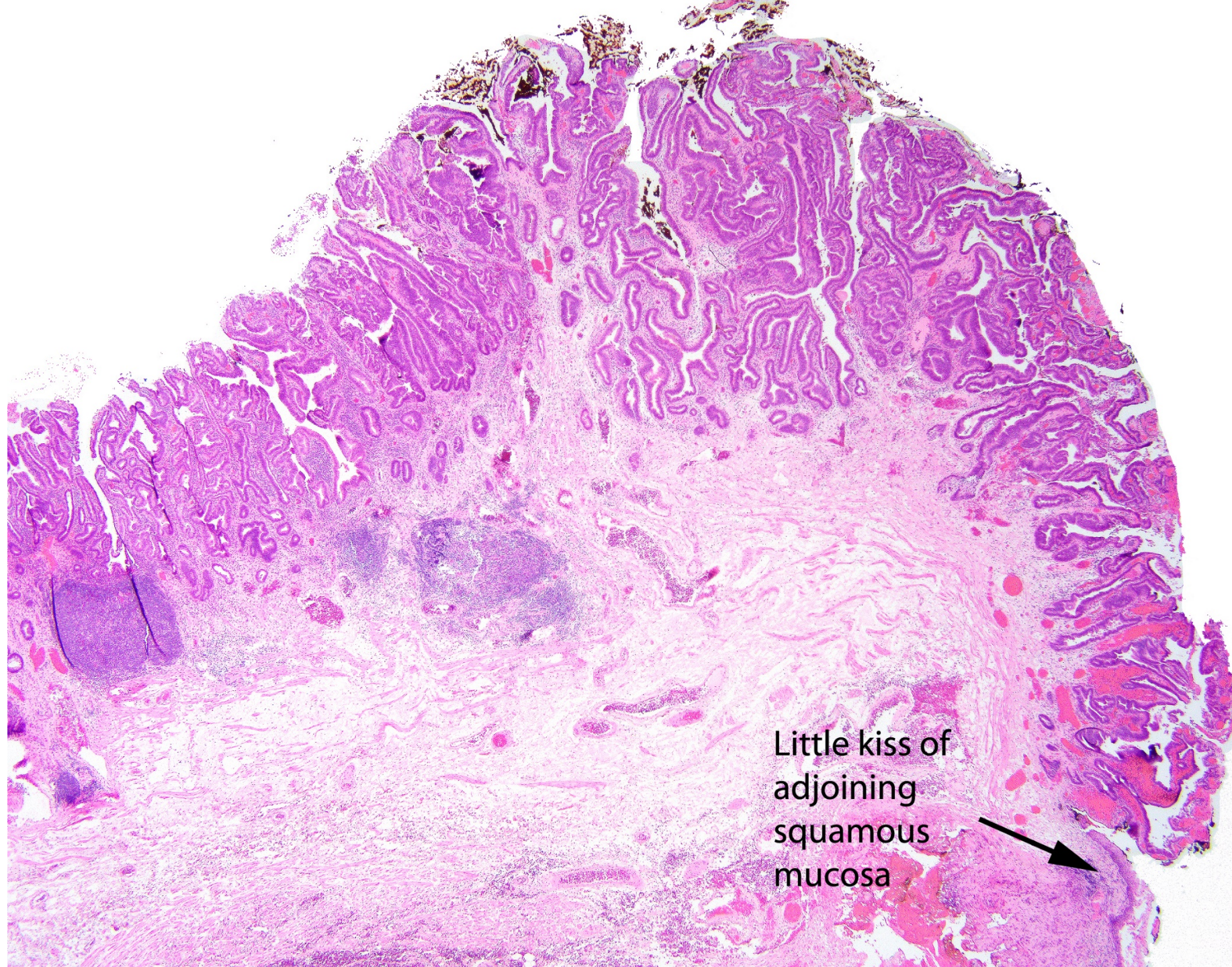
Anus

- 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

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.

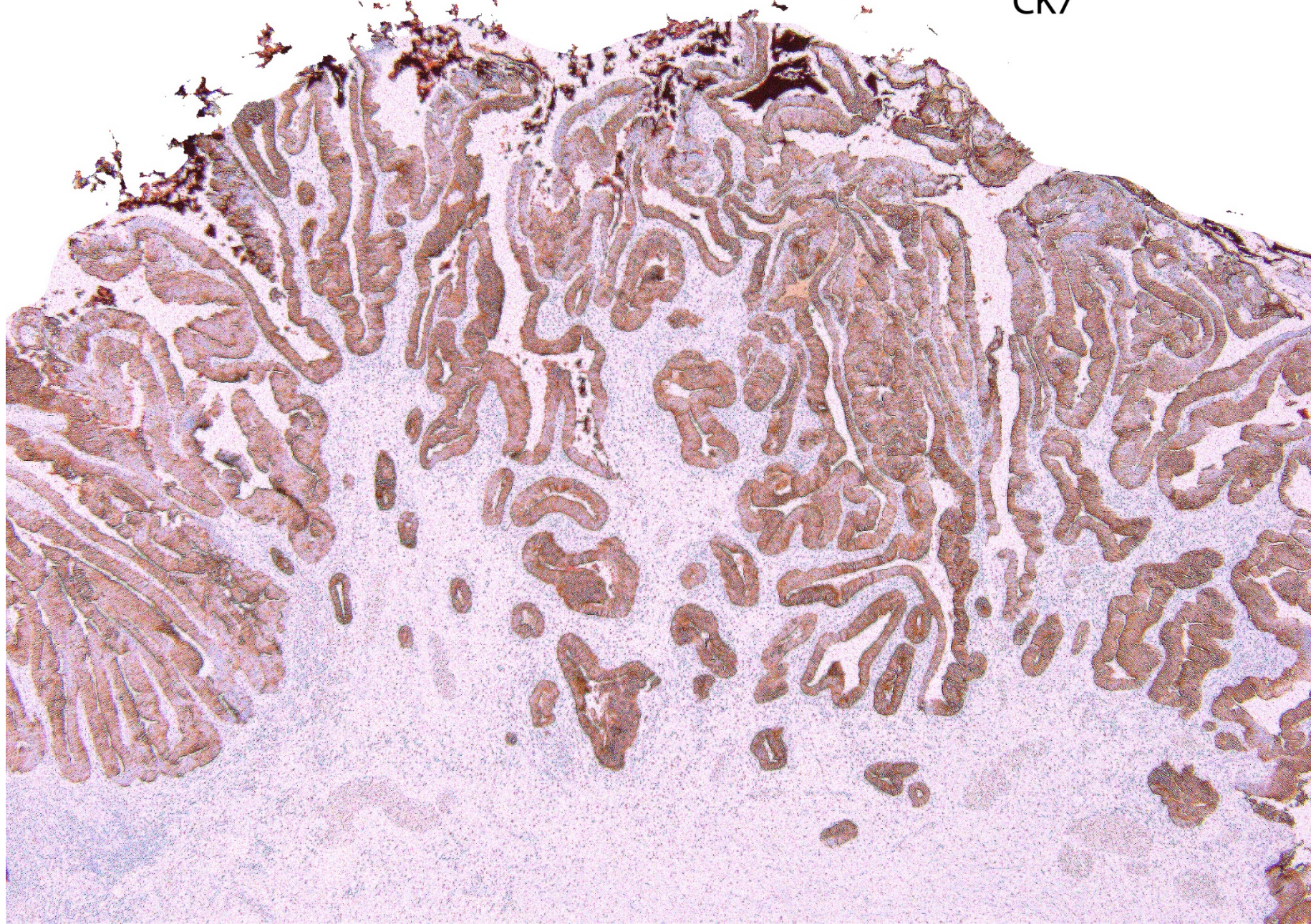
Sooooooooo

- Let's try something new and cool:
- 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*. 2019 Dec 19. doi: 10.1038/s41379-019-0437-z. [Epub ahead of print] PubMed PMID: 31857682.

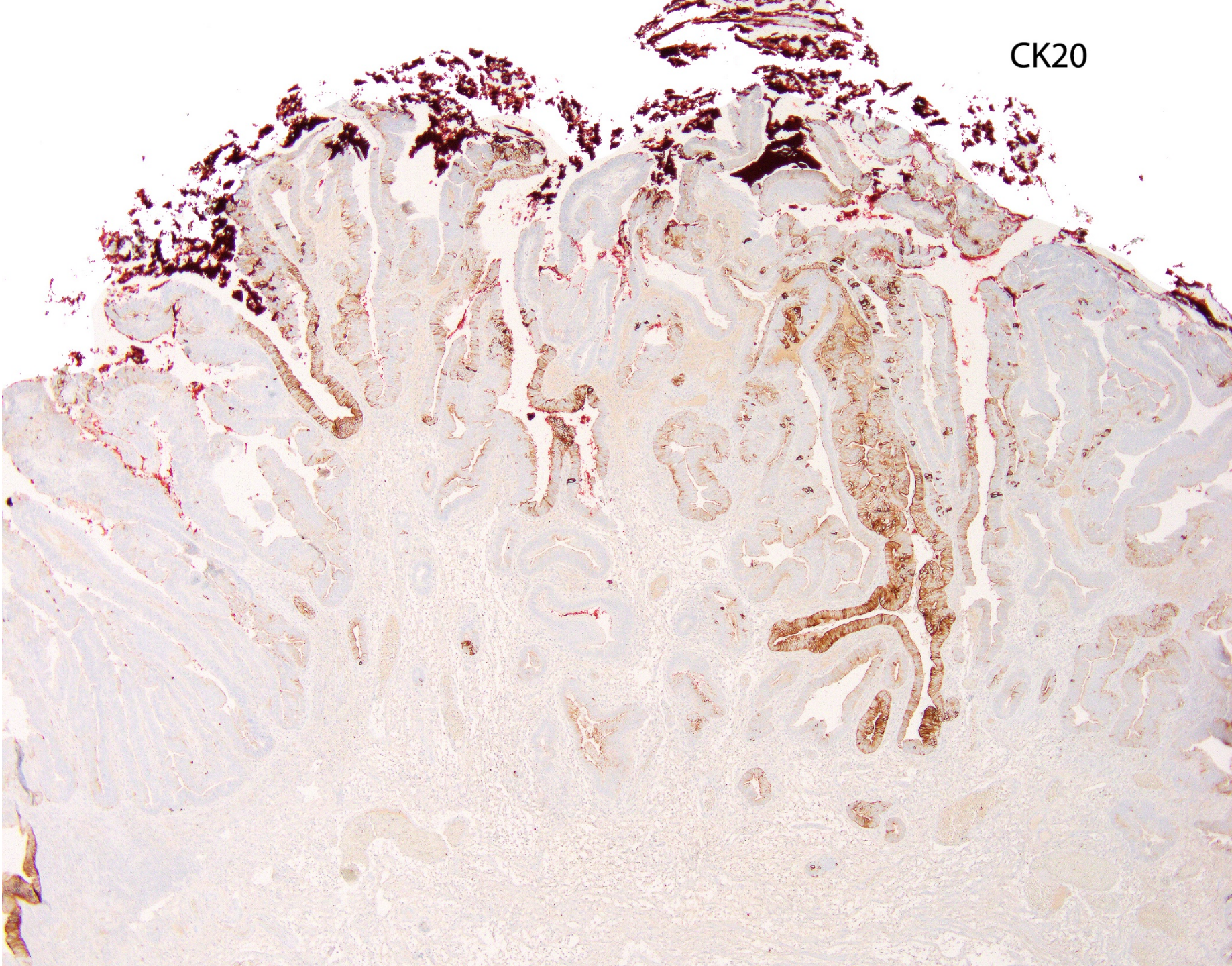


Little kiss of
adjoining
squamous
mucosa

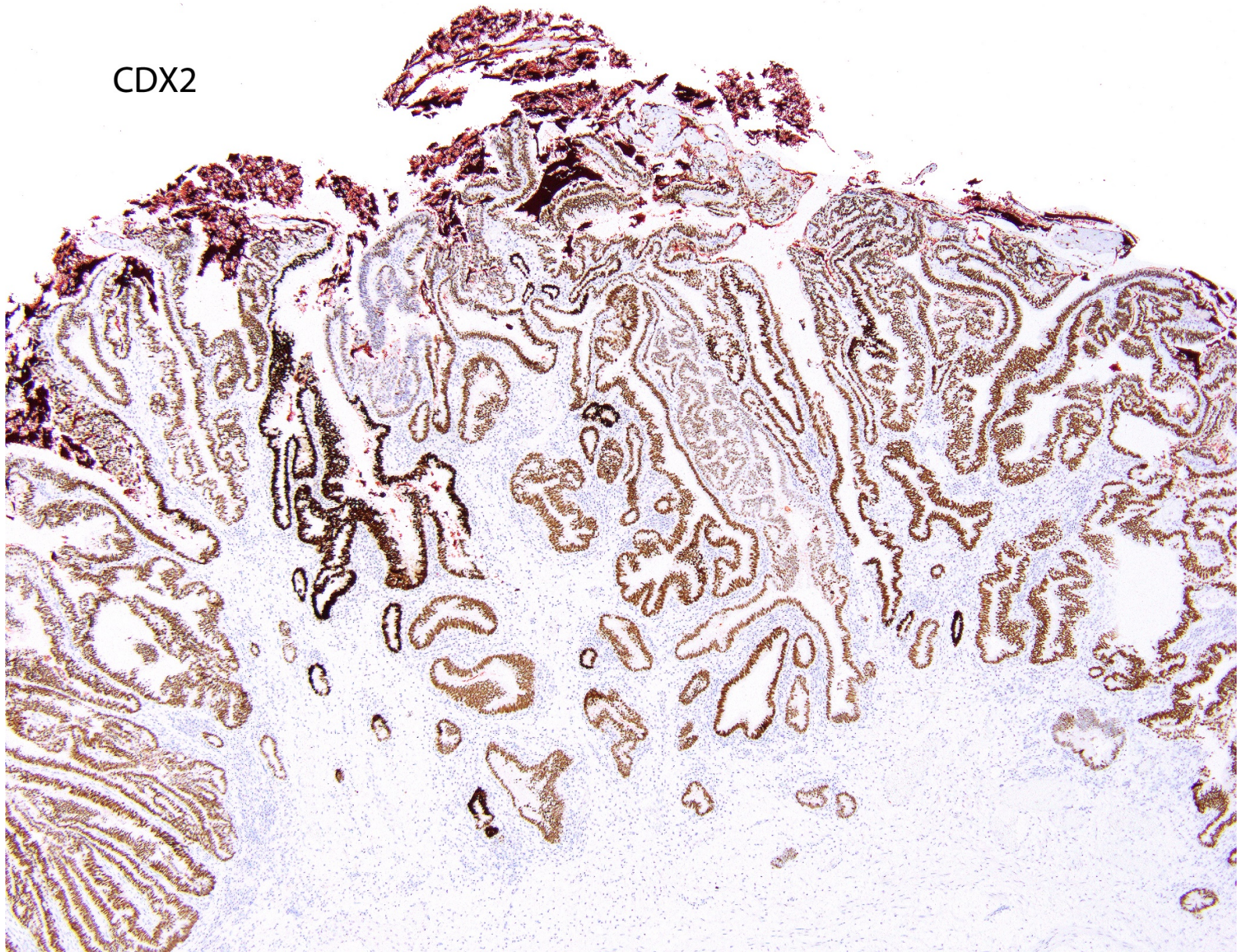
CK7



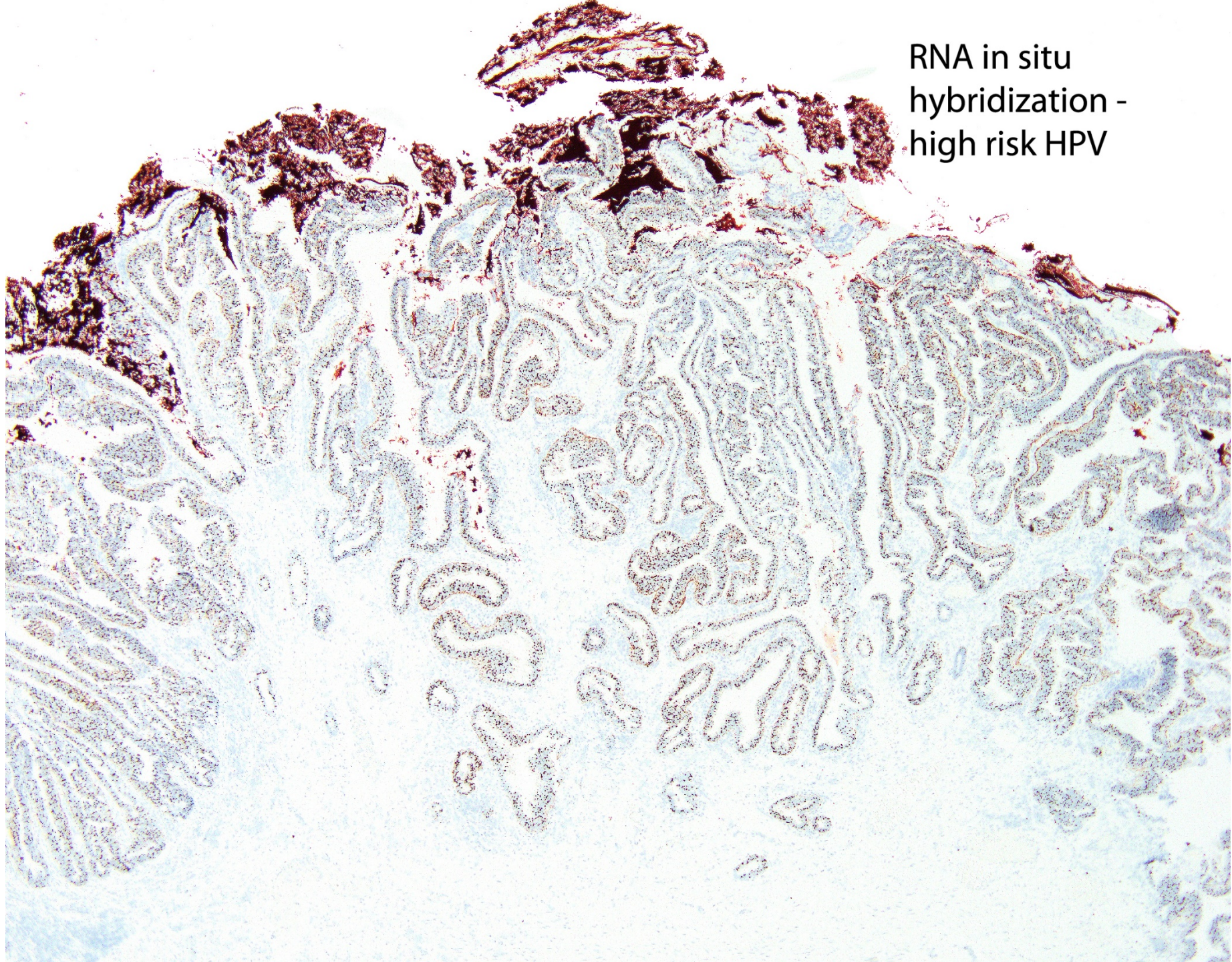
CK20

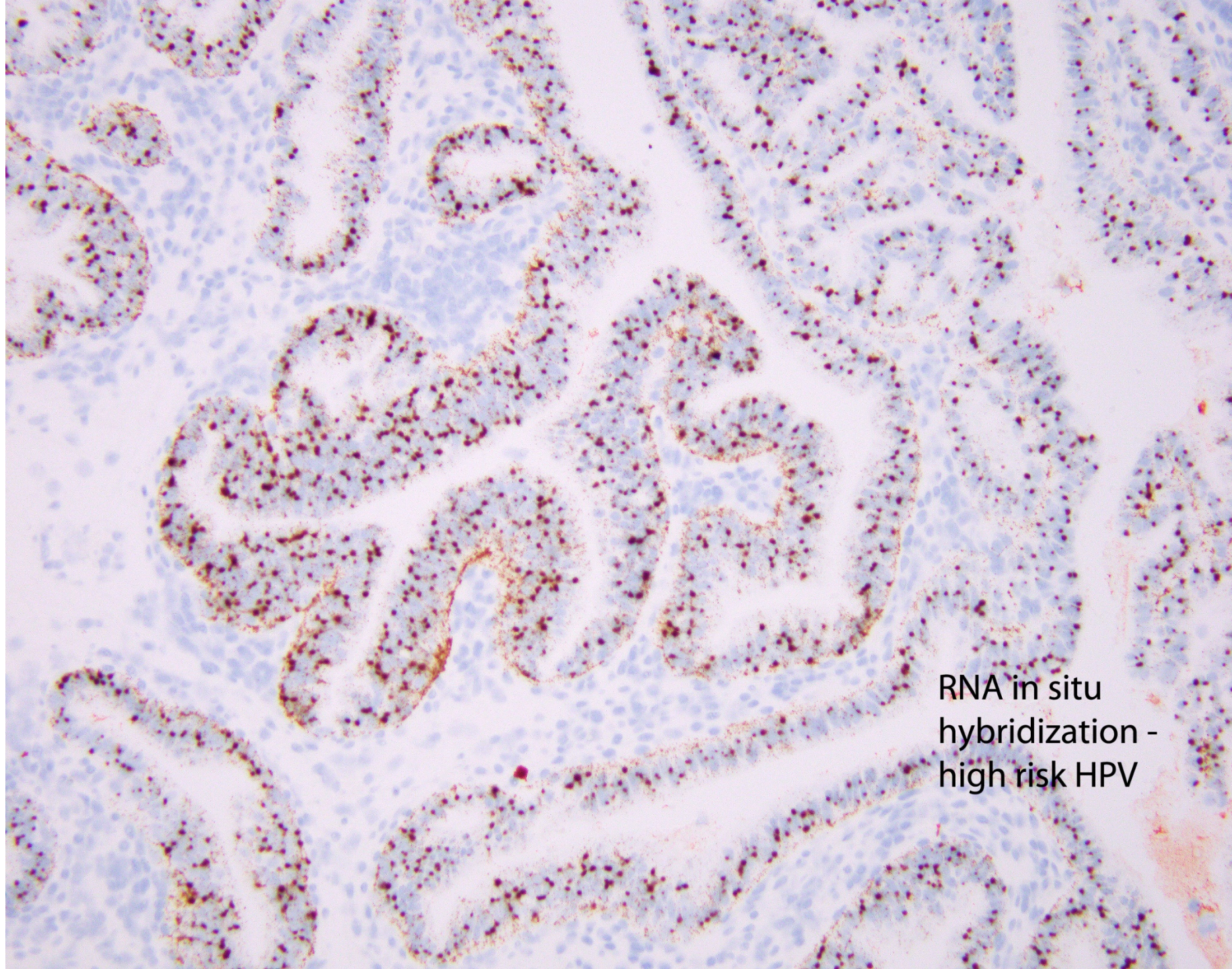


CDX2



RNA in situ
hybridization -
high risk HPV





RNA in situ
hybridization -
high risk HPV

Summary

- We have discussed tips for addressing reactive versus dysplastic lesions in the esophagus and stomach
- We have discussed an interesting potential 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 a newly recognized anal lesion

Thank you