

"NEW TRENDS IN GASTRIC POLYPS: EVOLVING CLASSIFICATION AND PATHOGENESIS"

Gregory Y. Lauwers, MD

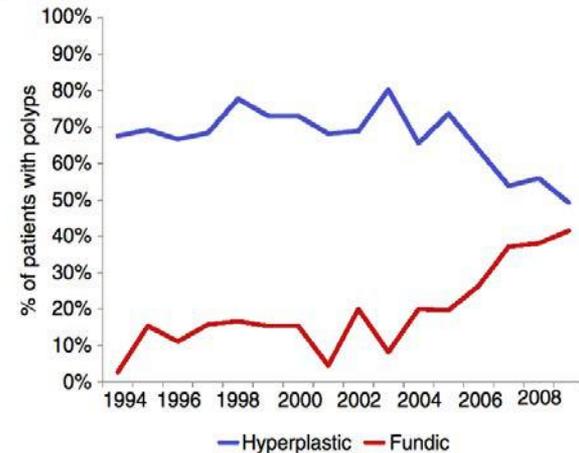
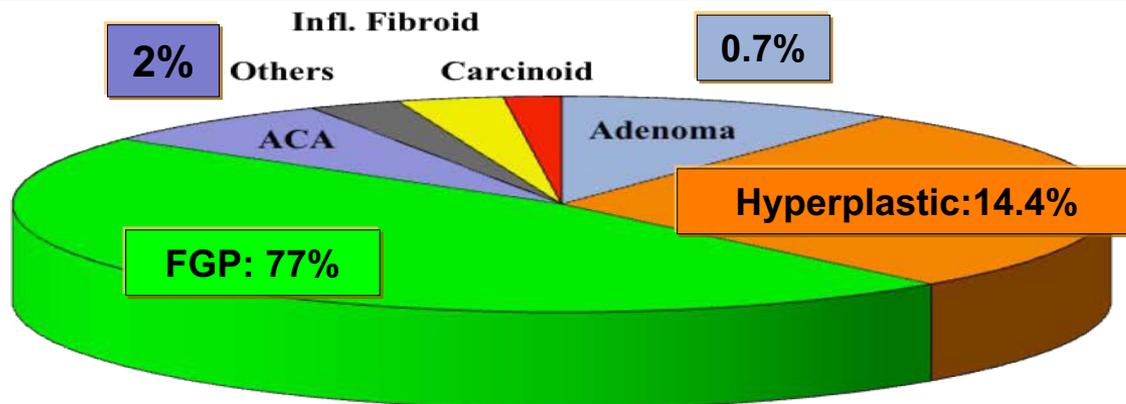
Senior Member

H. Lee Moffitt Cancer Center & Research Institute

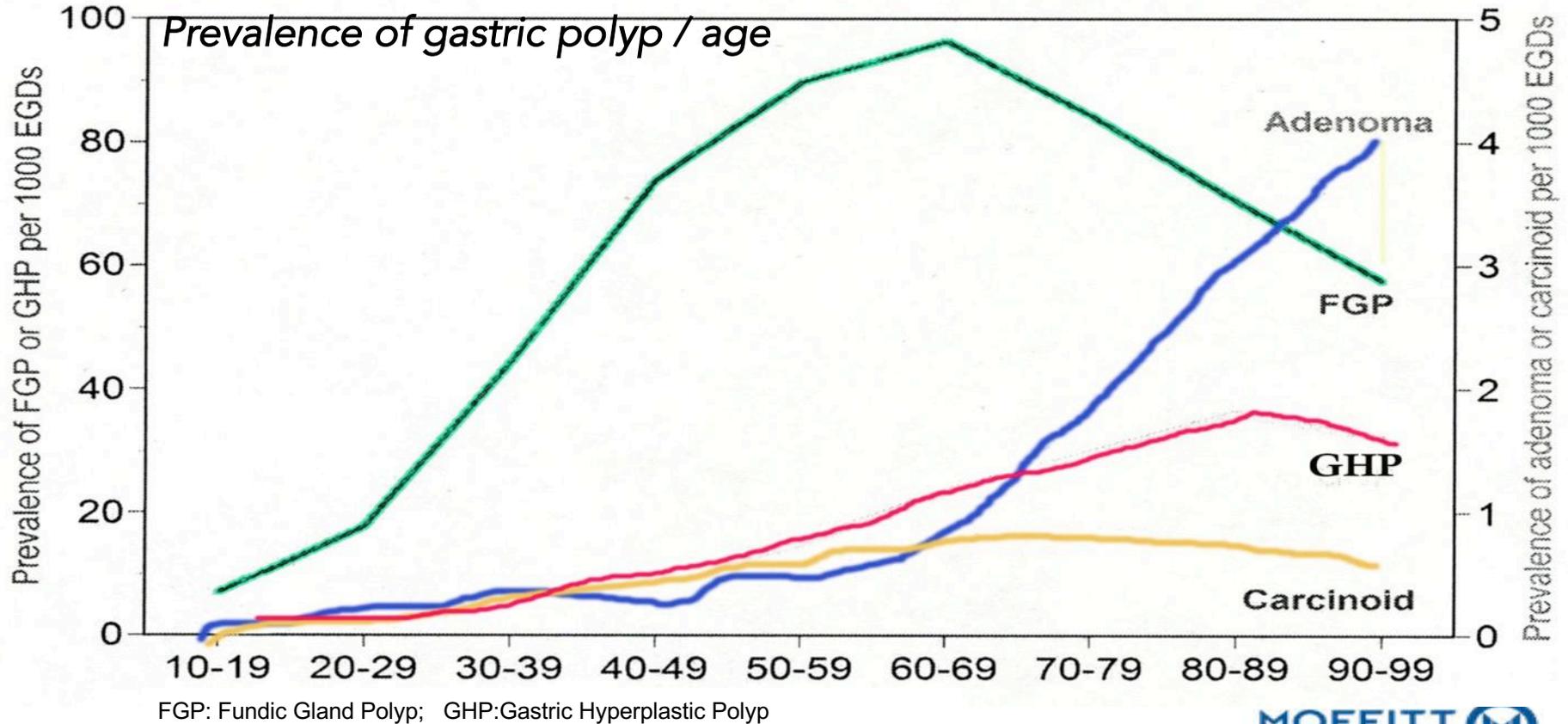
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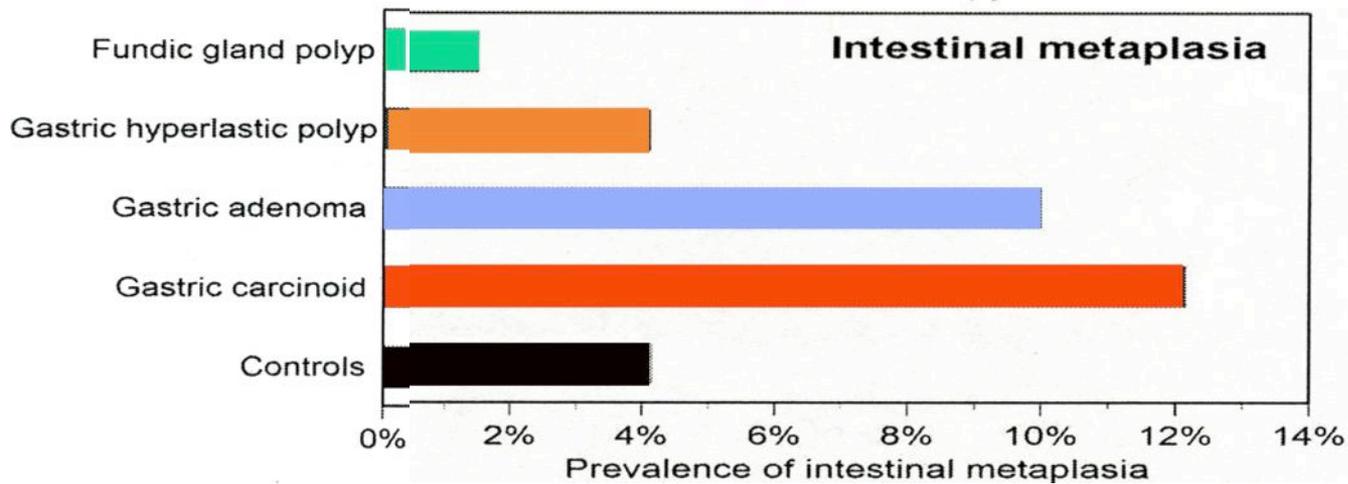
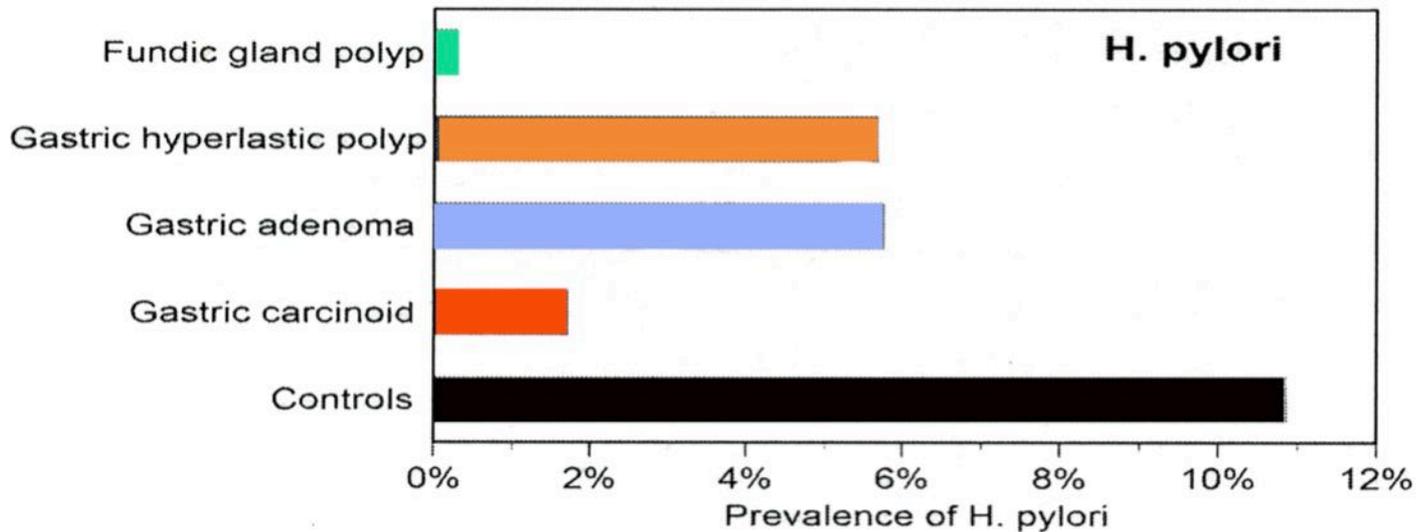
Gregory.Lauwers@Moffitt.org

General category	Subtype	Usual location	Malignant potential
Epithelial	Hyperplastic/inflammatory	Antrum and lower body	Low ^a
	Hamartomatous		Low
			Low ^a
			Unknown
	Neoplastic		Fundic gland polyp
	Polypoid dysplasia (adenoma)	Antrum and body fundus	High
	Neuro-endocrine tumor	Body fundus	Low to moderate
Mesenchymal	Inflammatory fibroid polyp	Antrum	None
	Others ^c		
Miscellaneous	Cronkhite–Canada		Unknown
	Xanthoma		None
	Gastric heterotopic pancreas		Very low



Prevalence of gastric polyps: 3.75%





OUTLINE

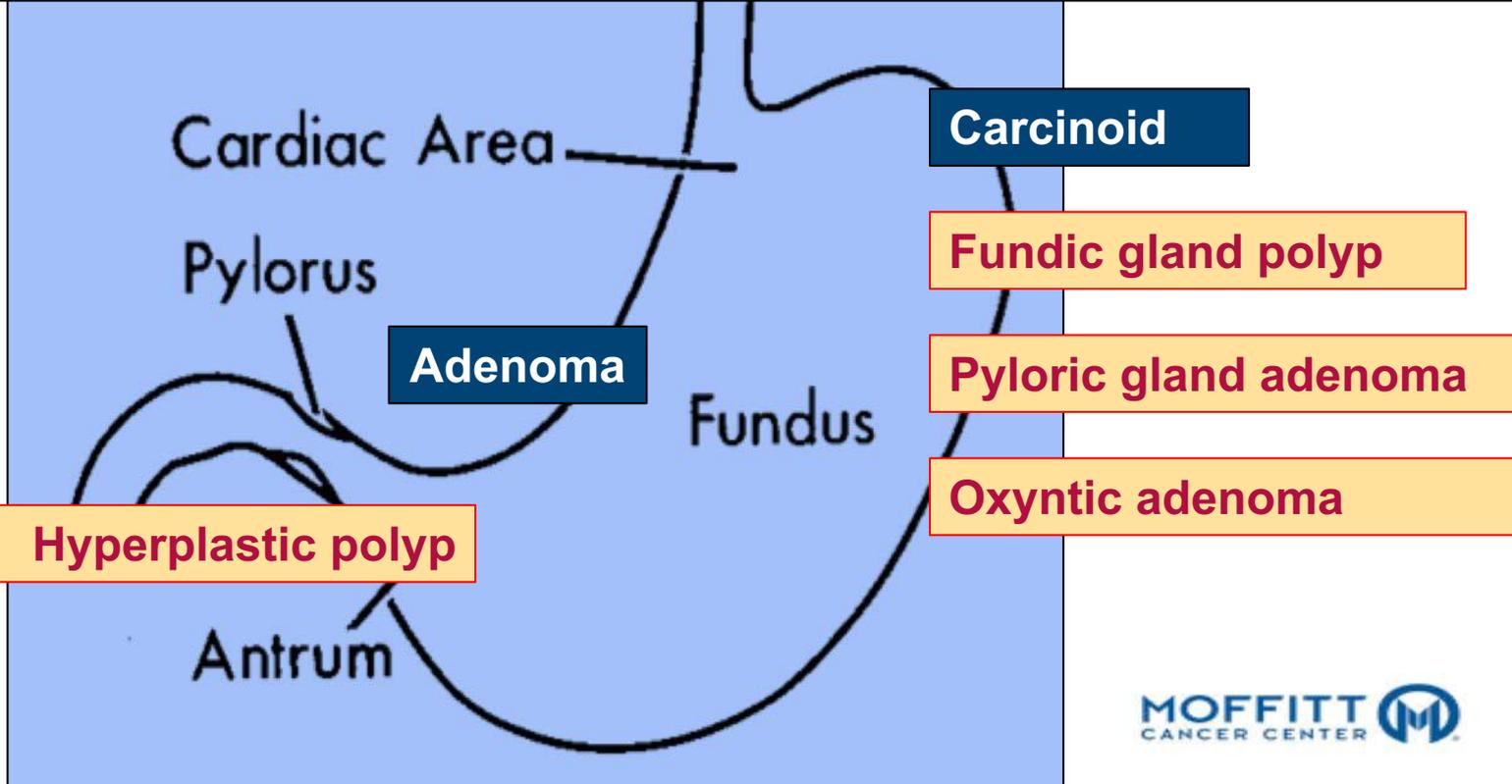
- **Fundic Gland Polyps**
 - Familial Adenomatous Polyposis
 - Gastric Adenocarcinoma & Proximal Polyposis [GAPPS]
- **Hyperplastic Polyps**
 - *Prolapse* and *Inverted* Variant
 - 'Syndromic' Differential Diagnosis On Pinch Biopsies
- **Pyloric Adenoma**
- **Gastric Adenocarcinoma Fundic Gland Type/ Oxyntic Adenoma**

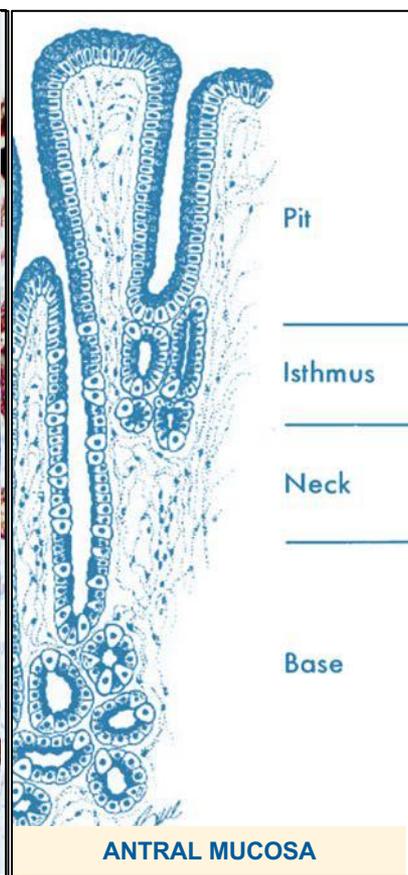
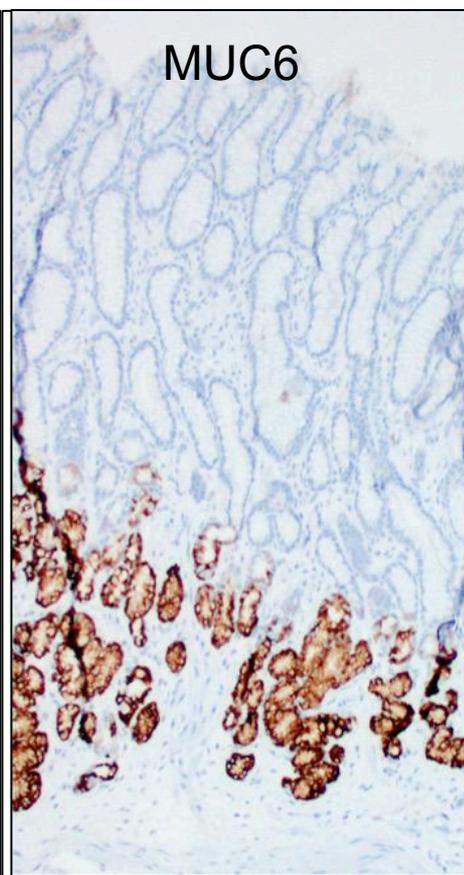
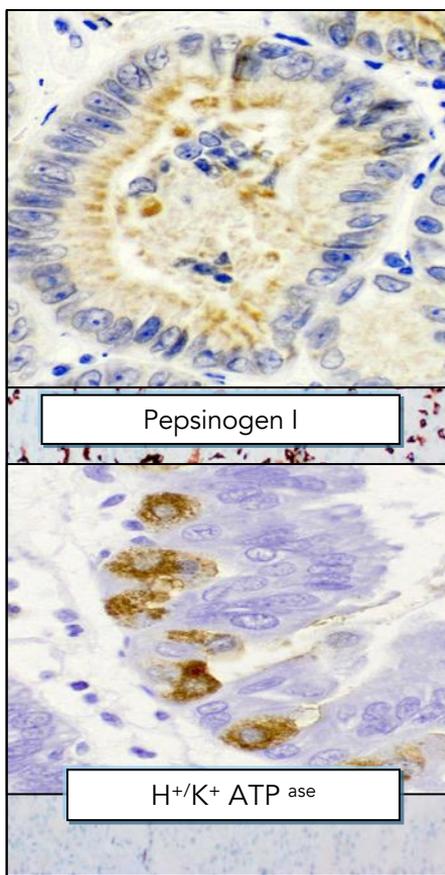
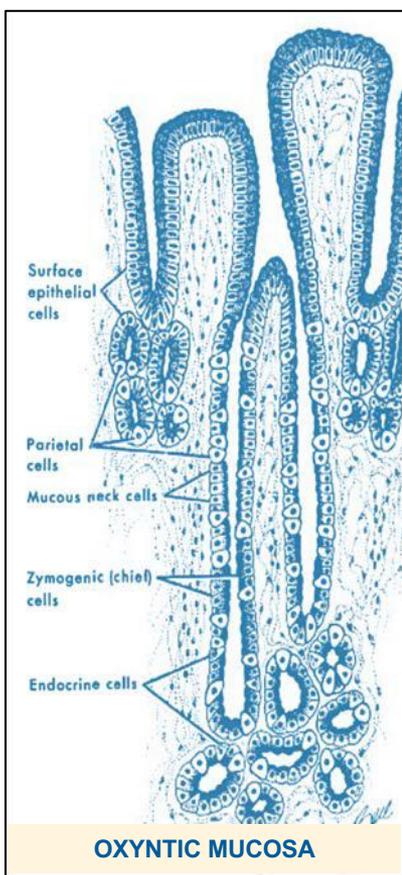
Gastric Polyps

-just

like real estate, it's all about location

Adapted from Voltaggio & Montgomery





MUC5AC /MUC6

Secretory

Stomach / Intestine

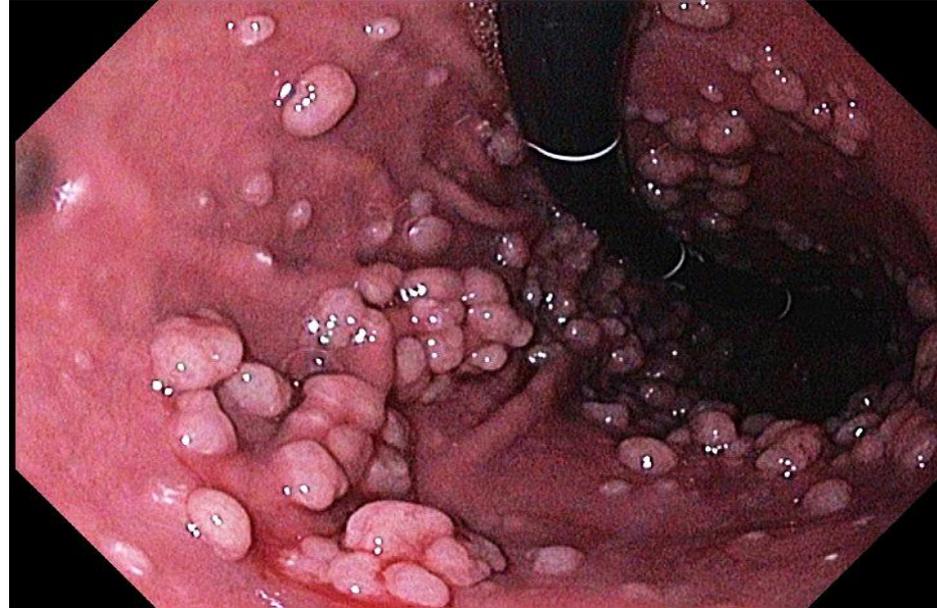
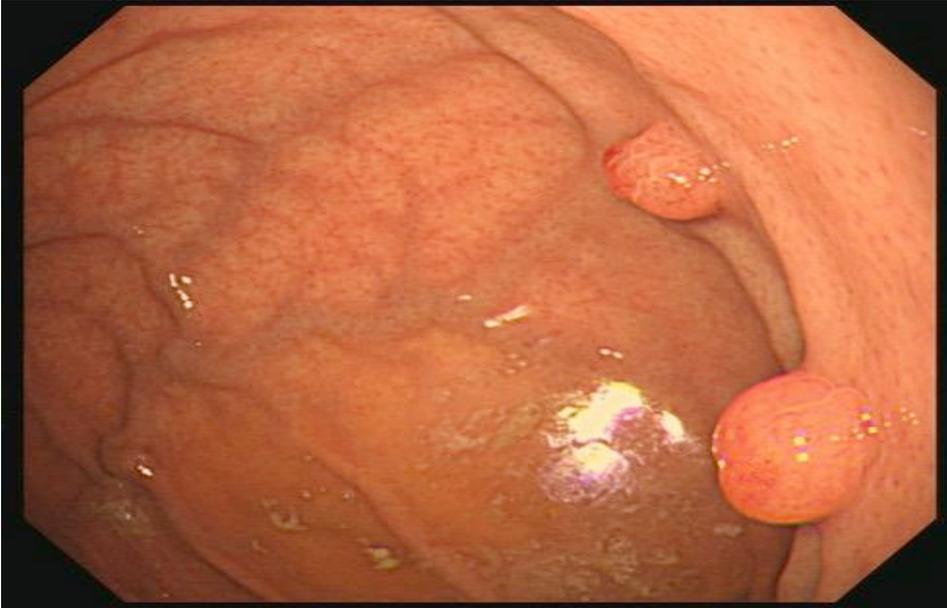
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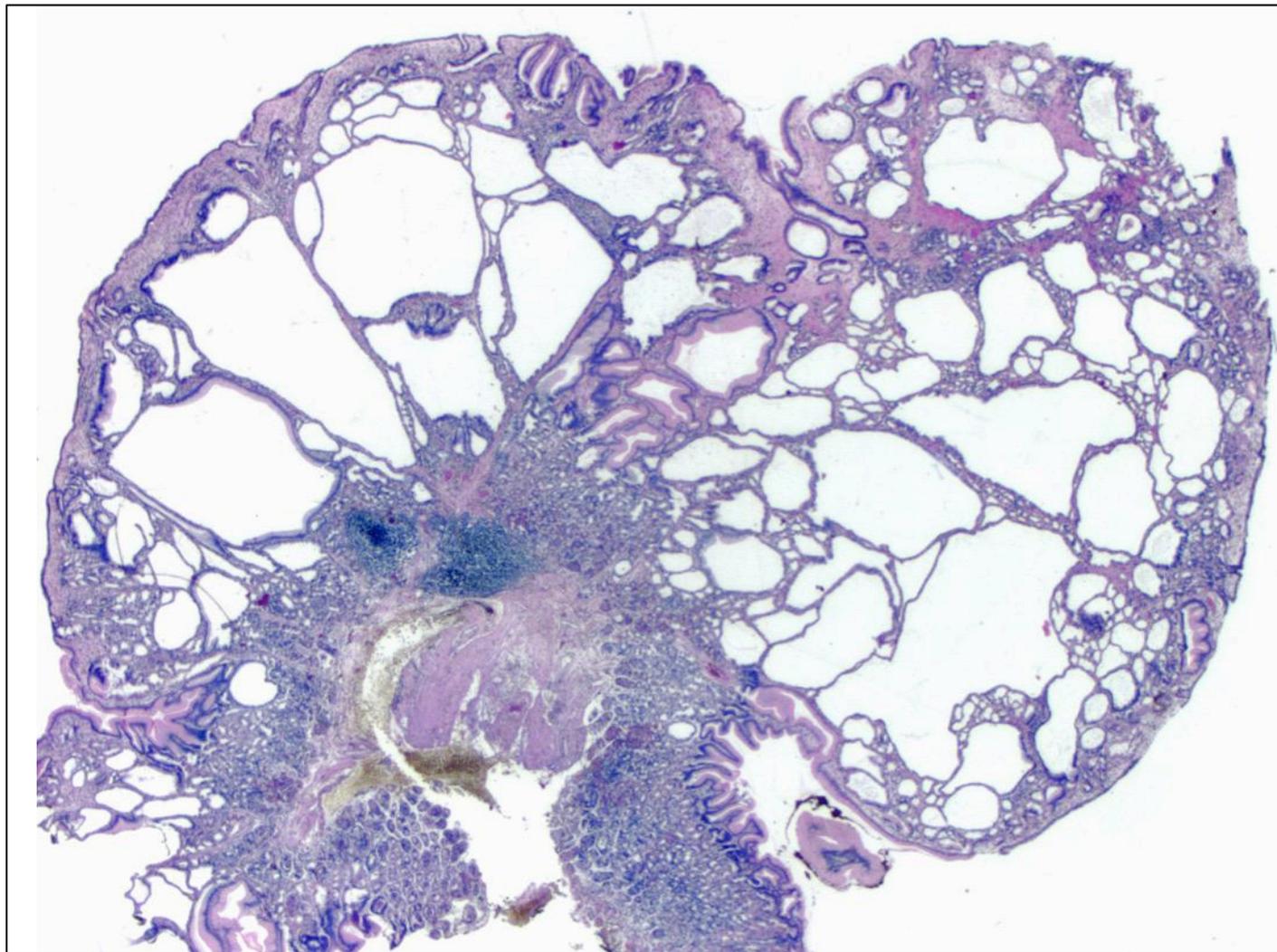
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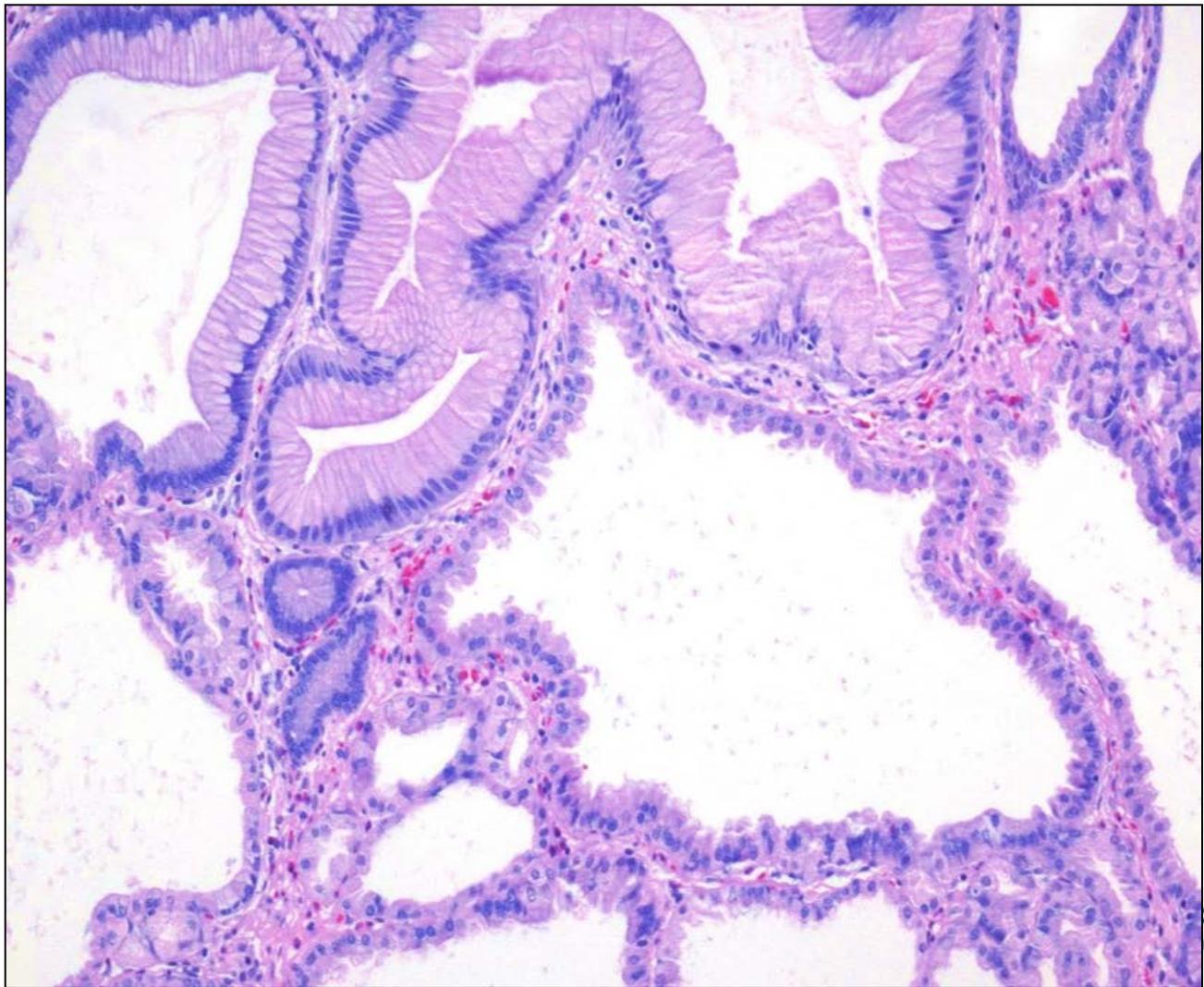
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Fundic Gland Polyp



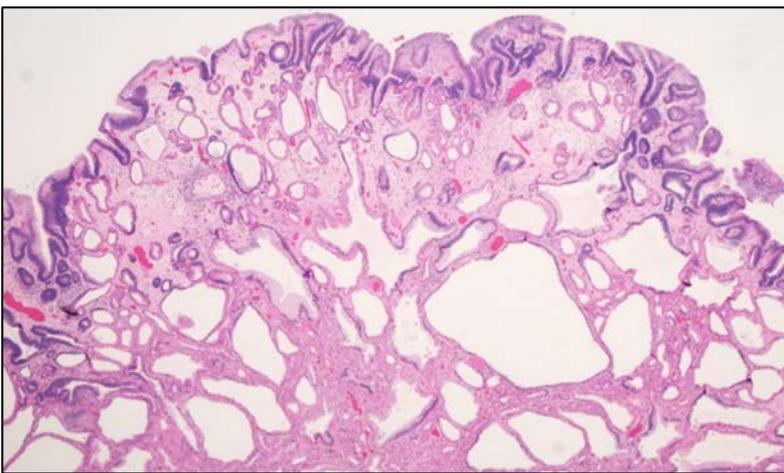
- Oxyntic mucosa
- Sessile: 1-5 mm
- Multiple (40-60%)
- 40-50% are labile overtime



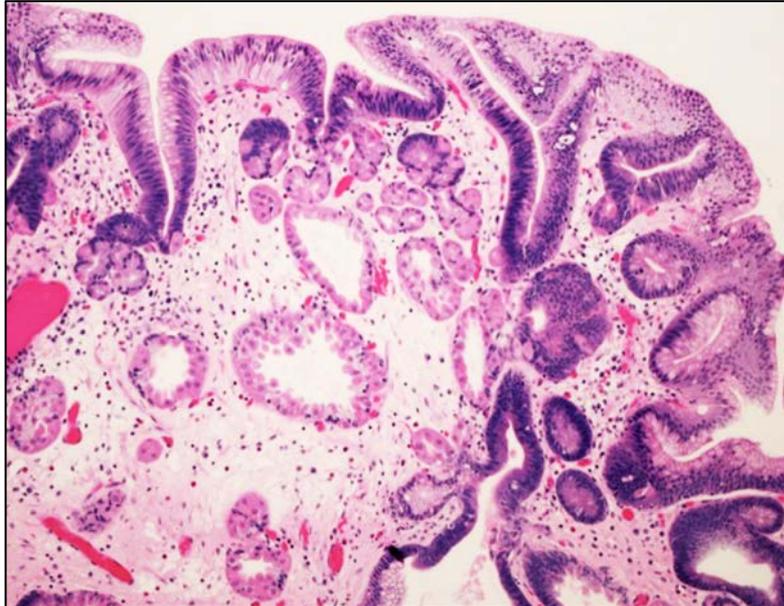


Fundic Gland Polyps

- Proton pump inhibitors
 - *Time and dose dependent manner (mean interval:32 months)*
- Sporadic (0.09 to 5% of endoscoped pts; Female +)
 - *Activating β catenin mutation (60%-90%)*
- FAP (prevalence 51% to 88%)
 - *Inactivating APC mutations [codons 1982-1983 asso^{ciated} w/ profuse gastric polyposis]*
- GAPPS (Gastric Adenocarcinoma & Proximal Polyposis)
 - *Point mutations in YY1 binding site of APC promoter 1B*
 - *Unique β catenin activation (via GNAS mutation)*
- MUTYH associated polyposis



Sporadic FGP: Dysplasia is rare (1%)
FAP patients: 25-48% (LGD>HGD [0-12%])
Risk increase w/ the size of polyps and severity of *duodenal polyposis*
Rare cases of ACA

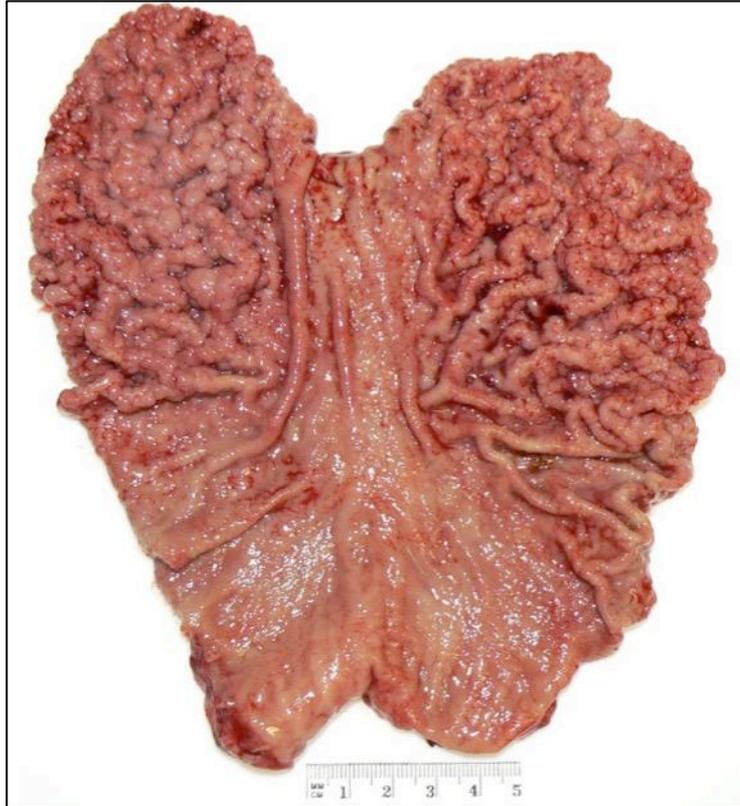


Series of 24 FAP pts [follow-up of 6 yrs]
87% *persisted* (54%) or *regressed* (33%)
13% *progressed* to HGD/IMC
(sporadic LGD progression rate: 5-14%)

- **Recommendations:**
 - *Sporadic: no follow-up*
 - *FAP: Follow q. 2/3 years (suggested):*
 - Look for large polyps (>1cm)
 - Sample extensively

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): a new autosomal dominant syndrome

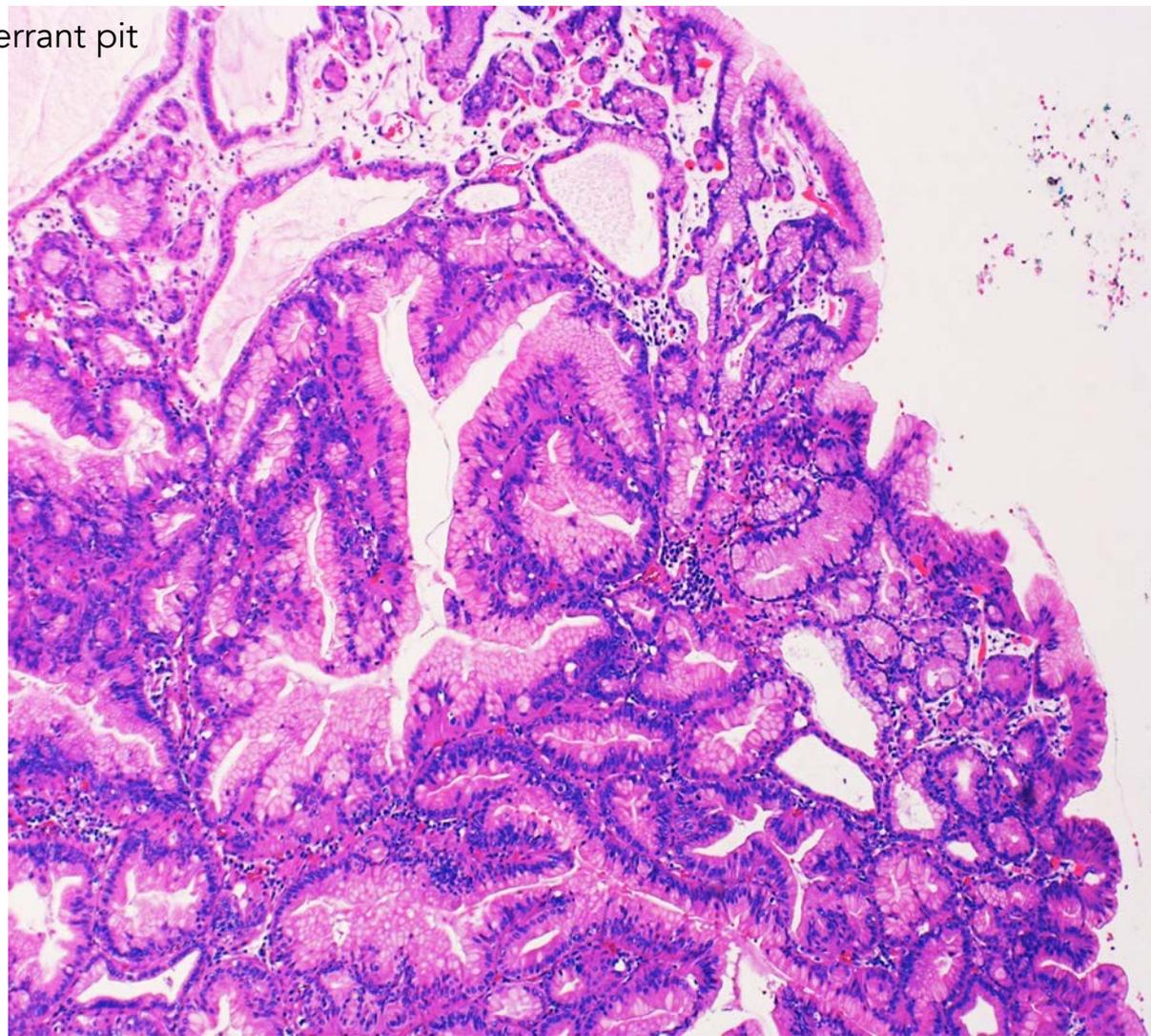
D L Worthley,¹ K D Phillips,² N Wayte,³ K A Schrader,⁴ S Healey,⁵ P Kaurah,⁴



✧ Key features:

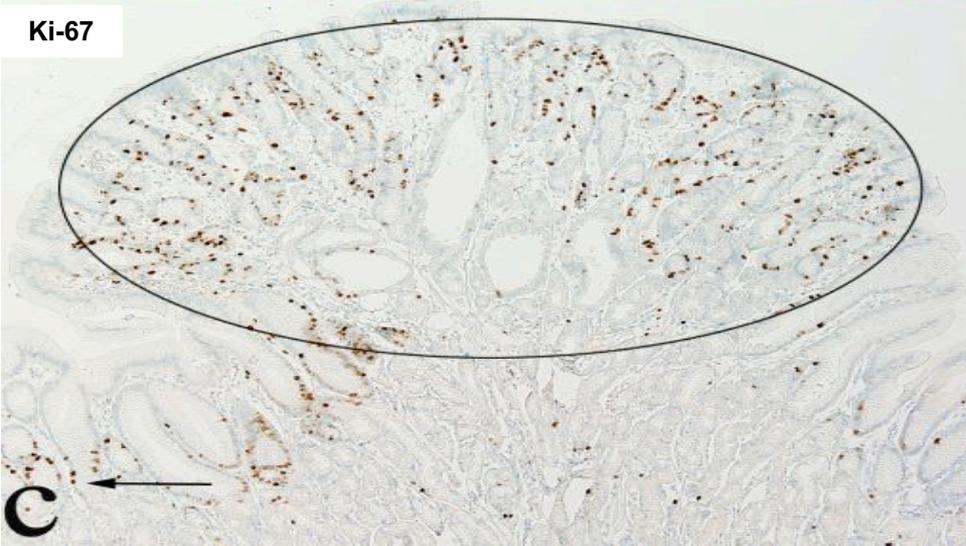
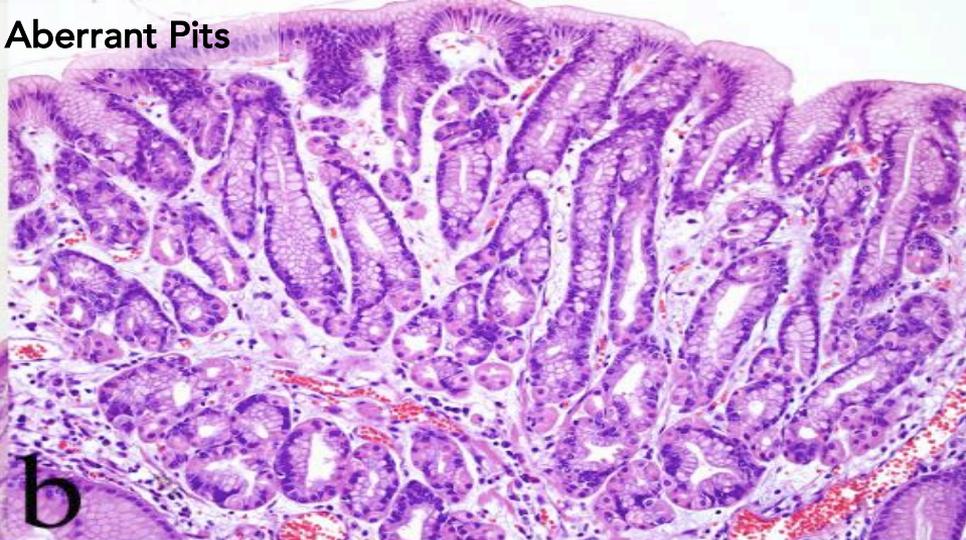
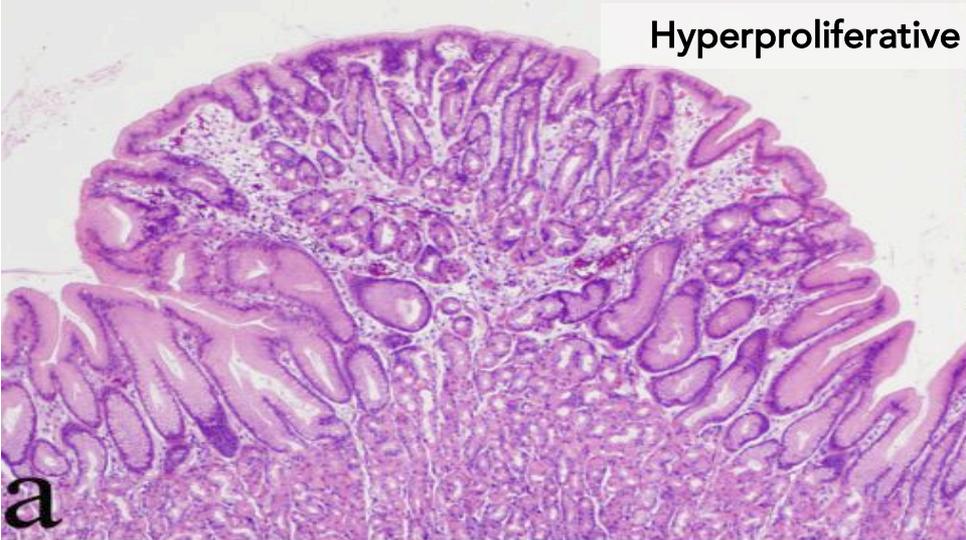
- FG polyposis w/occasional hyperplastic* & adenomatous polyps [**hyperproliferative aberrant pits & flat dysplasia in 100% of cases*]
 - sparing the antrum
 - intestinal type gastric cancer
- Autosomal dominant inheritance (Incomplete penetrance)
- No (rare ?) colonic adenomas

Hyperproliferative aberrant pit
w/ inverted foveolar
hyperplasia (+/- FGP)

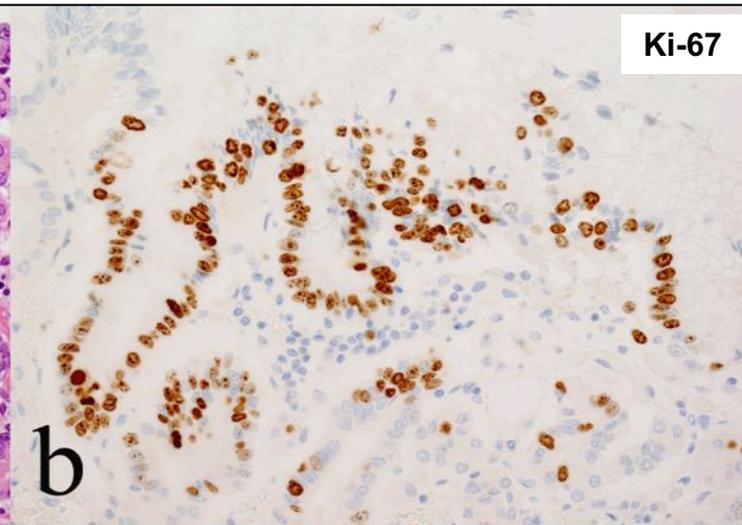
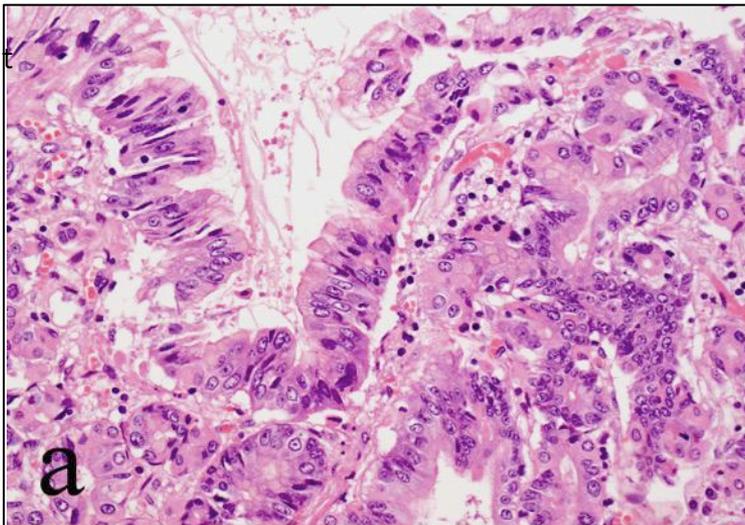


Courtesy of P. Kumarasinghe

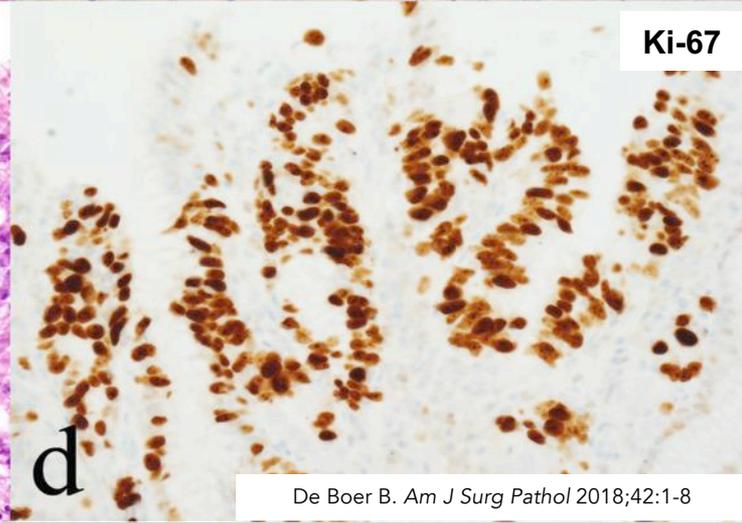
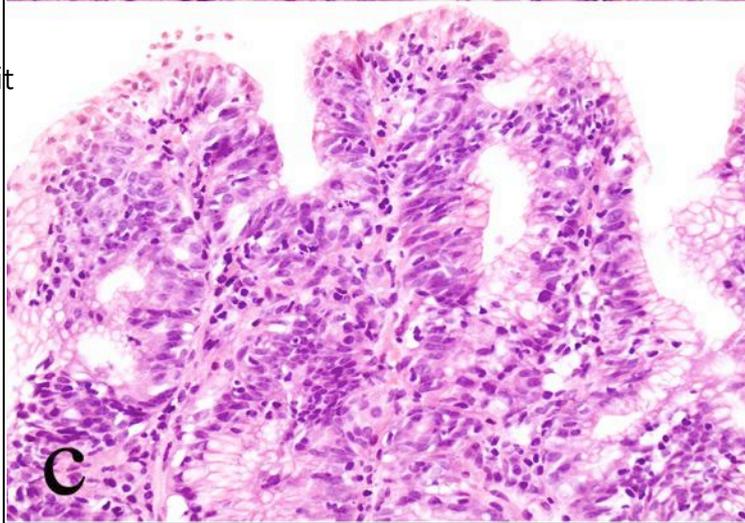
Hyperproliferative Aberrant Pits



Flat LGD in the setting of hyperproliferative aberrant pit



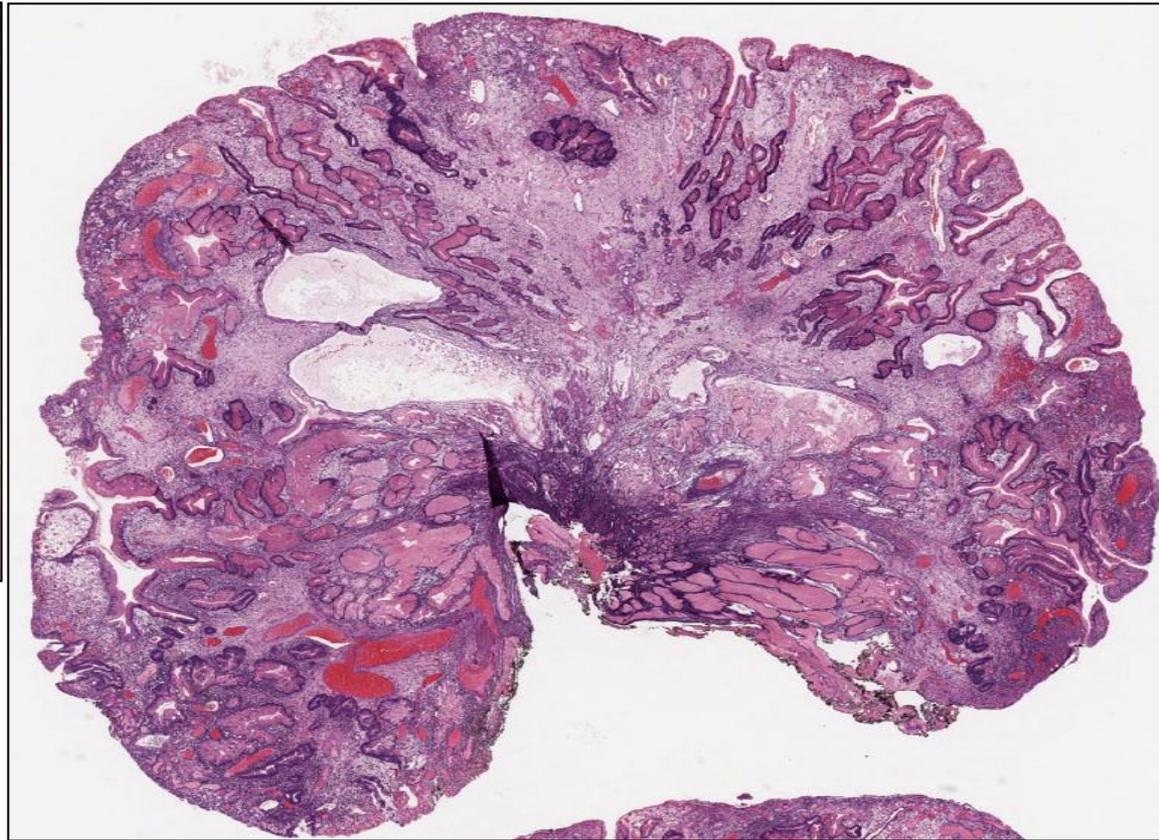
Flat HGD in the setting of hyperproliferative aberrant pit



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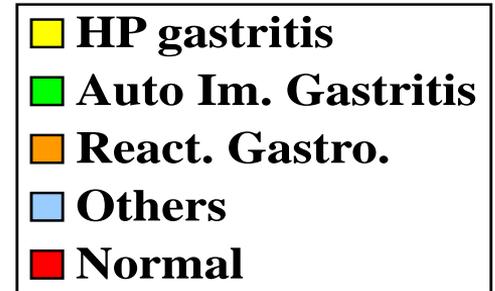
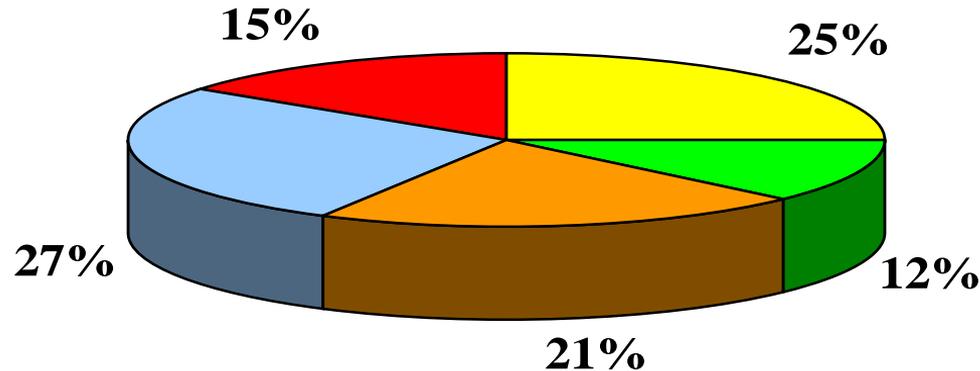
Hyperplastic Polyp



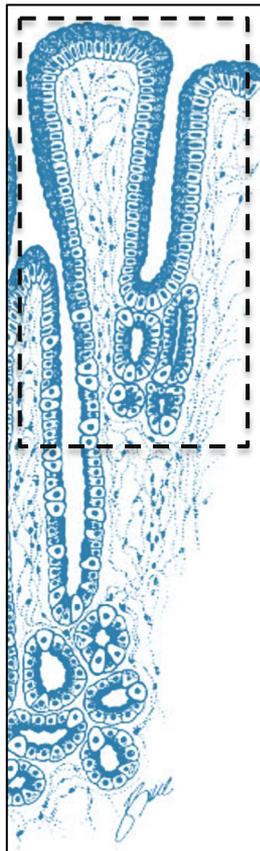
Mean age: 65yrs - Antrum:60%.

Sessile/pedunculated - Multiplicity: 20%.

Mucosal background of Hyperplastic Polyps



Hyperplastic Polyp

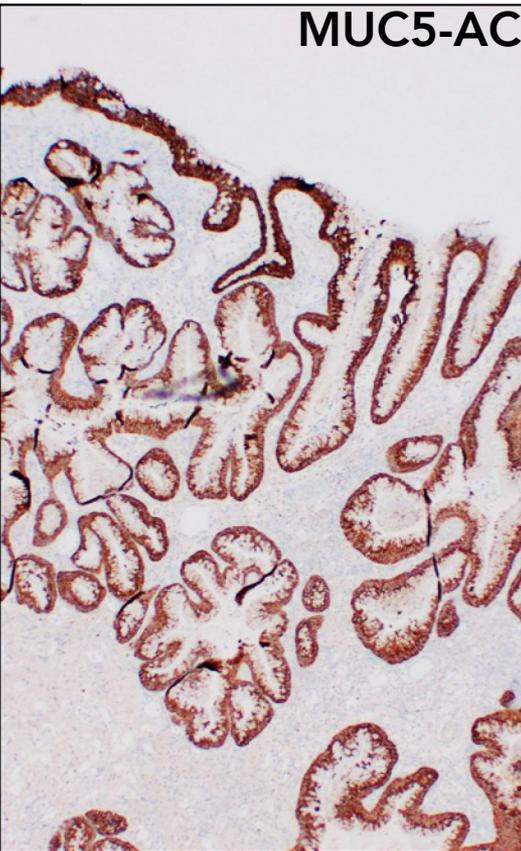
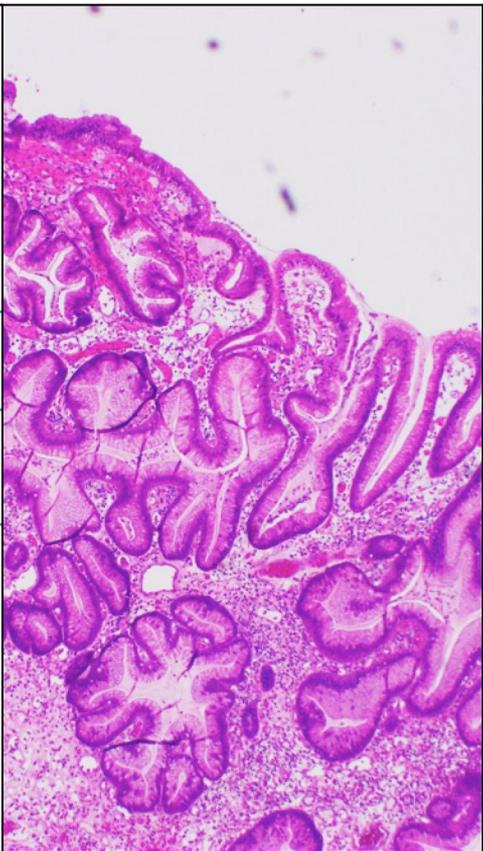


Pit

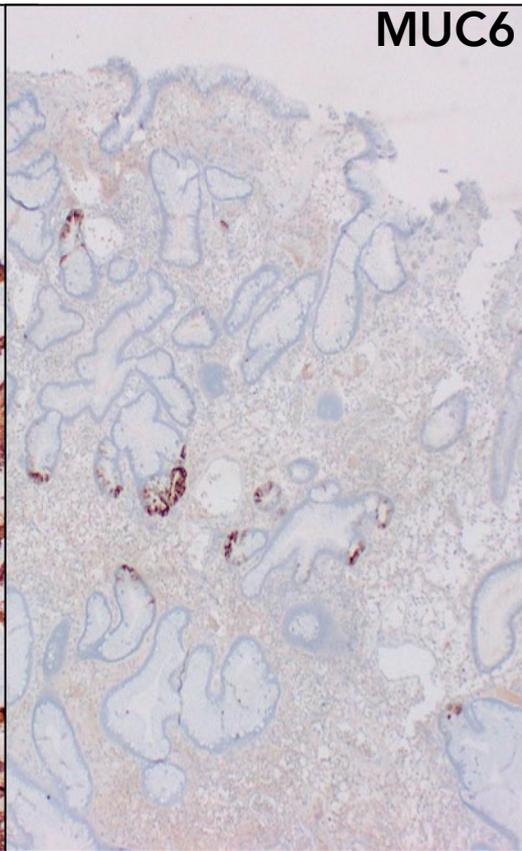
Isthmus

Neck

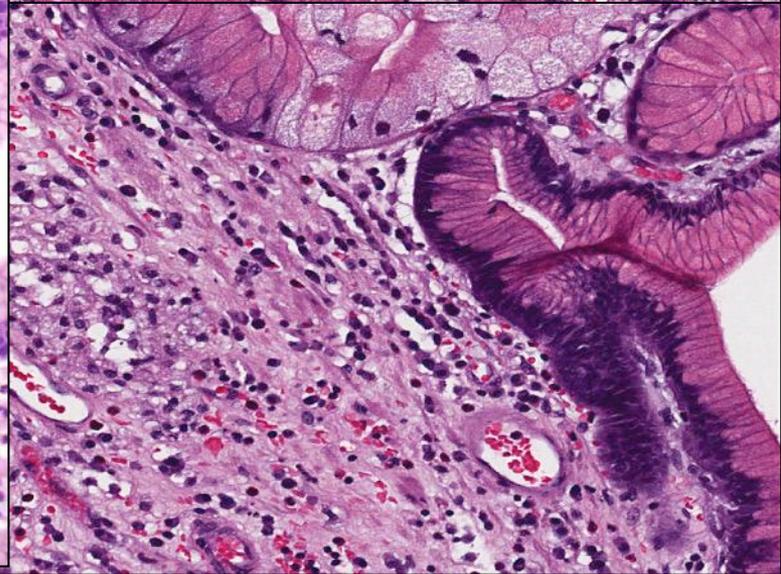
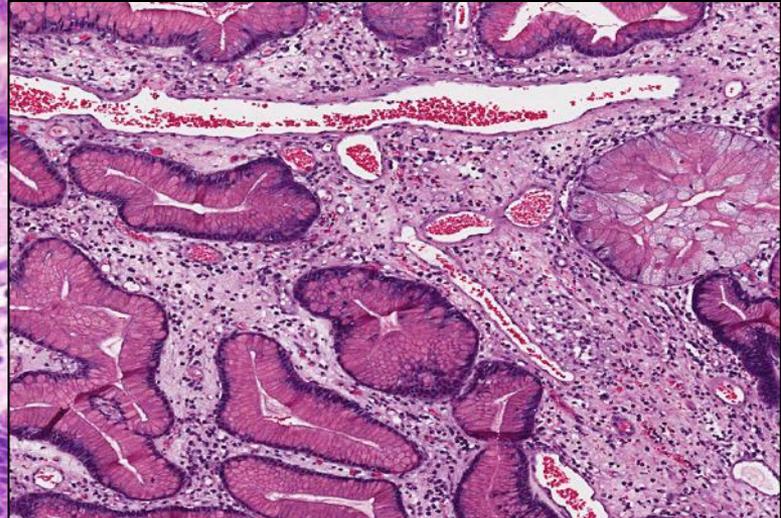
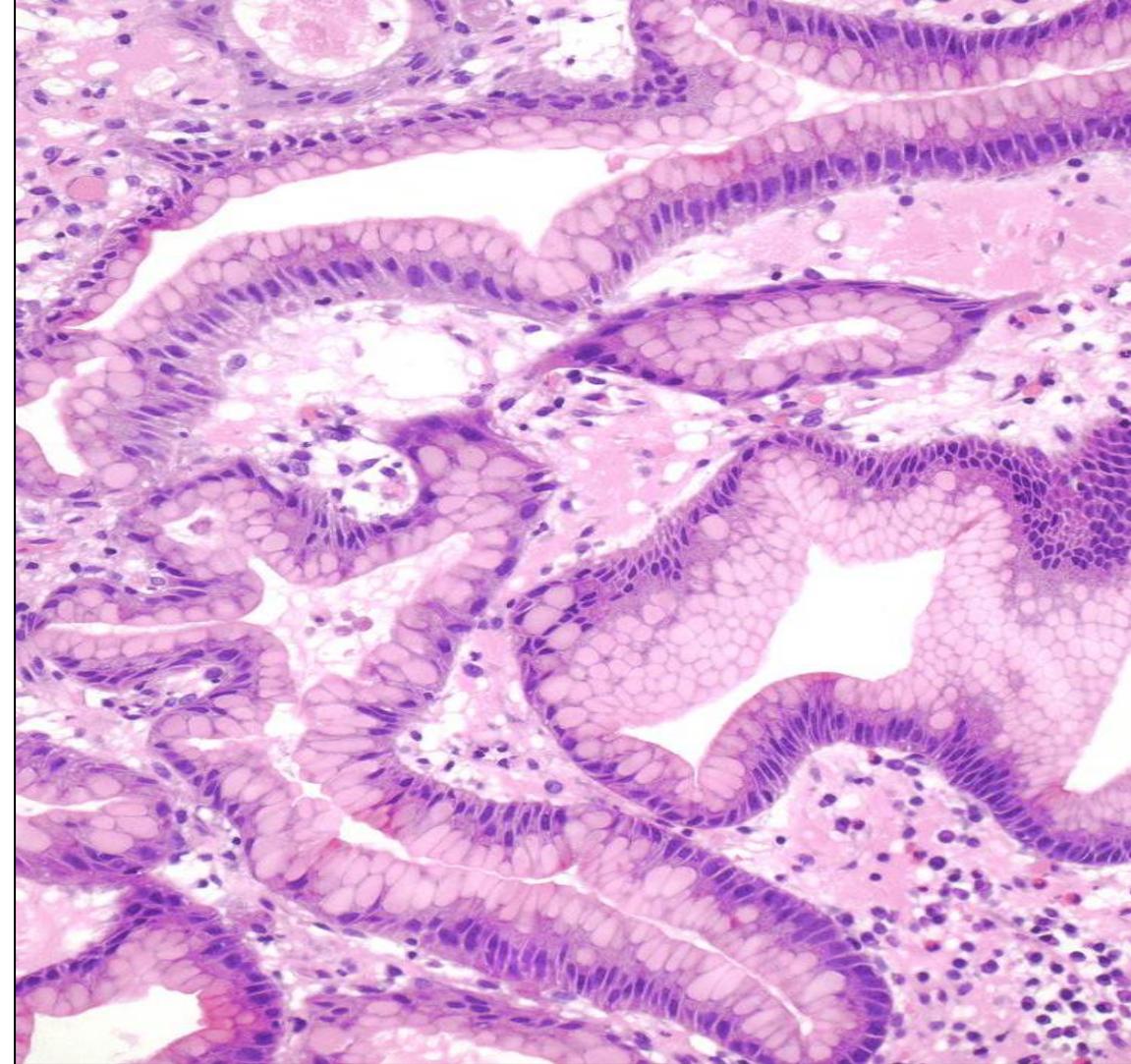
Base



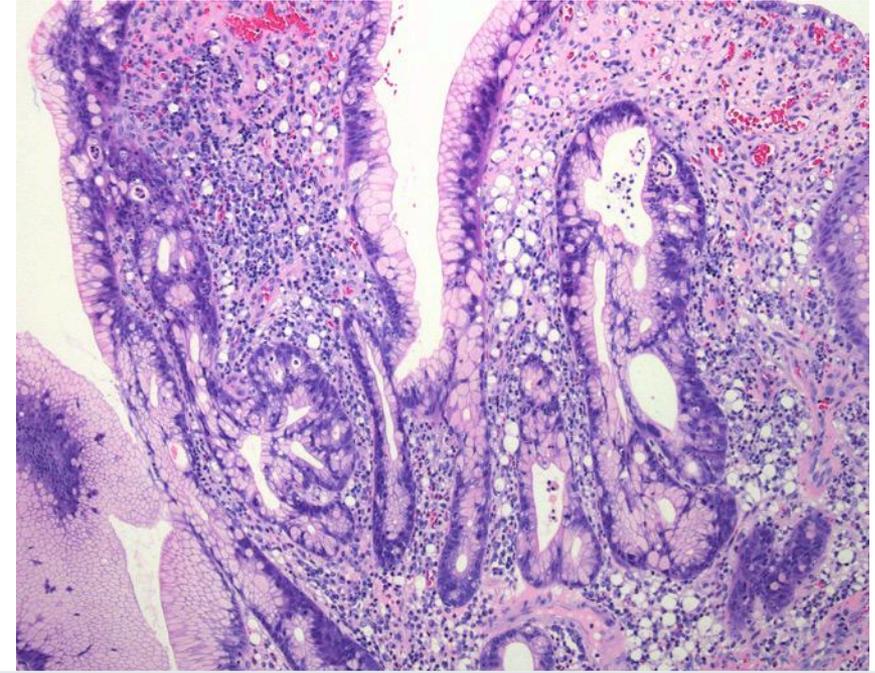
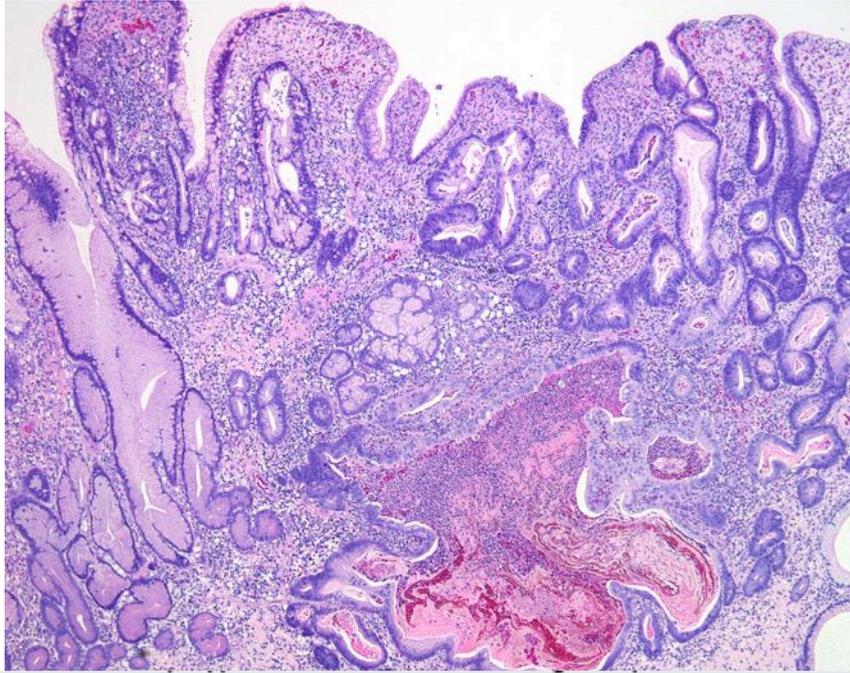
MUC5-AC



MUC6

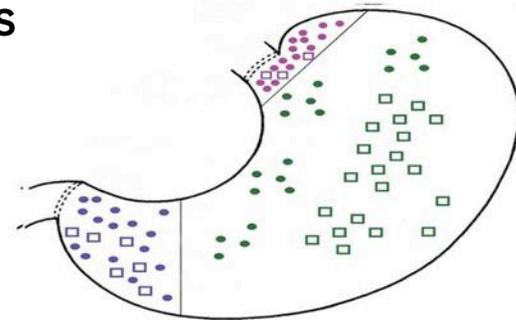
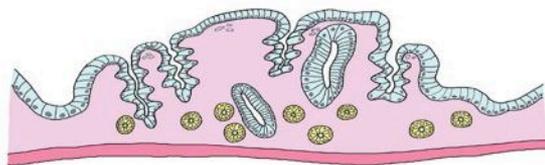
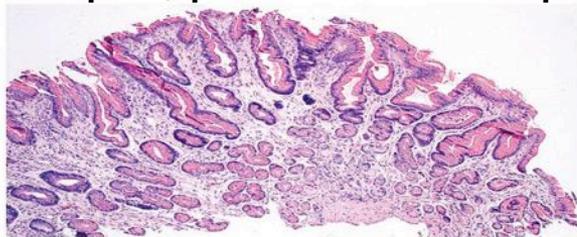


Dysplasia:1.8-16.4%; Carcinoma:0.3-7.1% (avg 2.1%) (> 2.0 cm)

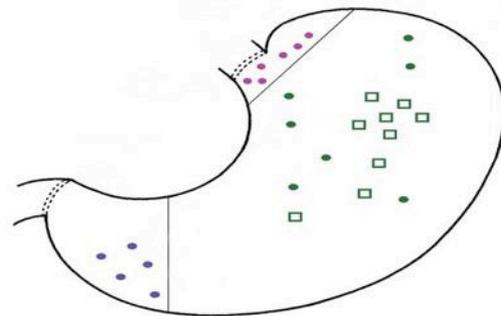
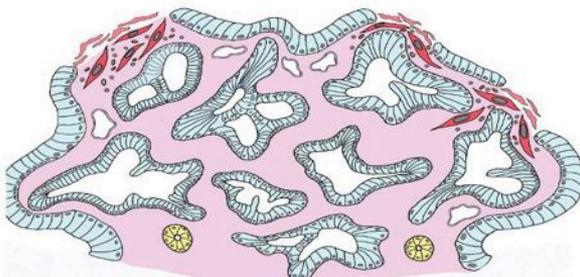
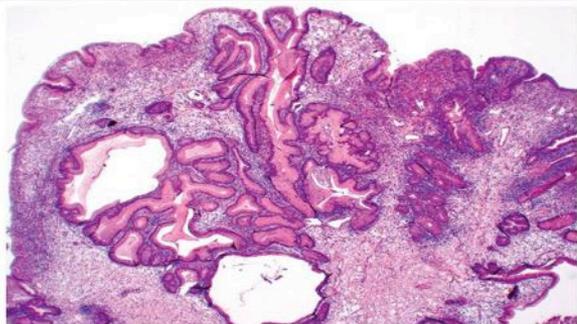


Polyp type	Usual number and size	Usual site	Malignant potential of polyp	Malignant potential of background mucosa	Management
Hyperplastic	Single 1–2 cm	Antrum	Low but significant	Low	Remove polyp if dysplastic Eradicate <i>H pylori</i> Repeat OGD 1 year
	Multiple <1 cm	Lower body	Low but significant	Low	Eradicate <i>H pylori</i> Repeat OGD 1 year

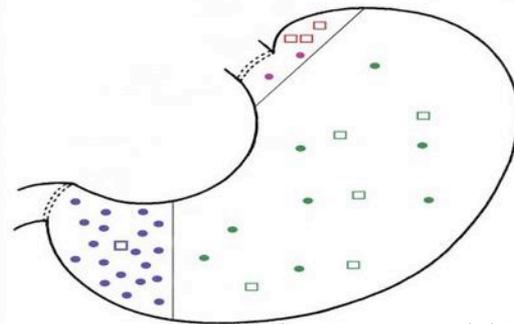
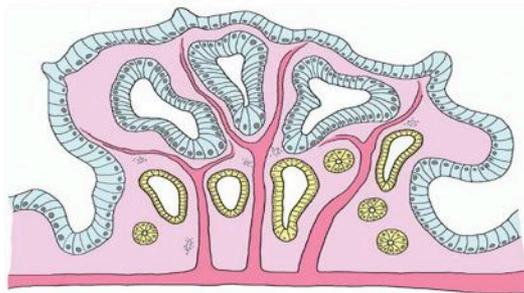
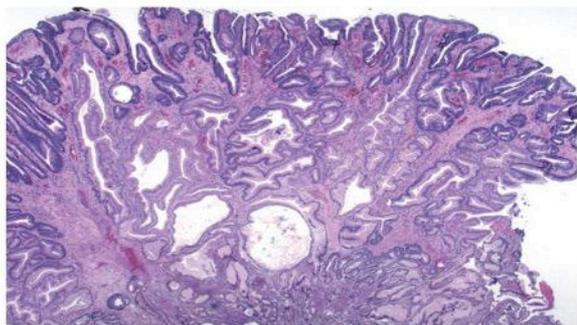
208 polypoid lesions reported as *hyperplastic* polyps



Polypoid fov. hyperplasia:49%

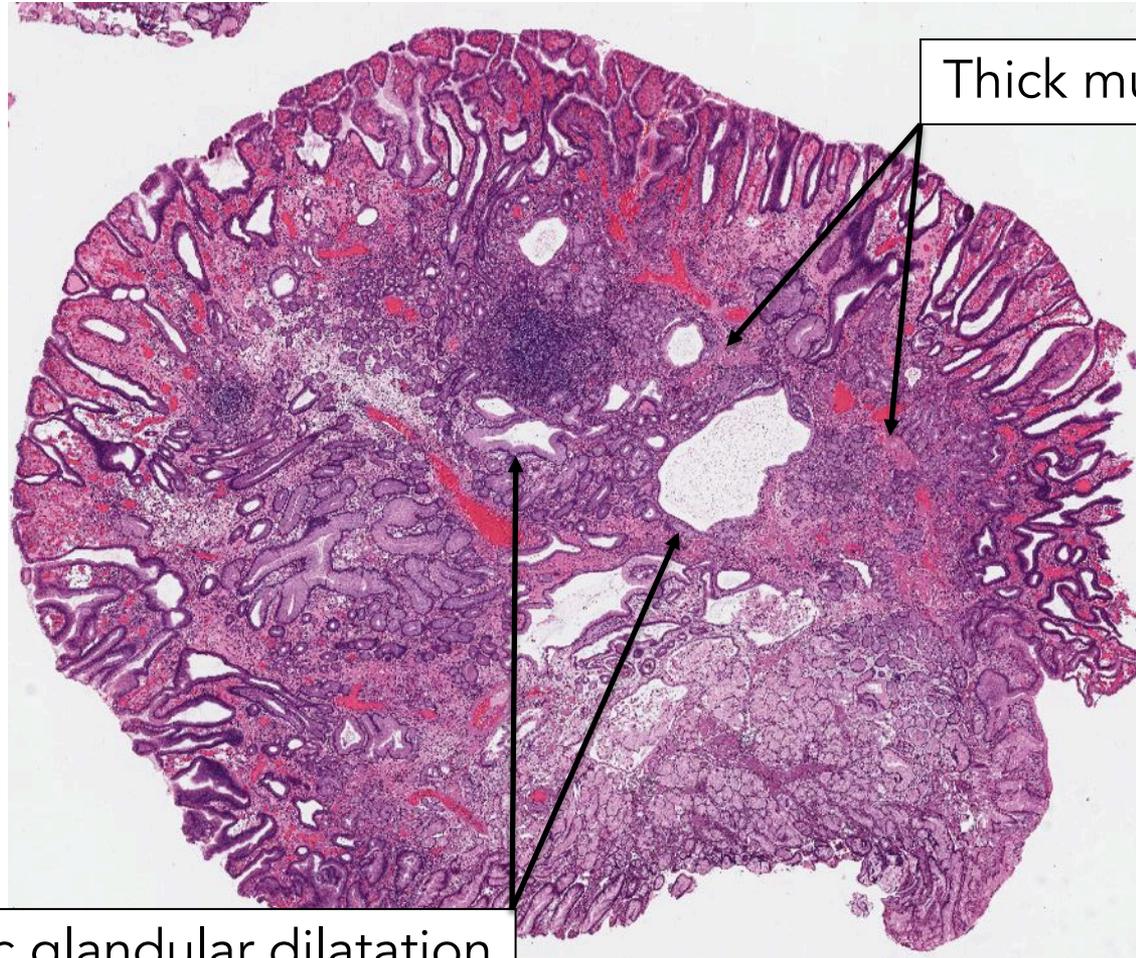


Hyperplastic polyp:31%



Prolapse polyp:20%

Prolapse Variant of Hyperplastic Polyp

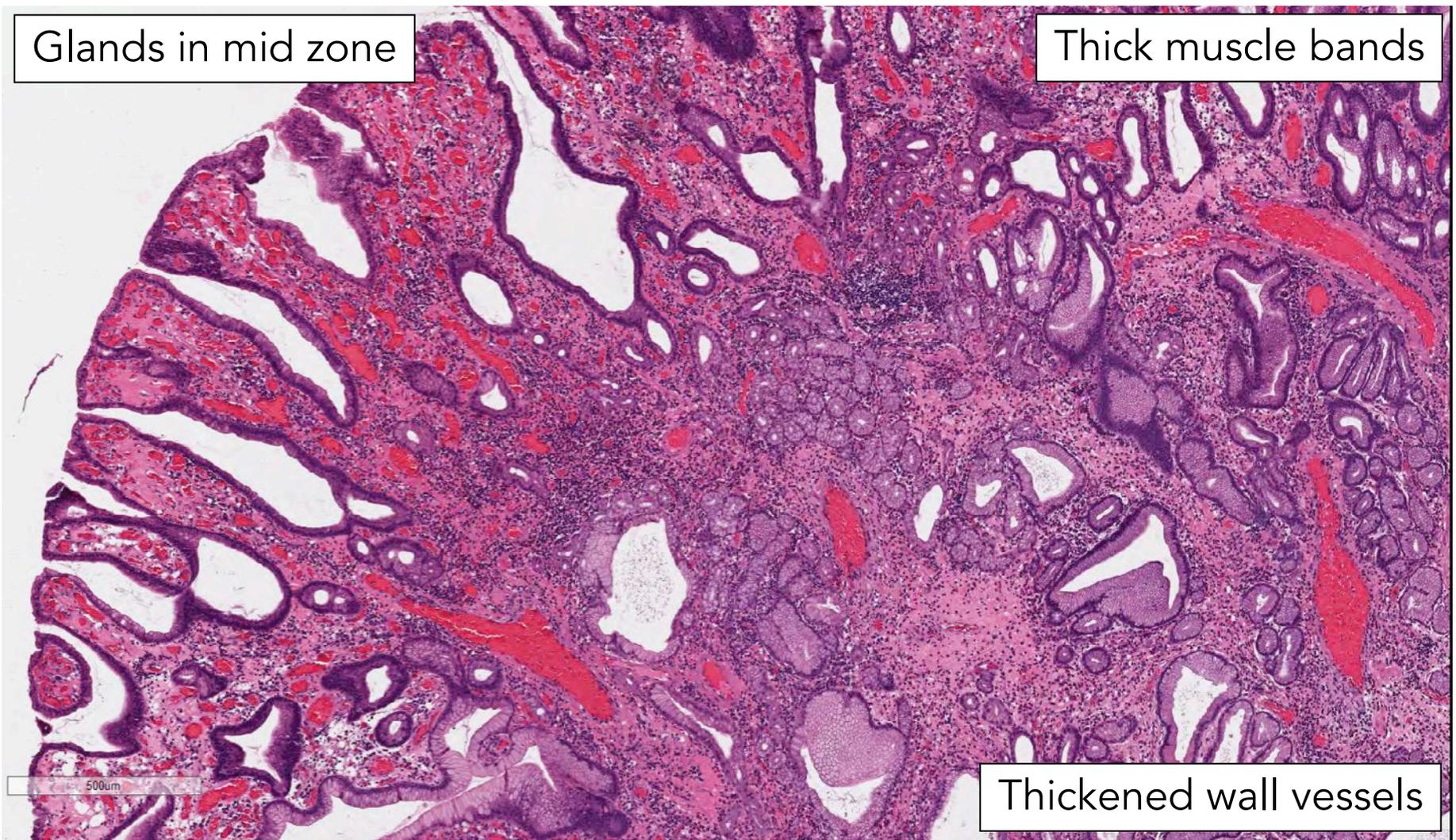


Thick muscle bands

Cystic glandular dilatation

Glands in mid zone

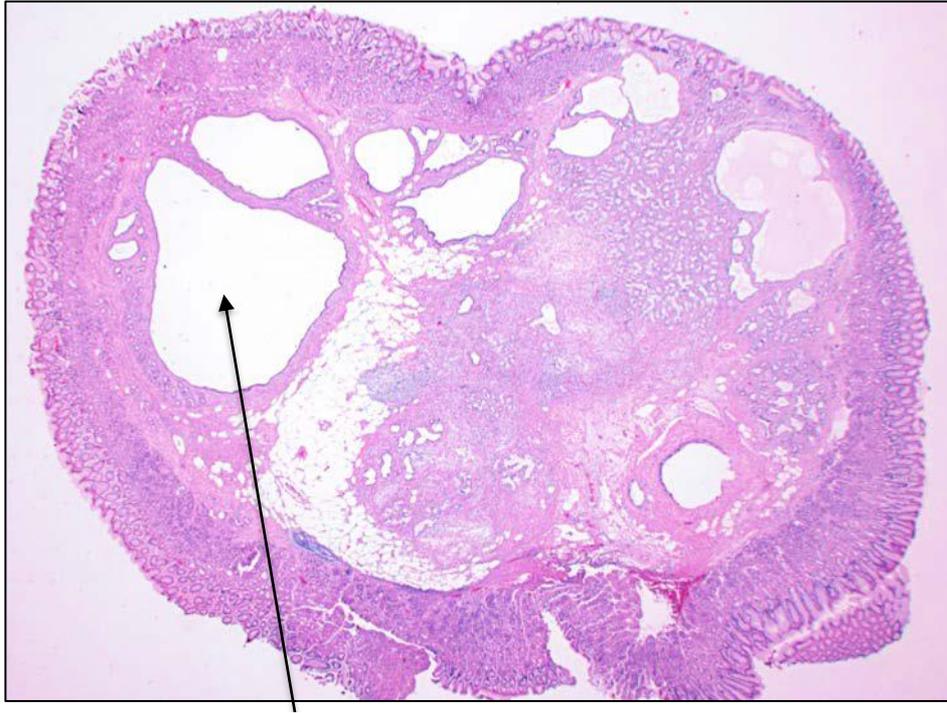
Thick muscle bands



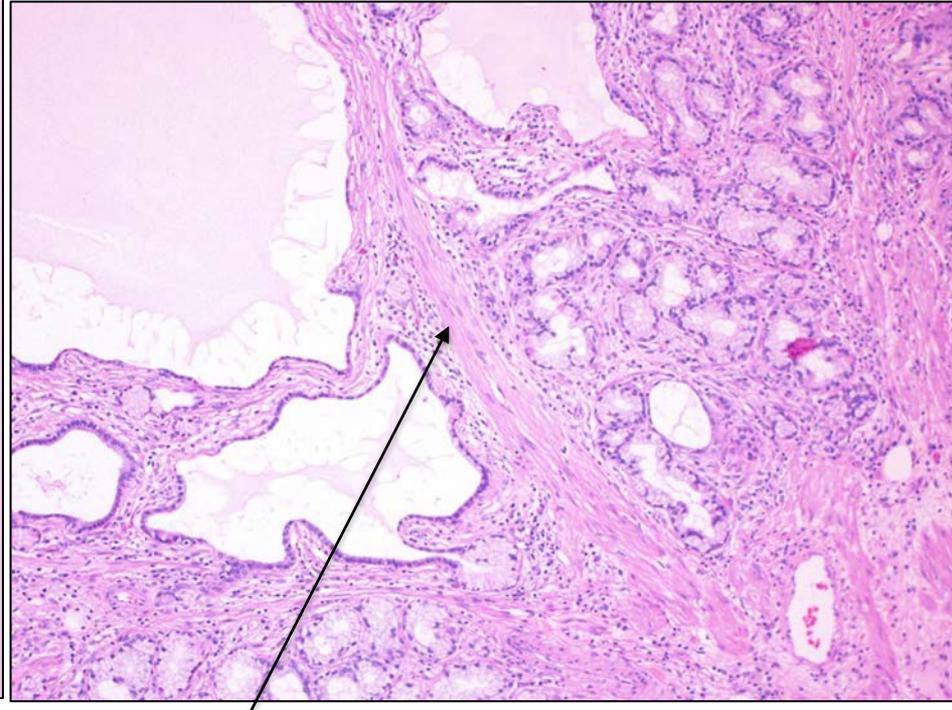
500um

Thickened wall vessels

Inverted Hyperplastic Polyp (hamartomatous inverted polyps) *Pathogenesis?*

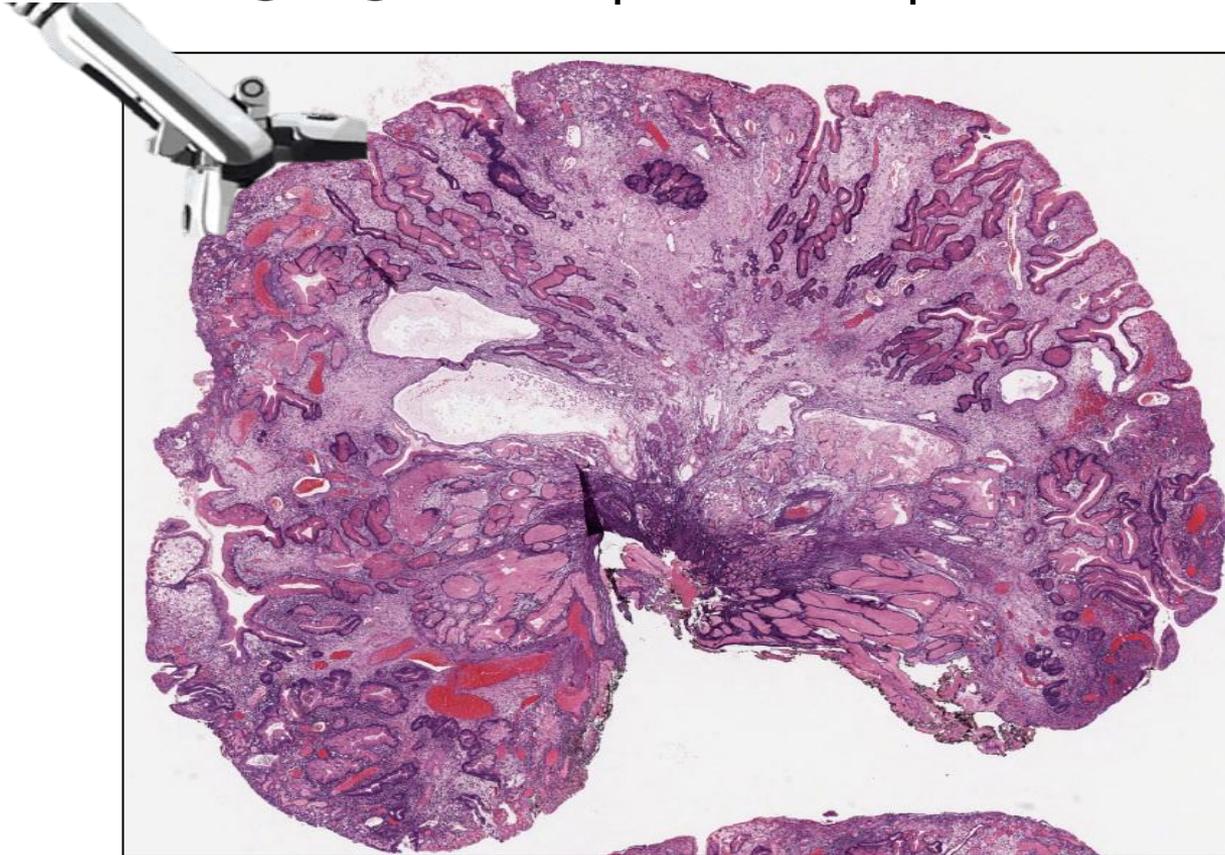


Submucosal glandular proliferation



Branching smooth muscles fascicles

Differential diagnosis of hyperplastic polyps is challenging on superficial pinch biopsies



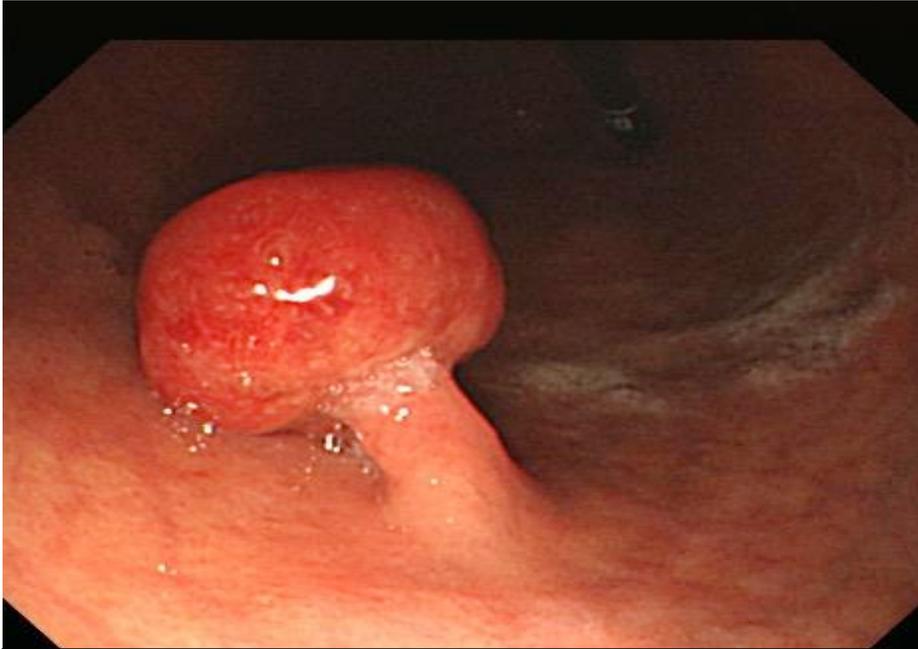
Hyperplastic Polyps – Diff. Dx

	Juvenile polyposis	Peutz-Jeghers Syndrome	Cowden's Disease	Cronkhite-Canada Syndrome
Inheritance	autosomal dominant	autosomal dominant	autosomic dominant	non-inherited (sporadic)
Gene	SMAD4 or BMPR1A	STK11/LKB1	PTEN	None
Gastric location	infrequent (15~25%)	25~50%	common	common
Location of polyp	antrum > body or fundus	random	random	random
Size of polyp	variable	usually small (<1cm)	usually small (<1cm)	variable
Lifetime risk of gastric Ca.	15~20%	30%	rare	about 10%

•Other differential dx:

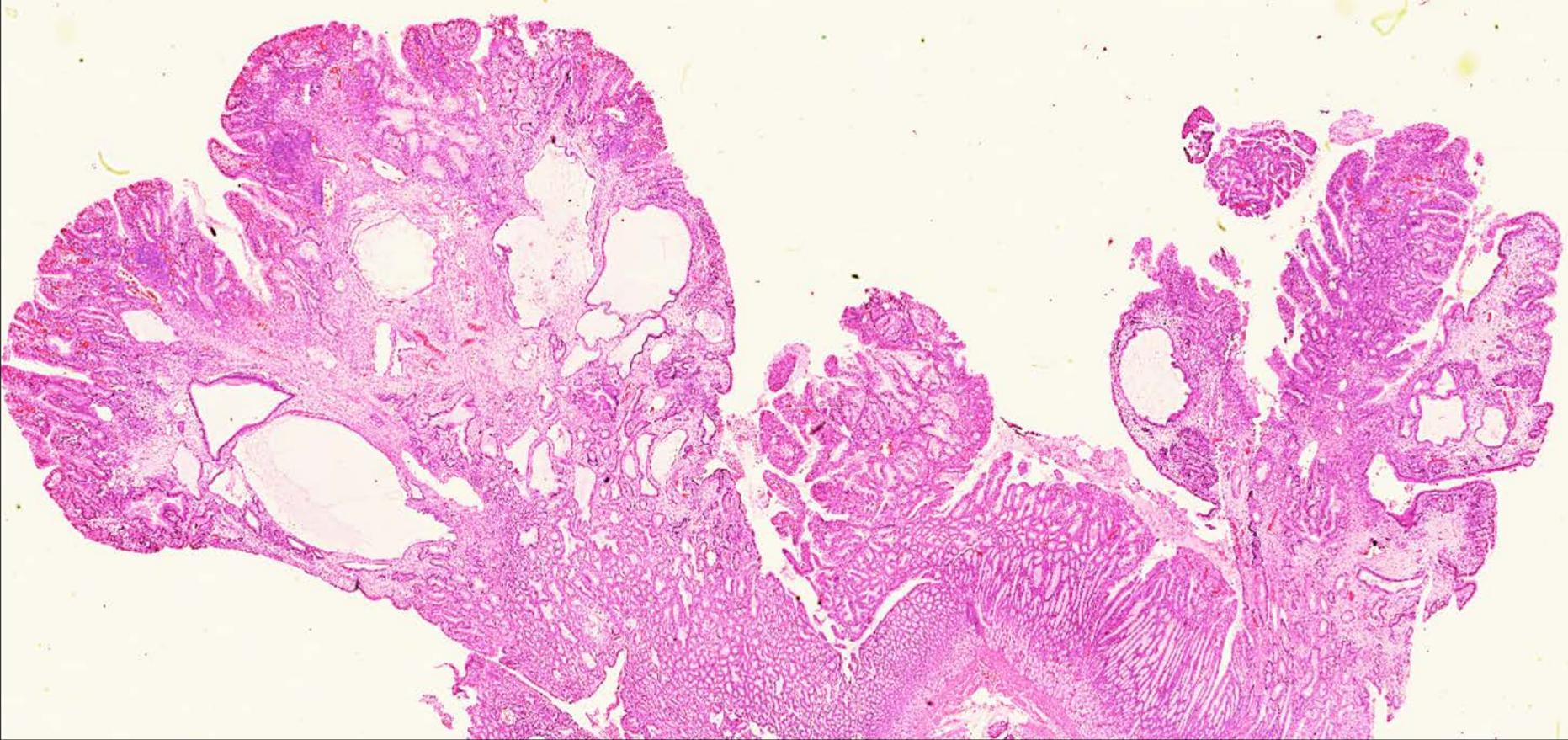
- Menetrier's disease
- Bile reflux/ post surgery gastritis
- Gastritis Polyposa Cystica

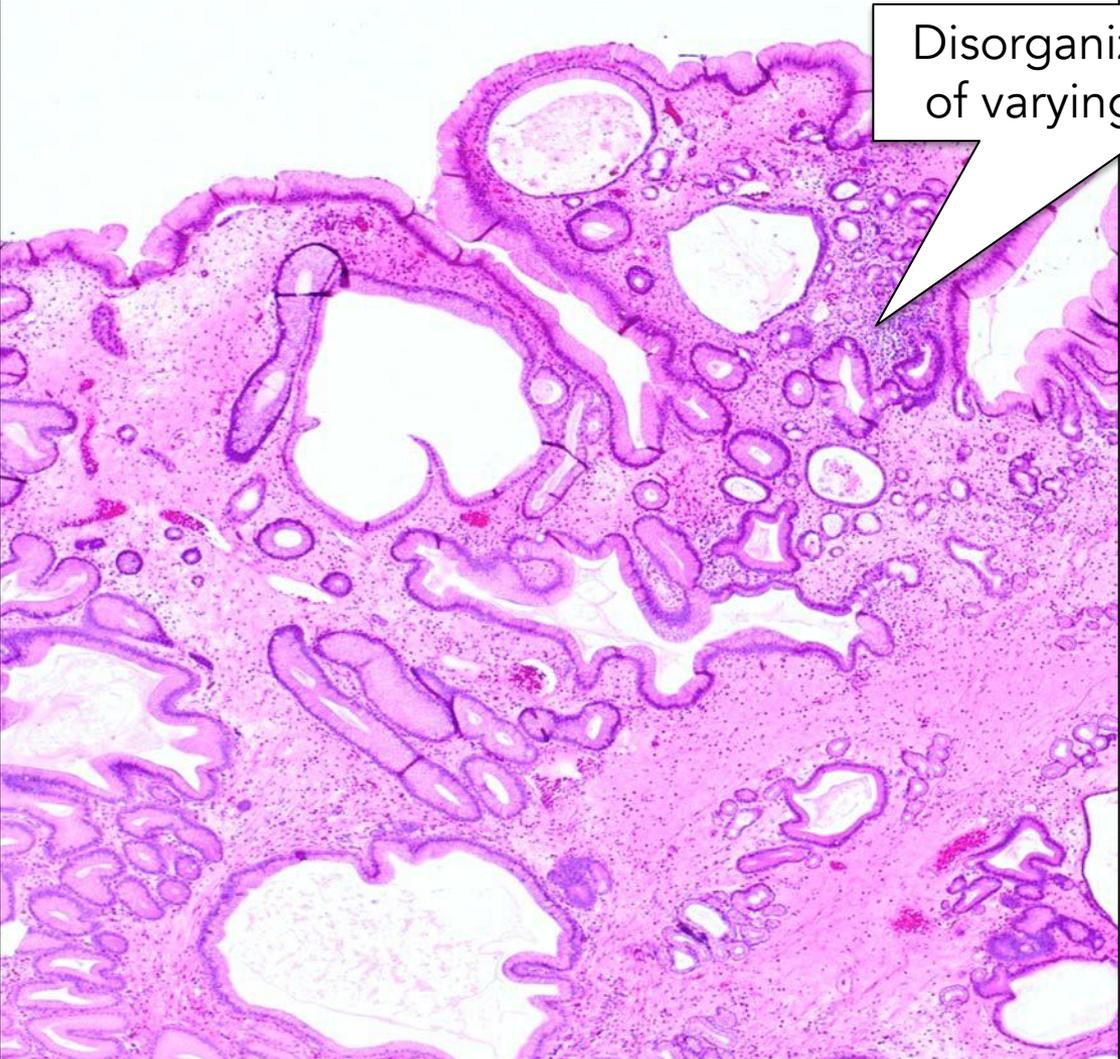
Juvenile Polyps [Polyposis]



- Median age of pts presenting w/ gastric polyps ~40 years (identified as early as 7)
- Rounded & sessile when small. Pedunculated w/lobular appearance as they enlarge
- 59% >1 gastric JPs polyp & can develop massive gastric polyposis without lower GIT involvement
- Dysplasia can be detected in up to 14% of polyps

Juvenile Polyp

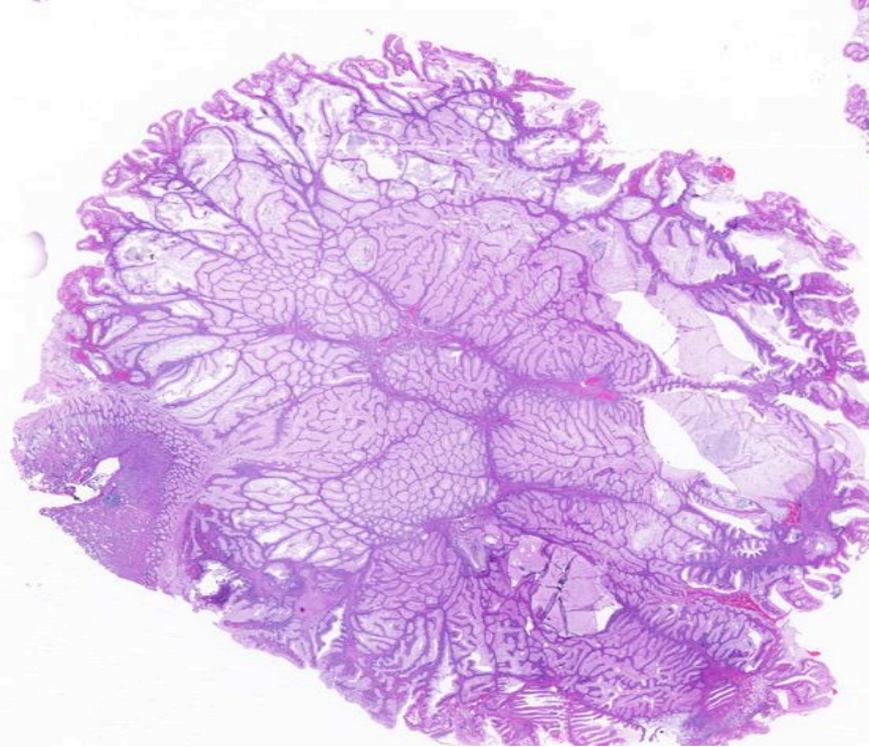




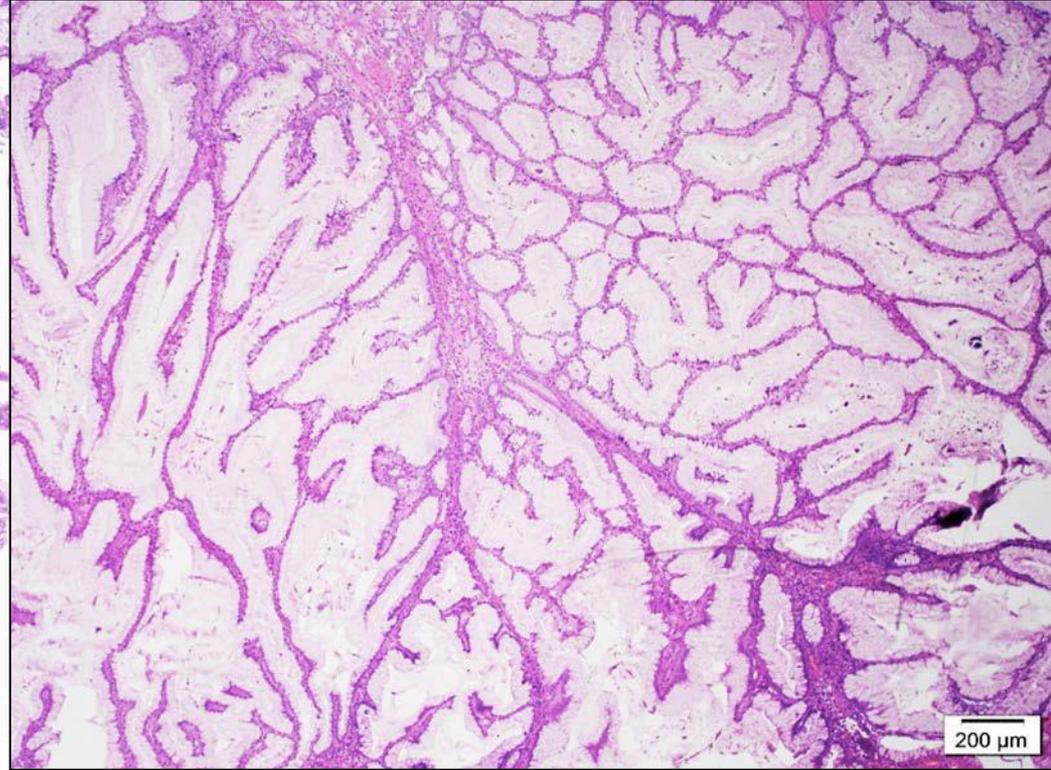
Disorganized pits / glands
of varying sizes & shapes

No smooth
muscle fibers

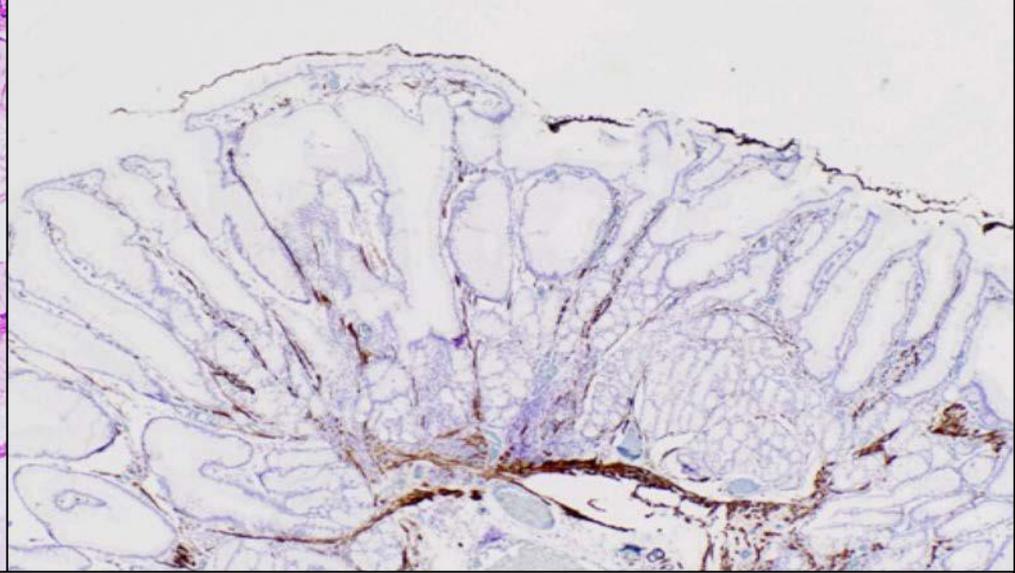
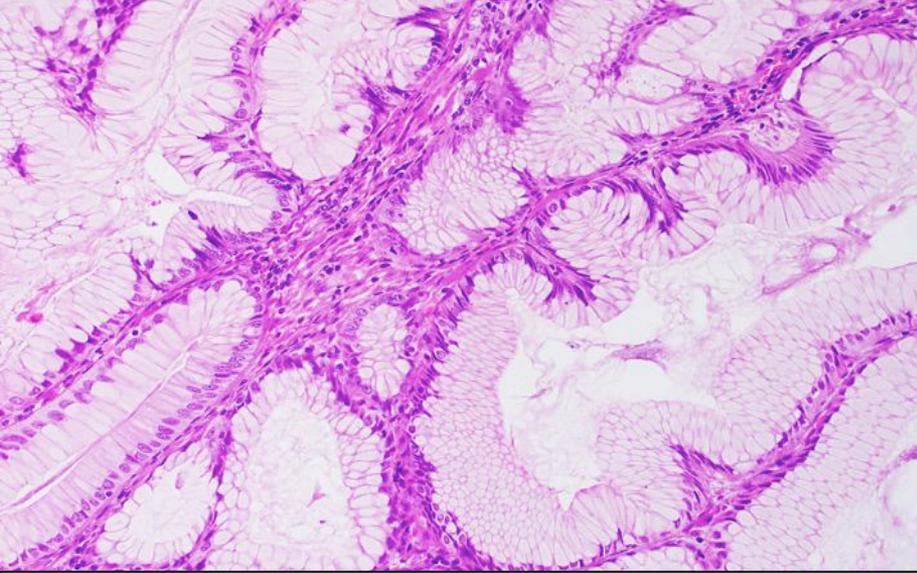
Peutz Jeghers Polyps



Median age of Dx:16 yrs
(rarely, PJS type polyp can arise spontaneously)



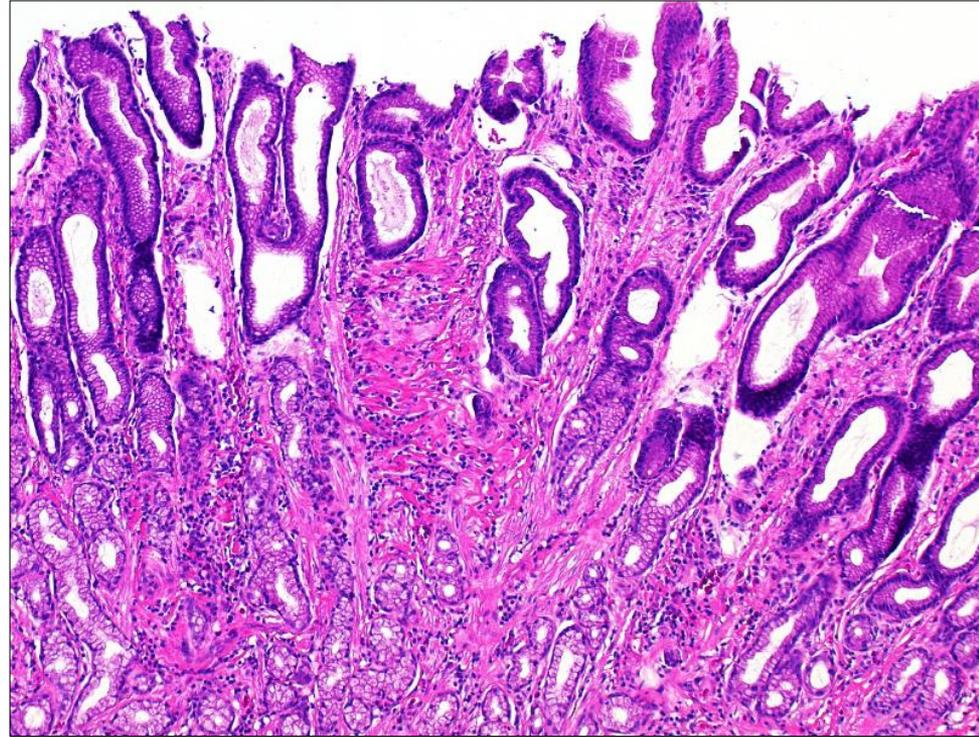
Pits & glands are grouped/ packeted;
Unremarkable epithelium



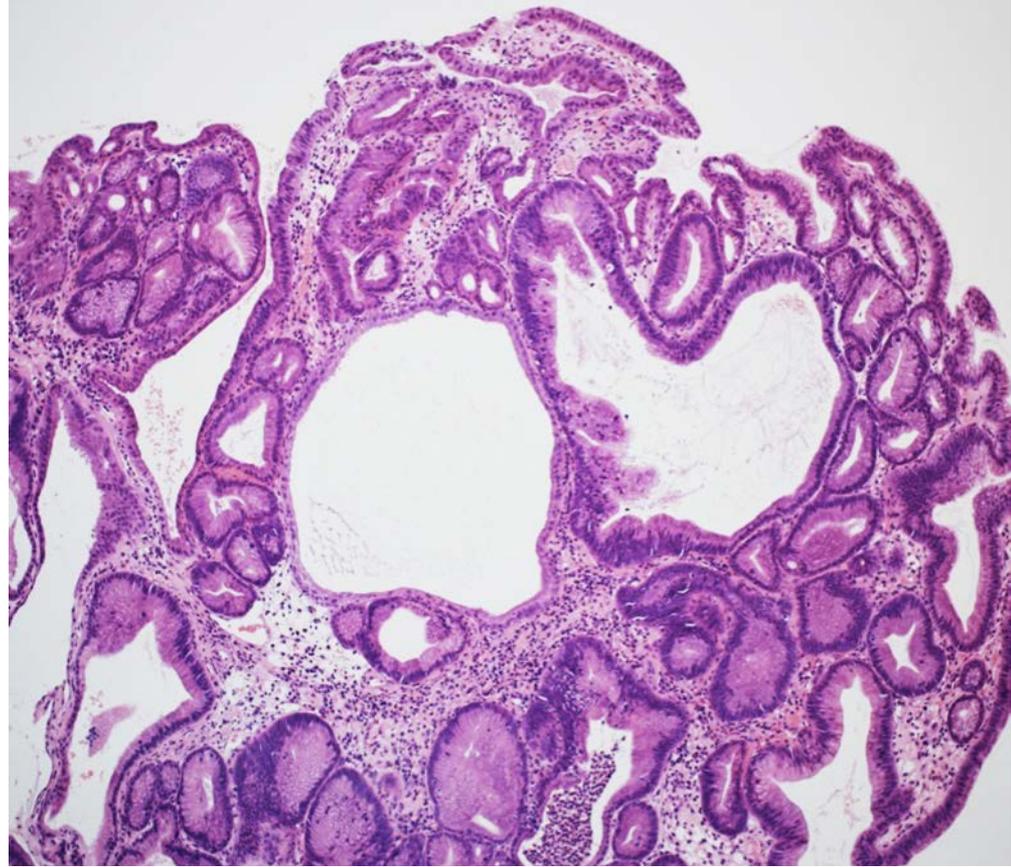
- Dysplasia is noted in 2-3% of PJ polyps.
- Increased risk of GI cancer through the hamartoma-adenoma-carcinoma sequence and *de novo* malignant change.
- Lifetime risk of gastric cancer estimated at 29%

Cowden's syndrome

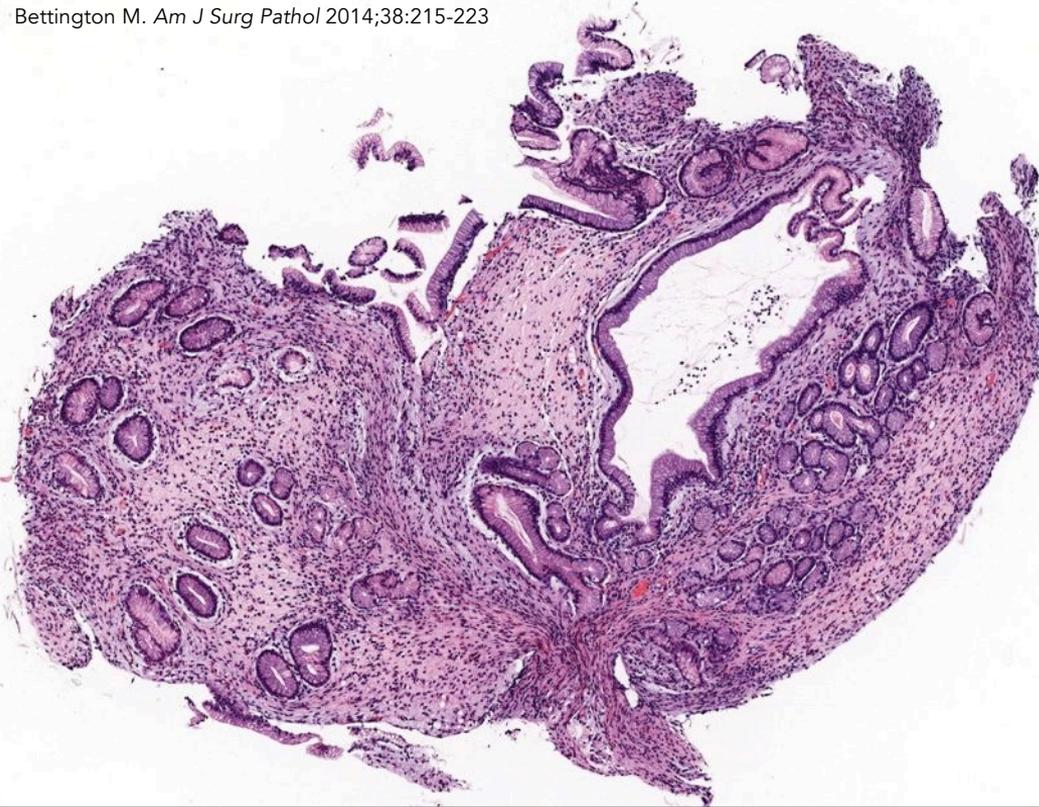
- GI polyps in 35–65% of cases.
- Series of 23 patients with upper endoscopy:
 - 56.5% w/ polyps resembling hyperplastic polyps
 - *Yet differed from typical hyperplastic polyps with an abundant fibrous stroma (hamartomatous)?*
 - FGPs (n=4), dysplasia (n=1).



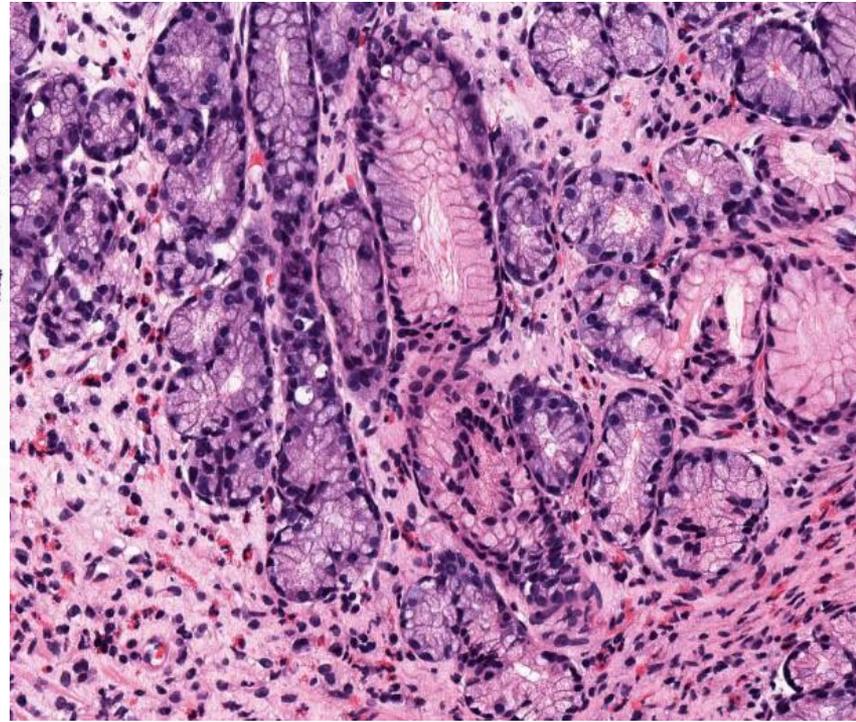
Cronkhite Canada Syndrome



Frequently delayed diagnosis / ectodermal frequently follow GIT by weeks to months



- Broad based polyp w/ marked stromal edema & unevenly spaced glands.



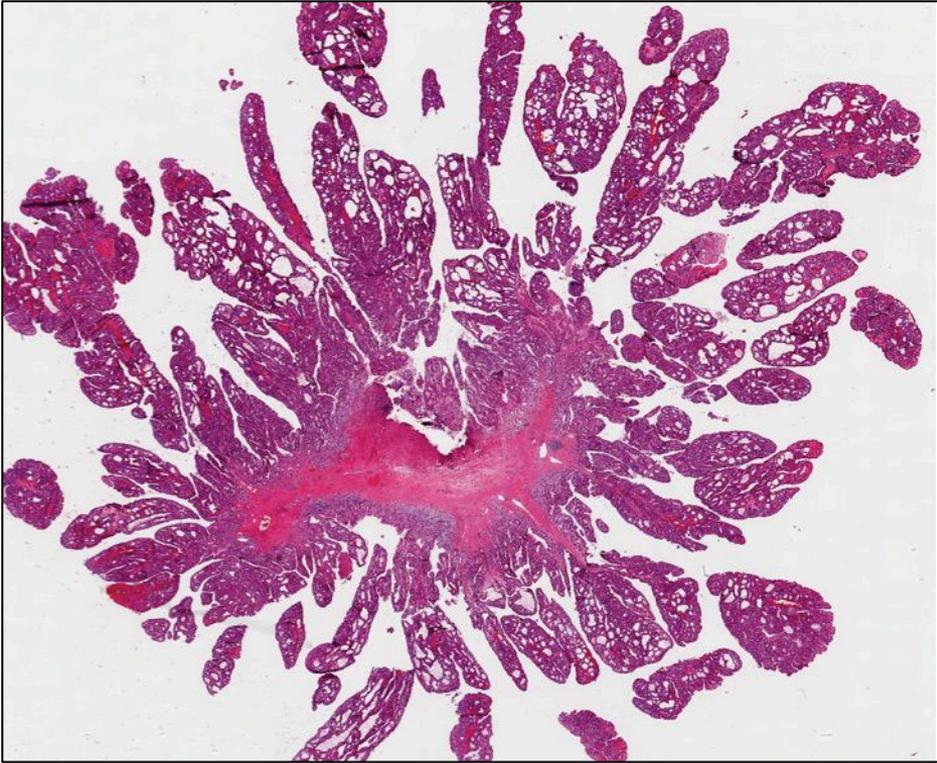
- Mixed inflammatory infiltrate w/ prominent eosinophilia

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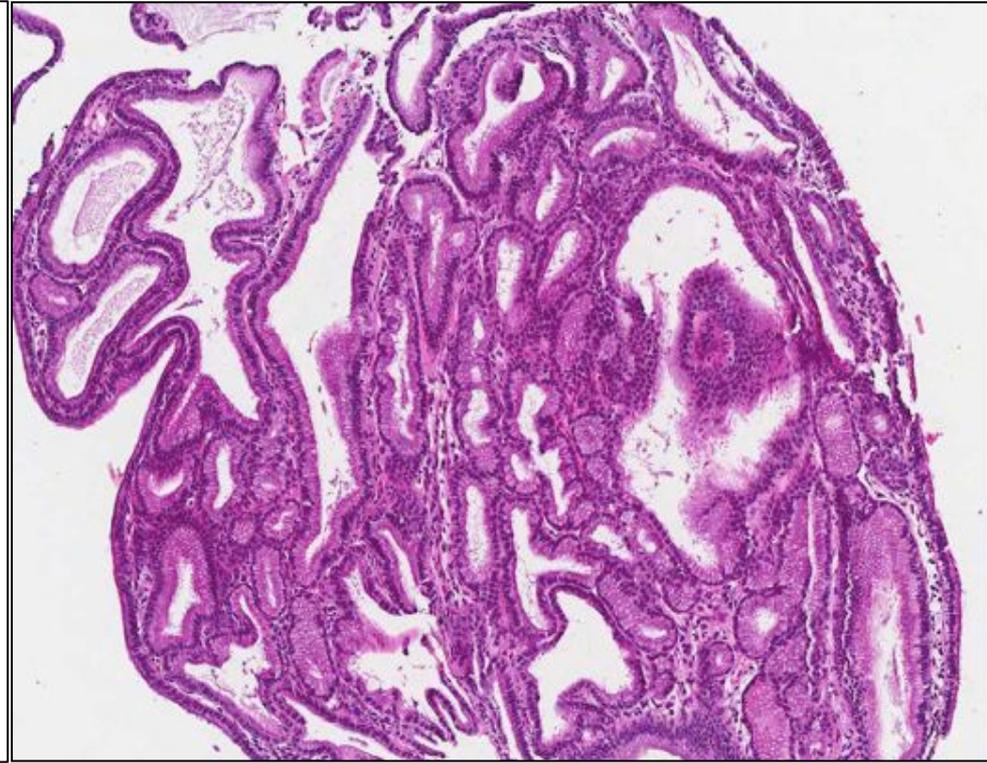
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Pyloric Gland Adenoma (<3% of all polyps)

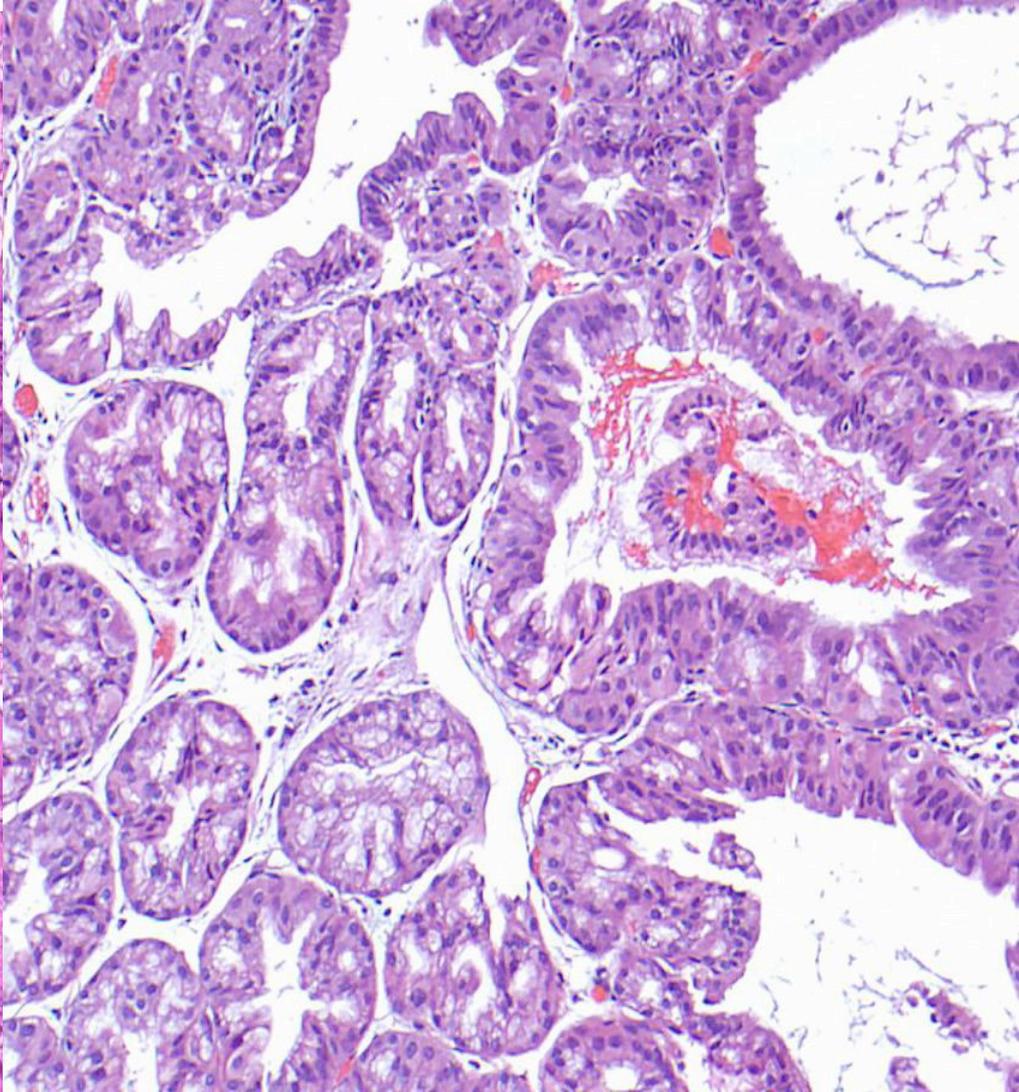
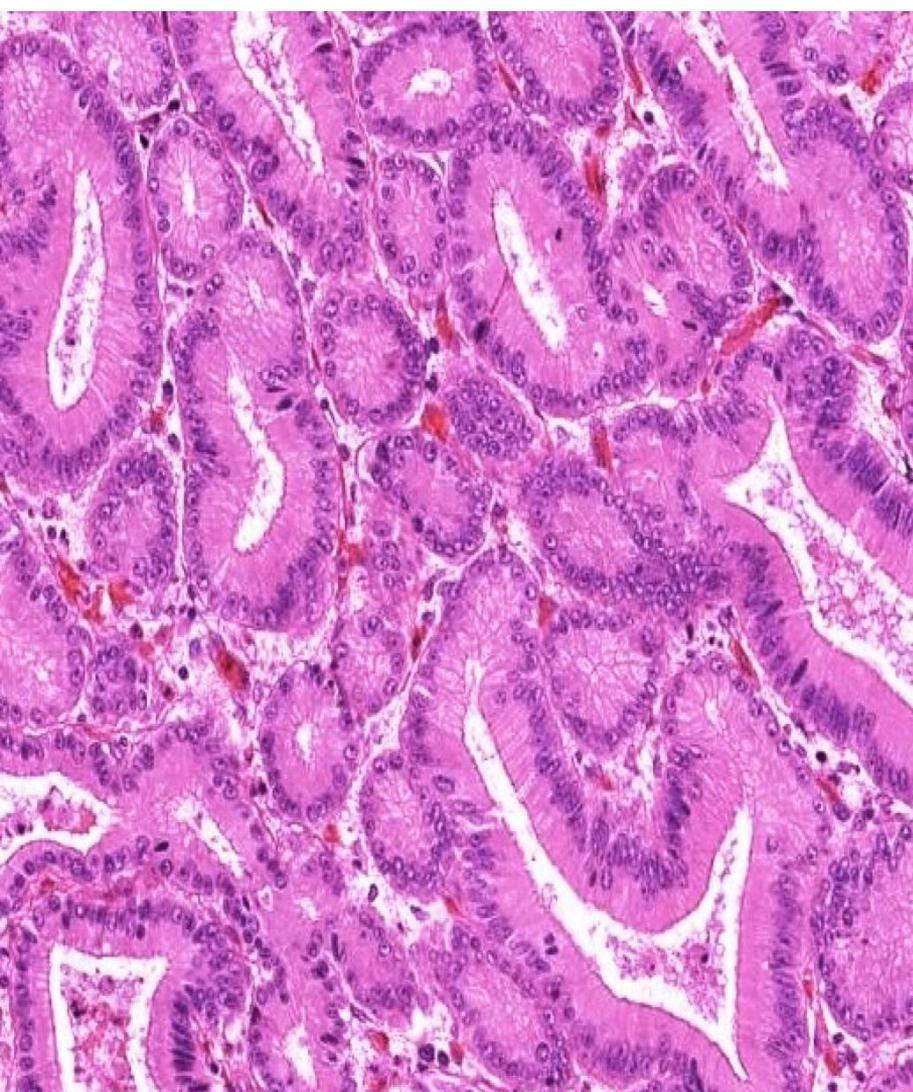
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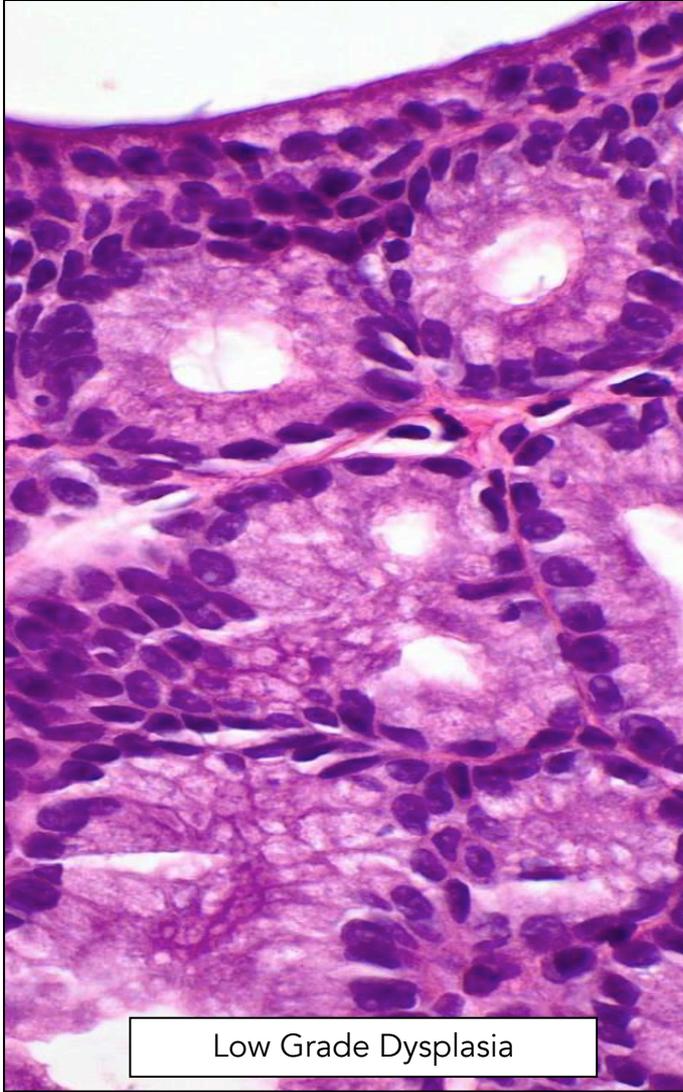


Tubulo-villous Pyloric gland adenoma

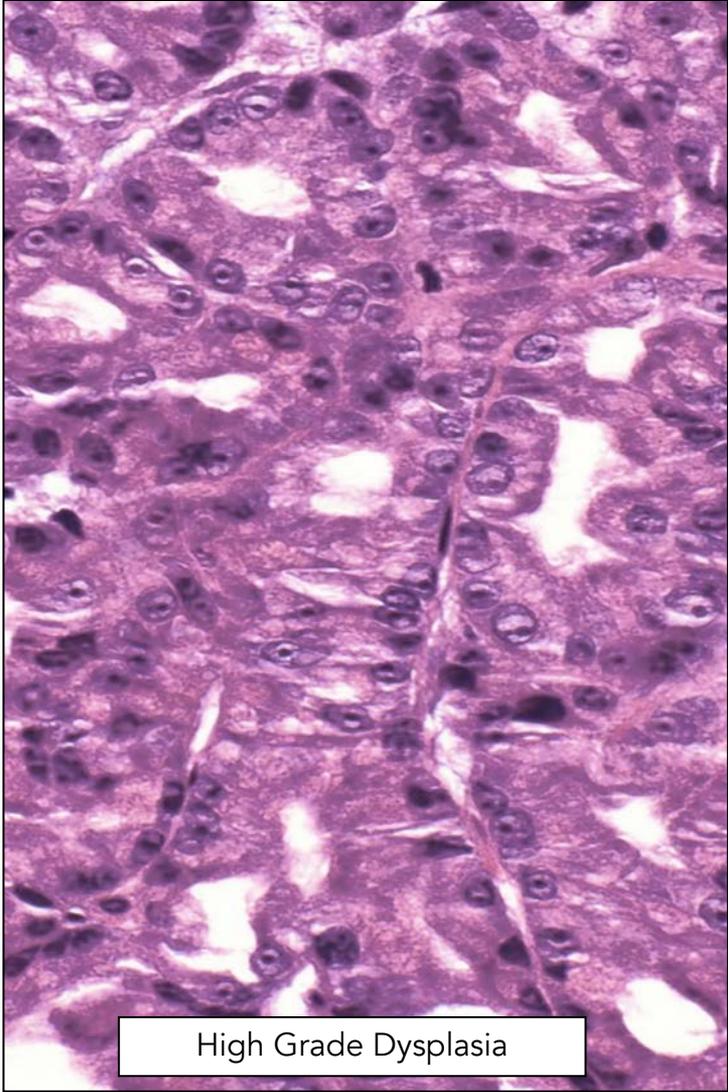


Tubular Pyloric gland adenoma



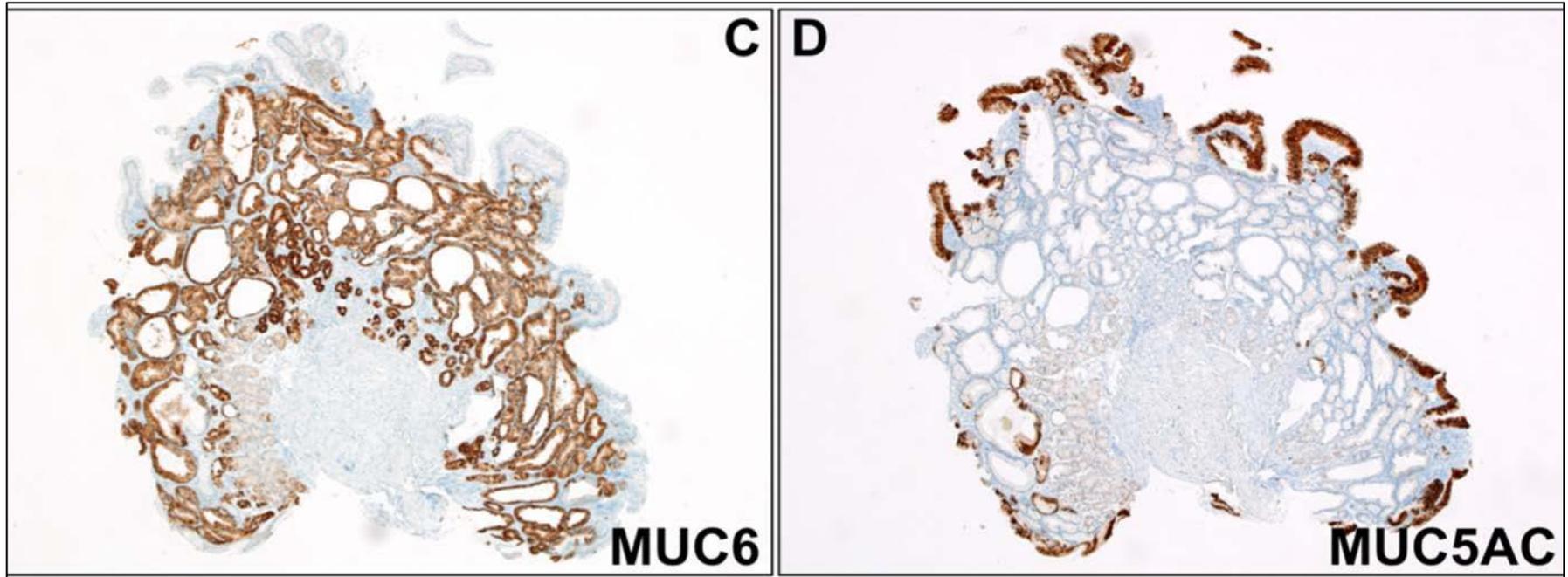


Low Grade Dysplasia



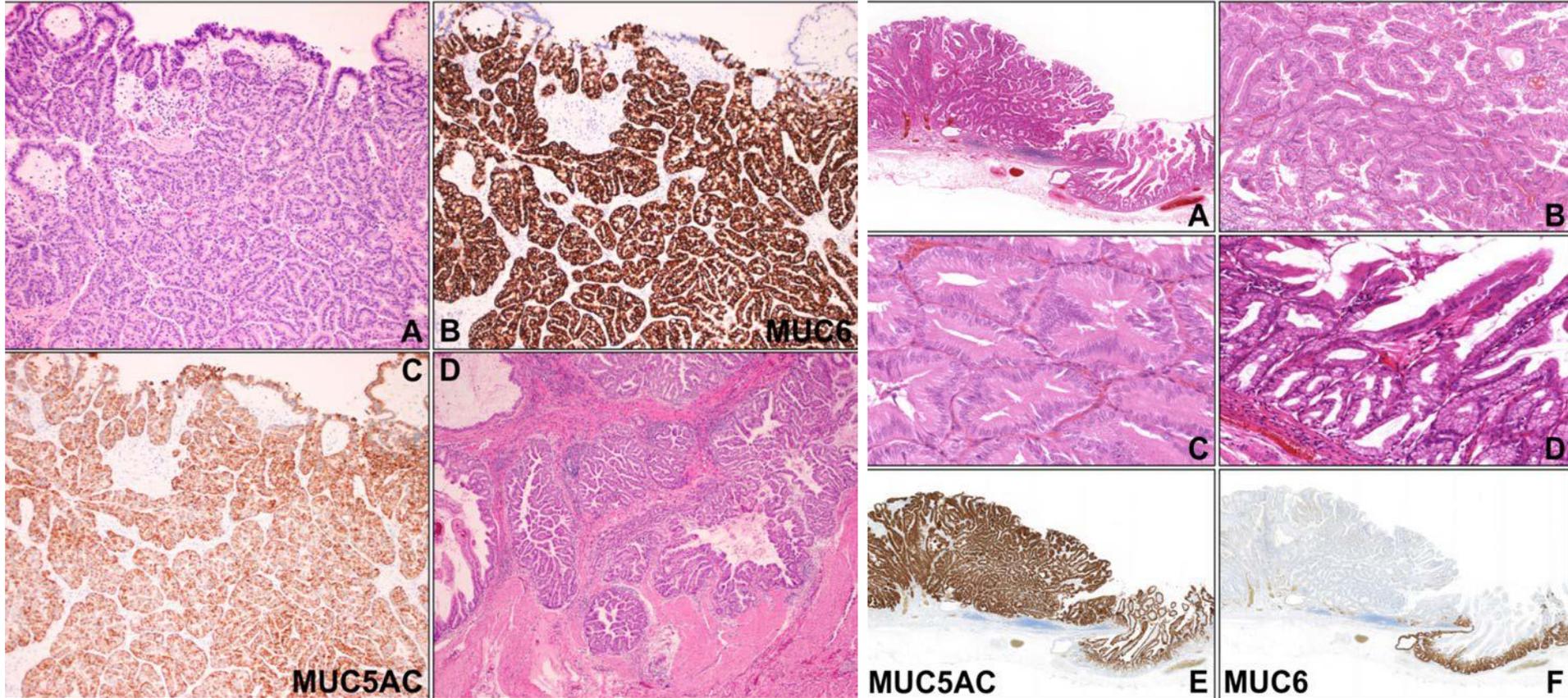
High Grade Dysplasia

Classic immunophenotype of pyloric gland adenoma



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

Pyloric gland adenomas w/ aberrant phenotype



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)
- Pyloric-phenotype (MUC6+)
- < 30% MUC5AC+

What is new about PGA

- Antrum (6%), pylorus (3%)
- 73% not associated with AIG
 - 36% in normal mucosa
- 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 1 year

Journal of Pathology

J Pathol 2013; 229: 579–587

Published online 4 February 2013 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1111/j.1365-2451.12153

ORIGINAL PAPER

48%

41%

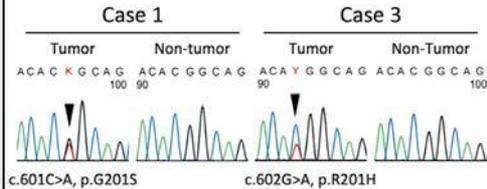
Frequent *GNAS* and *KRAS* mutations in pyloric gland adenoma of the stomach and duodenum

Akiko Matsubara,¹ Shigeki Sekine,^{2*} Ryoji Kushima,¹ Reiko Ogawa,² Hirokazu Taniguchi,¹ Hitoshi Tsuda¹ and Yae Kanai²

Original Article

Kushima R.
Pathology International 2013

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



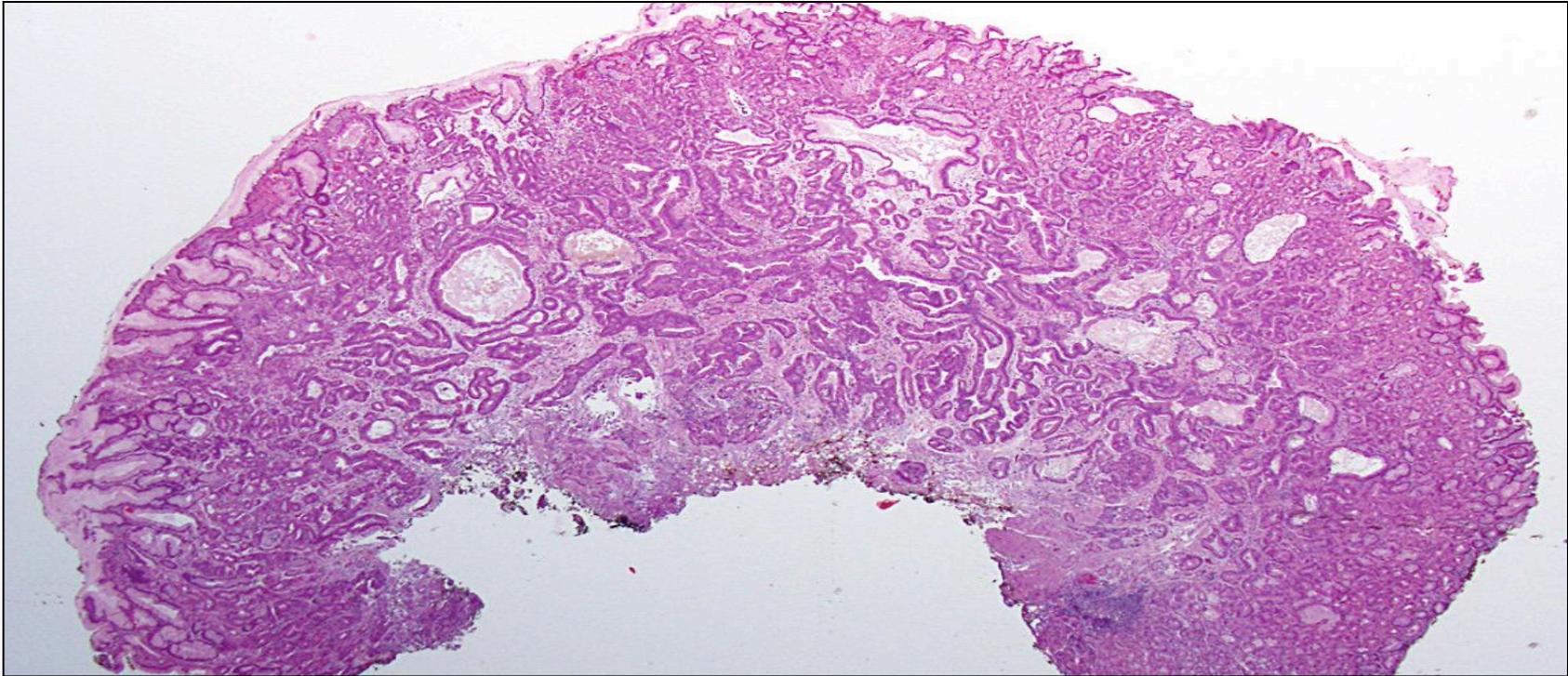
← *GNAS*
mutation

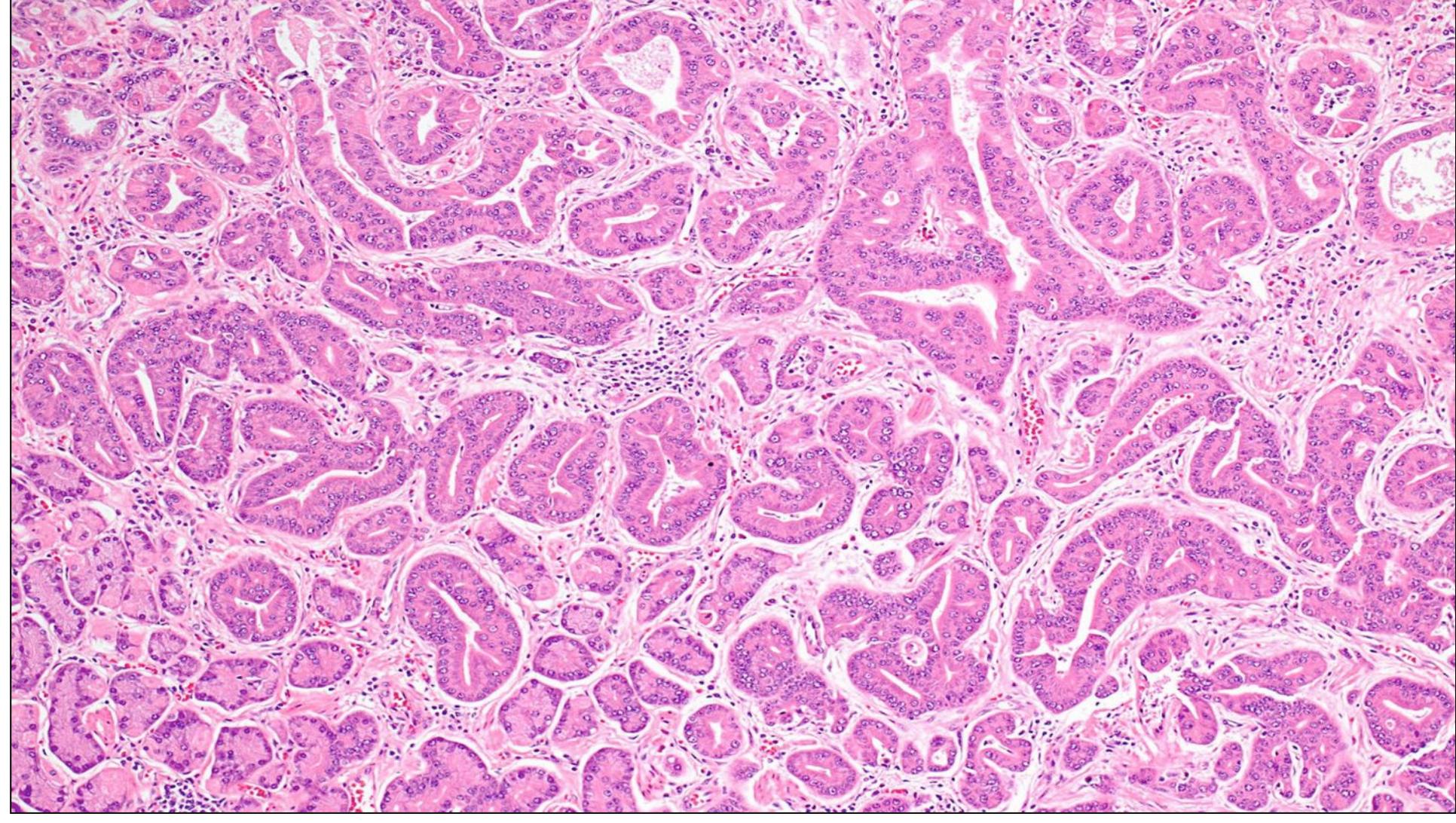
OUTLINE

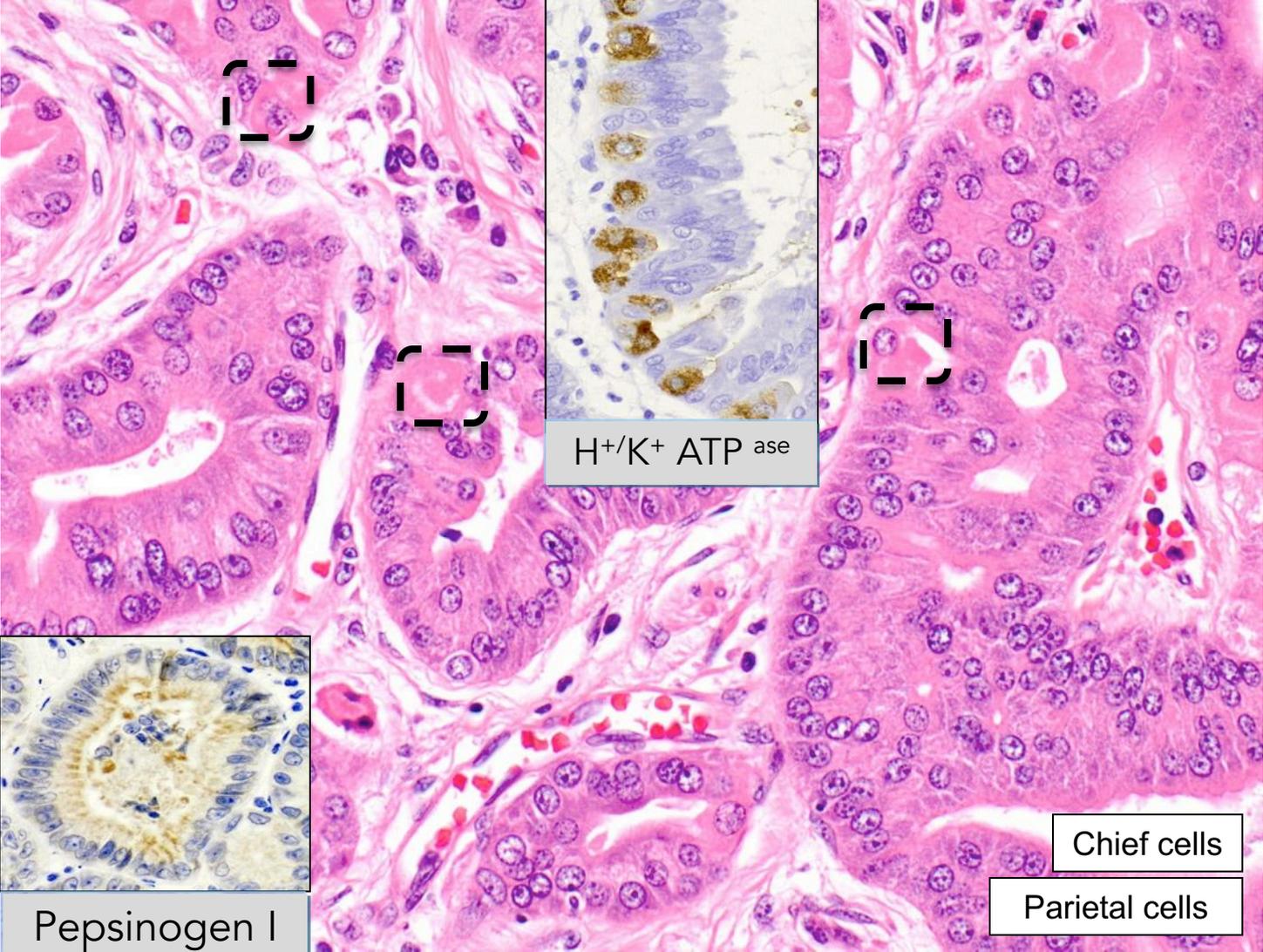
- **Fundic Gland Polyps**
 - Familial Adenomatous Polyposis
 - Gastric Adenocarcinoma & Proximal Polyposis [GAPPS]
- **Hyperplastic Polyps**
 - *Prolapse* and *Inverted Variant*
 - 'Syndromic' Differential Diagnosis On Pinch Biopsies
- **Pyloric Adenoma**
- **Gastric Adenocarcinoma Fundic Gland Type/ Oxyntic Adenoma**

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

Uyema H AJSP. 2010;609-619.







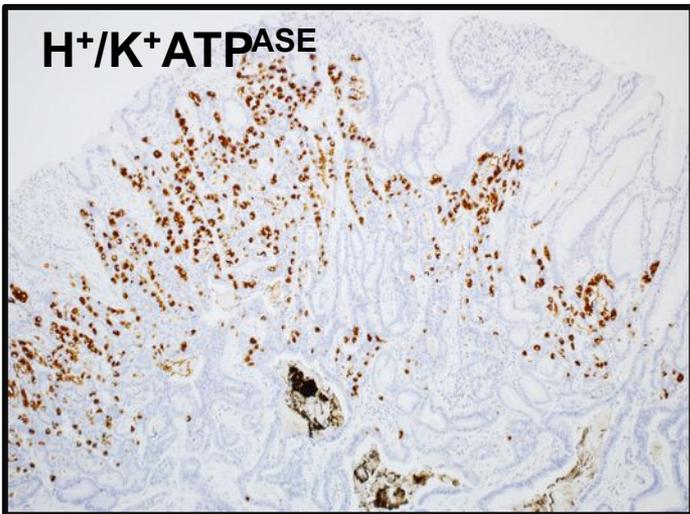
H⁺/K⁺ ATP_{ase}

Pepsinogen I

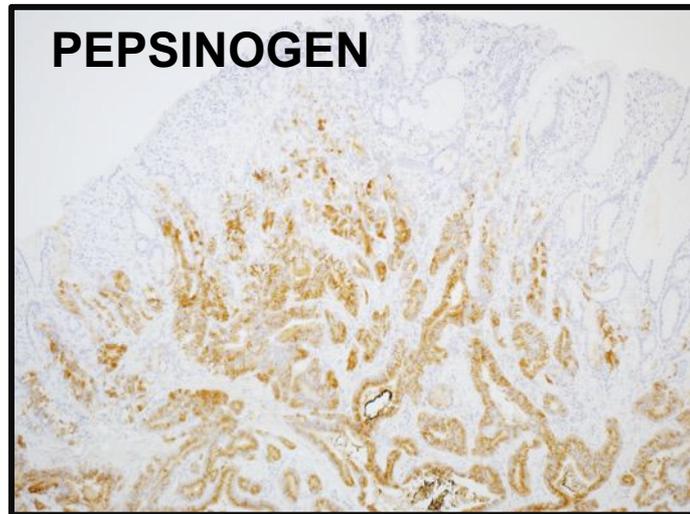
Chief cells

Parietal cells

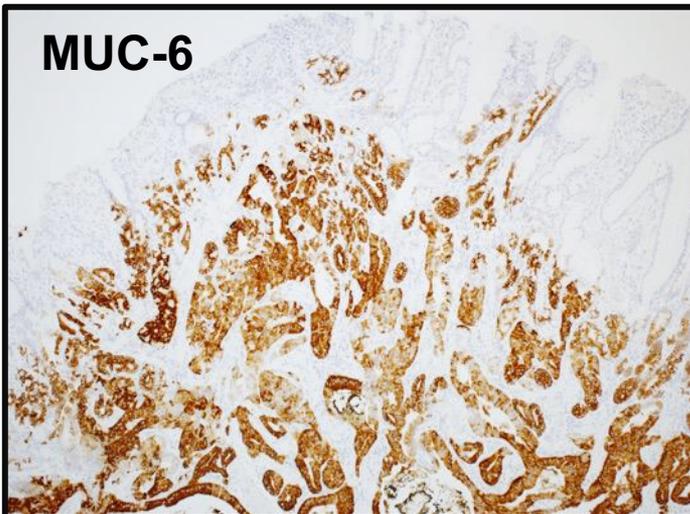
H⁺/K⁺ATPASE



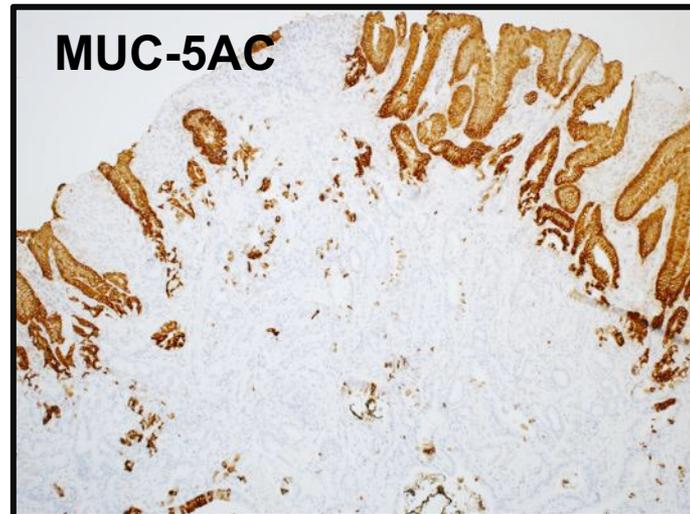
PEPSINOGEN

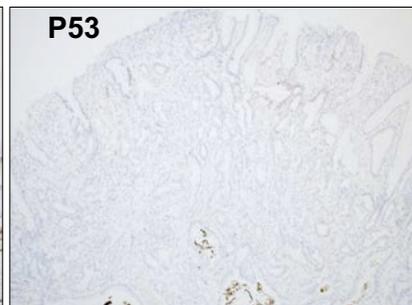
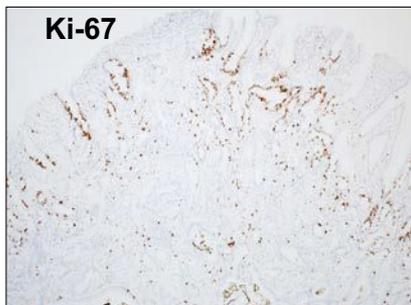
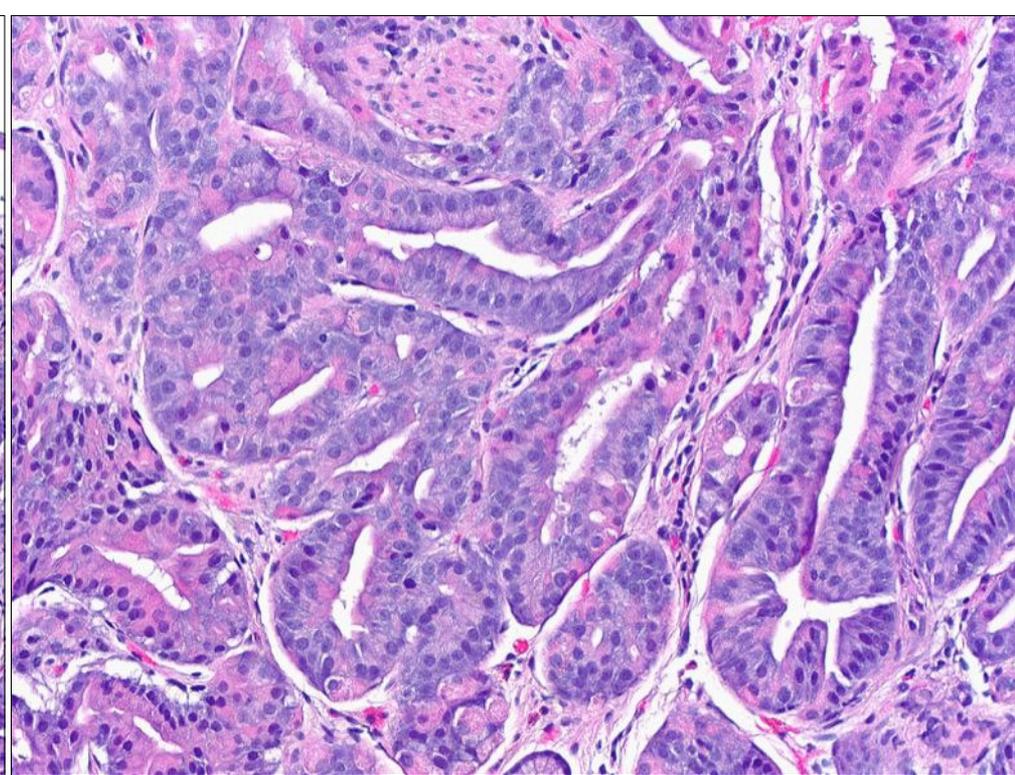
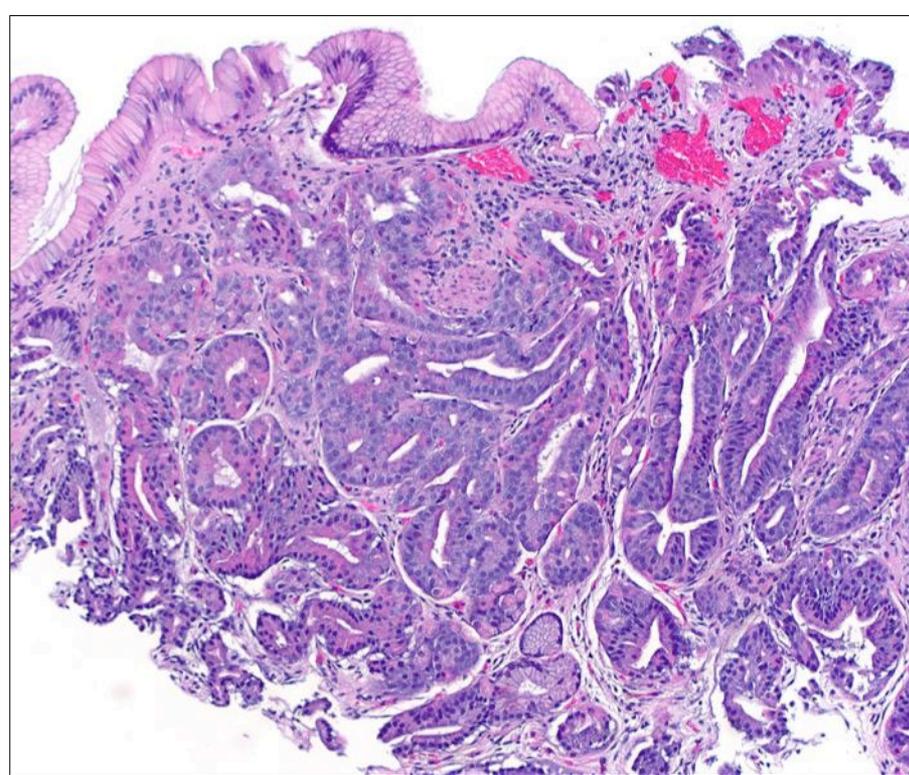


MUC-6



MUC-5AC





“Gastric *adenocarcinoma* with chief cell differentiation”?

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 Lauwers⁵ & Marian Priyanthi
Kumarasinghe^{1,6}

A morphologic continuum.....
Anastomosing glands (55%);
Mild atypia (58%)
Desmoplasia (16%)
Necrosis (8%)

Lympho-vascular invasion & nodal metastases. Ueo T. *Dig Endosc.* 2014;26(2):293-294

SUMMARY: NEW TRENDS IN GASTRIC POLYPS

- **Fundic Gland Polyps**
 - Familial Adenomatous Polyposis
 - *Frequently dysplastic but low rate of progression*
 - Gastric Adenocarcinoma & Proximal Polyposis [GAPPS]
 - *'Atypical' lesions (Hyperproliferative Aberrant Pits)*
- **Hyperplastic Polyps**
 - New Variants
 - *Prolapsed and inverted of limited clinical significance*
 - 'Syndromic' Differential Diagnosis on Pinch Biopsies
 - *Better characterization of upper GIT lesions*
- **Pyloric Adenoma**
 - *Expanding clinical associations; spectrum from LGD to HGD and natural history*
- **Gastric Adenocarcinoma Fundic Gland Type/ Oxyntic Adenoma**
 - *Spectrum of lesions; predominantly 'low grade'; GNAS mutation shared w/ PGA*