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# Update on pyloric gland adenomas
## *[of stomach, duodenum & gall bladder]*

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Histopathology

# Gastric pyloric gland adenoma: a multicentre clinicopathological study of 67 cases

Won-Tak Choi, Ian Brown, Tetsuo Ushiku, Masato Yozu, Namrata Setia, Amitabh Srivastava, Melanie Johncilla, Rish K Pai, Ryan M Gill, Masashi Fukayama, Joseph Misdraji, Gregory Y Lauwers ✉, ... See fewer authors

Histopathology 2018;72:1007-1014

# Clinicopathologic features of duodenal pyloric gland adenoma – an analysis of 20 cases

Gregory Miller, Wajiha Sufyan, Gregory Y Lauwers, Ian Brown. University of Queensland, Brisbane Australia; Darwin Hospital, Northern Territory, Australia: Moffitt Cancer Centre, Tampa Florida; Envoi Pathology, Brisbane, Australia.

USCAP Vancouver 2018

# Pyloric Gland Adenoma (PGA) of the Gallbladder

## *A Unique and Distinct Tumor from PGAs of the Stomach, Duodenum, and Pancreas*

*Cong He, MD,* Yuki Fukumura, MD, PhD,* Akane Toriyama, MD, PhD,† Kanako Ogura, MD, PhD,‡ Noriko Sasahara, MT,* Keiko Mitani, MT,* and Takashi Yao, MD, PhD**

AJSP 2018;42:1237-1245

# Pyloric Gland Adenoma [PGA]

- Neoplasms with pyloric gland differentiation.
- Risk for malignant transformation.
- Most frequently identified in the stomach.
- Also : gallbladder, duodenum, bile duct, & esophagus.
- In pancreas, the terms IPMNs of the gastric type, pyloric gland variant & IPMN w/ pyloric gland features have been coined.

Kushima R, Pathol Res Pract. 1996;192:963–969;. Bakotic BW. Am J Surg Pathol. 1999;23:227–231.Kushima R,. Virchows Arch. 1999;435:452–457.Vieth M,. Vircho s Arch. 2003;442:317–321. Albores-Saavedra J, Am J Surg Pathol. 2004;28(2):233–238.; Yamaguchi H, J Pathol. 2013;231(3):335–341.

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# Morphologic characteristics

- Tightly packed tubular glands.
- Cuboidal or columnar cells.
- Eosinophilic to amphophilic cytoplasm.
- Round to oval nuclei.
- Occasional prominent nucleoli.

# Special stains & IHC

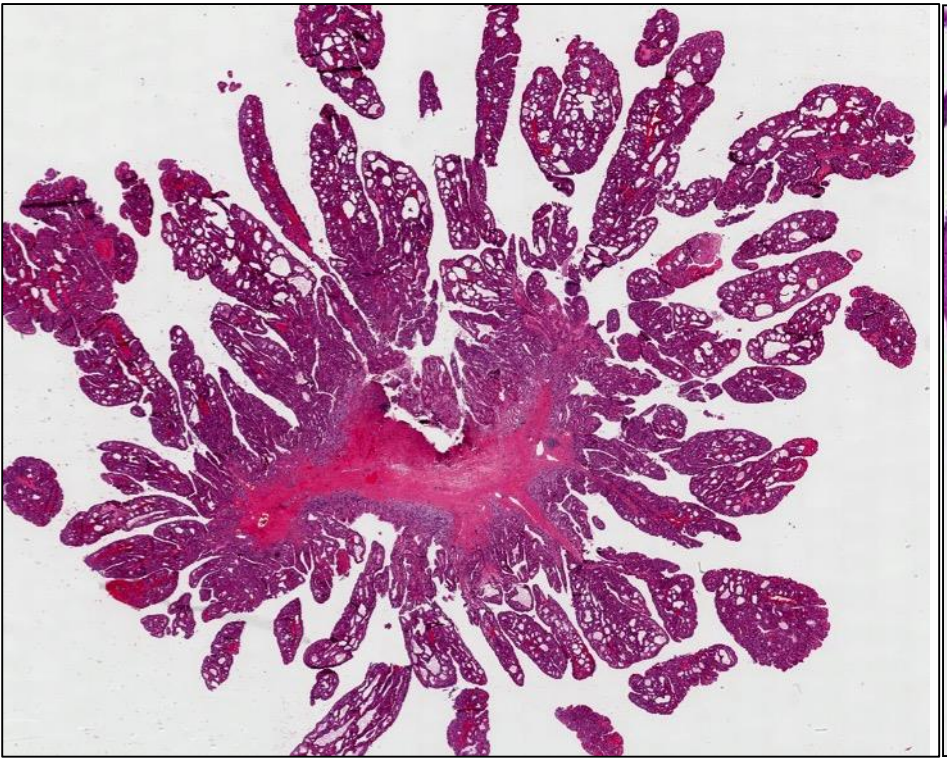
- PAS/AB shows granular cytoplasmic staining.
- No PAS+ mucin cap identified (vs foveolar epithelium)
- Positivity for apoprotein MUC6 and MUC5AC confirm gastric differentiation.
  - MUC6 is more specific since MUC5AC is expressed by both foveolar-type adenomas and PGAs.
- Focal intestinal differentiation with labeling by CDX2 and/or intestinal MUC2 staining.

Wani Y. Virchows Arch. 2008; 453:521–527.

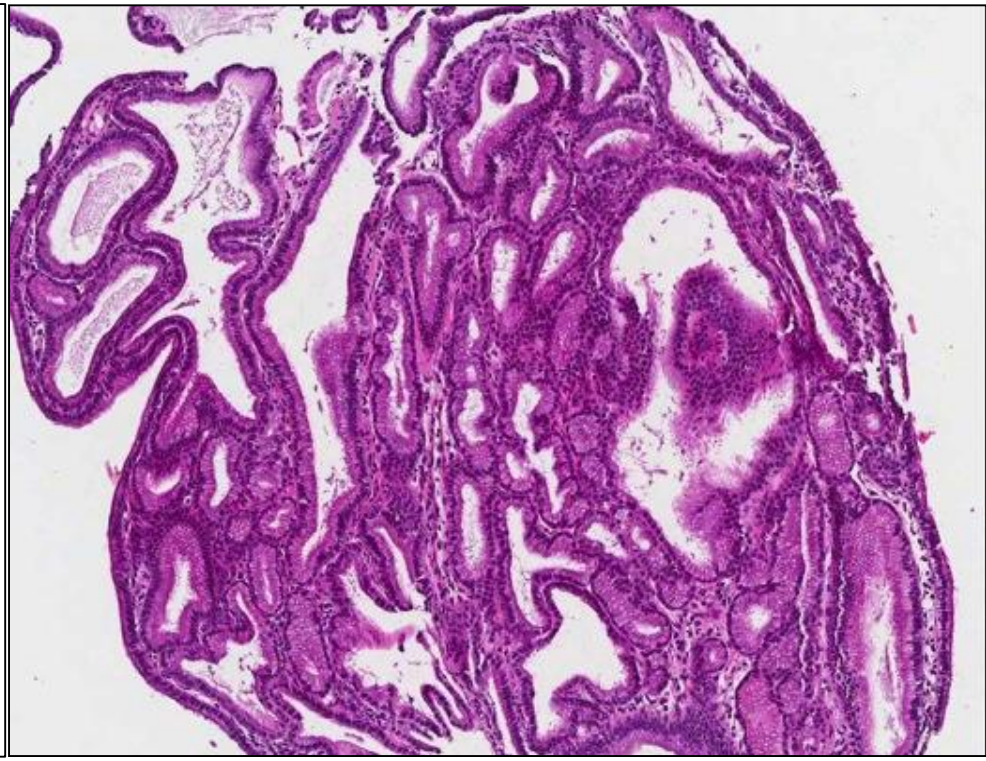
# STOMACH

## Pyloric Gland Adenoma (<3% of all polyps)

Oberhuber G. Virchows Archiv; 2000; 437:581-90



Tubulo-villous Pyloric gland adenoma



Tubular Pyloric gland adenoma

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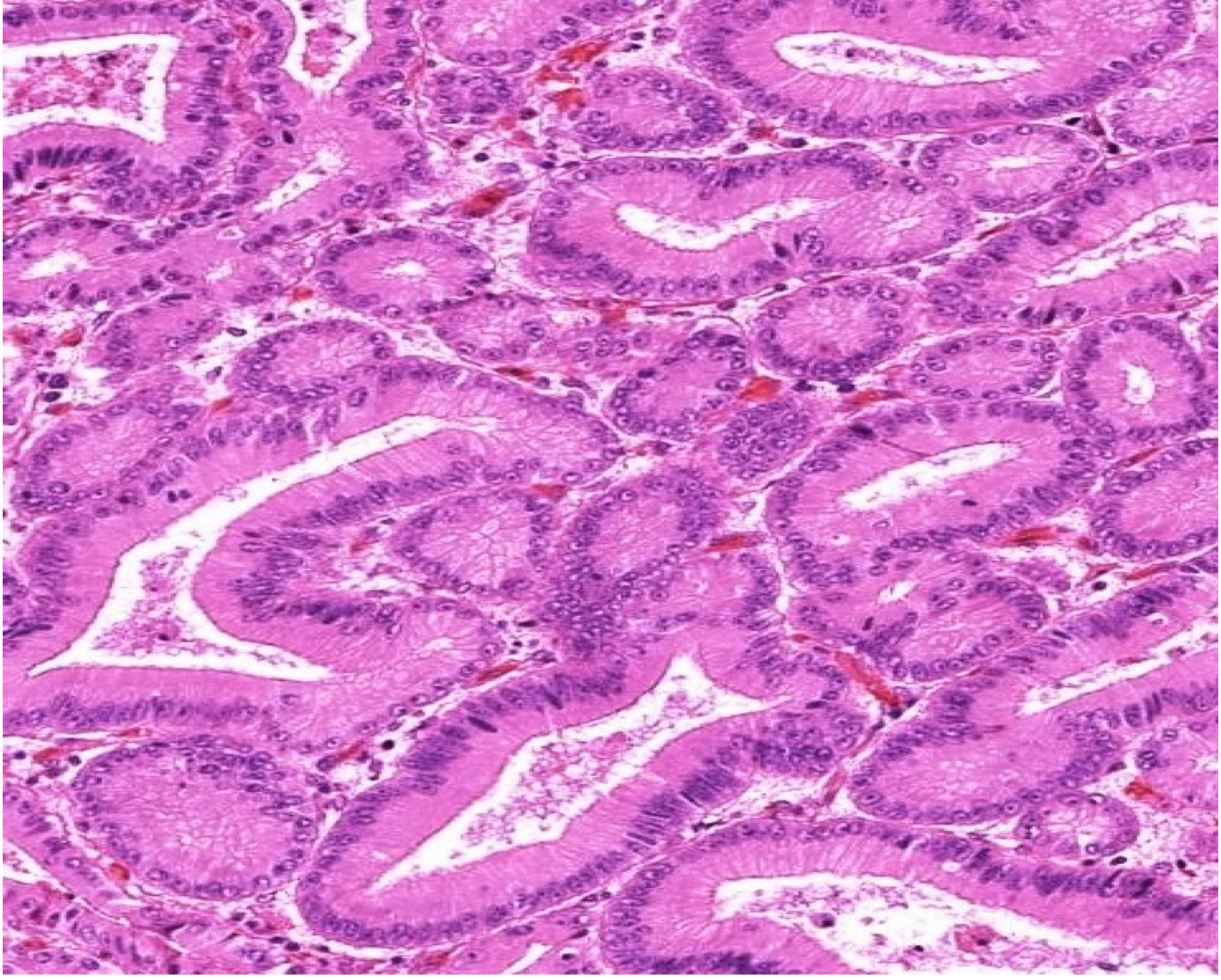
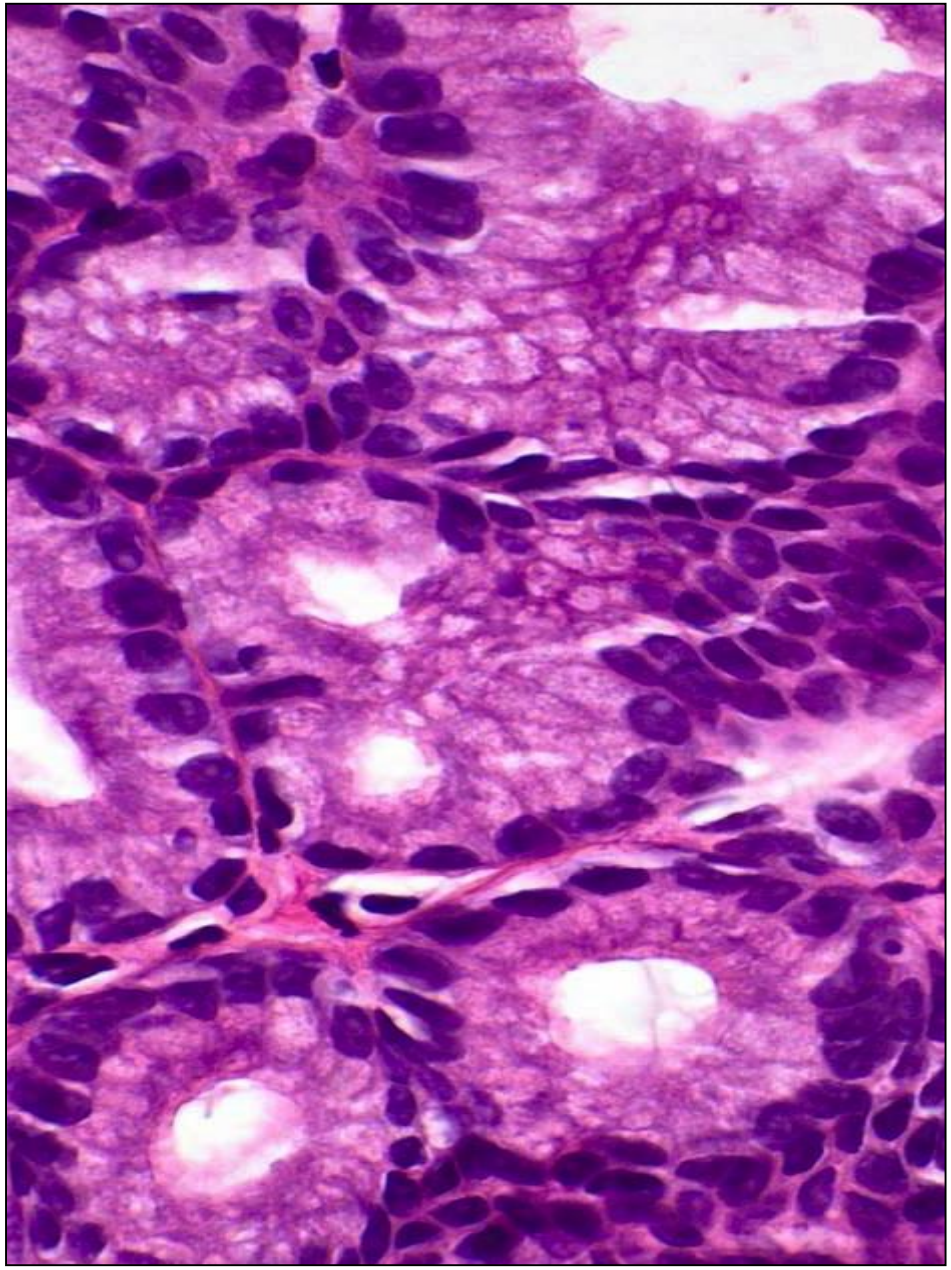
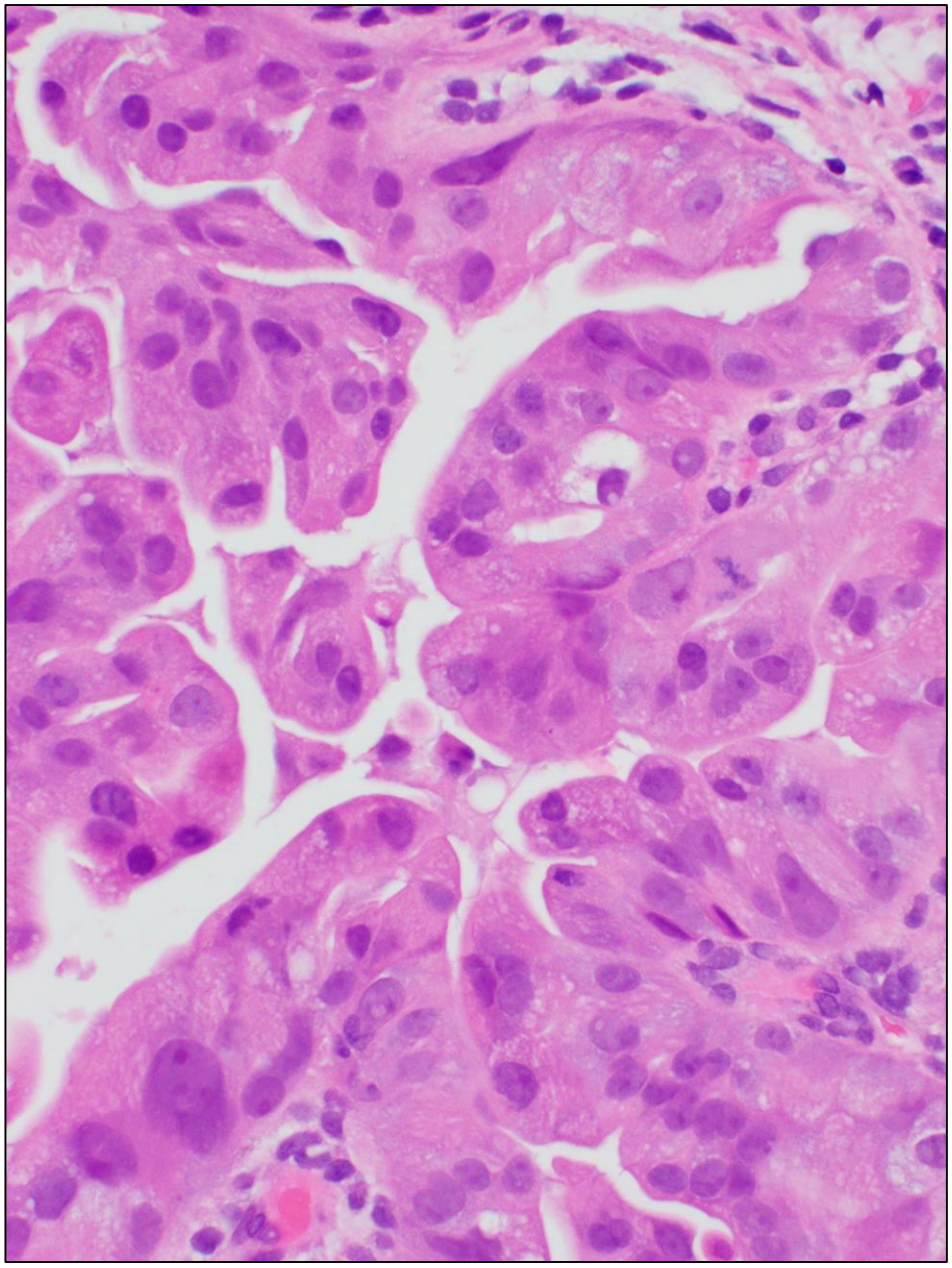


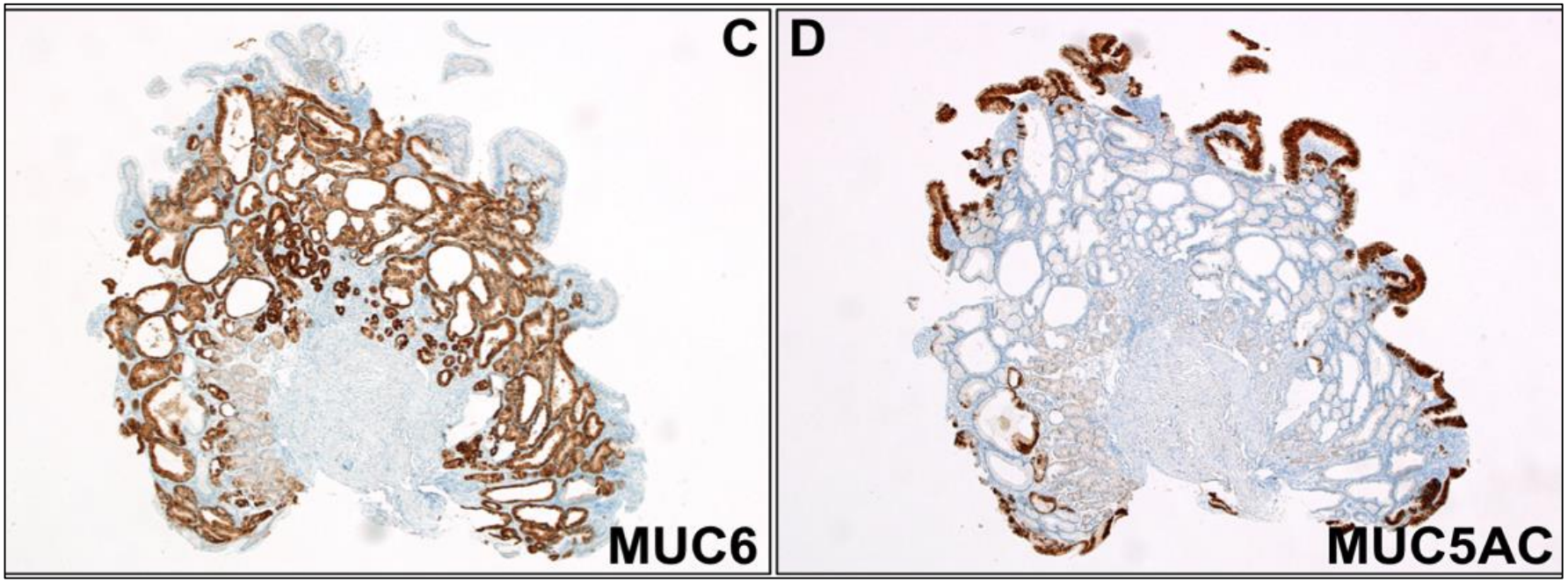
LGD



HGD



# *Classic* immunophenotype of PGA




TFF2 is also diffusely expressed [MST1 and pepsinogen can be focally expressed]

Choi WT. Histopathology 2018;

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## What we know about PGA

- Older pts (mean age: 70 yrs)
- Females > males (3:1)
- Oxyntic mucosa
- Autoimmune gastritis +
- FAP; Lynch Sd.
- 53% with HGD (23 cases)
- Freqt. assoc. of gastric PGAs w/ CAs, ranging from 12% to 30% .4,7
- Pyloric-phenotype (MUC6+)
- < 30% MUC5AC+

## What is *new* about PGA

- Antrum (6%), pylorus (3%)
- 73% not associated with AIG
  - *36% in normal mucosa*
- Parietal cells noted in all FAP associated PGAs
- 55% LGD [avg:1.7 cm]; 37% HGD [avg:3.4 cm]
  - *TVA pattern more commonly asso.ted w/ in HGD (52%) than LGD*
- 51% co-expressed MUC5AC in an intermixed pattern
- 7% w/ recurrence at 1year

Vieth . J Clin Pathol 2014;38:784-792 Choi WT. Histopathology 2018; Hackeng WM. Histopathology 2017

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# Molecular Pathogenesis

- P53+ in 22.3% of cases [85.7% in intestinal-type adenomas]
  - Some w/ high-grade dysplasia.
- Frequent p53 expression in 82.1% of PGAs associated with CA vs 59.3% for those *without* associated CA.
- Infrequent loss of MMR expression: 4.3% (1/23) showing loss of both MLH1 & PMS2.

Kushima R. Virchows Arch. 1996; 428(4–5):223–227. Vieth M. Virchows Arch. 2010; 457(5):529–536. Matsubara A. J Pathol. 2013;229(4):579–587.

# Molecular Pathogenesis

- 63% of PGAs show activating mutations of GNAS.
- ***no*** GNAS mutations in foveolar-type adenomas, intestinal type adenomas, or adenocarcinomas.
- KRAS mutations in 41% of cases
  - vs 9% of foveolar & intestinal-type adenomas
- 37% have dual-activating mutations in both GNAS and KRAS.

Matsubara A. J Pathol. 2013;229(4):579–587.

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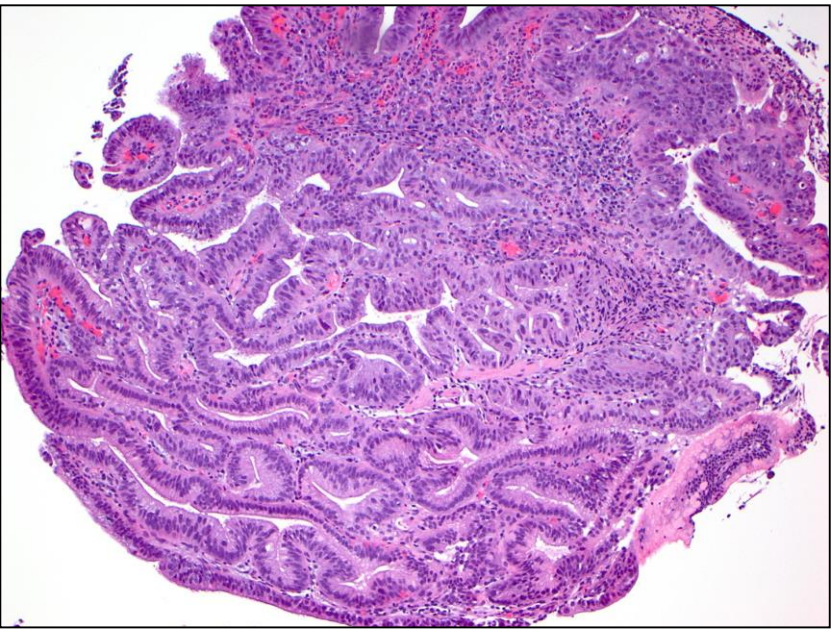
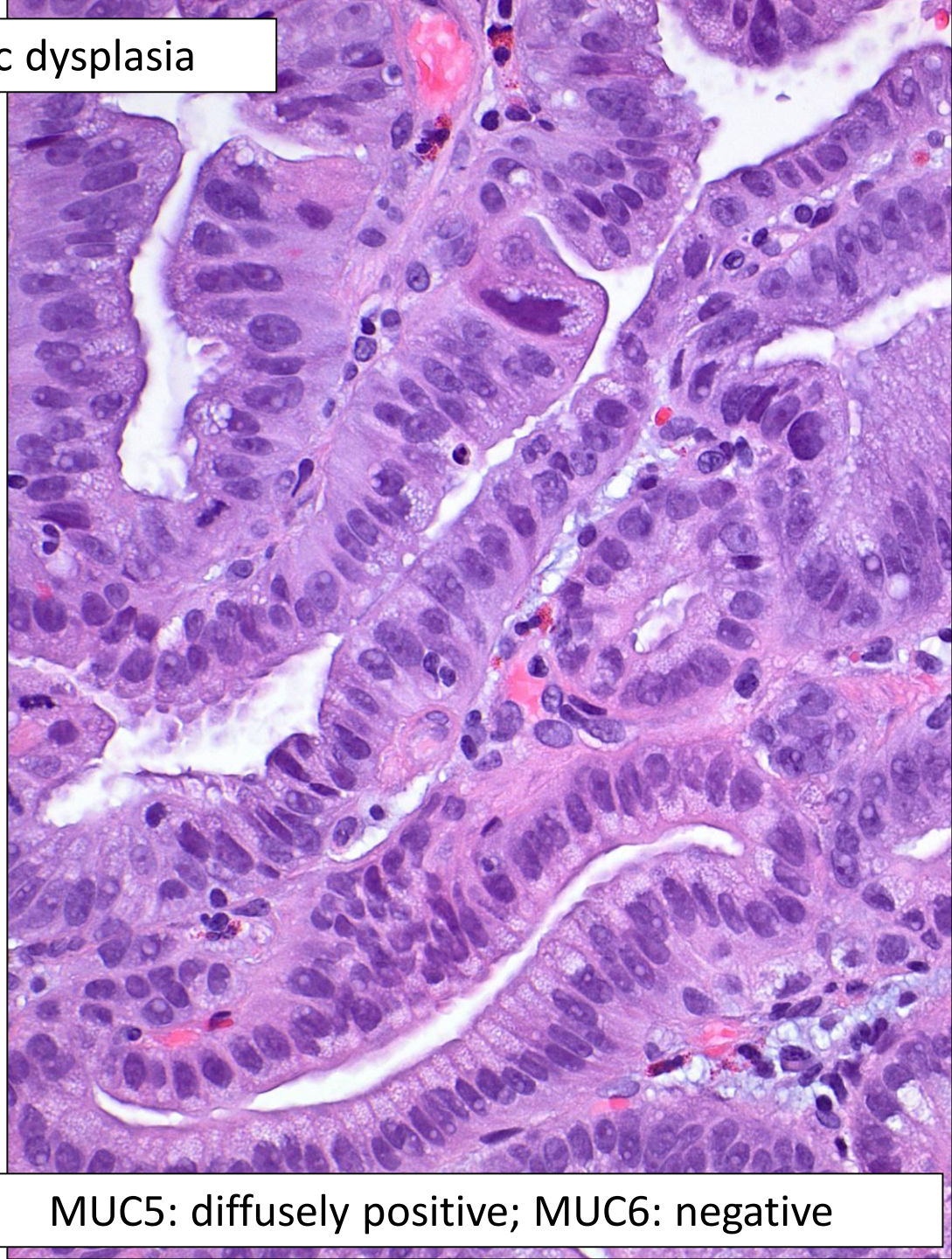
DDX: Polypoid foveolar type gastric dysplasia





MUC5: diffusely positive; MUC6: negative

# Gastric Adenocarcinoma of Fundic Gland Type (Chief Cell Predominant Type): Proposal for a New Entity of Gastric Adenocarcinoma

Uyema H AJSP. 2010;609-619.

# Gastric Adenocarcinoma With Chief Cell Differentiation

*A Proposal for Reclassification as Oxyntic Gland Polyp/Adenoma*

Singhi A AJSP. 2012;1030-1035.

Histopathology

*Histopathology* 2016, **68**, 825–833. DOI: 10.1111/his.12859

## Chief cell-predominant gastric polyps: a series of 12 cases with literature review

Karen Chan,[1,2] Ian S Brown,[3] Trevor Kyle,[4] Gregory Y Lauwers[5] & Marian Priyanthi Kumarasinghe[1,6]

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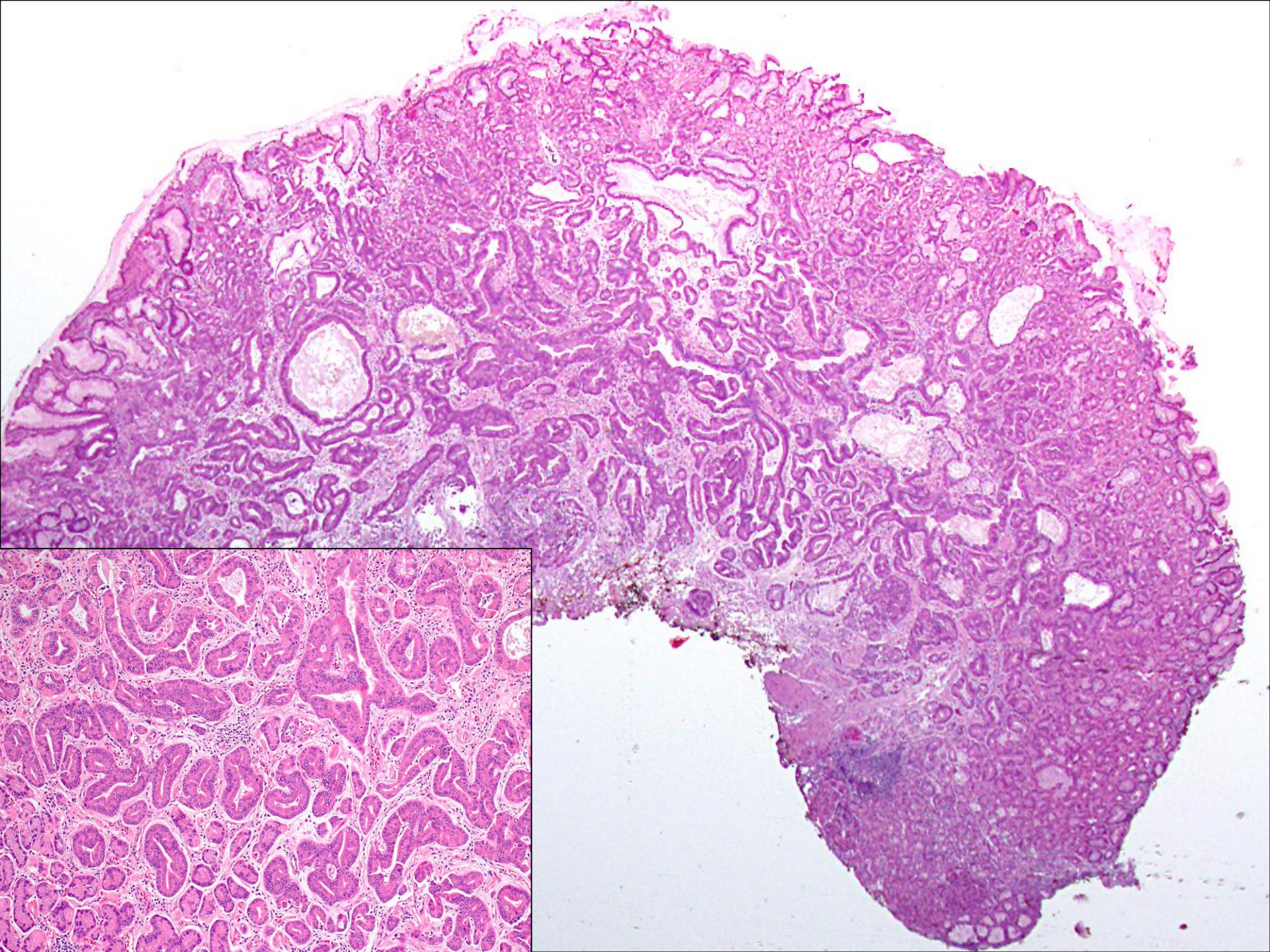
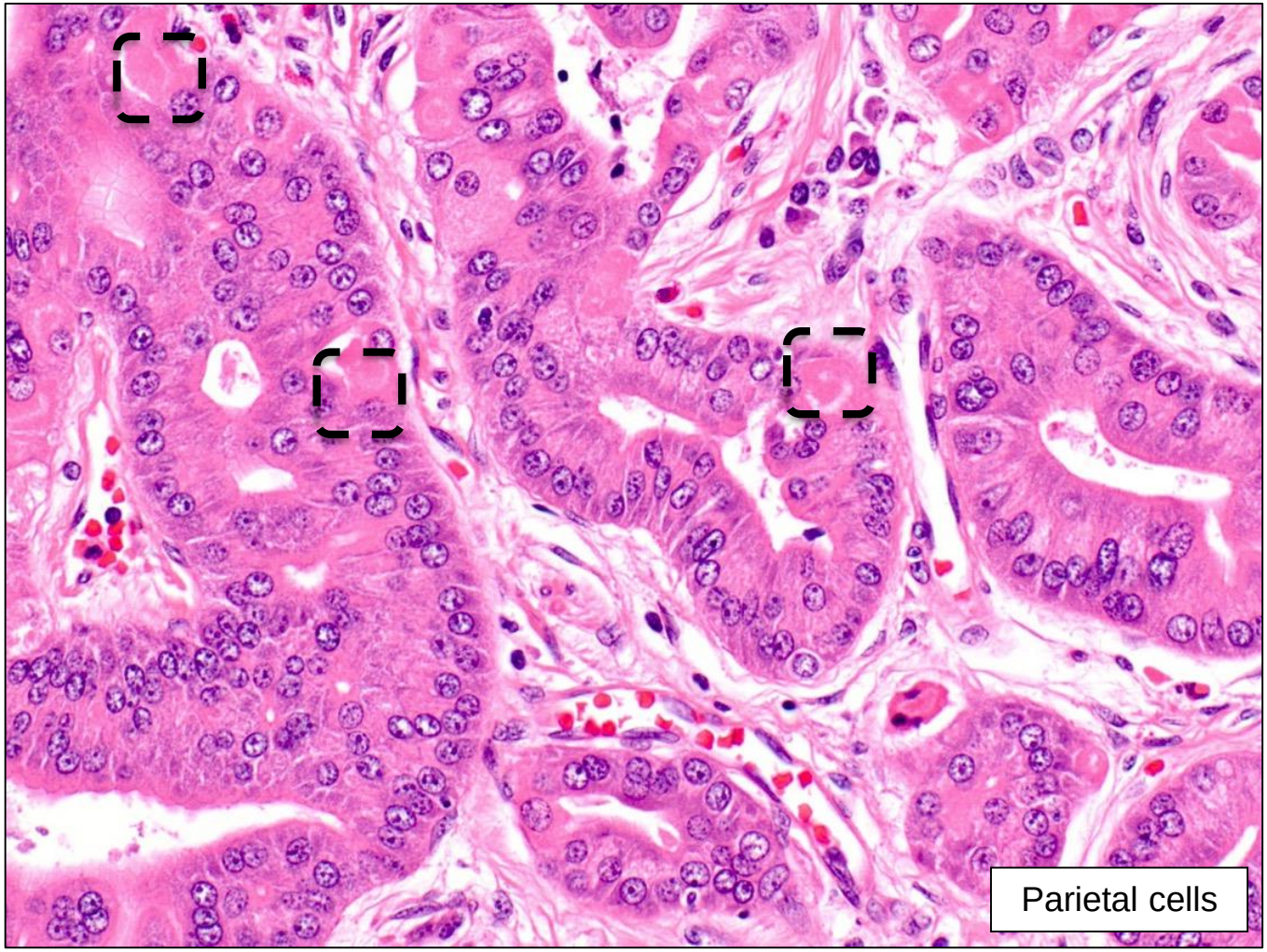
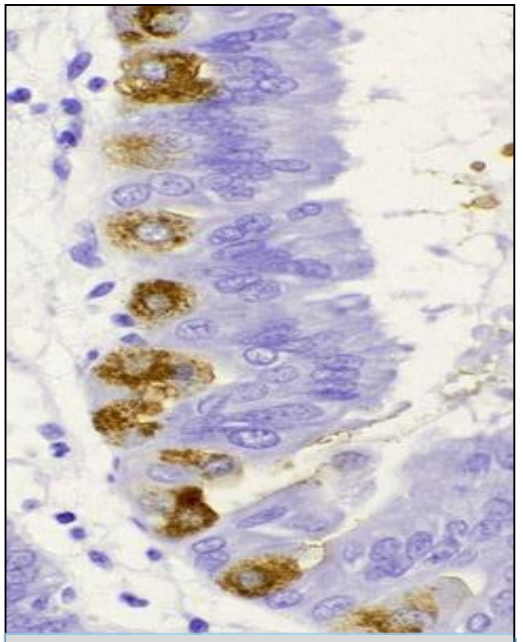
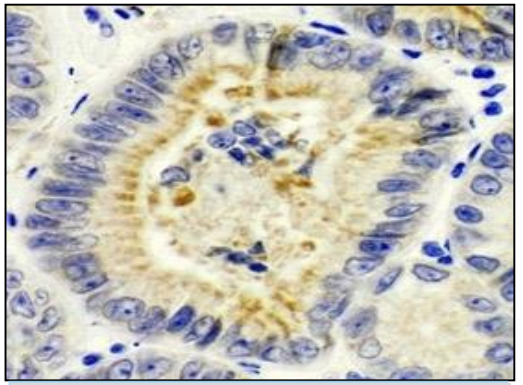




$H^+/K^+$ ATP $^{ase}$



Pepsinogen I

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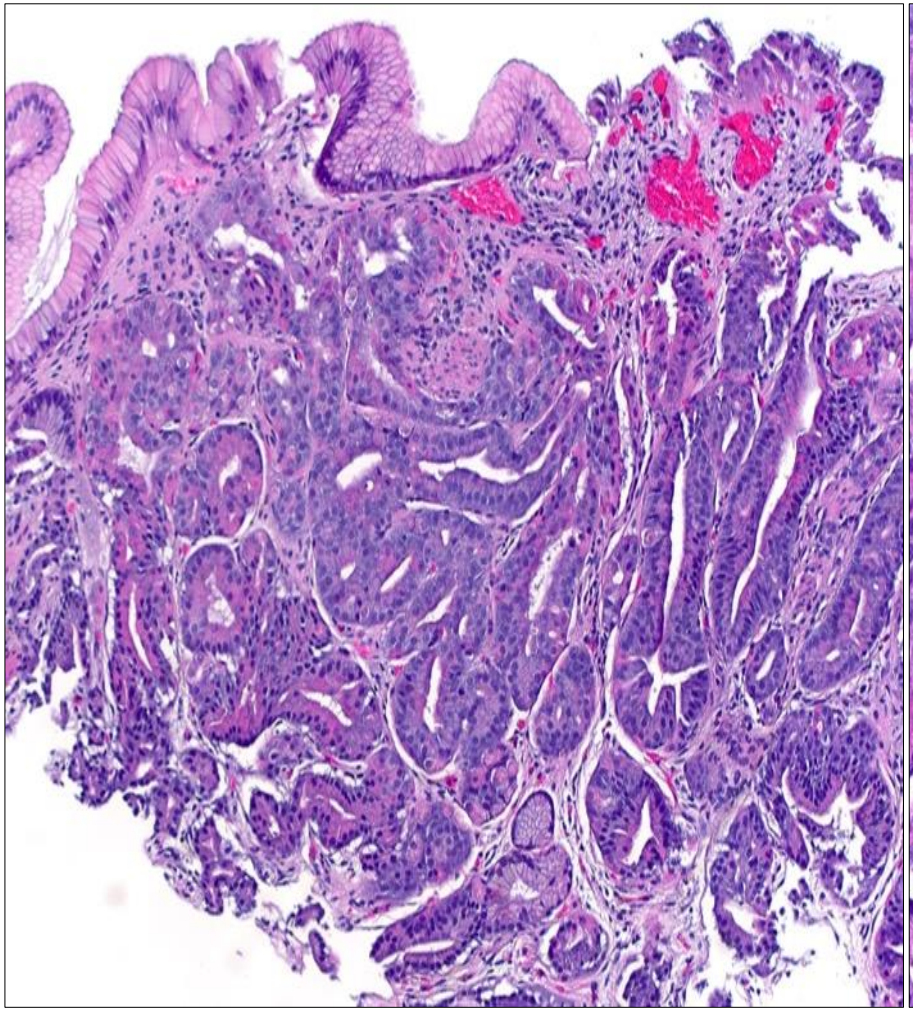

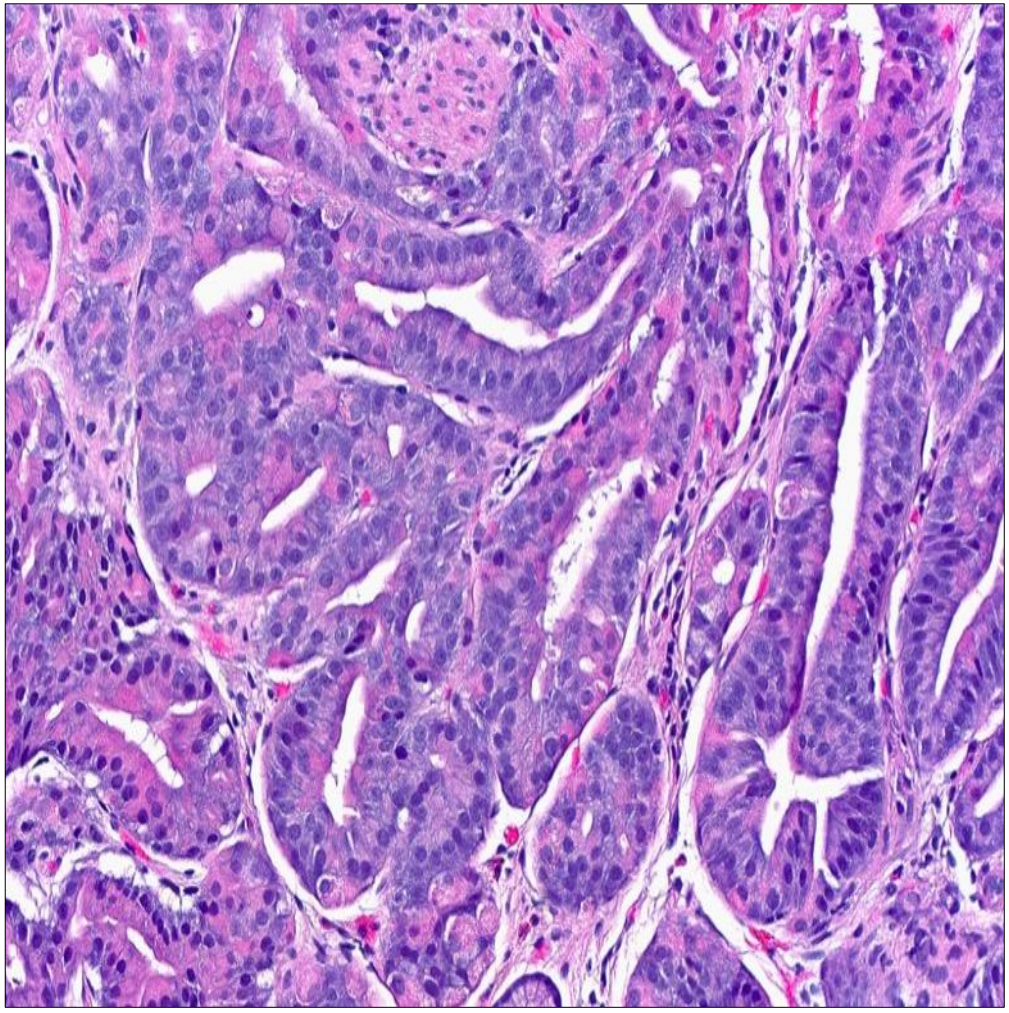

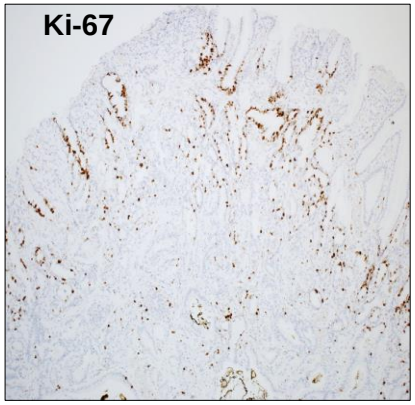


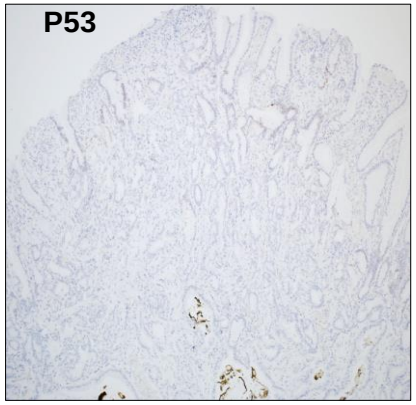


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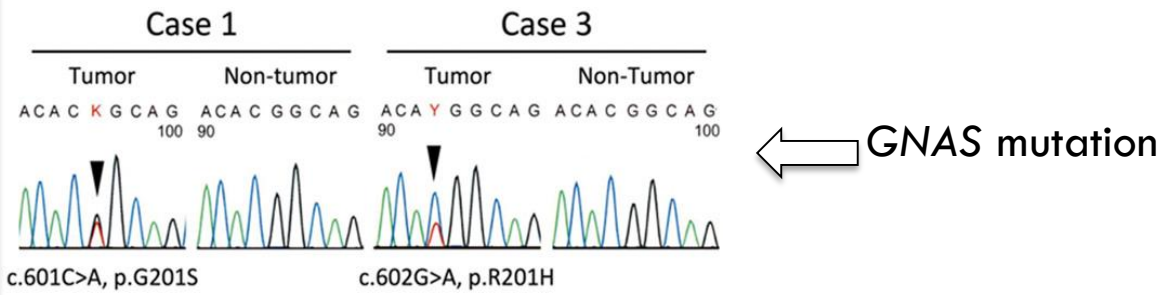
# Relationship between PGAs & Oxyntic adenoma

- Frequent detection of parietal cells in PGAs (syndromic AFP)
- Expression of chief cell markers in some PGAs

Kushima R. Pathology International 2013

Original Article

**Gastric adenocarcinoma of the fundic gland type shares common genetic and phenotypic features with pyloric gland adenoma**




Hackeng WM. Histopathology 2017;

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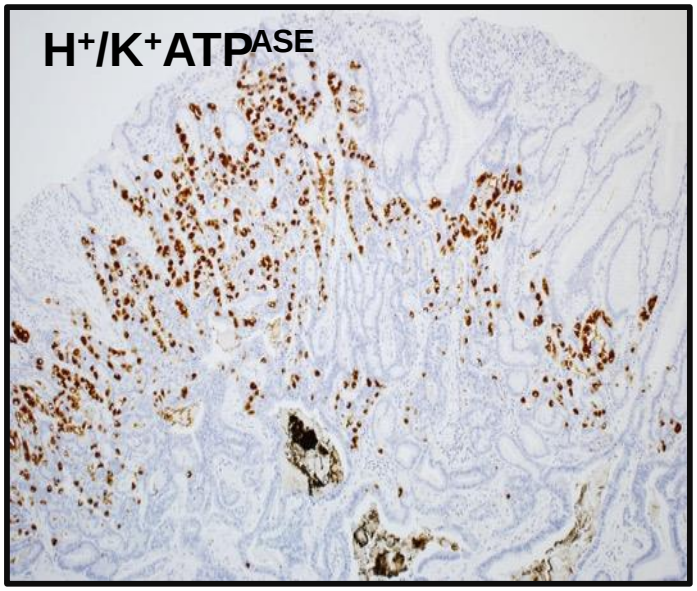
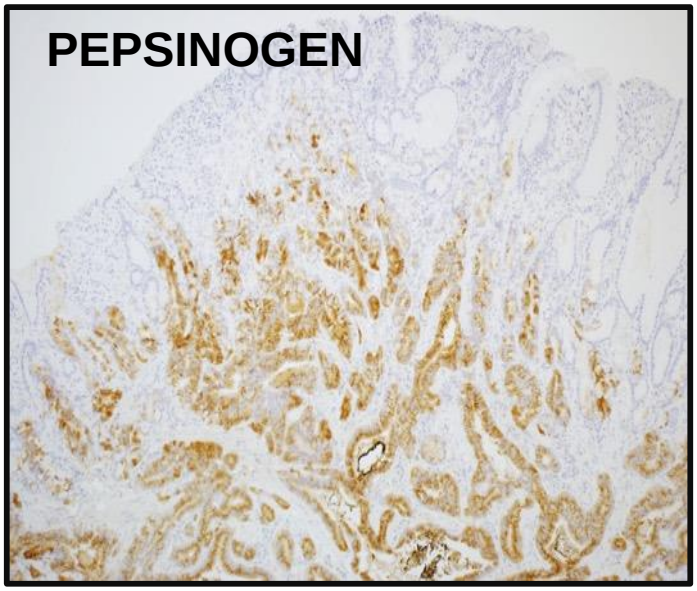
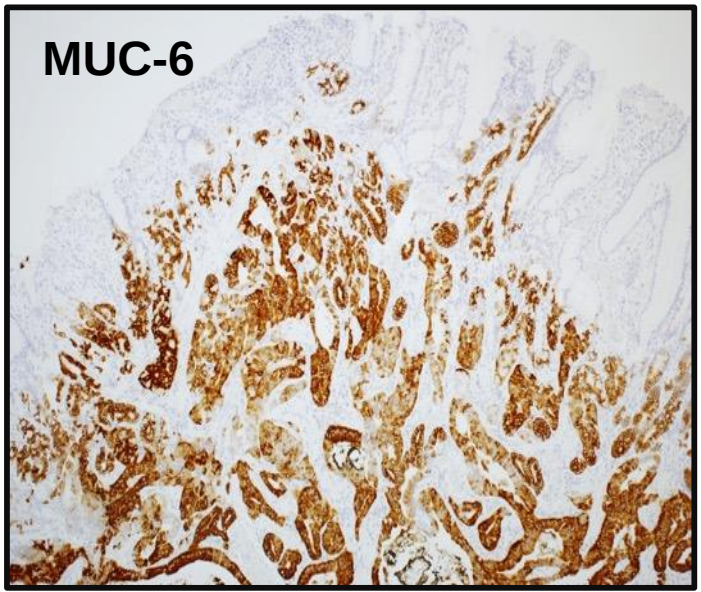
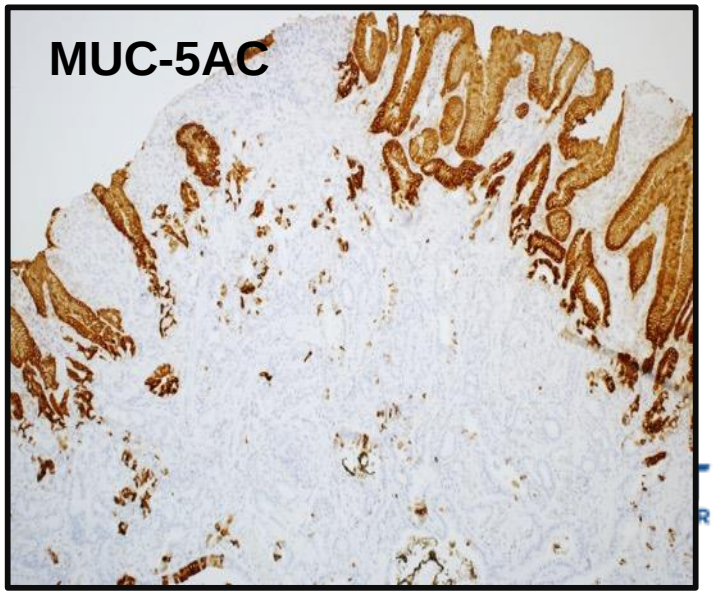
# Relationship between PGAs & Oxyntic adenoma

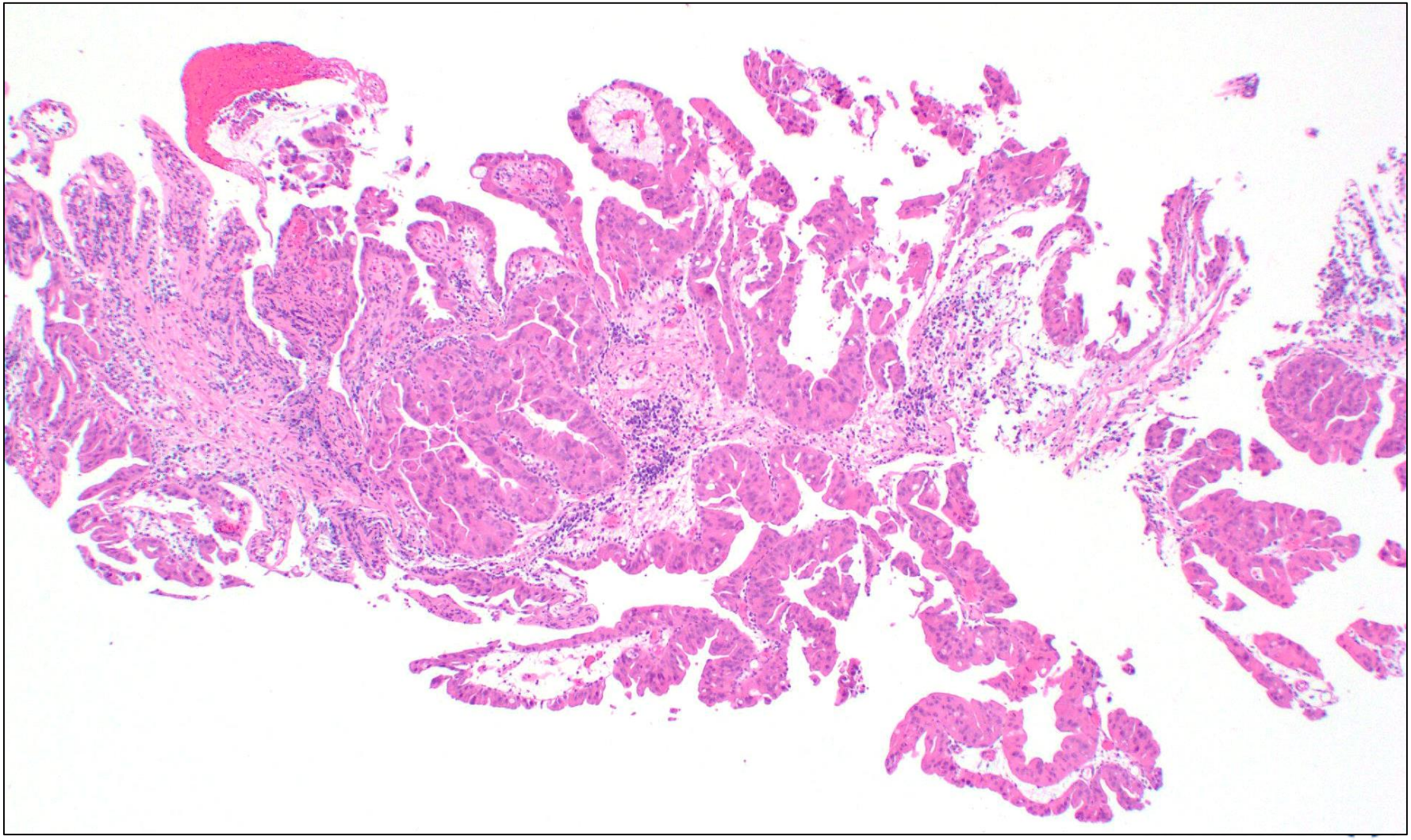


# PGAs in DUODENUM



# Duodenal Pyloric Gland Adenoma [n=42]

| | | **LGD** (n=25) | **HGD** (n=17) | |
|---|---|---|---|---|
| **Age,** (range) | | 73.4 (54-85) | 69.8 (51-77) | |
| **Sex, male (%)** | | 13 (52) | 9 (56.5) | |
| **Location** | **D1** | 9 | 10 | |
| | **D2** | 4 | 6 | |
| | **D3** | 1 | 1 | |
| | Unknown | 11 | 0 | |
| **Size, mm** (range) | | 9.5 (2-37) | 19.6 (7-60) | *P:0.008* |

Miller G et al. *in preparation*

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# Duodenal Pyloric Gland Adenoma [n=42]

| | | LGD (n=25) | HGD (n=17) |
|---|---|---|---|
| **Gastric heterotopia (%)** | | 4 (16) | 4 (23.5) |
| **Architecture** | **Tubular (%)** | 17 (68) | 7(37.5) |
| | **Tubulovillous (%)** | 8 (32) | 10 (62.5) |
| **MUC staining pattern** | **Pyloric (%)** | 5 (21.7) | 4 (28.6) |
| | **Mixed (%)** | 18 (78.3) | 10 (71.4) |
| **Recurrence** | | 1 | 1 |
| **Associated carcinoma** | | 0 | 4 |

Miller G et al. *in preparation*

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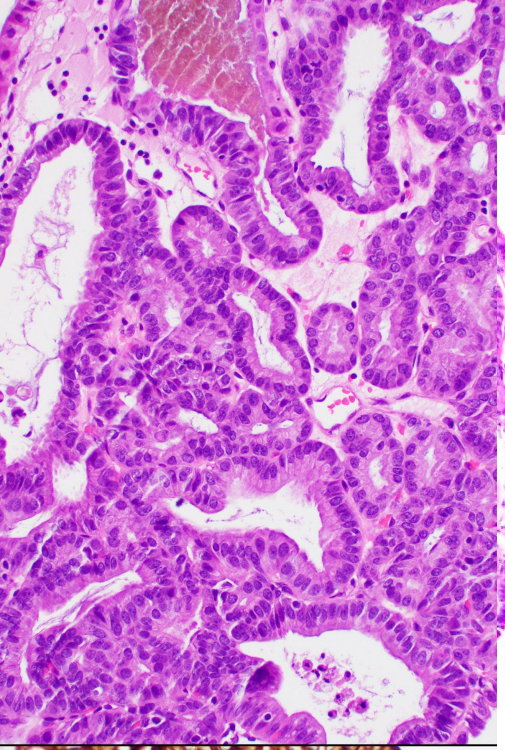
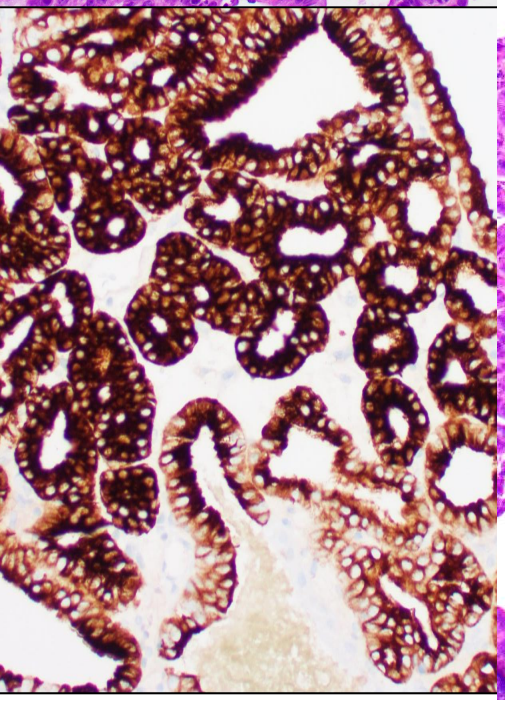
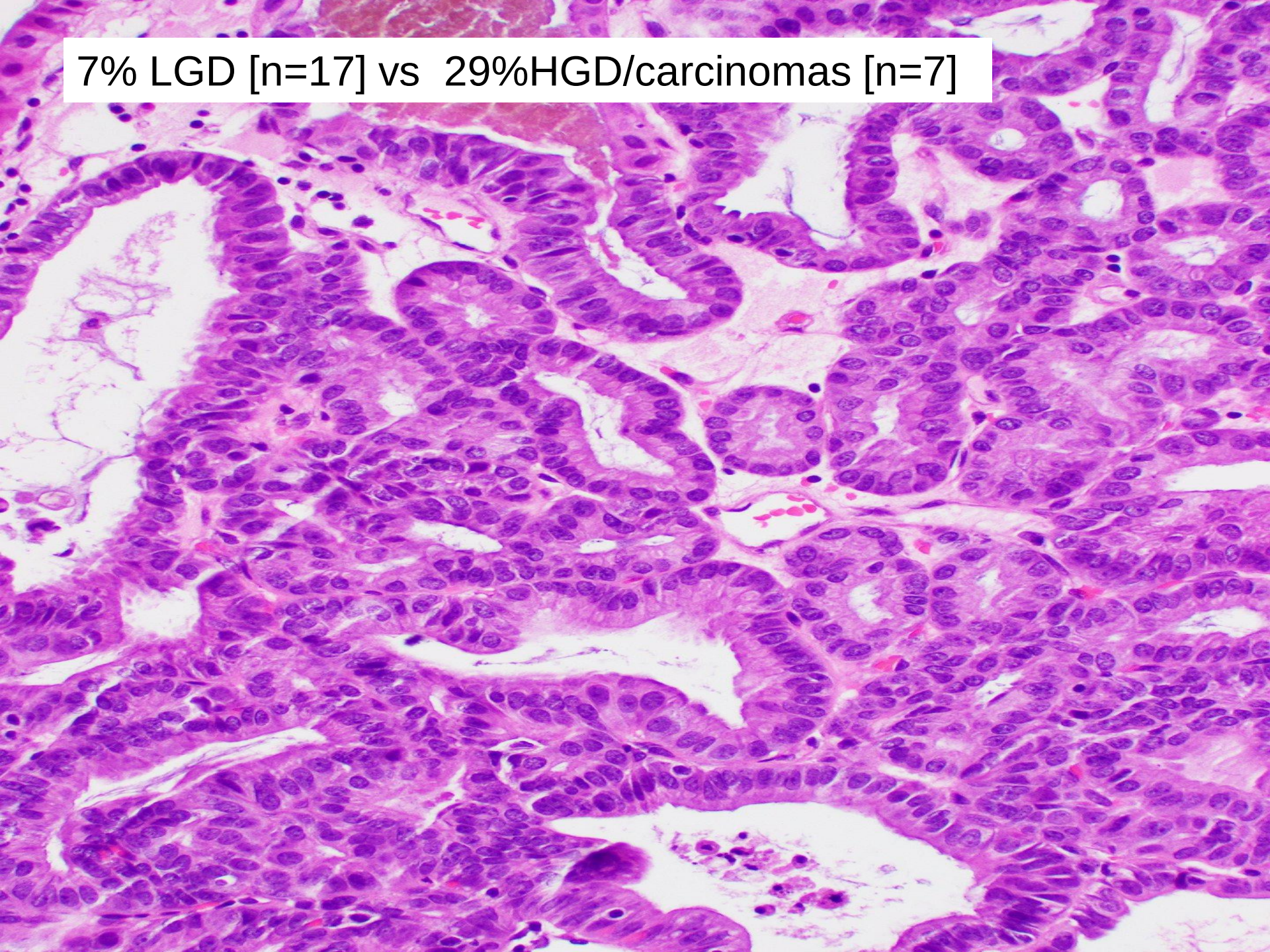
# PGAs in GALL BLADDER

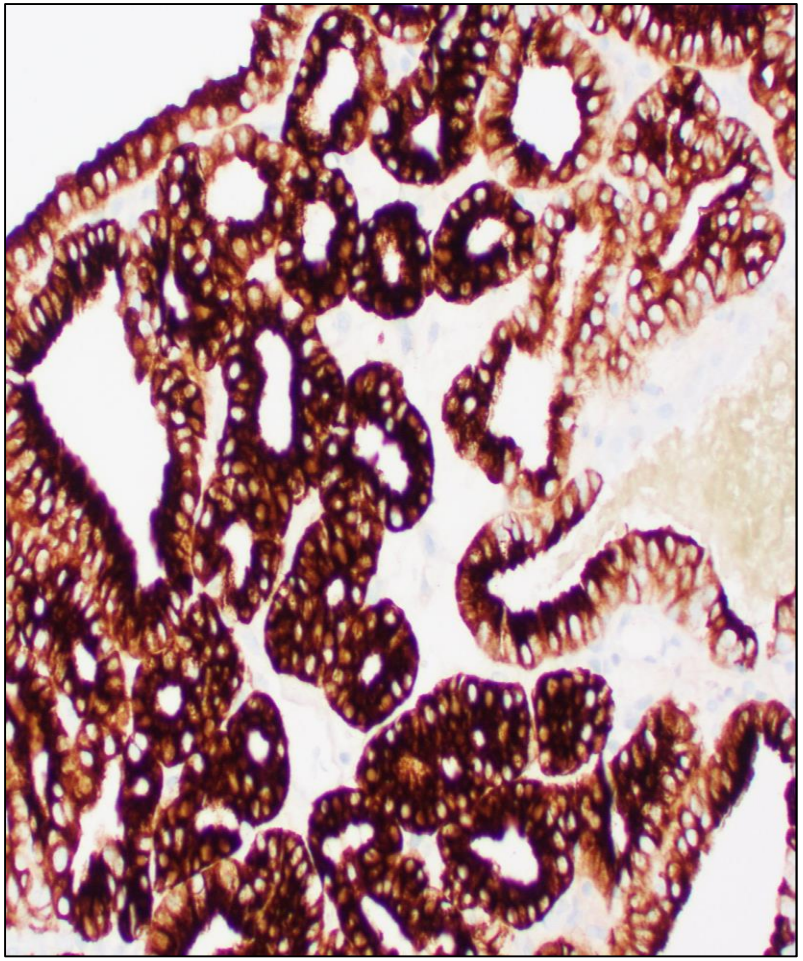




2/3 sessile


7% LGD [n=17] vs 29%HGD/carcinomas [n=7]

# Diffuse positivity for MUC6



- Focal detection
  - MUC2: 50% of cases
  - MUC5AC: 70.8% of cases
  - CDX2:100% of cases
- PAS staining:
  - 11 (45.8%) mucin-rich type
  - 13 (54.2%) mucin-poor type.

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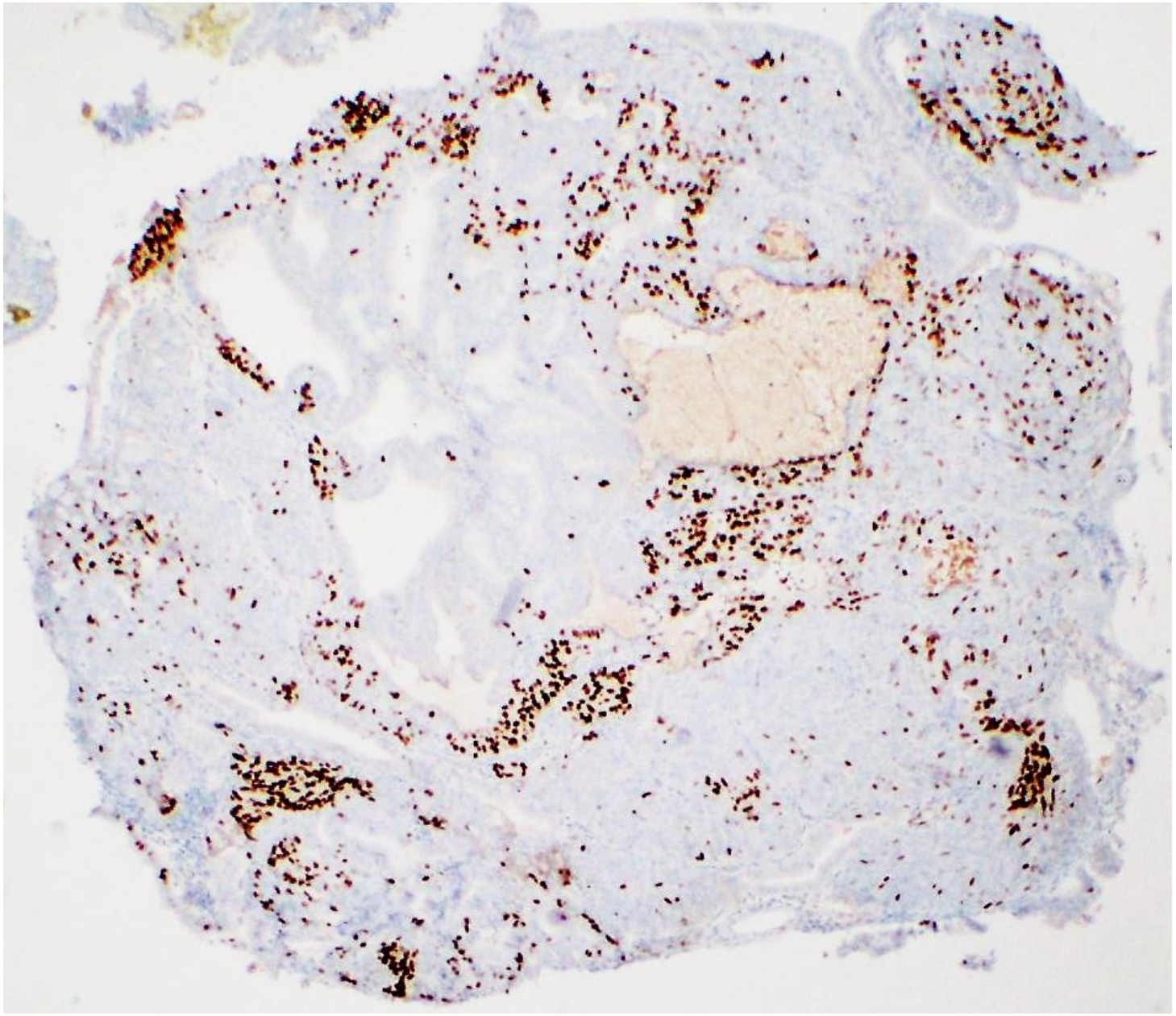
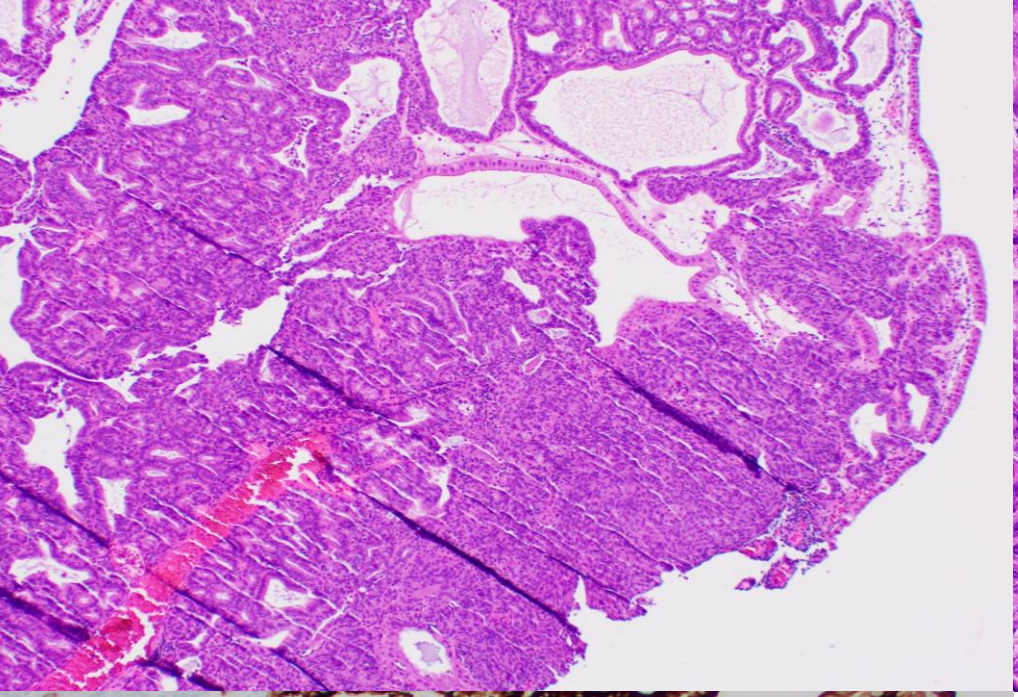
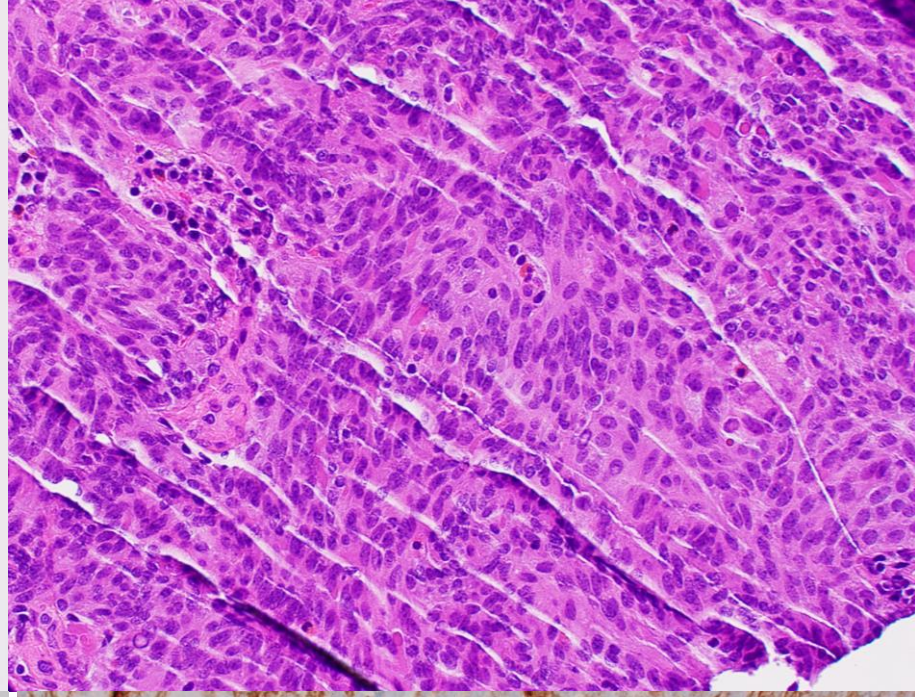
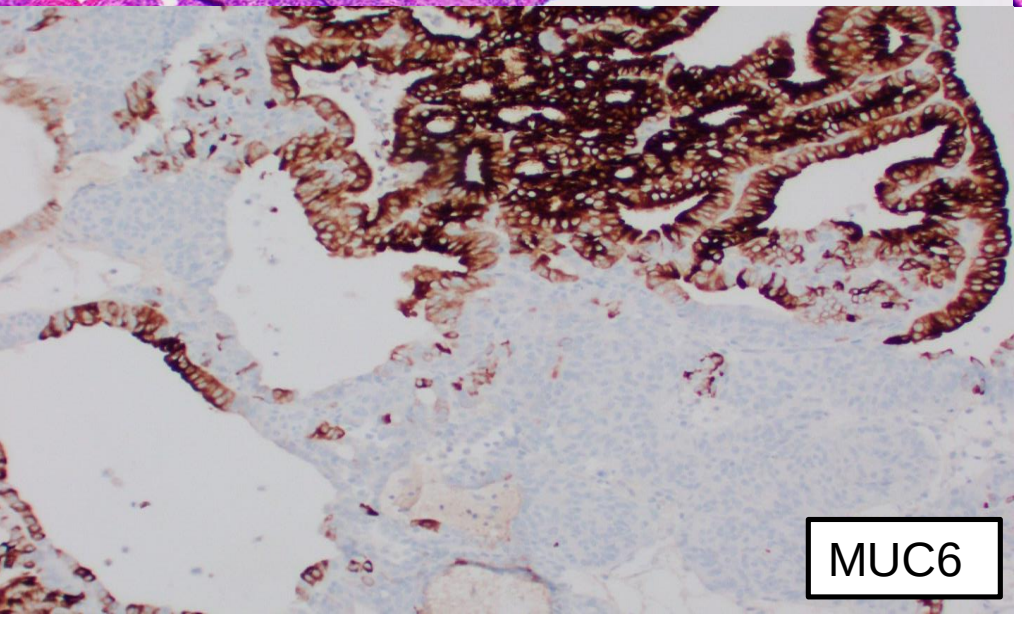
He C. AJSP 2018;42:1237-1245

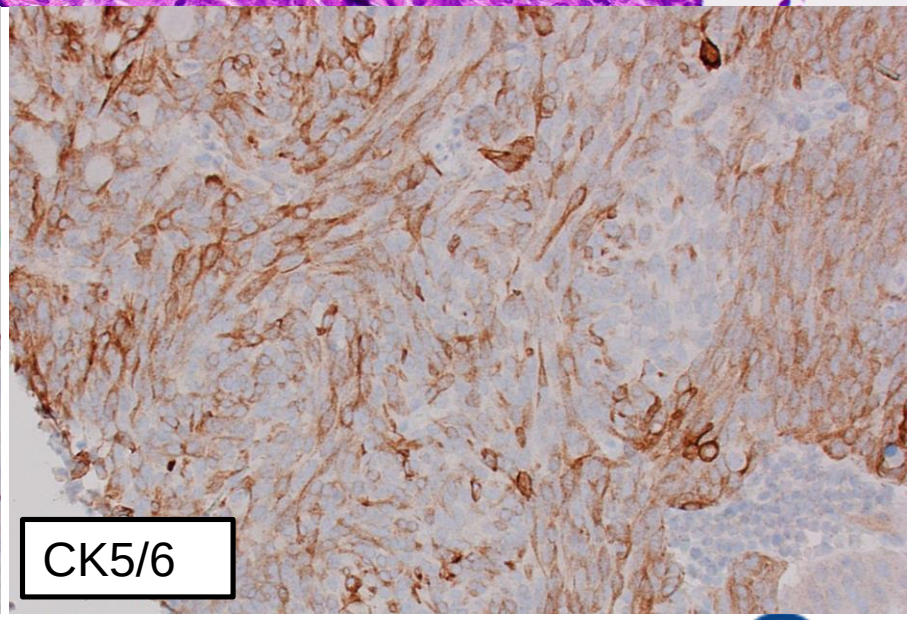


CDX2 [+] in goblet cells, Paneth cells, squamous morules








squamoid morules in 25% cases [mucin-poor PGAs];

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# Molecular Pathogenesis

- CTNNB1 missense mutations in all cases (21/21)
  - *but* β catenin staining varies: 10% to 90%.
  - β -catenin signaling pathway plays an essential role in induction of transdifferentiation toward morule-formation
- KRAS missense mutation in one case (4.2%).
- ***No*** GNAS missense mutation detected.

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He C. AJSP 2018;42:1237-1245

# UPDATE in PGAs

- *Gastric PGAs*
  - Not all associated with AIG
  - Low malignant potential
  - OGA and PGA: ? same spectrum w/ subtle changes?
- *GB – PGAs vs Gastric / Duod*
  - Can differentiate toward foveolar and intestinal phenotype.
  - Frequent CTNNB1 mutations.
    - Variable nuclear accumulation of β-catenin.
  - Infrequent or no KRAS or GNAS-mutations.

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