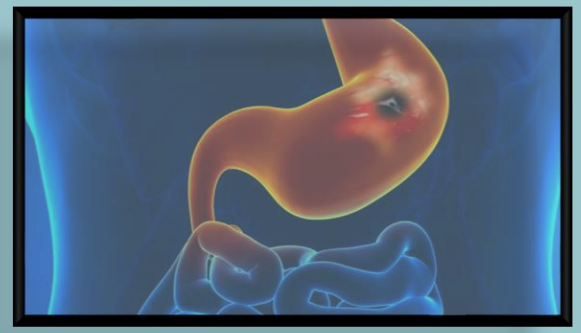
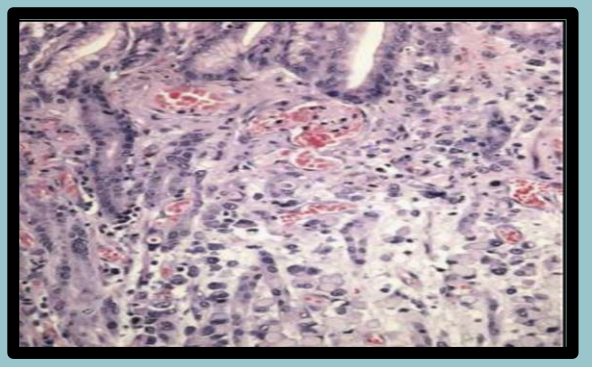
PREMALIGNANT GASTRIC LESIONS





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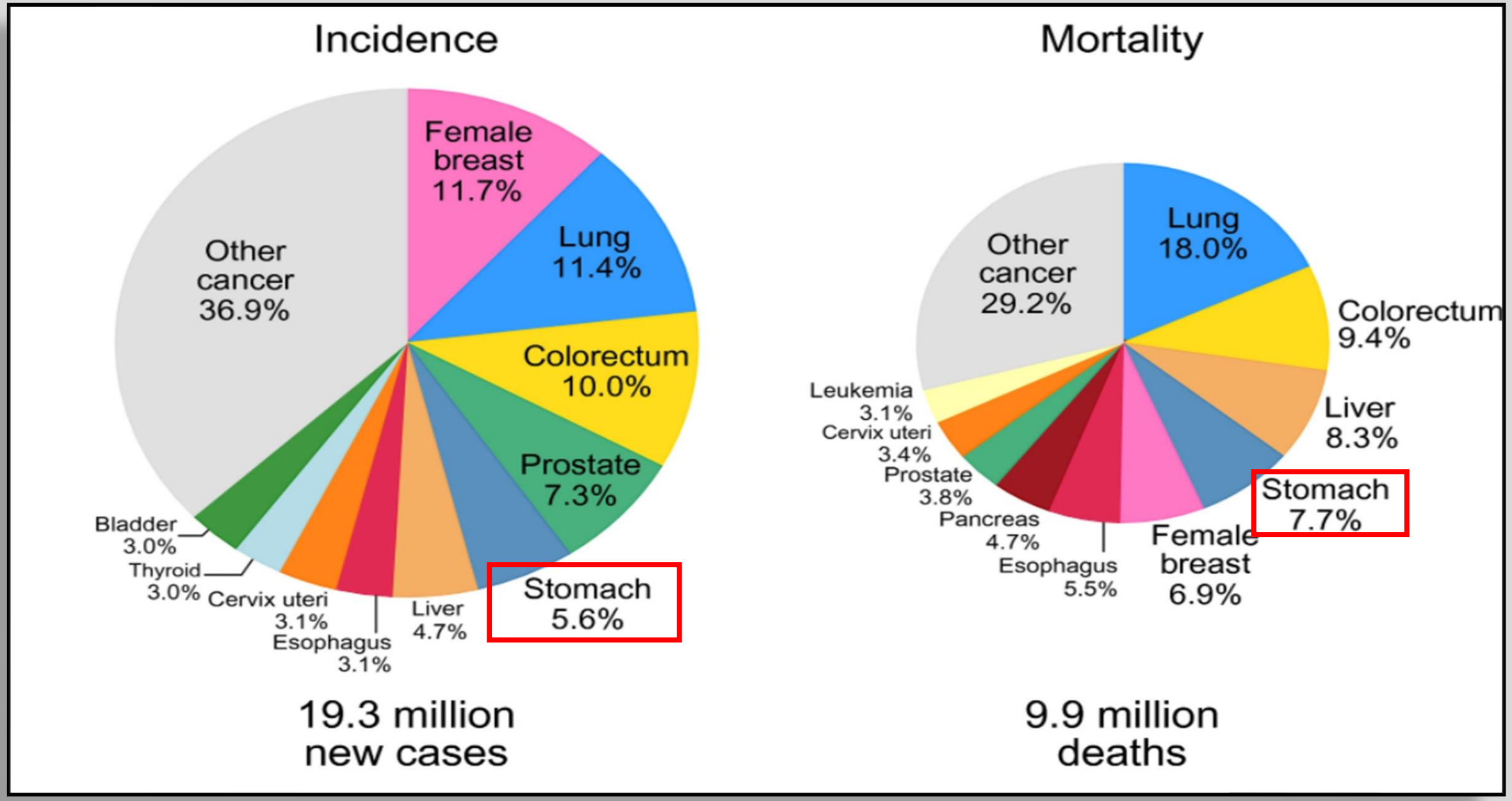
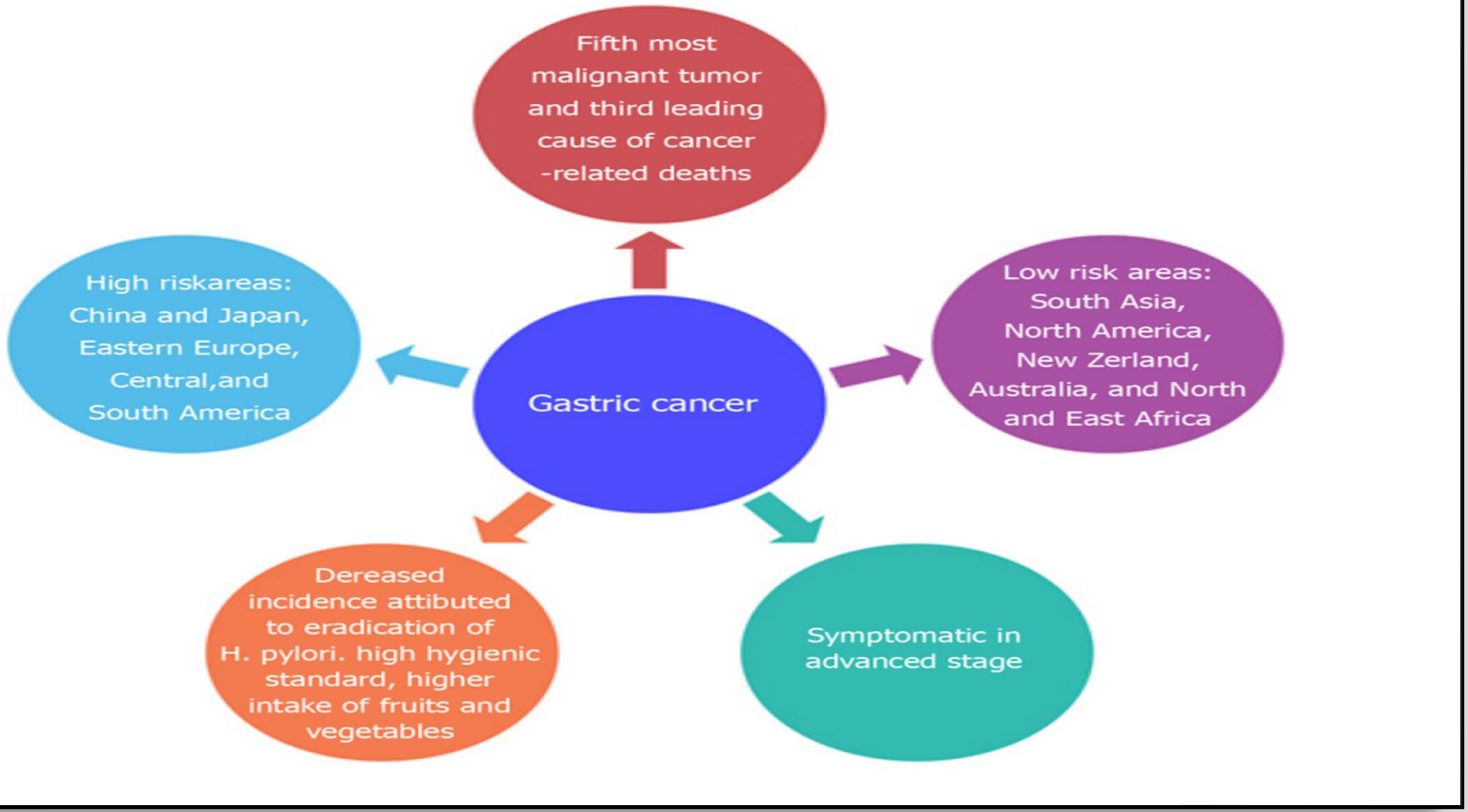


CA CANCER J CLIN 2021;71:209–249



Bonelli P et al. Precision medicine in GC

EPIDEMIOLOGY

- Sx - advanced stage
- 5yr survival rate – **Japan (90%) early diagnosis** and **tumor resection**.
- 5yr survival **25%** globally
- **High incidence**:
  - China, Japan and S.Korea,
  - E.Europe, Central and S.America
- **Low incidence**:
  - Aus and NZ
  - N.America, W.Europe
  - **Most parts of Africa**
- M:F (2:1)

HISTOLOGICAL CLASSIFICATION

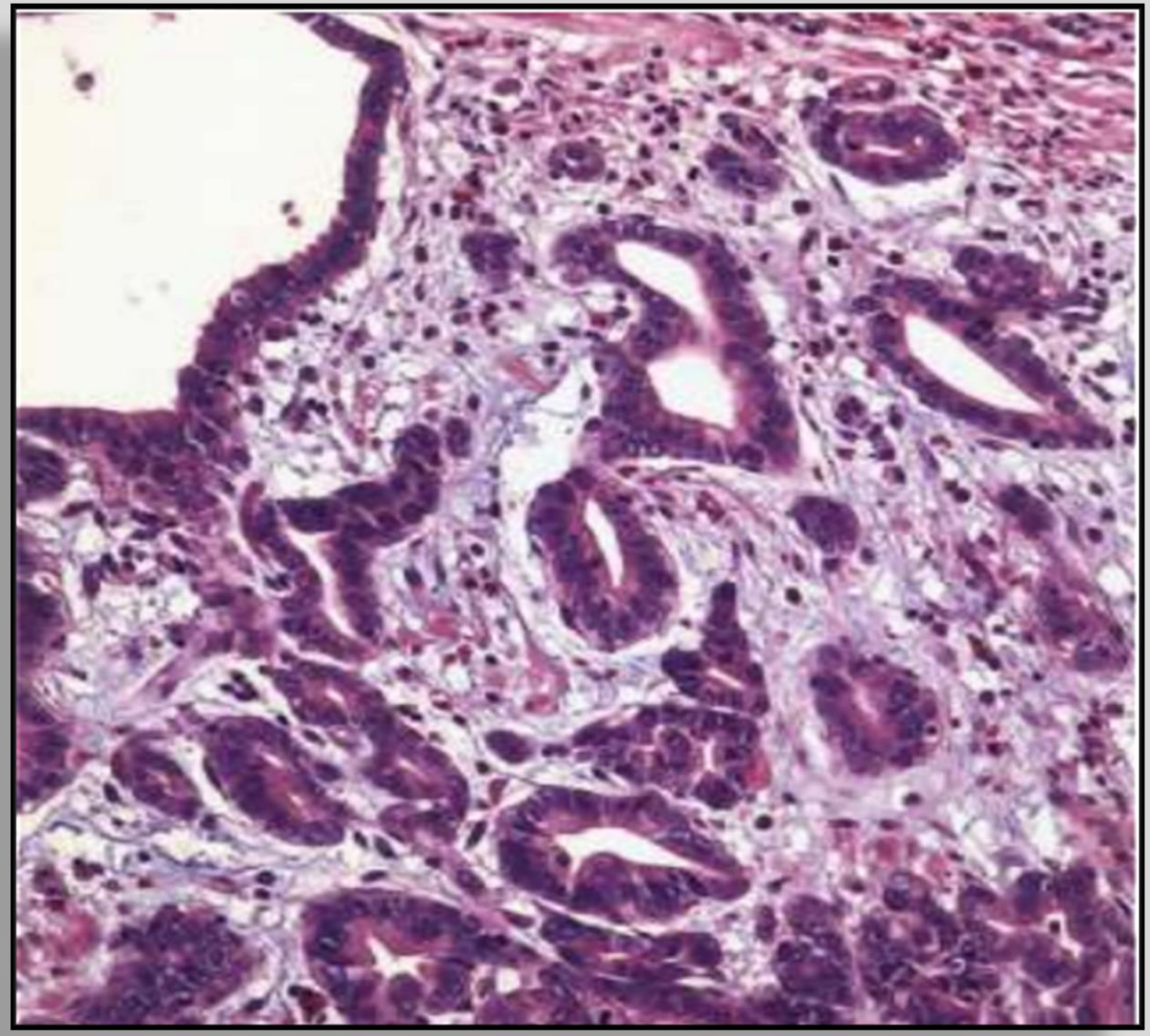
- Majority of GC – **adenocarcinomas**

- **LAUREN CLASSIFICATION - 3 distinct subtypes (INCLUDING MIXED)**

1. **INTESTINAL Type**
   - **Elderly - environmental/dietary factors**
   - **DISTAL STOMACH – "premalignant lesion"**

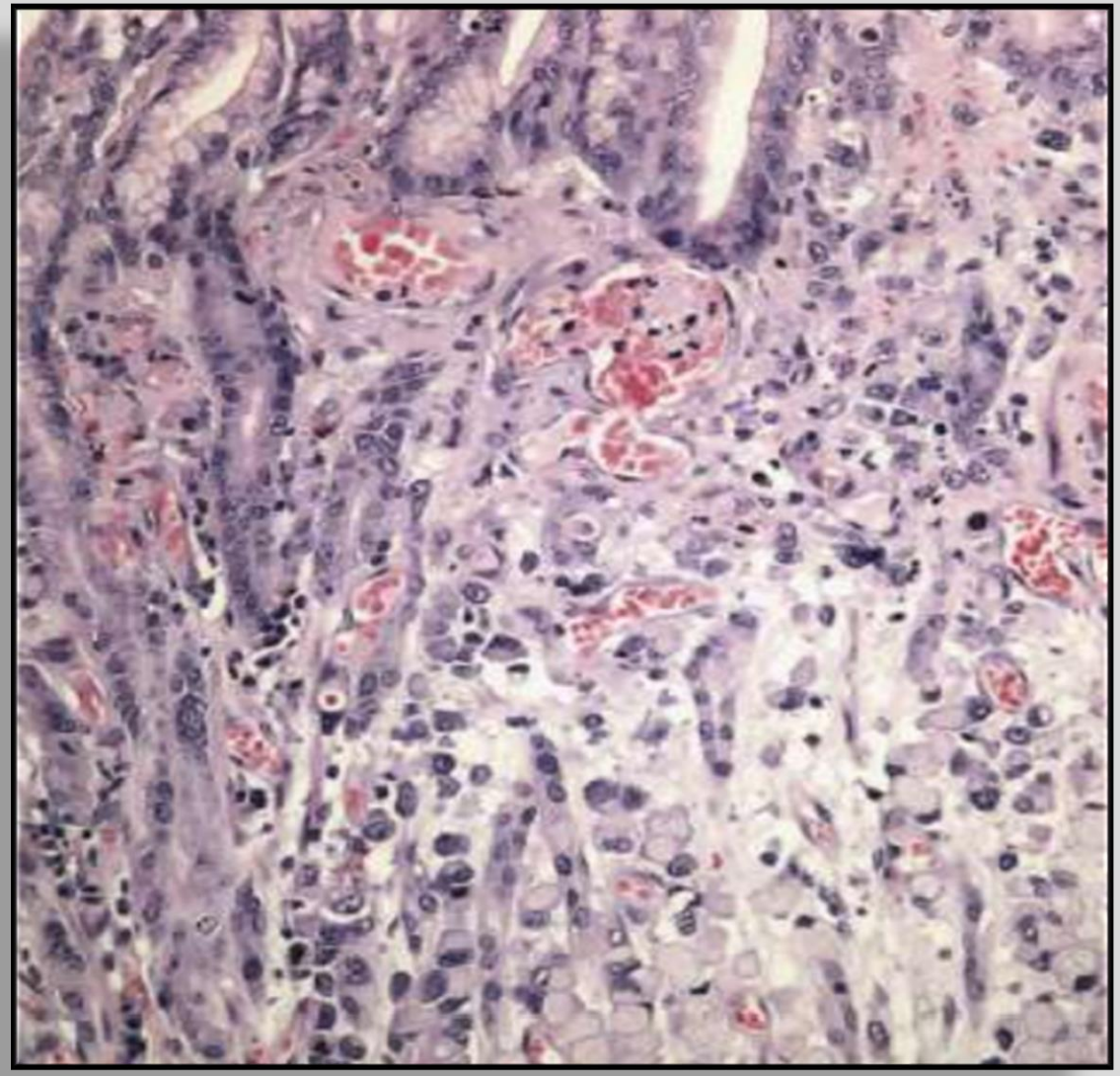
2. **DIFFUSE Type** - lacks glandular structure
   - **Signet-ring cells**, special mucin-filled cells
   - **YOUNGER PTS** AND **WORSE PROGNOSIS**
   - Diffuse involvement – poorly distensible **"linnitis plastica"**

INTESTINAL TYPE



gland-like tubular structures

DIFFUSE TYPE



lacks glandular structure

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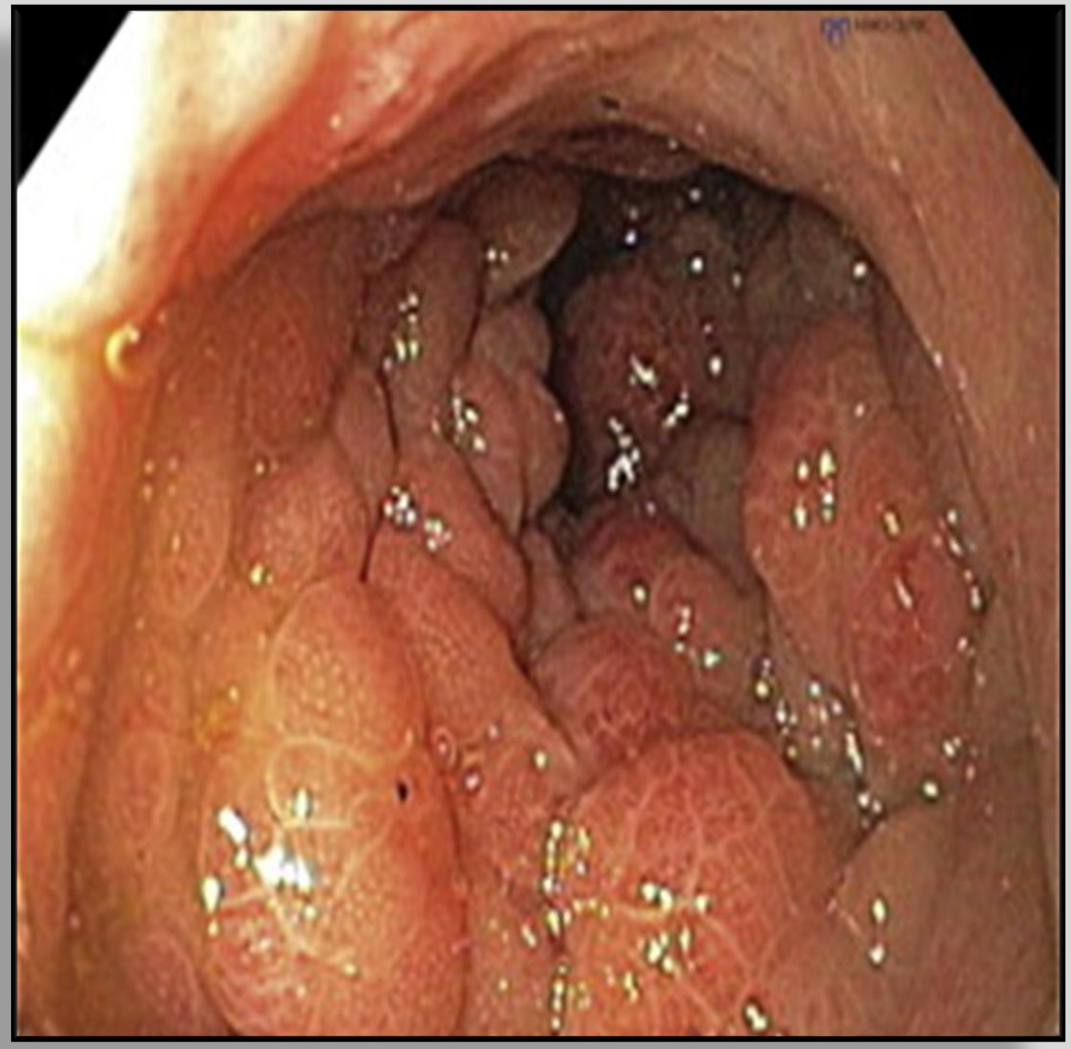
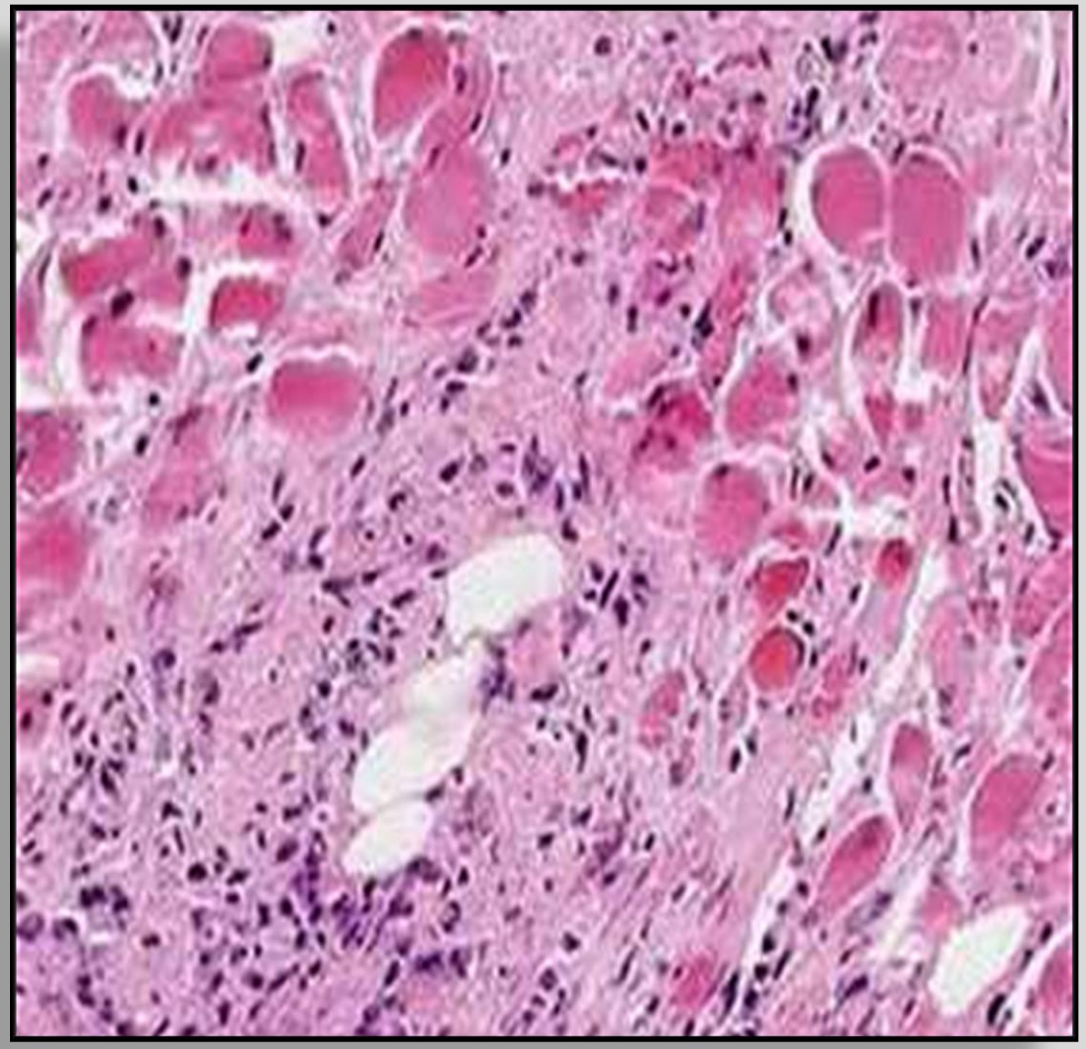
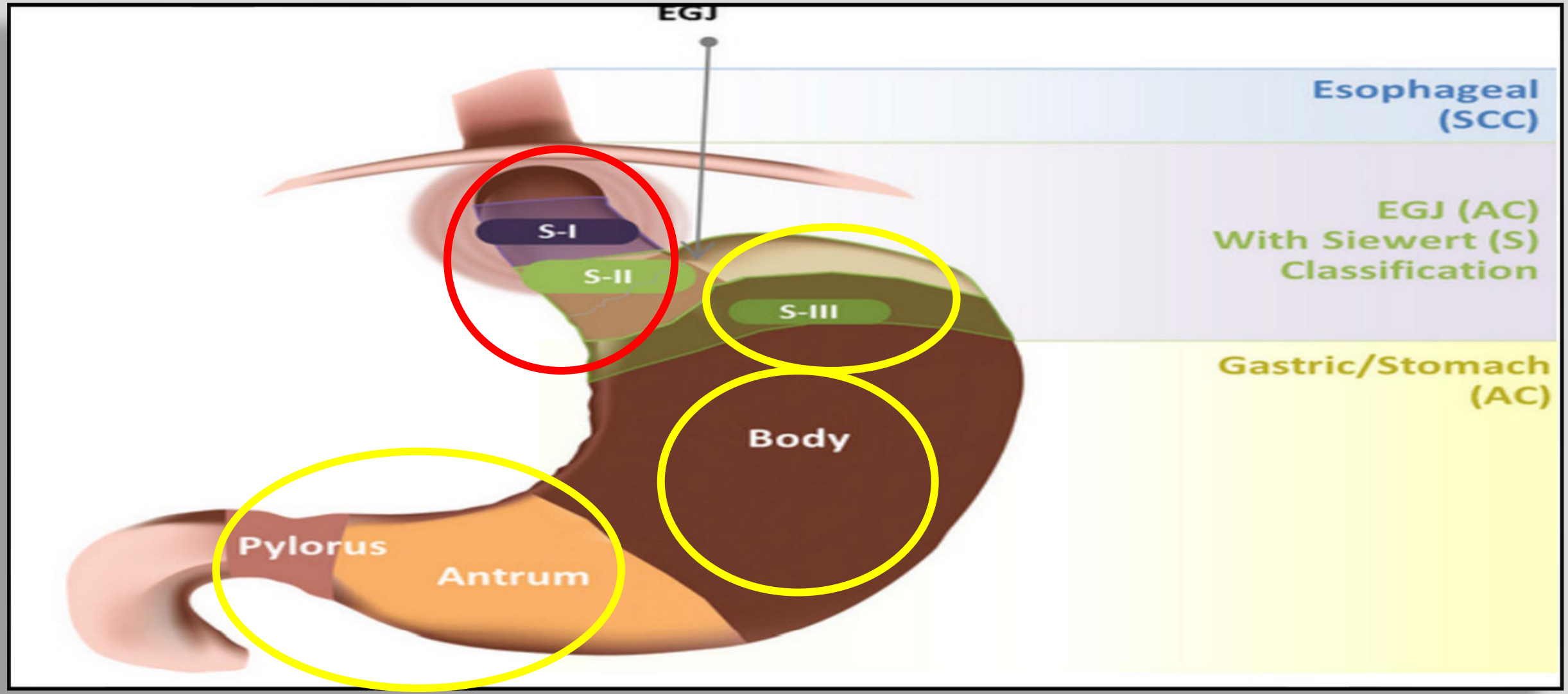
LINNITIS PLASTICA



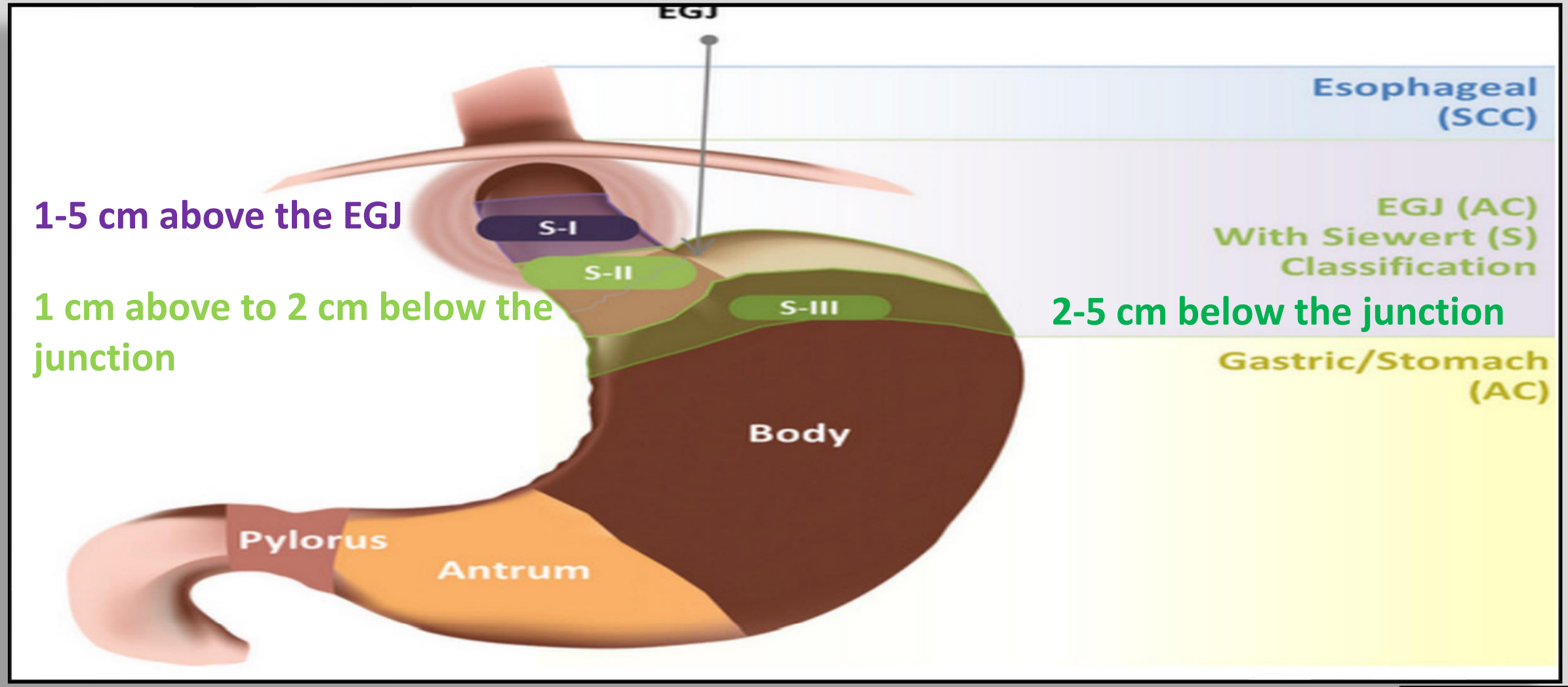


PROXIMAL VS DISTAL (NON-JUNCTIONAL)



Discovery Medicine, volume 16, Number 87, Pages 103-111, September 2013

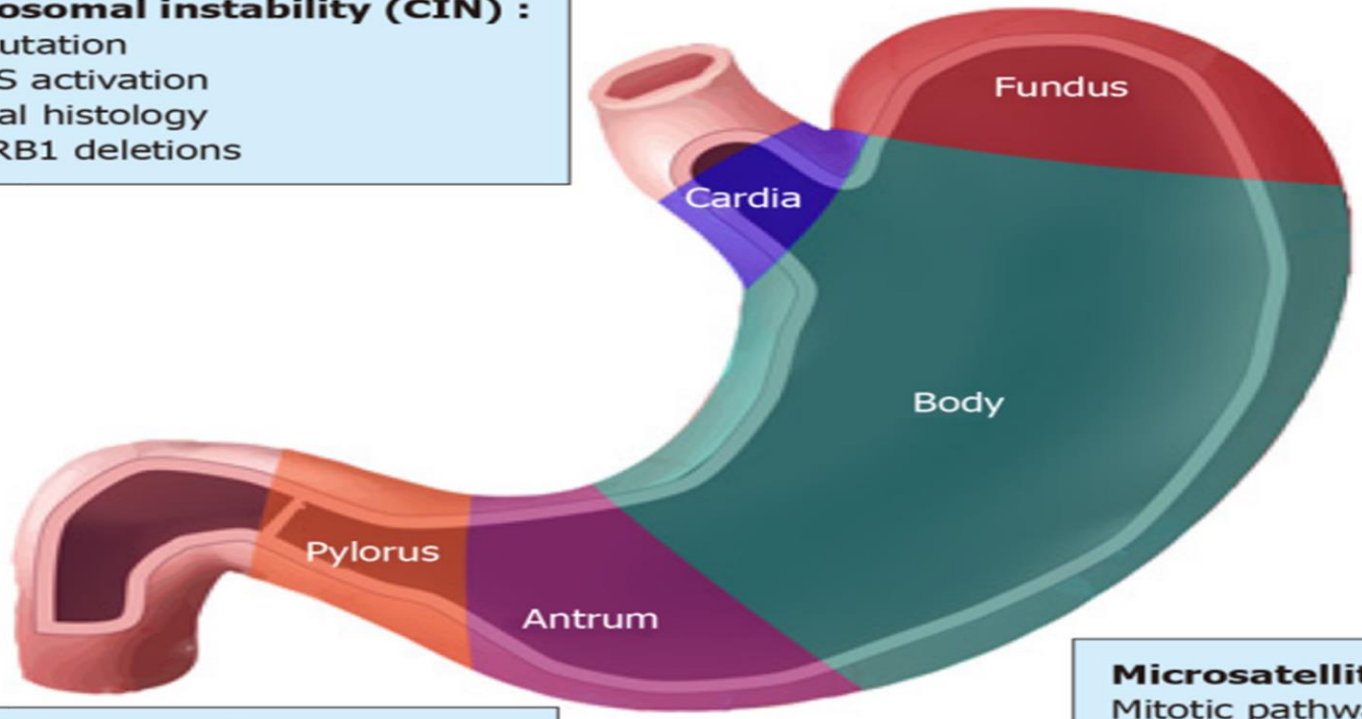
JUNCTIONAL TUMOURS – SIEWERT CLASSIFICATION



Discovery Medicine, volume 16, Number 87, Pages 103-111, September 2013

MOLECULAR SUBTYPES

Chromosomal instability (CIN) :
TP53 mutation
RTK-RAS activation
Intestinal histology
CDH1, RB1 deletions



Epstein-Barr virus (EBV) :
CDKN2A silencing
PIK3CA mutation
JAK2 amplification
PDL-1/2 overexpression

Genomically stable (GS) :
CDH1, RHOA, ARDI1A, mutations
CLDN18-ARHGAP fusion
Diffuse histology
Cell adhesion

Microsatellite instable (MSI) :
Mitotic pathways activated
Methylation of DNA mismatch repair genes (MLH1 silencing)
Hypermutation of PI3KCA, ERBB3, RNF43, PTEN, KRAS, TP53, ARID1A

World J Gastrointest Oncol 2019 October 15; 11(10): 804-829

PREMALIGNANT LESIONS

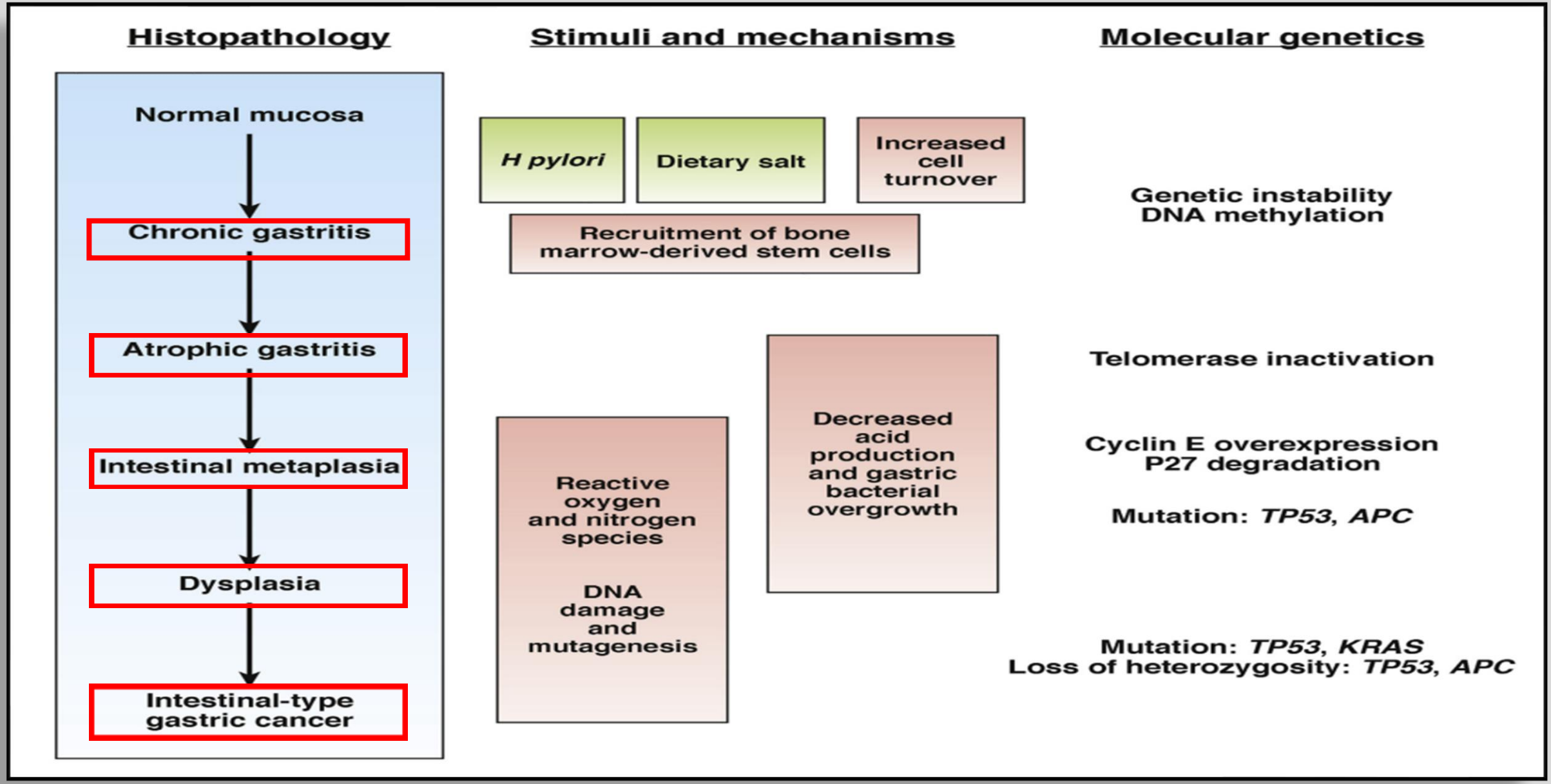
1. **CHRONIC GASTRITIS**
2. **CHRONIC ATROPHIC GASTRITIS**
3. **INTESTINAL METAPLASIA**
4. **DYSPLASIA**
5. **GASTRIC POLYPS**
6. **PREVIOUS GASTRECTOMY**
7. **PUD**
8. **MENETIERS DISEASE**

INTRODUCTION

- Complex interplay - Genetic and Environmental factors
- **H. pylori** - **most significant** risk factor for GC
  - >90% of Chronic gastritis
  - ≥70% Non-Cardia – **CagA and VacA**
- **Genetic and Epigenetic alterations**
  - Hypermethylation of DNA
  - Mutations APC and TP53
  - KRAS proto-oncogene and GTPase (KRAS)

WHAT IS THE INCENTIVE?

1. How premalignant lesions lead to GC?
2. Improve risk stratification
3. Improve survival



Cellular and Molecular Gastroenterology and Hepatology Vol. 3, No. 2

DEFINITE RISK FACTORS

1. Chronic Hp
2. CAG – *Th1 (robust)*
3. Cigarette smoking
4. Adenomatous gastric polyps
5. Dysplasia
6. EBV
7. Billroth II
8. IM

GENETIC FACTORS

1. Fam. Hx GC (1st-deg)
2. Female (5x)
3. FAP-FG
4. HNPCC
5. Juvenile polyposis
6. PJS

PROBABLE RISK FACTORS

1. NaCl intake – 1.5-2 fold
2. Hx of GU
3. BMI ≥ 35
4. Pernicious anemia
5. Snuff tobacco – 1.4x

POSSIBLE RISK FACTORS

1. Diet - nitrates
2. Heavy EtOH
3. Low socioeconomic status
4. Ménétrier disease
5. Hyperplastic/FG polyps

HELICOBACTER PYLORI

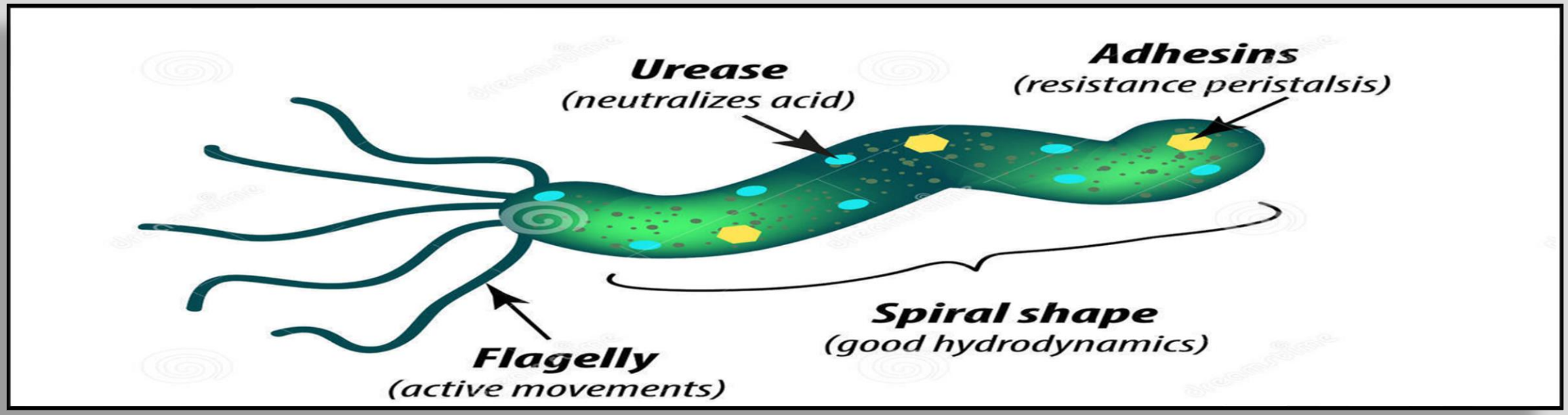


Table 1. The Three Cohort Studies That Led to the Classification of *H pylori* as a Class 1 Carcinogen in 1994

Study	Cohort description	Time from cohort inception to cancer, mean	Cases of *H pylori* seroprevalence, n (%)	Controls with *H pylori* seroprevalence, n (%)	Odds ratio (95% CI)
Forman et al,[24] 1991	British men	6 y	29 (69)	116 (47)	2.8 (1.0–8.0)
Parsonnet et al,[25] 1991	Californian men and women	14 y	109 (84)	109 (61)	3.6 (1.8–7.3)
Nomura et al,[26] 1991	Japanese–American men in Hawaii	13 y	109 (94)	109 (76)	6.0 (2.1–17)

GASTROENTEROLOGY Vol. 134, No. 1

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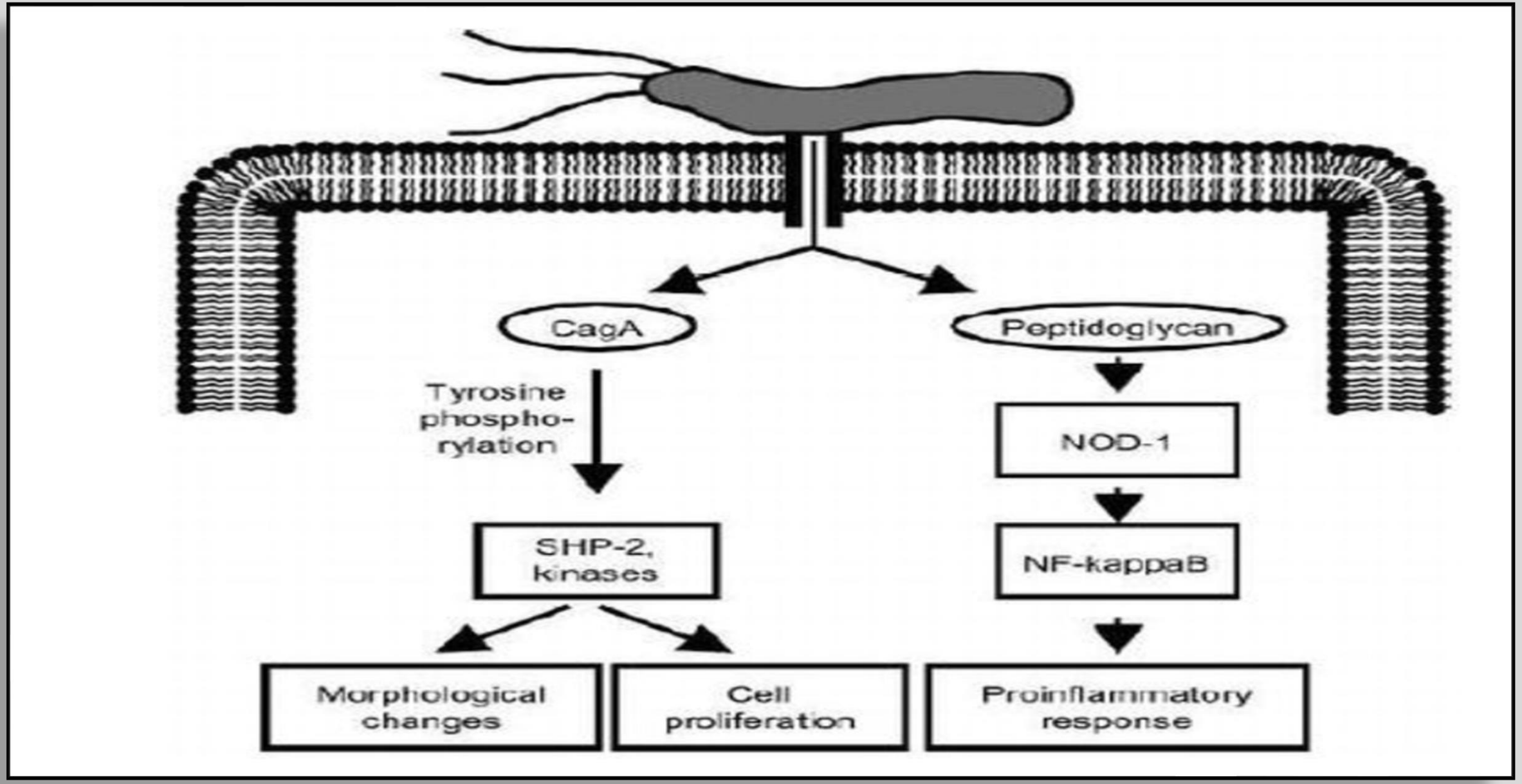
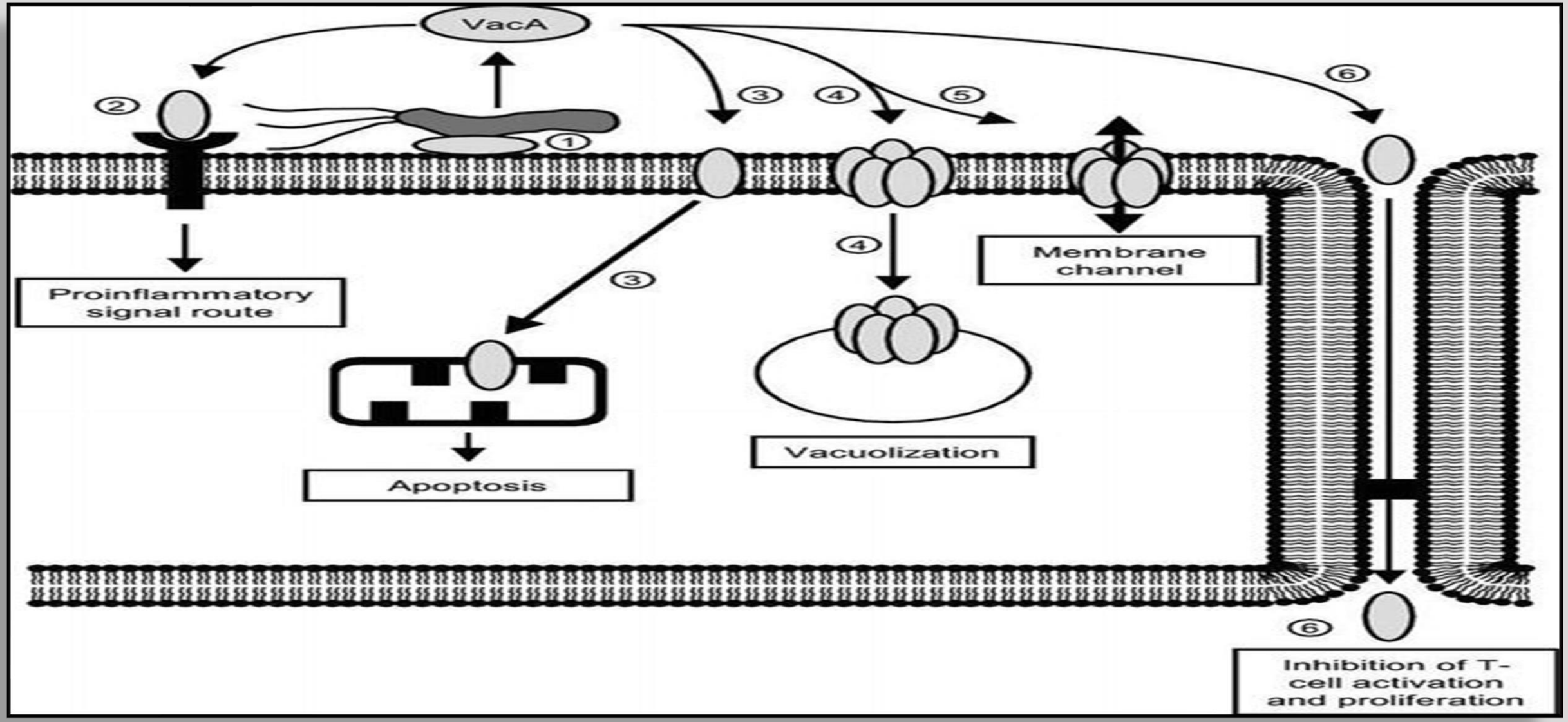


Dawood, K., Mamdooh, I., 2021, 'Pathophysiology of H. pylori. Esophagitis and Gastritis - Recent Updates.



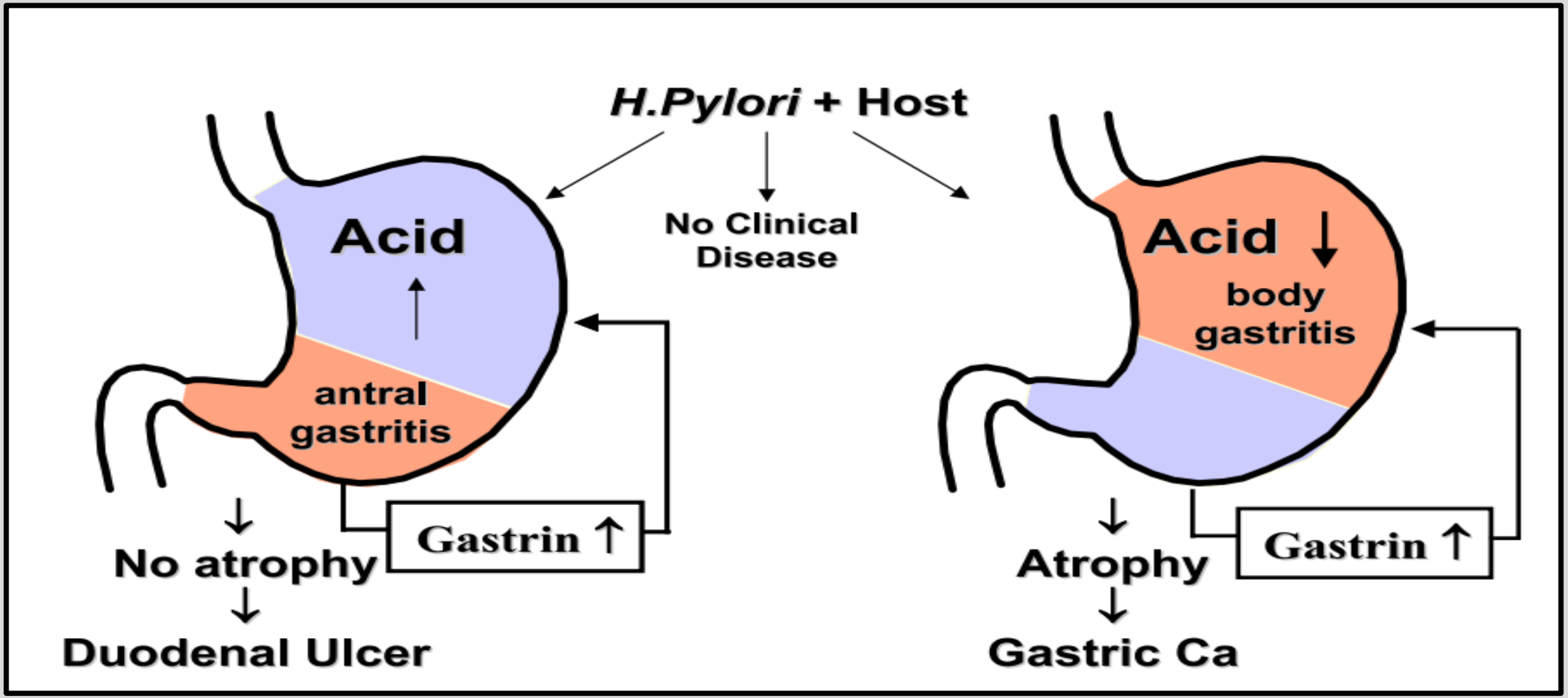
Dawood, K., Mamdooh, I., 2021, 'Pathophysiology of H. pylori. Esophagitis and Gastritis - Recent Updates.

CHRONIC GASTRITIS

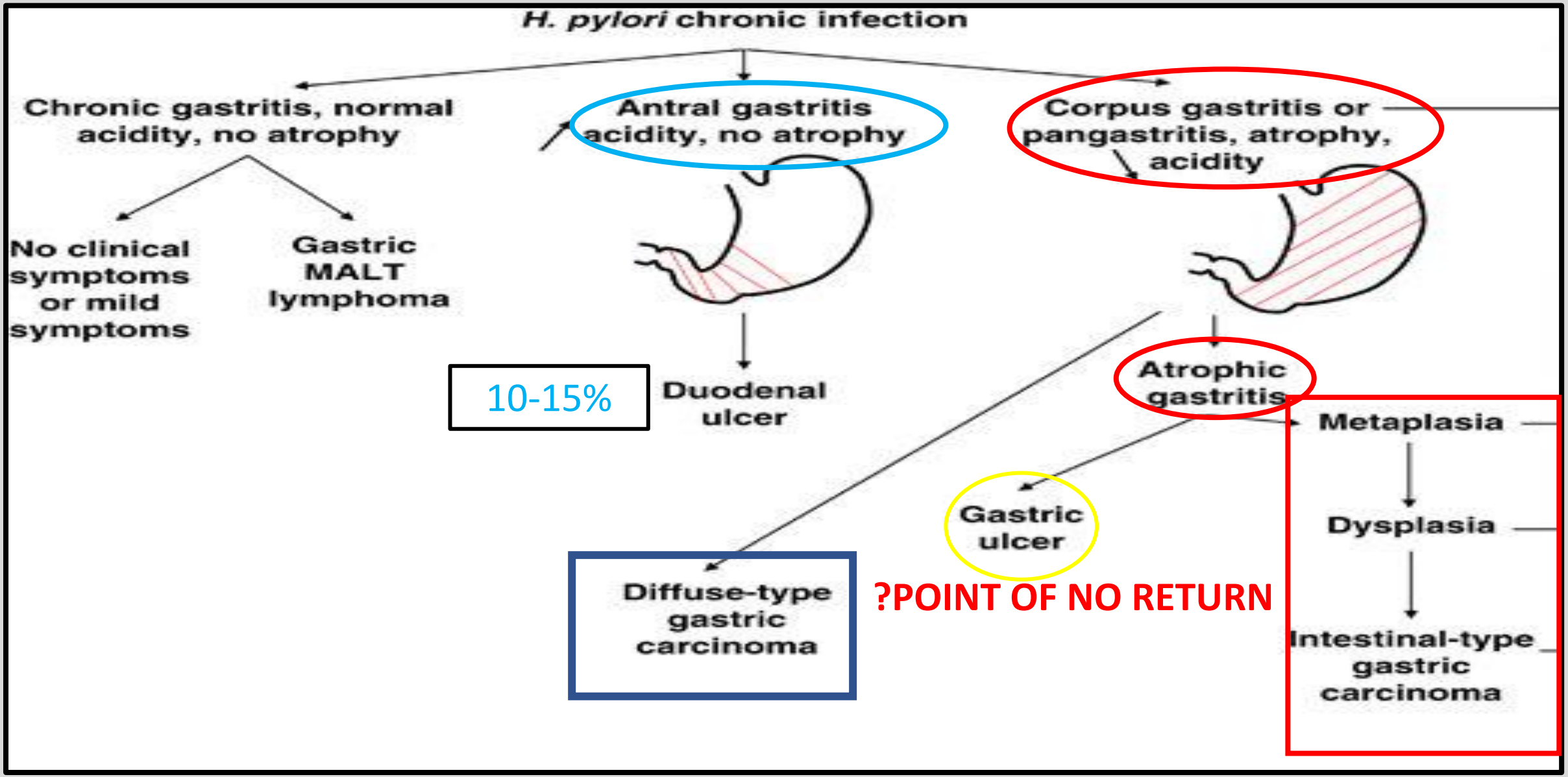
- **DIFFUSE ANTRAL** GASTRITIS – ***H.Pylori related***
  - ***M>F (2:1)***

- **ENVIROMENTAL METAPLASTIC** ATROPHIC GASTRITIS (EMAG)

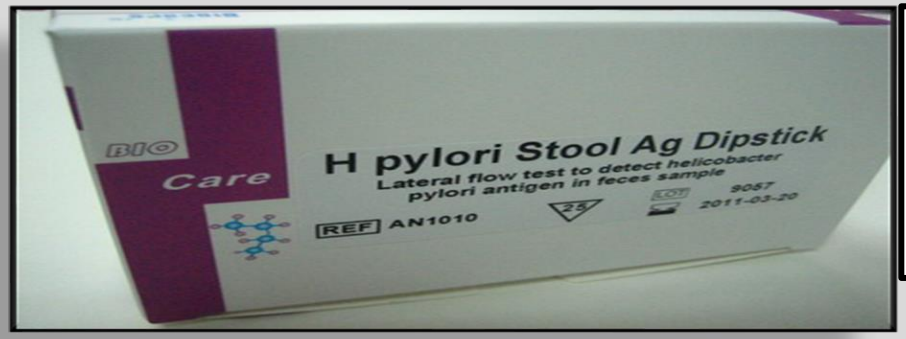
- **AUTOIMMUNE METAPLASTIC** ATROPHIC GASTRITIS **(AIMAG)**
  - AIT and T1DM
  - Age
  - F>M
  - Pernicious Anaemia – **late stage (Vit B12 deficiency)**



CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2005;3:1180 –1186



NON-ENDOSCOPIC TESTS



Stool antigen test

Advantages: Active infection, Before and after Tx

Disadvantages: Antibiotic use

Urea Breath test

Advantages: Active infection, Before and after Tx

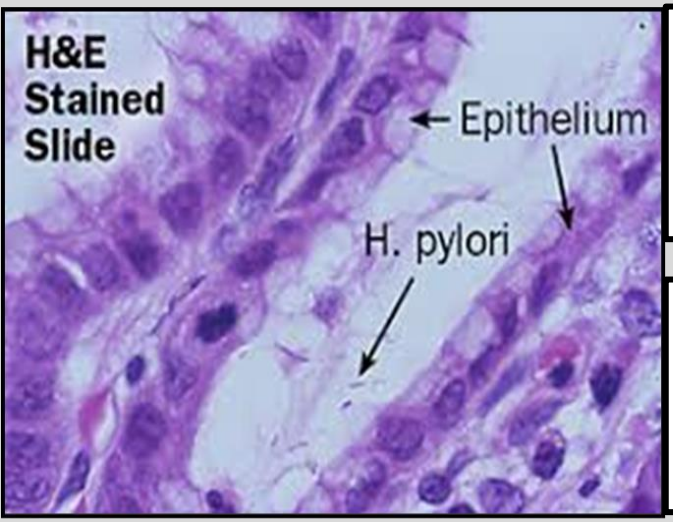
Disadvantages: Availability, Antibiotic use, Radiation-14C

Serology (quantitative IgG Antibodies)

Advantages: Widely available, Inexpensive, Good NPV

Disadvantages: Poor PPV (low prevalence), After treatment

ENDOSCOPIC TESTS



Histology

Advantages: Excellent S&S, Mucosal Information

Disadvantages: Expensive, accuracy affected by antibiotic use

Culture

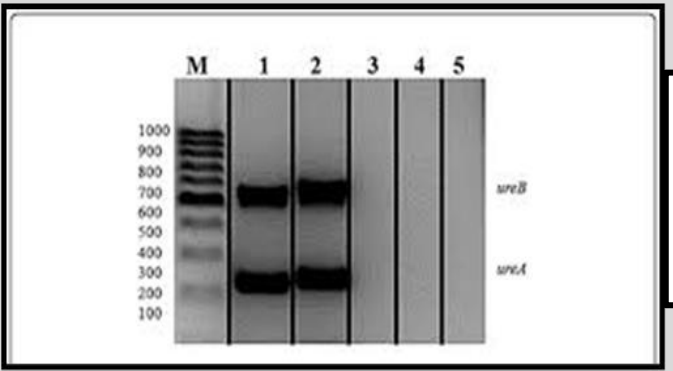
Advantages: 100% sensitivity, allows antibiotic sensitivity testing

Disadvantages: Technically difficult, expensive, not widely available

Rapid Urease test (CLOtest)

Advantages: Rapid and cost effective, accurate – off PPI or antibiotics

Disadvantages: After treatment or PPI use



PCR assay

Advantages: Excellent S&S, Detects antibiotic resistance

Disadvantages: Not widely available, expensive, no standardized technique

DIAGNOSIS

- EGD PROCEDURE OF CHOICE
- Non-healing GU – 6-8 Bx (edge and base)
- AGA RECOMMENDATION:
  - **>55 yr** - new-onset dyspepsia
  - **<55 years** who have “alarm” symptoms
  - **Failure** - Empirical trial of PPIs and eradication of Hp to relieve Sx’s
- Chromoendoscopy
- Magnification endoscopy
- Narrow band imaging are used alone or in combination

HELICOBACTER PYLORI ERADICATION

- **Limit chronic inflammation** and **oxidative stress**
  - **Reverse** premalignant progression to GC

- RCT placebo controlled trial **China** (n = 587) with **Hp eradication reduced risk of progression of IM**

Journal of Gastroenterology and Hepatology 34 (2019) 1287–1295

EVIDENCE FOR ERADICATION

- **Recent meta-analysis**:
  - **35% reduction** – GC risk
  - Benefit – post GC **"multifocal dysplasia"**
- **Open-label RCT by *Fukase et al.,***
  - **Resected early GC** followed by **Hp eradication -** risk reduction metachronous GC
- **Parsonnet and colleagues**
  - High Risk – Hp attributible GC (30%)

Journal of Gastroenterology and Hepatology 34 (2019) 1287–1295

Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.14646

REVIEW

Chemoprevention of gastric cancer by *Helicobacter pylori* eradication and its underlying mechanism

Nayoung Kim*,†,‡

*Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, †Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine and ‡Tumor Microenvironment Global Core Research Center, Seoul National University, Seoul, South Korea

Table 1 The effect of *Helicobacter pylori* eradication history on gastric cancer in South Korea[29]

	Non-cardiac GC (*n* = 879)	Intestinal-type NCGC (*n* = 494)	Diffuse-type NCGC (*n* = 352)
Uninfected	0.30 (0.23 to 0.39)	0.35 (0.25 to 0.49)	0.22 (0.15 to 0.32)
Infected, eradication history (+)	0.35 (0.27 to 0.47)	0.50 (0.36 to 0.70)	0.20 (0.13 to 0.31)
Infected, eradication history (–)	1	1	1

Journal of Gastroenterology and Hepatology 34 (2019) 1287–1295

HESITANCY TO ERADICATE

- **Inverse relationship: *H pylori*** and **esophageal adenocarcinoma**
- **RCT placebo controlled trial in Mexican adults**
  - **NO benefit** of Hp eradication - preventing histologic progression.
- **NNT to prevent a case of GC:**
  - **HR** - Chinese men **(15)** vs **LR** – USA females **(245)**
- **China (n=1630) "healthy" Hp-positive individuals eradicated - ?reduce the incidence of GC**
  - **No overall group benefit -** receiving Hp eradication
  - **Reduction in GC -** who did not already precancerous lesions - **?POINT OF NO RETURN**

Gastroenterology 2021;160:1831–1841

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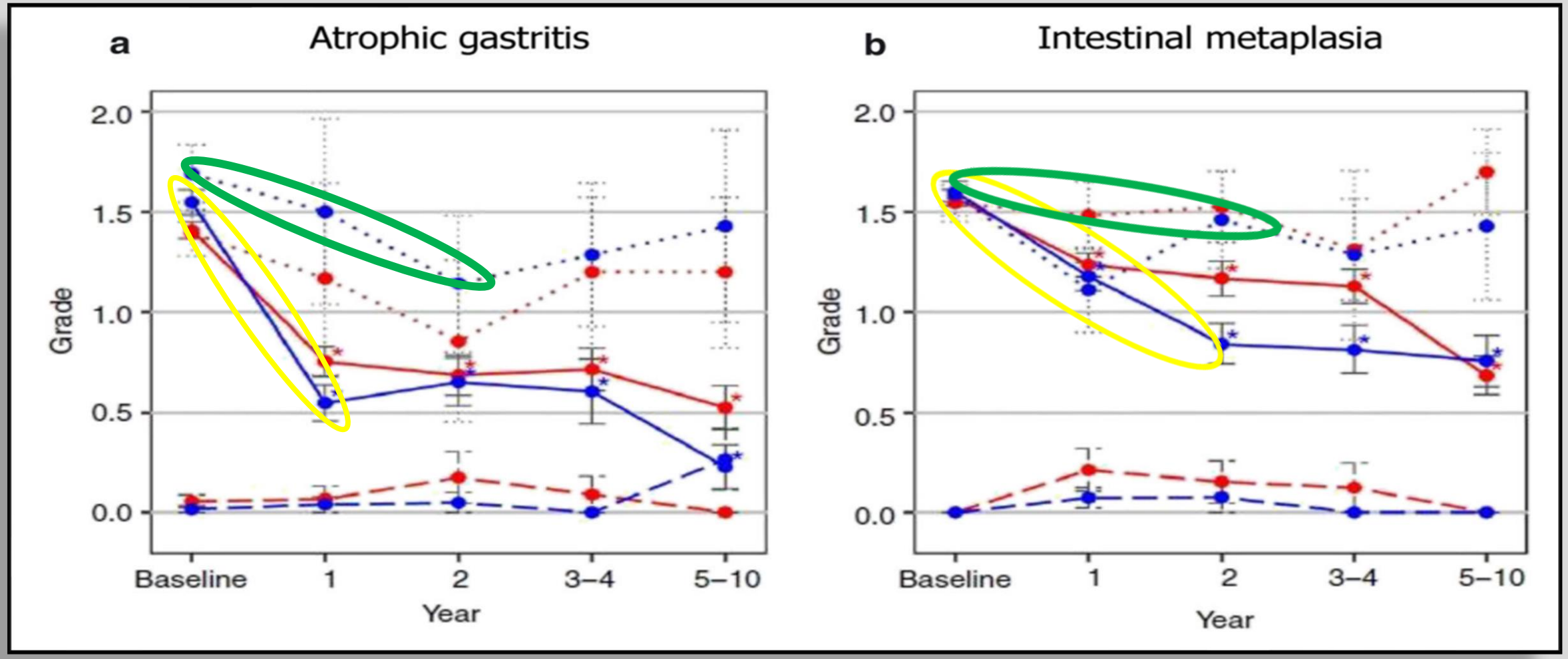
“?POINT OF NO RETURN”



Gastroenterology 2021;160:1831–1841

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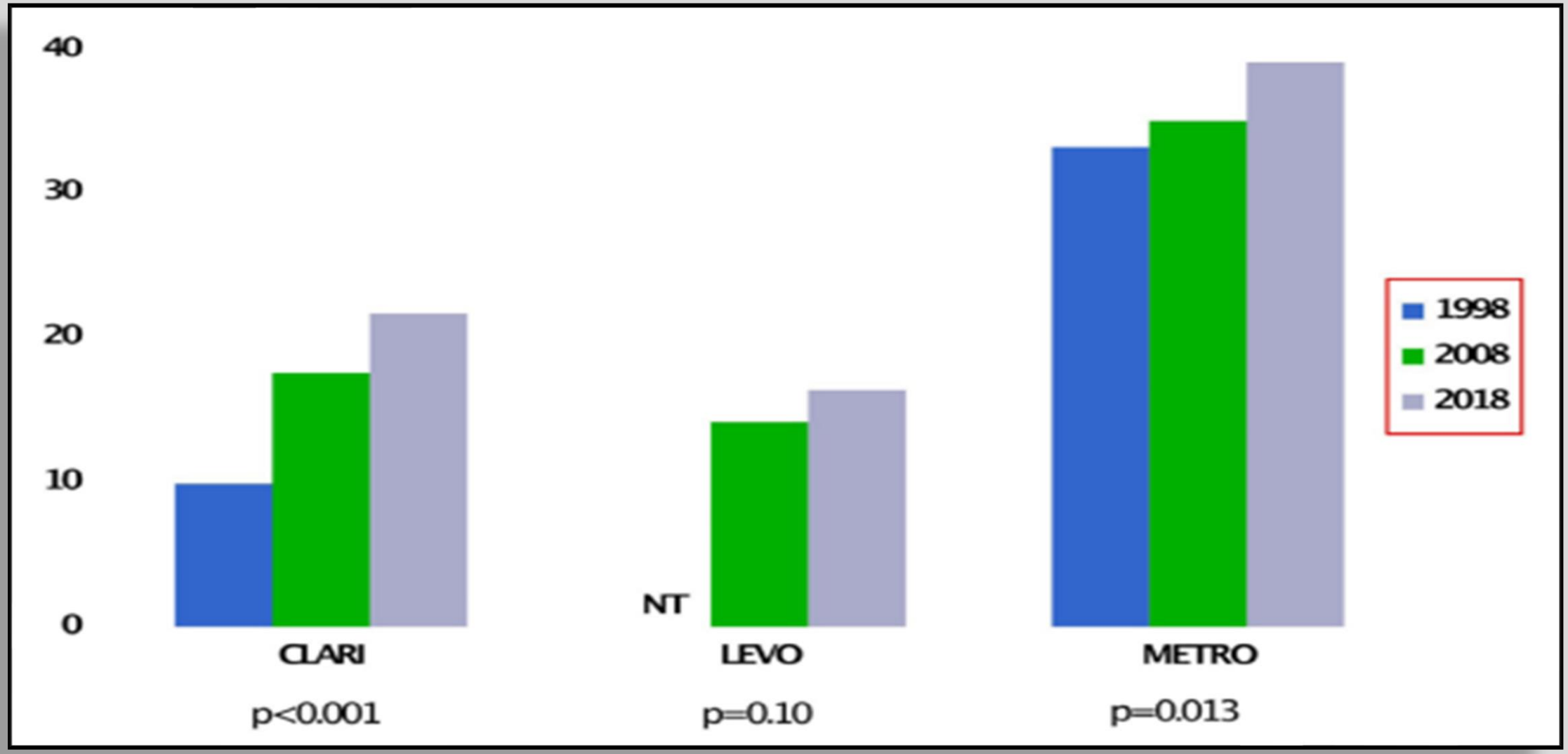
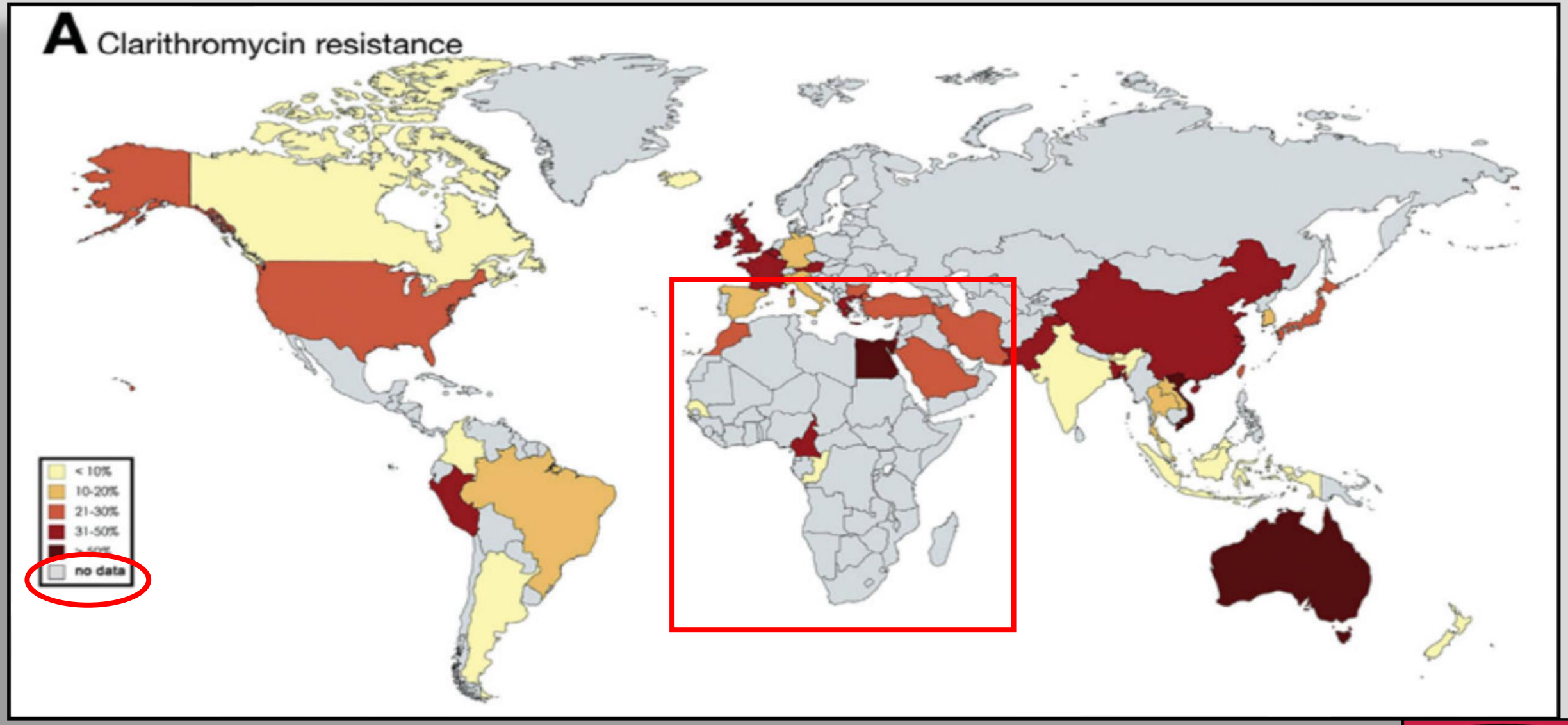
H.PYLORI RESISTANCE PATTERNS IN EUROPE



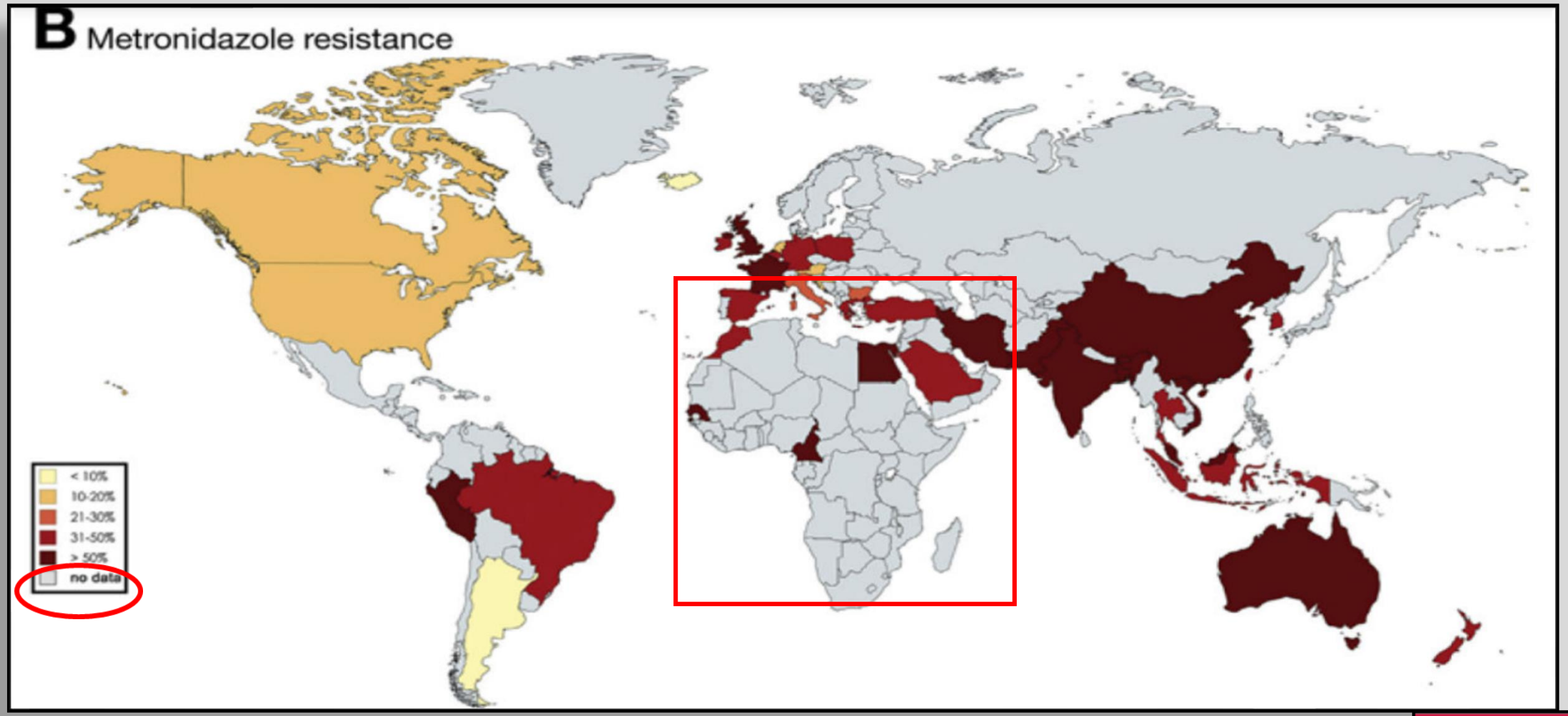
Megraud F, et al. Gut 2021;70:1815–1822.

GLOBAL RESISTANCE PATTERNS



Gastroenterology. 2018 November ; 155(5): 1372–1382.

GLOBAL RESISTANCE PATTERNS



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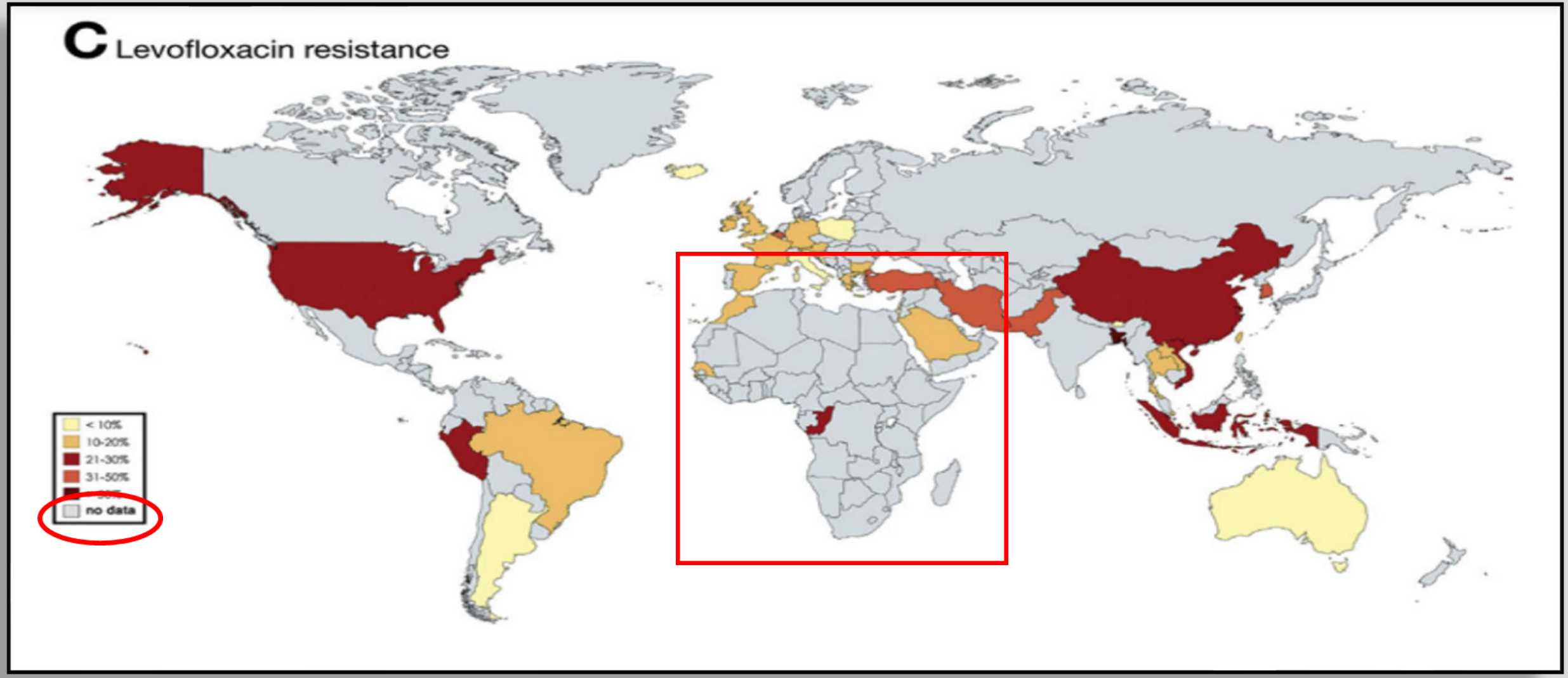
GLOBAL RESISTANCE PATTERNS



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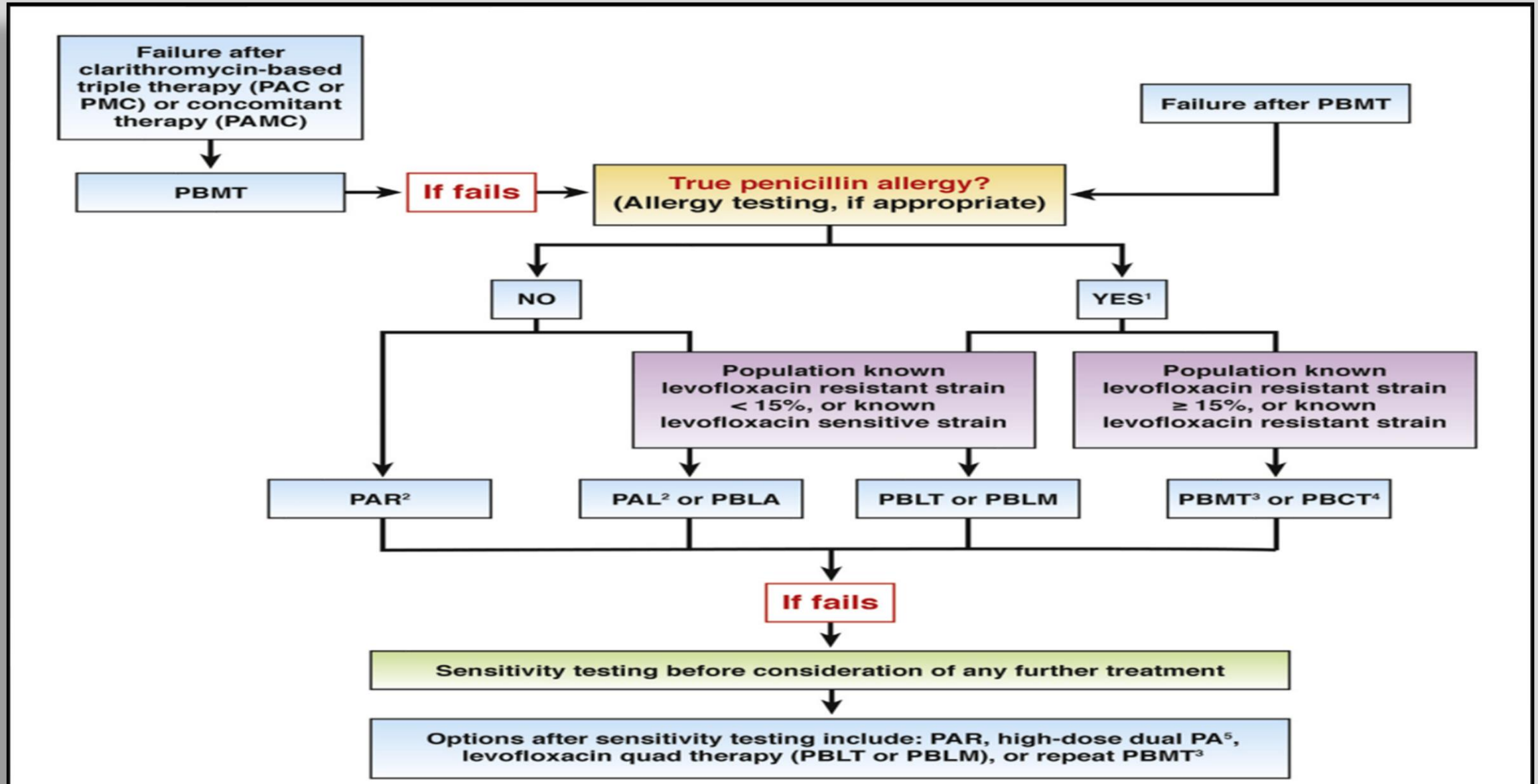
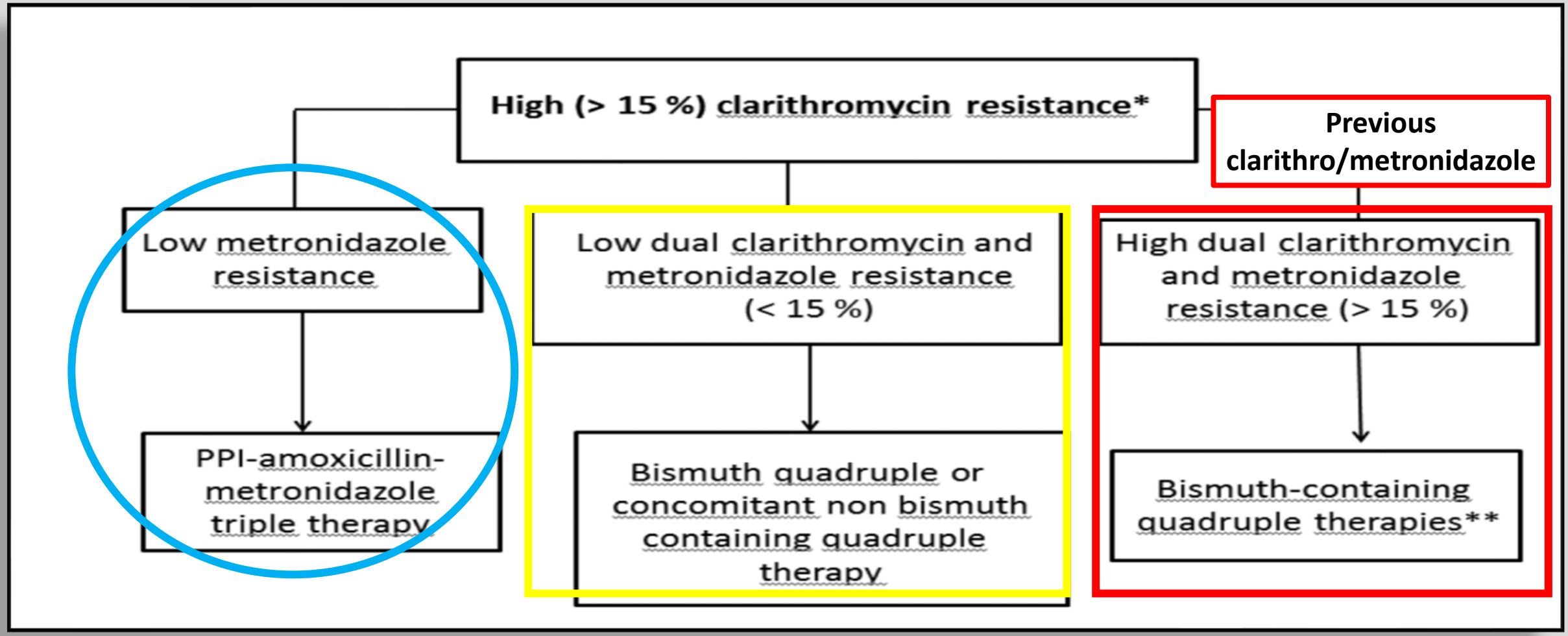
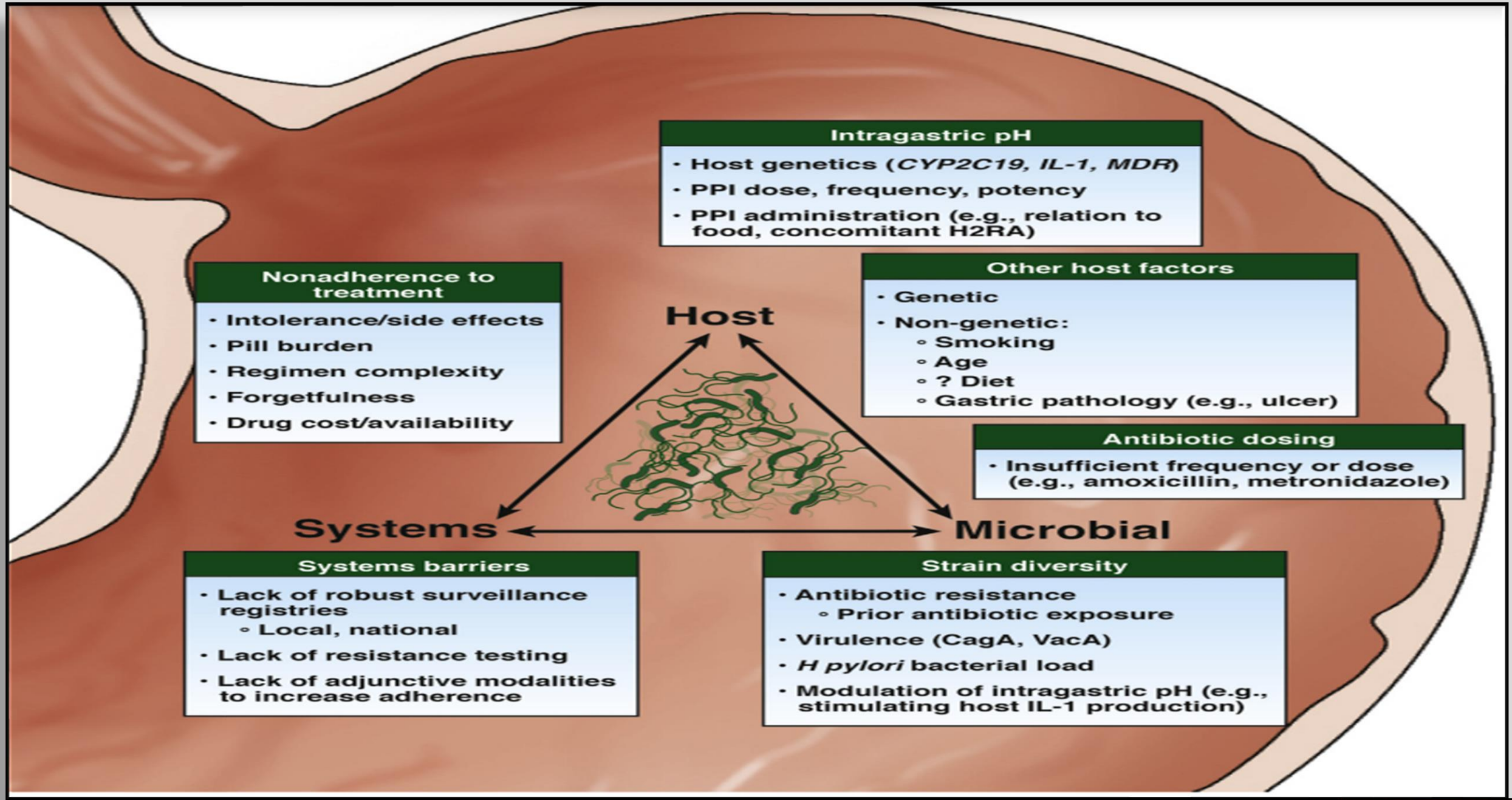


Gastroenterology 2021;160:1831–1841

ERADICATION STRATEGIES



Malfertheiner P, et al. Gut 2017;66:6–30



Gastroenterology 2021;160:1831–1841

PROTECTIVE FACTORS

- ✓ Regular aspirin or other NSAID use
  - COX-2 expression (70% GC)
  - UK – no benefit to aspirin only NSAIDS
  - No regression in IM after 2 yrs selective COX-2 inhibitors
  - Hp eradication plus COX-2 inhibitor (24mo) – CAG regression
  - Aspirin (10-20yrs) – to derive benefit
- ✓ High ascorbate intake
- ✓ High intake of fresh fruits and vegetables
- ✓ Statin use – antiproliferative and proapoptotic effects
- ✓ High green tea consumption ?

ATROPHIC GASTRITIS

- Loss of **gastric glands ± metaplasia**
- Chronic inflammation –***H.pylori*** vs **autoimmunity.**
- Reduction/absence - **IF** and **HCL** (***hypochlorhydria/achlorhydria***) as well as pepsinogen

- Risk AG to GC (0.1-0.3%) annually

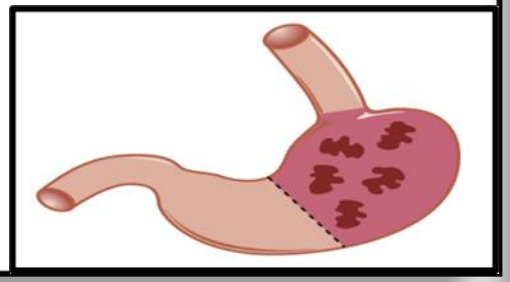
- Depending on AG severity
  1. **Extent**
  2. **Concomitant IM**

- **PA - corpus-predominant AG -** several years
  - **7-fold** higher RR of GC in pts with PA

- CAG especially AIG **(corpus-predominant atrophy)**
  - Risk of type I NETs.
  - PC loss ⟶ reduced gastric acid secretion ⟶ hypergastrinemia ⟶ ECL hyperplasia ⟶ ECL dysplasia and gastric NETs

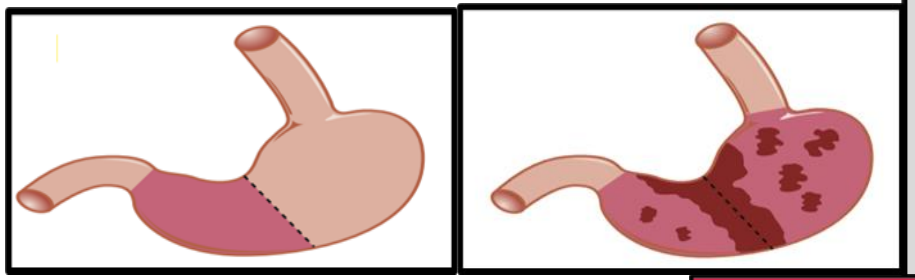
AMAG

- **T and B/plasma**
- Autoimmune overlap
- Antral sparing
- ↓Serum PGI &↓PGI/PGII ratio
- Hypergastrinemia (can be marked)
- Gastric carcinoid tumours



EMAG

- **Hp gastritis (Current, past)**
- Potentially reversible
- Antral involvement
- Serum PG levels more variable
- Normal or slight increase in serum gastrin

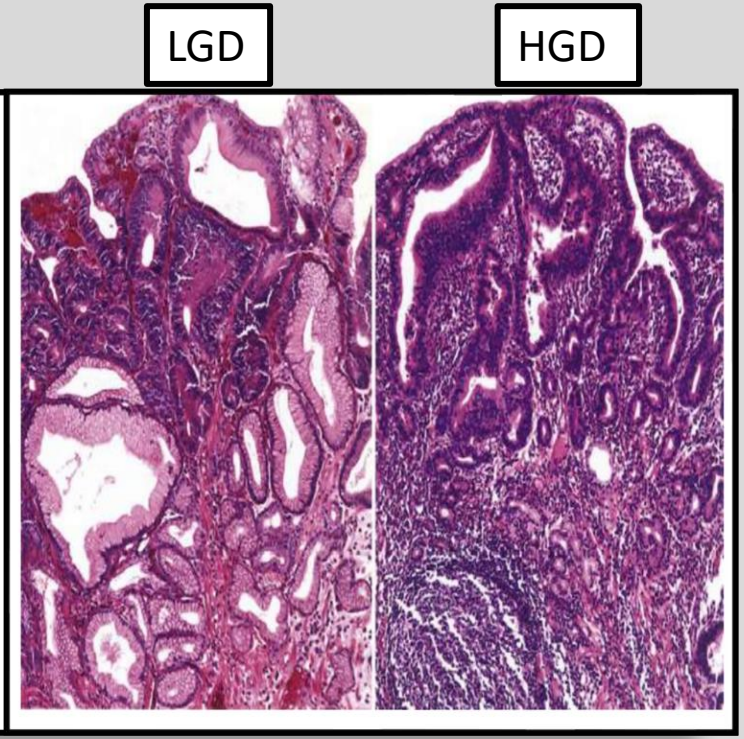


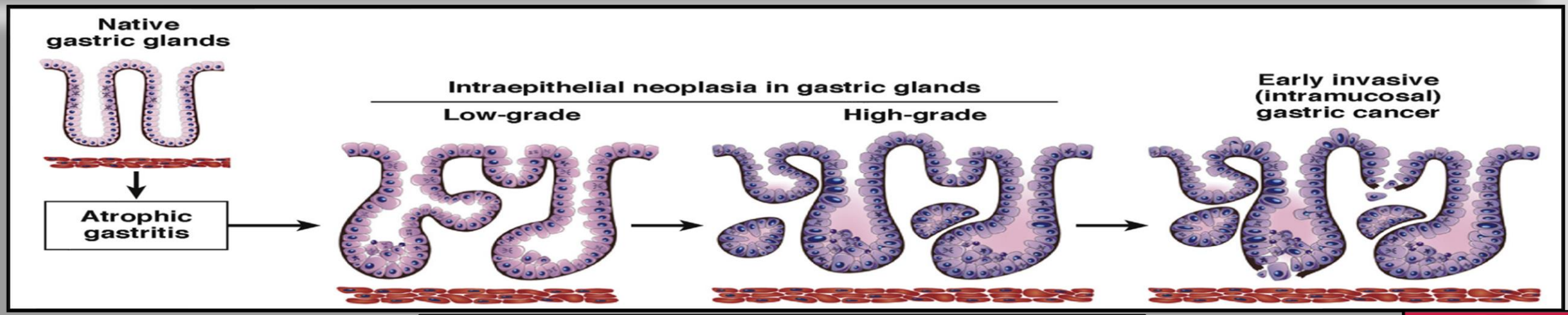
GASTRIC INTESTINAL METAPLASIA

1. **3 CATEGORIES:**
    1. **Type I (complete)** - goblet cells - mature **(NOT A RISK FOR GC)**
    2. **Type II (incomplete)** few absorptive cells “intermediate” various stages of differentiation.
    3. **Type III (incomplete)** even less differentiated than **Type II**
        1. **Type II and III 20 FOLD INCREASE RISK OF GC**
        2. **Early GC in Type III (42%) – 5yrs F/U**
2. **Metaplasia induction prerequisite -** Loss acid secreting parietal cells
3. **?Metaplasia - ?attempt to repair in the face of chronic inflammation**

GASTRIC DYSPLASIA

- **LGD** - **Regress (60%)** VS **Progress (10-20%)**
- **HGD** rarely regresses
  - ➢2-6% Annual incidence - GC
  - ➢**40-fold** – RISK OF PROGRESSION
  - ➢**SYNCHRONOUS/UNIFOCAL OR MULTIFOCAL**





Clinical Gastroenterology and Hepatology 2017;15:1833–1843

ENDOSCOPIC EVALUATION

- **Ensure excellent mucosal visualization**
  - color and texture
  - appearance of submucosal blood vessels
  - architecture of the gastric rugae
- **Defoaming and mucolytic agents** - simethicone and 1 % N-acetylcysteine
- **Targeted examinations of focal abnormalities** - HD-WLE/NBI
- **Photographic documentation**
  1. cardia and fundus
  2. lesser and greater curvature of corpus and antrum
  3. incisura angularisand pylorus

OLGA/OLGIM RISK SCORE

Atrophy Score		Corpus			
		No Atrophy (score 0)	Mild Atrophy (score 1)	Moderate Atrophy (score 2)	Severe Atrophy (score 3)
Antrum	No Atrophy (score 0) (including *incisura angularis*)	STAGE 0	STAGE I	STAGE II	STAGE II
	Mild Atrophy (score 1) (including *incisura angularis*)	STAGE I	STAGE I	STAGE II	STAGE III
	Moderate Atrophy (score 2) (including *incisura angularis*)	STAGE II	STAGE II	STAGE III	STAGE IV
	Severe Atrophy (score 3) (including *incisura angularis*)	STAGE III	STAGE III	STAGE IV	STAGE IV

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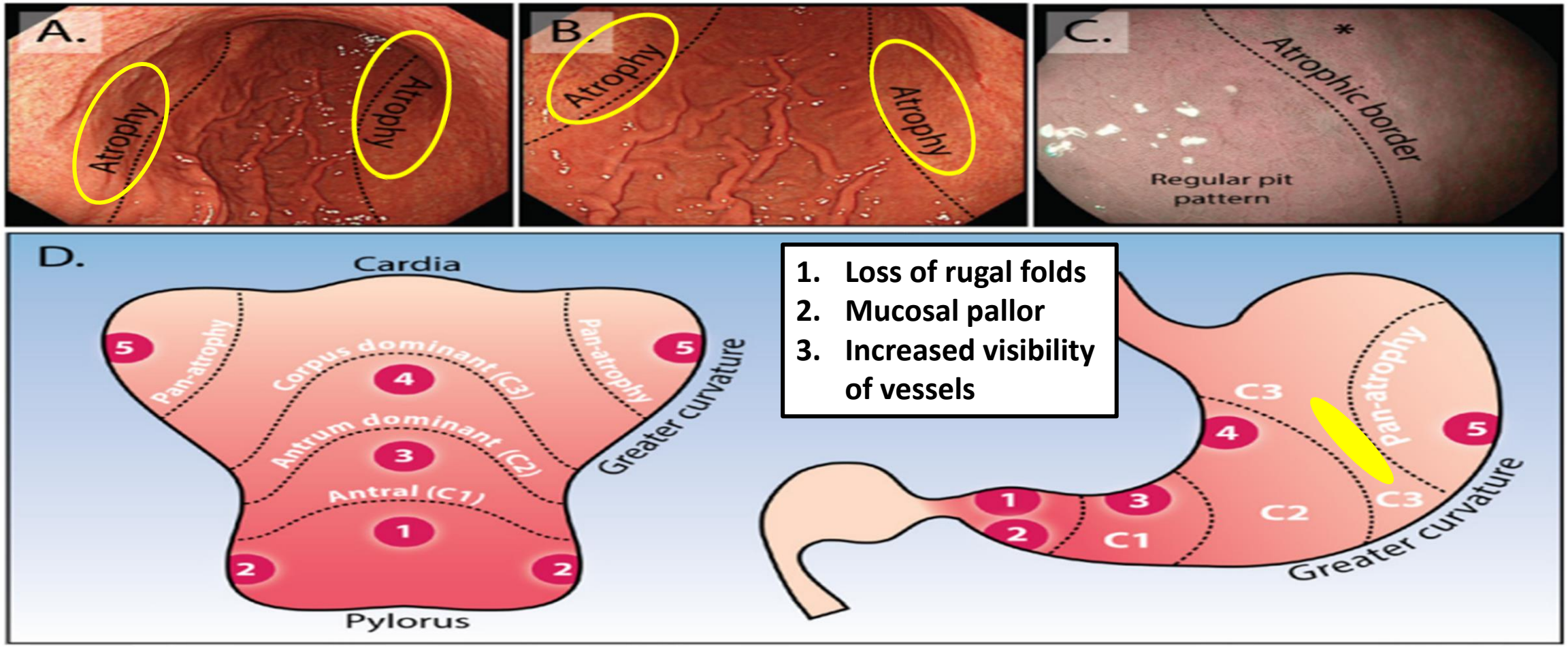
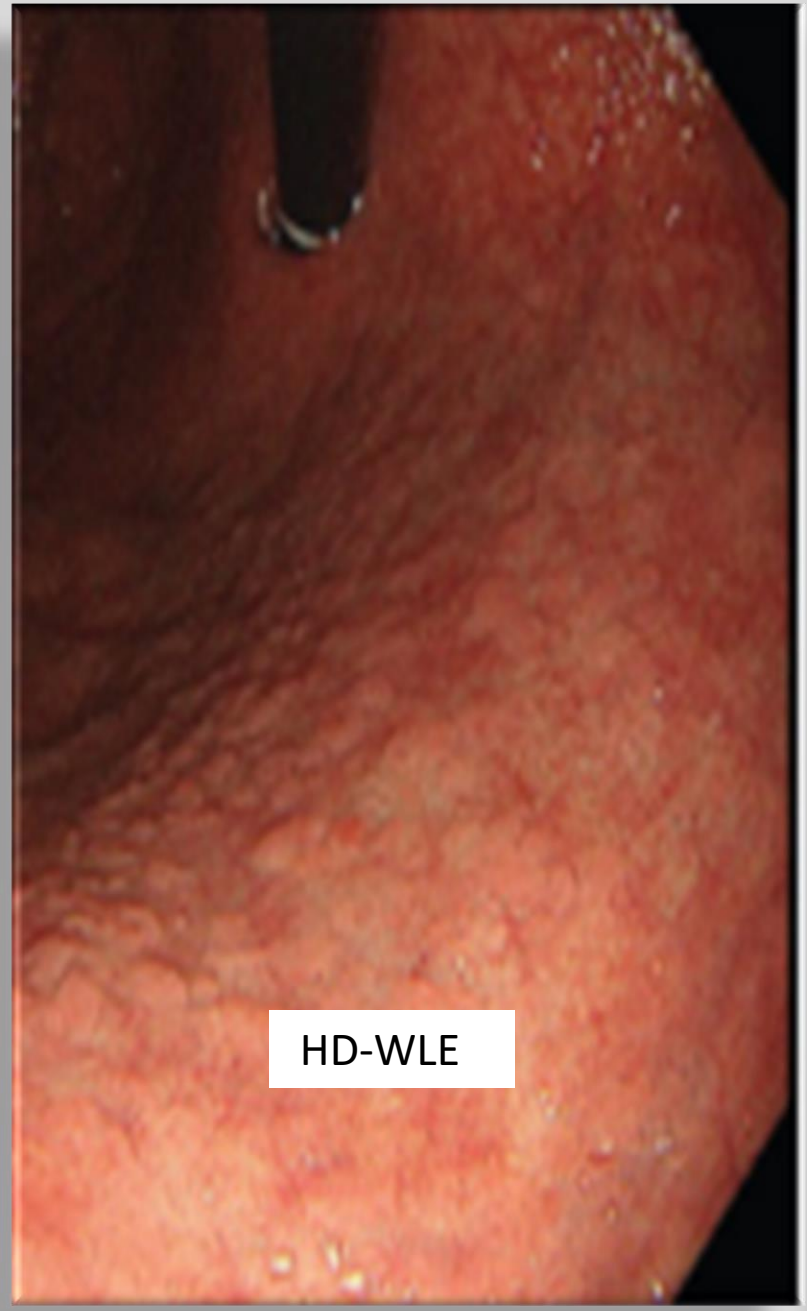
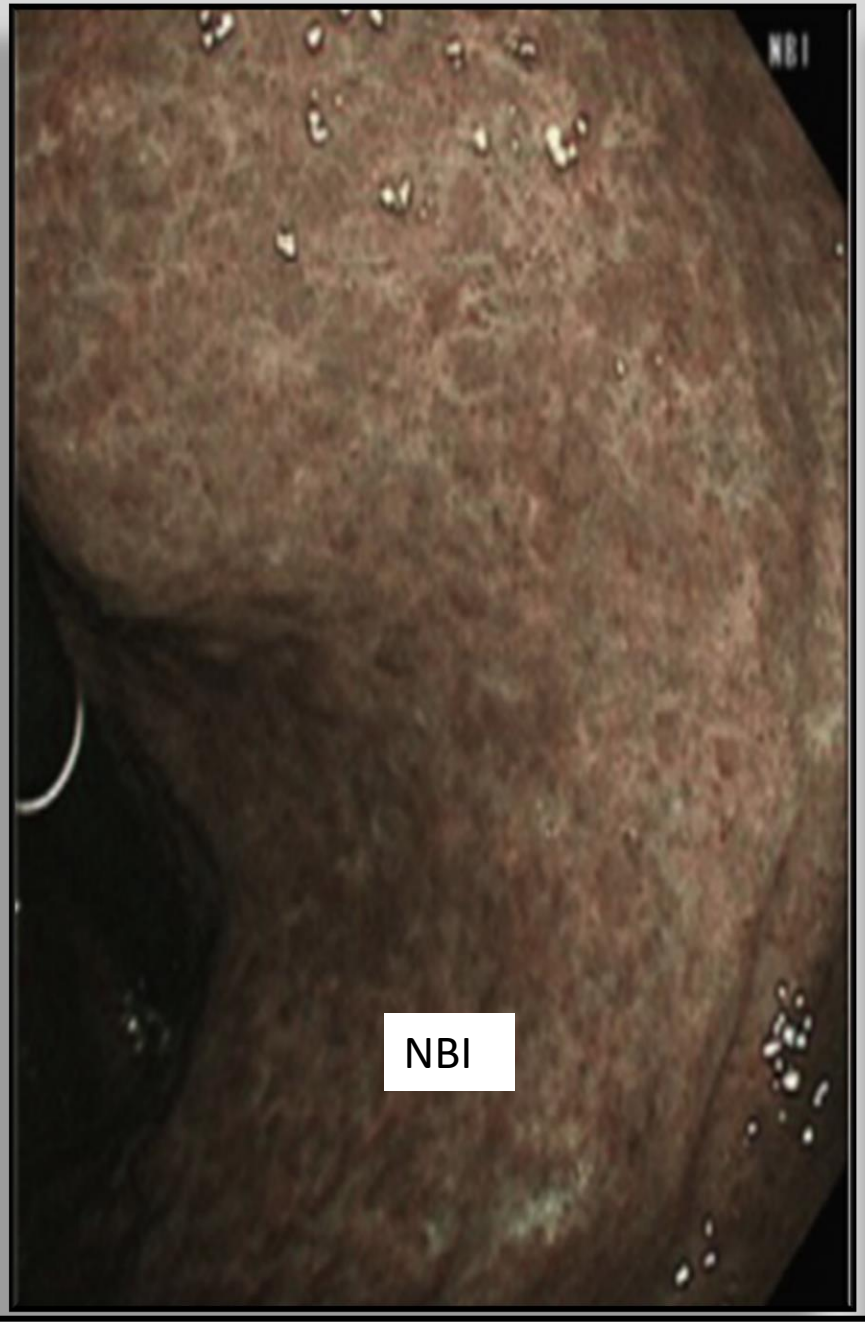
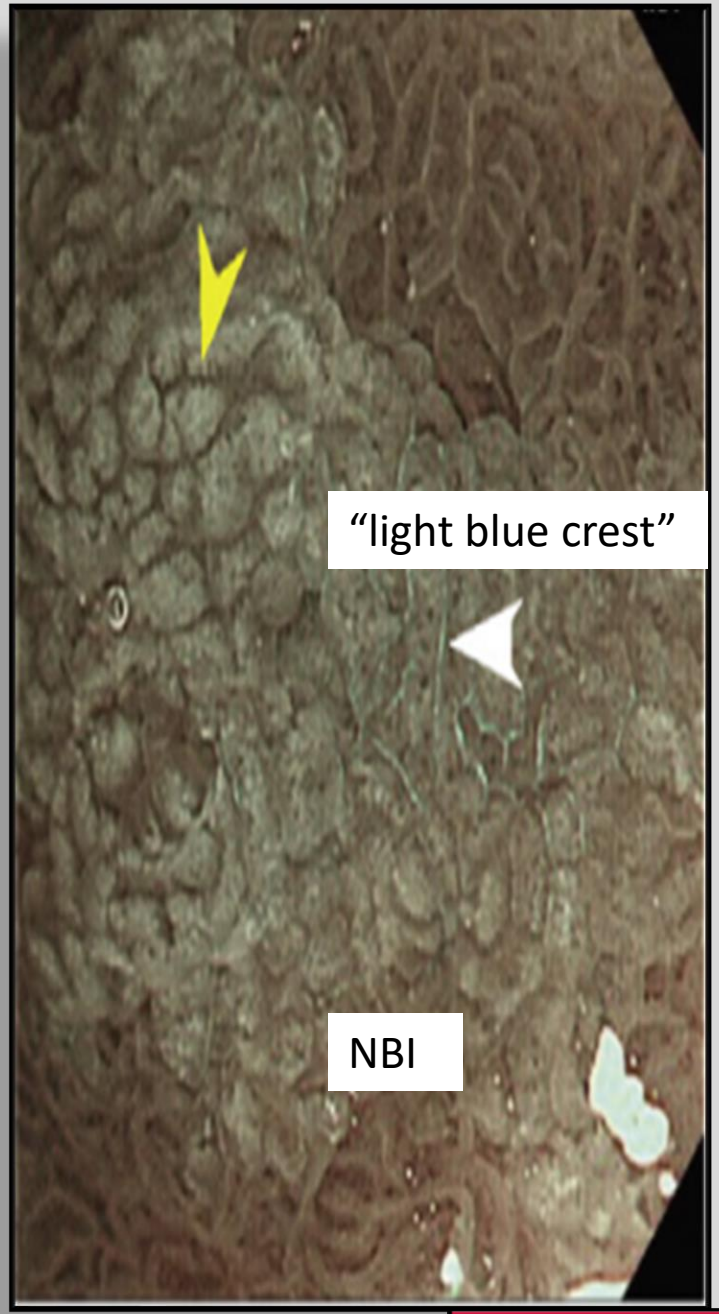
Modified Kimura–Takemoto classification system



Waddingham W, et al. Frontline Gastroenterology 2021;12:322–331



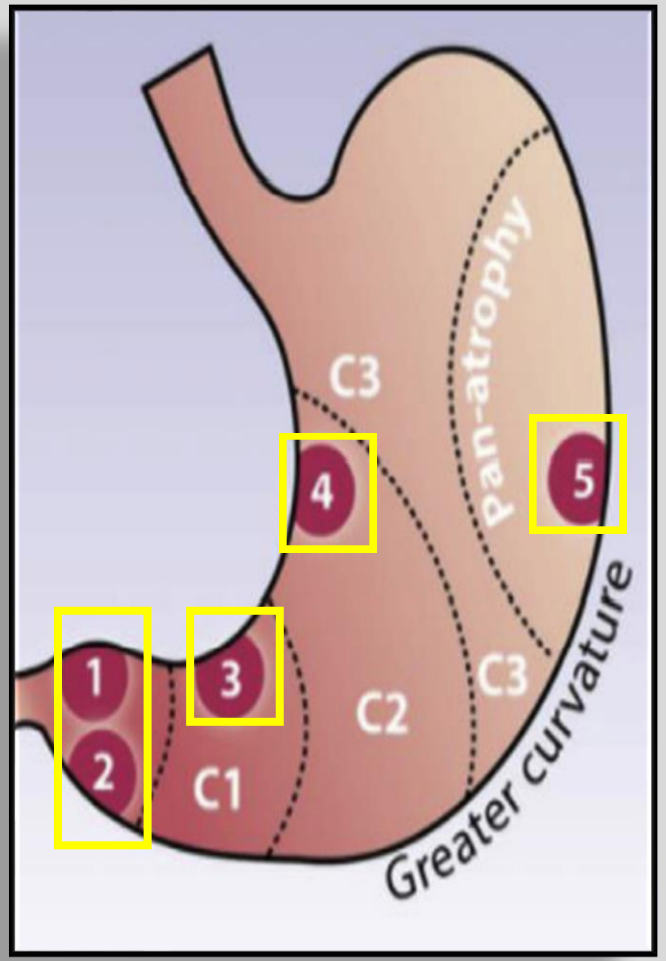




Gastroenterology 2021;161:1325–1332

SYDNEY BIOPSY PROTOCOL

- **5 gastric biopsies** - separately labeled jars
- **2 antrum** along the lesser and greater curvature
  - within 2–3cm of the pylorus
- **1 incisura angularis**
- **2 gastric corpus**
  - 1 lesser curvature at 4 cm proximal to the incisura angularis
  - 1 middle portion of the greater curvature of the gastric body at 8 cm from the cardia



Waddingham W, et al. Frontline Gastroenterology 2021;12:322–331.

International Padova Classification

1 Negative for noninvasive neoplasia (NiN)

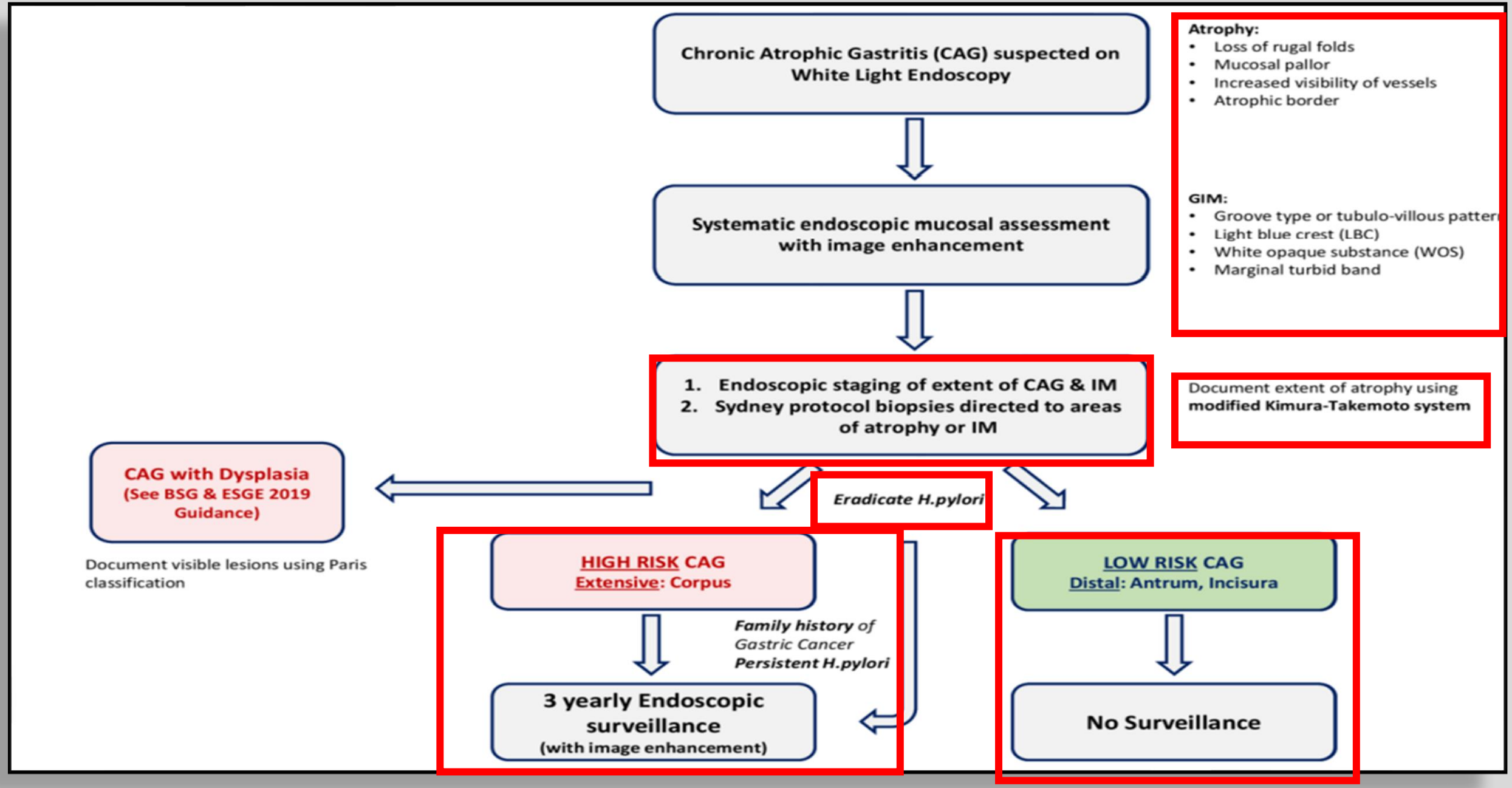
2 Indefinite for noninvasive neoplasia
- 2.1 Foveolar hyperproliferation
- 2.2 Hyperproliferative intestinal metaplasia

3 Noninvasive neoplasia (NiN)
- 3.1 Low-grade noninvasive neoplasia
- 3.2 High-grade noninvasive neoplasia

4 Noninvasive neoplasia coexisting with features suggesting invasive carcinoma

5 Invasive adenocarcinoma of the stomach

Clinical Gastroenterology and Hepatology 2017;15:1833–184



Waddingham W, et al. Frontline Gastroenterology 2021;12:322–331.

Non-endoscopic

- Test for *H pylori*, treat if positive and confirm eradication
- Evaluate for anemia
- Evaluate for micronutrient deficiencies, such as iron and vitamin B12 (irrespective of anemia)
- In patients with AIG
  - Screen for autoimmune thyroid disease
  - Low threshold to evaluate other autoimmune diseases based on clinical presentation (e.g. type I diabetes)
- Check PCA and IFA in patients with endoscopic/ histologic findings consistent with AIG**

Gastroenterology 2021;161:1325–1332

Endoscopic

- Obtain topographical biopsies to determine anatomic extent and histologic severity for risk stratification

- Surveillance endoscopy should be considered in patients with*
  - Advanced AG: every 3 years
  - AIG: interval based on individualized assessment (see text)

- In patients with newly diagnosed PA, upper endoscopy should be considered for risk stratification and to evaluate for prevalent gastric neoplasia and NETs

- Evaluate for NETs and manage accordingly (see text)

Gastroenterology 2021;161:1325–1332

SERUM MARKERS

- **Low PGI levels**
- **Low ratios:** PGI **(corpus)** : PGII **(antrum, cardia, fundus)**
- **Hypergastraemia**
- **GA** progresses to corpus **PGI** is reduced relative to **PGII**
- PGI **<70 ng/mL**
- PGI:PGII **ratio <3**
- PCAs & IFA
- **S&S:**
  - GC Dx : **69%** and **73%**
  - AG – **69%** and **88%**
- **PG** screening at **age 50 yrs** reduced the lifetime **intestinal-type non-cardia GC risk 26.4%**
- **CEA** and **CA19.9** – low sensitivity

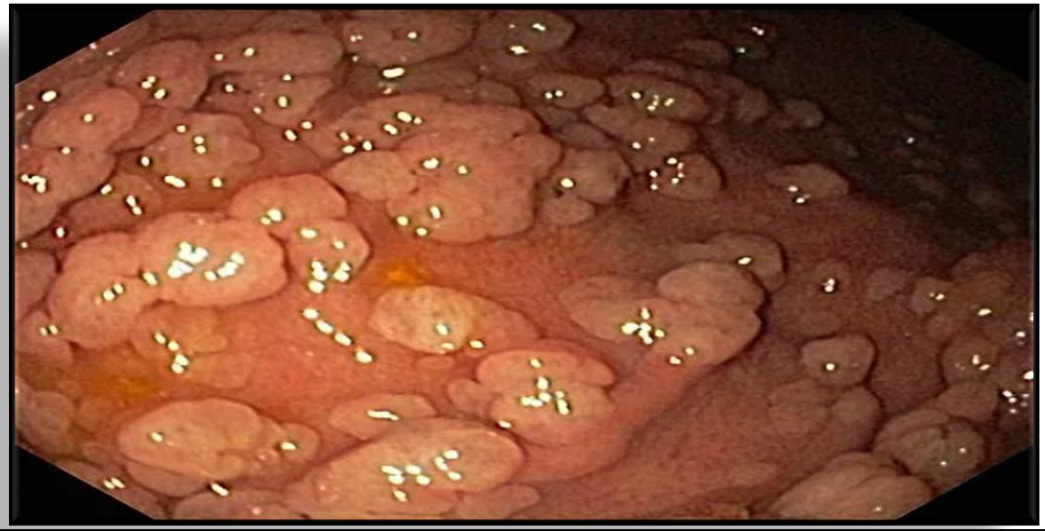
GASTRIC POLYPS

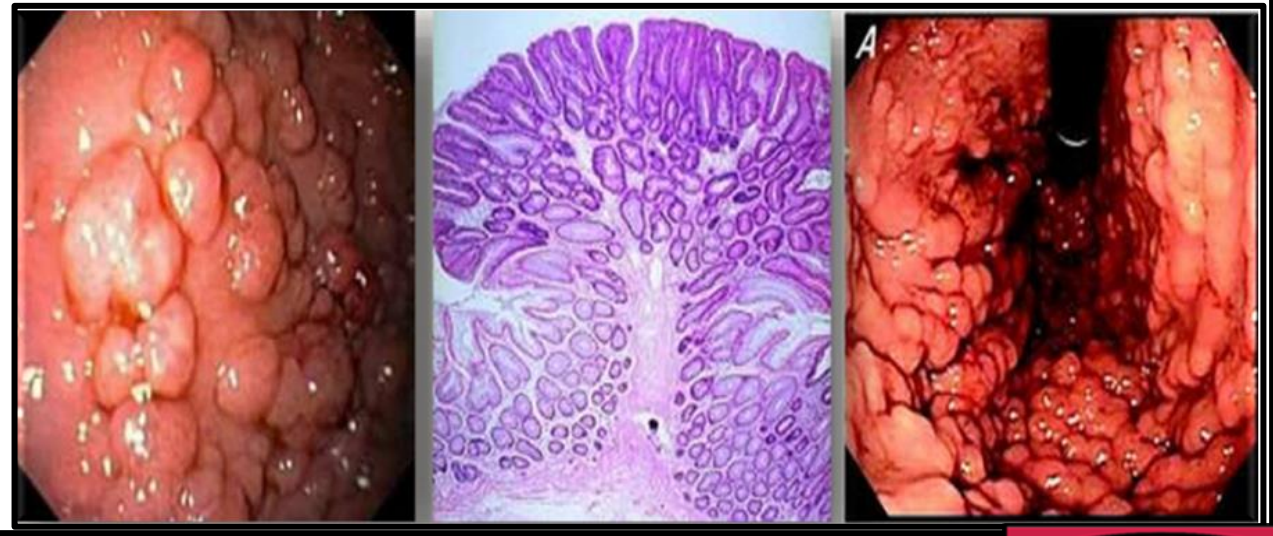
- **Gastric polyps:**
  1. Fundic gland polyps (≈50%) Dysplastic potential:
     - Sporadic **(<1%)** vs **FAP-FGP (25-40%)**
  2. Hyperplastic polyps (≈40%)
  3. Adenomatous polyps (≈10%)

H Pylori common PPI less common	H Pylori less common PPI common
Hyperplastic/ adenoma> Fundic	Fundic> Hyperplastic/ adenoma

FGP IN FAP

- **20-100%** with FAP
- **APC gene**
- **'carpet' the body of the stomach**
- **No evidence** as to how to **differentiate sporadic FGP vs FAP-associated** FGP at endoscopy
- 35 yrs (95%) - FAP have polyps (>100 adenomas)
- The mean age of colon cancer in untreated persons is 39 yrs





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RECOMMENDATION

- BIOPSY **unless ≥1cm** then consider polypectomy
- Polypectomy (sporadic FGPs)
- FGPs have reliable endoscopic features
  - Exclude dysplasia or adenocarcinoma (and possible FAP)
  - Exclude the need for polypectomy
- **Numerous FGP** - **<40 years of age** or **dysplasia**
  - Colonoscopy to exclude FAP (poor evidence)
- NO dysplasia – no follow-up
- Dysplasia – consider FAP (colonoscopy)

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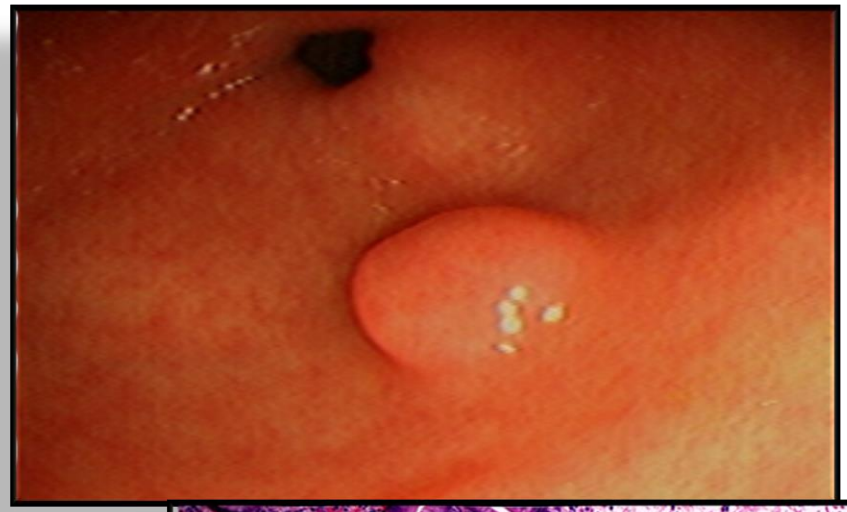
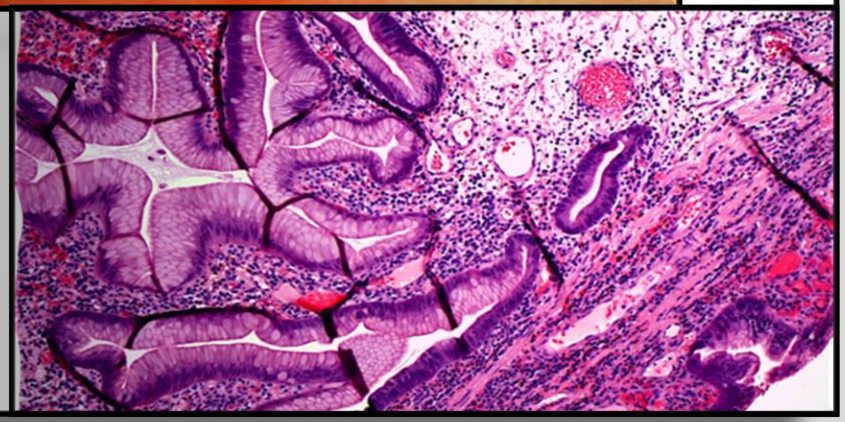
Project ECHO Gastroenterology Foundation of sub Saharan Africa

HYPERPLASTIC POLYPS

- Little neoplastic potential – ?Simply biopsied vs polypectomy
  - Dysplasia (1.9-19%)
  - Adenocarcinoma (0.6-2.1%)
- **sessile or pedunculated**
- Typically occur in the antrum





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RECOMMENDATION

- Biopsy unless >1cm -
- Testing for H pylori and eradication
- Surveillance - single repeat endoscopy at 1 year
- Polyp persist or dysplasia (polypectomy)
  - Repeat EGD in 1year
- No polyp or dysplasia (no F/U)

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ADENOMATOUS POLYPS

- **True neoplasms** and precursors to GC – **6-10%**
- **flat or sessile Tubular, villous and tubulovillous**
- Frequently **solitary**
- **No** proven association with **H pylori infection**
- **>2 cm** and have **villous histology** - neoplasia **(28-40%).**
  - **Tubular adenomas** (5%)
- **HGD** - invasive GC within the polyp & synchronous areas of the stomach

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RECOMMENDATION

- Complete removal of the adenoma
- An examination of the whole stomach should be made for mucosal abnormalities and any abnormalities biopsied
- Endoscopic follow-up is required following resection
  - 6 months for incompletely resected polyps
  - HGD
  - 1 year for all other polyps

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HARMATOUS POLYPS

Peutz–Jeghers'	>50% (extra-GI)	OGD every 2 years after age 18
		Biopsy >5 polyps
		Remove polyps >1 cm
Juvenile polyposis	>50%	OGD every 3 years after age 18
Cowden's	Rare	Eradicate *H pylori*
		No further OGD needed

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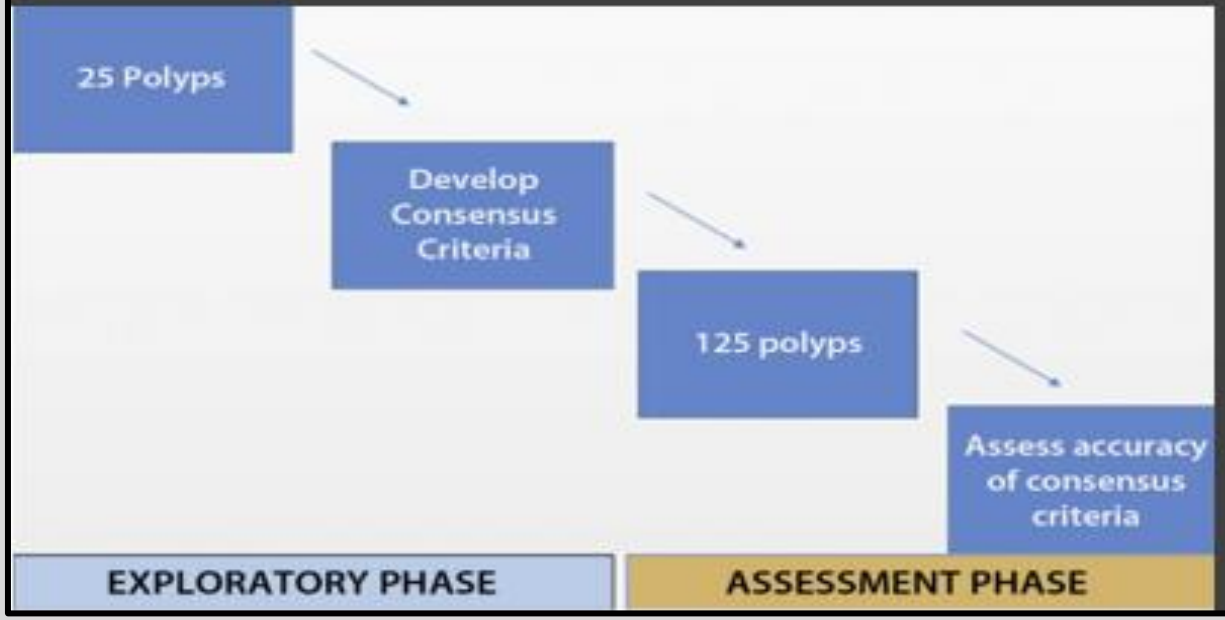
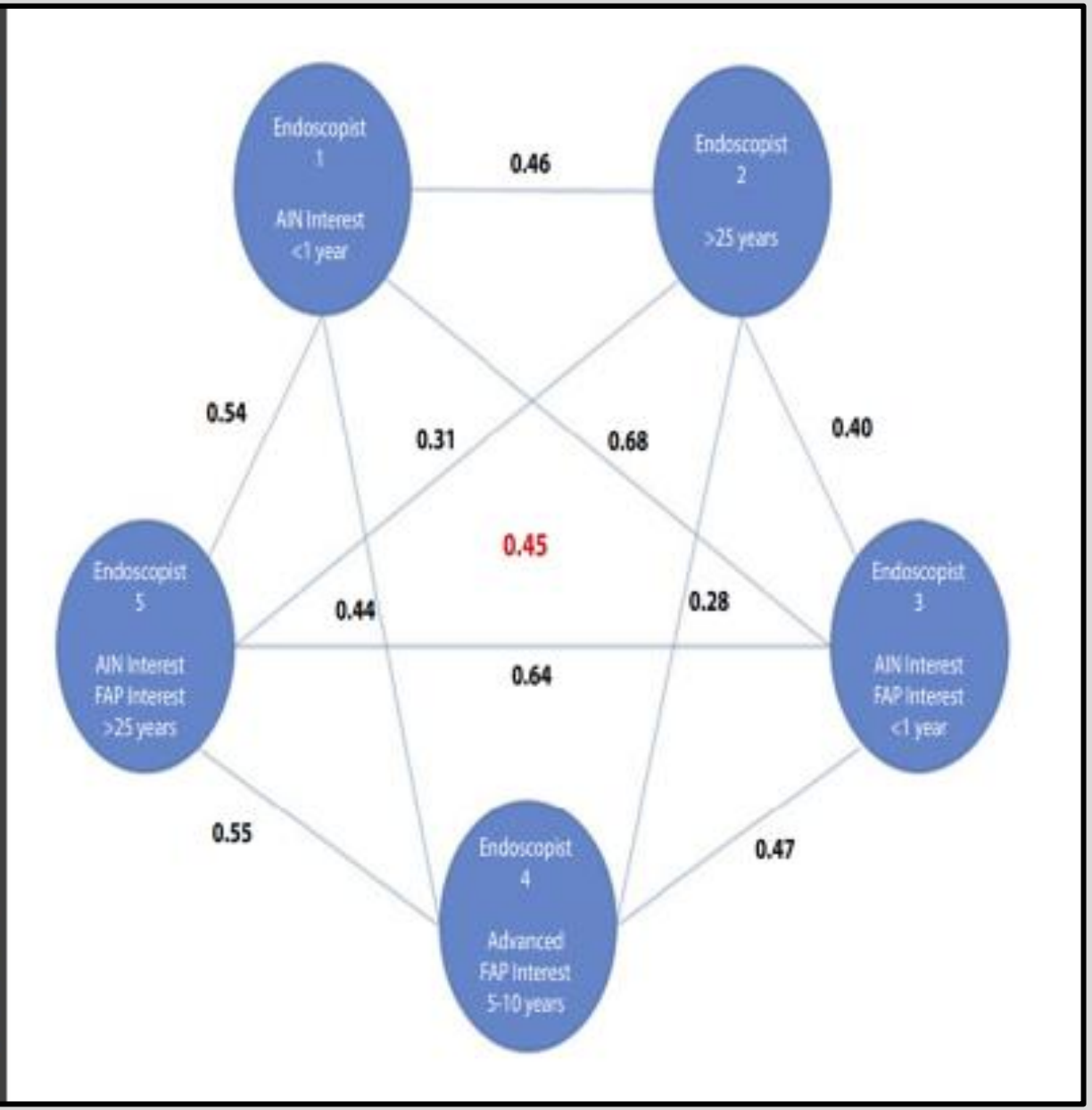
Surveillance for pathology associated with cancer on endoscopy (SPACE): criteria to identify high-risk gastric polyps in familial adenomatous polyposis

Gautam N. Mankaney, MD,[1,2] Michael Cruise, MD, PhD,[2,3] Shashank Sarvepalli, MD,[4] Amit Bhatt, MD,[1,2] Zubin Arora, MD,[1] Brian Baggot, MD,[1] Lisa Laguardia, RN,[2,5] Margaret O'Malley,[2,5] James Church, MD,[2,5] Matthew Kalady, MD,[2,5] Carol A. Burke, MD[1,2,5]

Cleveland, Ohio, USA





Criteria for Gastric Polyps

- Color in comparison to background mucosa - same, lighter, or darker
- Pitt pattern - open vs closed
- Surface - not smooth (irregular/bumpy/nodular) vs smooth
- NBI vs White light - same features seen on both vs NBI highlights more features

High Risk (pyloric gland adenoma, tubular adenoma, hyperplastic)

-Color - lighter or darker than surrounding mucosa

-Pitt pattern - open.

-Surface - not smooth (irregular, bumpy, nodular)

-NBI vs white light - appear similar

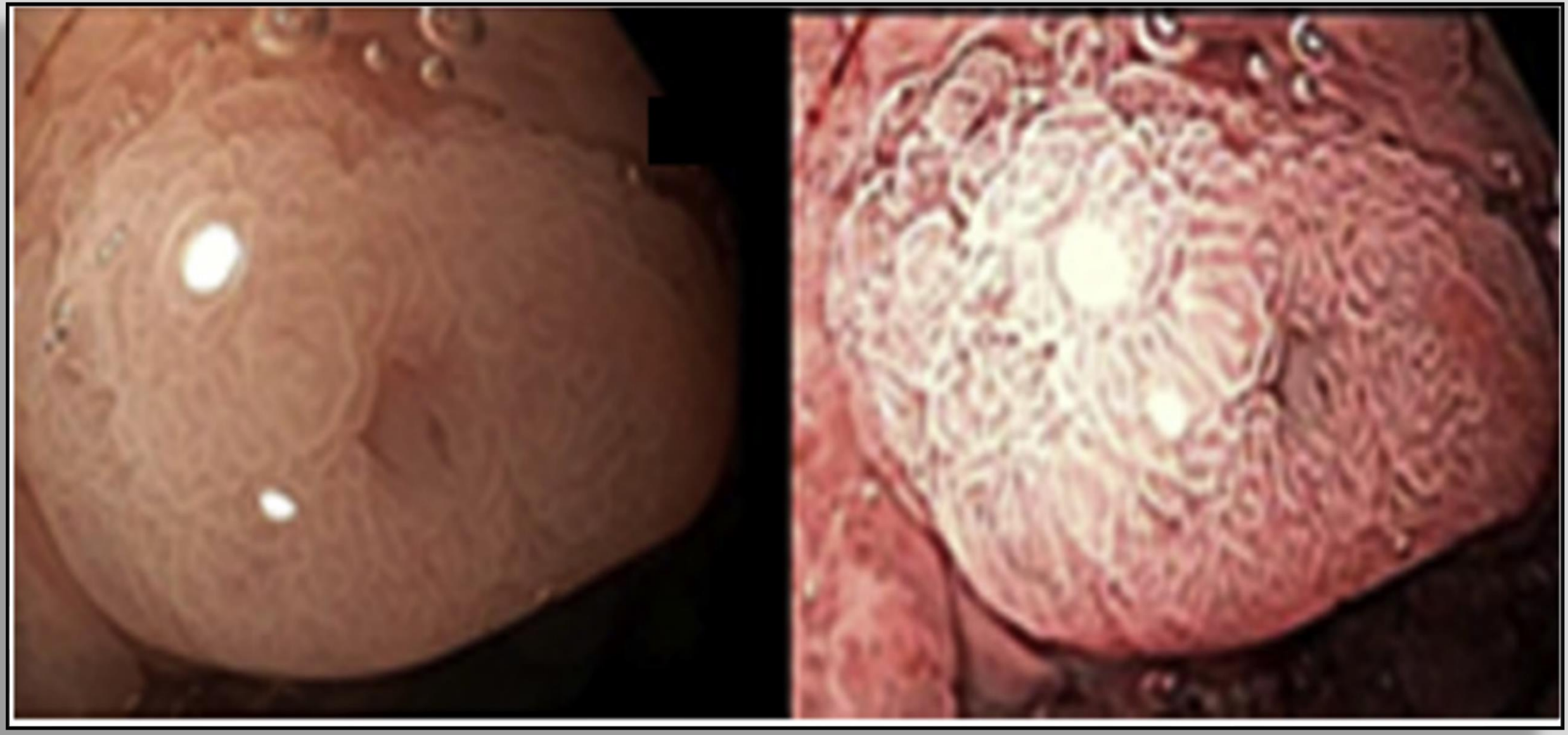
Low risk (gastric mucosa, fundic gland polyps with no to low grade dysplasia)

-Color - same as surrounding mucosa (or red)

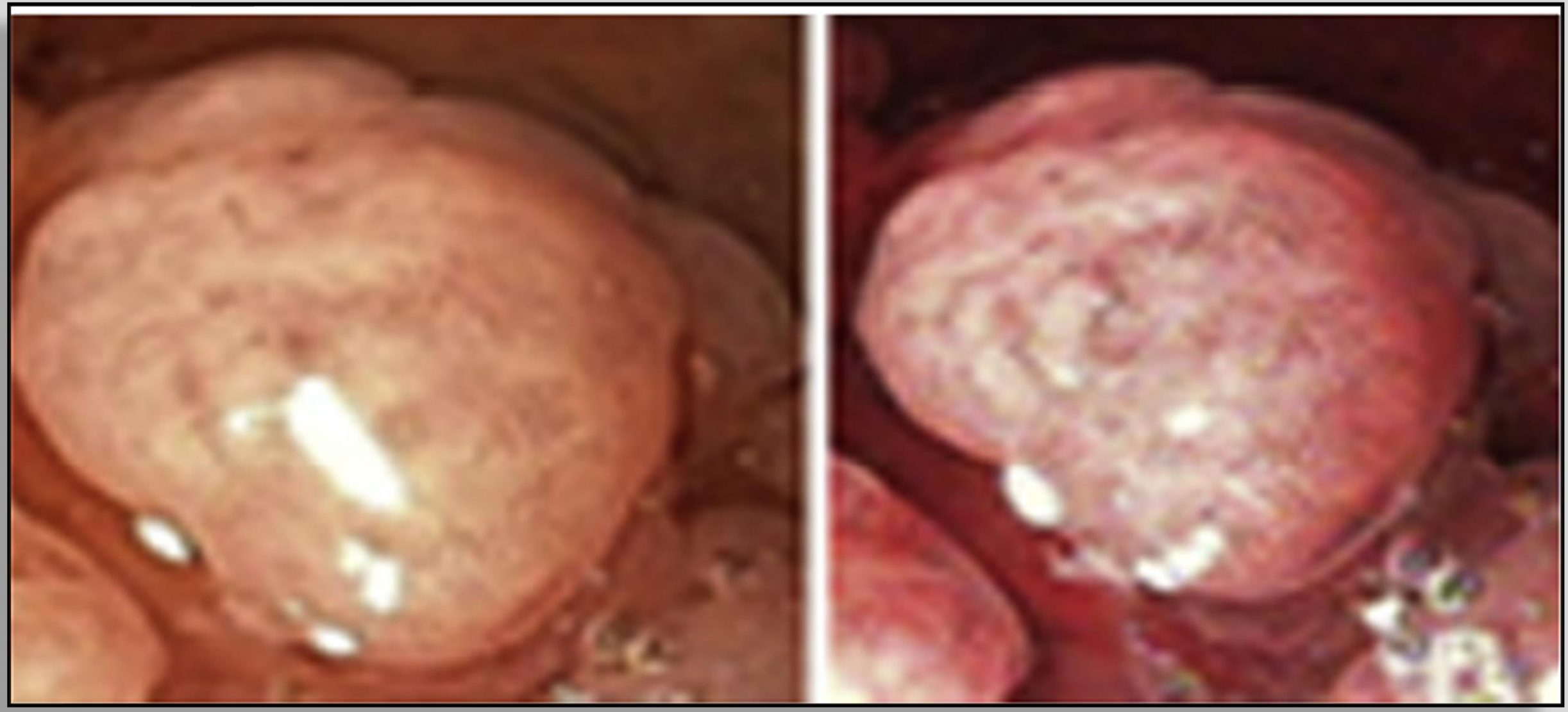
-Pitt pattern - closed.

-Surface - smooth

-NBI vs White light - more features seen with NBI



HIGH RISK - Pyloric gland adenoma (PGA) with low-grade dysplasia



Low Risk - FGPs without dysplasia

OTHER LESIONS

1. **Meneteriers**- rare with 15% GC
   - Enlarged gastric folds foveolar cell hyperplasia, edema, and variable degrees of inflammation
   - Hp, CMV, and HIV
   - No recommendations regarding endoscopic surveillance

2. **Previous gastrectomy** - 20 yrs post-op **(anastomosis site)**
   1. **Hypochlorhydria** – bacterial overgrowth (nitrites)
   2. **Chronic enterogastric reflux** of bile salts and pancreatic enzymes
   3. **Atrophy** remaining fundic mucosa due to low levels gastrin
      - **Billroth II with GJ > Billroth I with GD (4-fold) – BILE SALT REFLUX**
3. **PUD** Hx –1.8X risk GC

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TAKE HOME MESSAGE

- GC IS POTENTIALLY PREVENTABLE
- H.PYLORI RESISTANCE IS EMERGING
- PAUCITY OF DATA FOR OUR RESISTANCE
- METHODICAL APPROACH - DIFFICULT TO TREAT

THANK YOU FOR YOUR TIME

Project ECHO®
Gastroenterology Foundation of sub Saharan Africa