Richard D. McKenna 2020 Memorial Lecture

Rick Peek

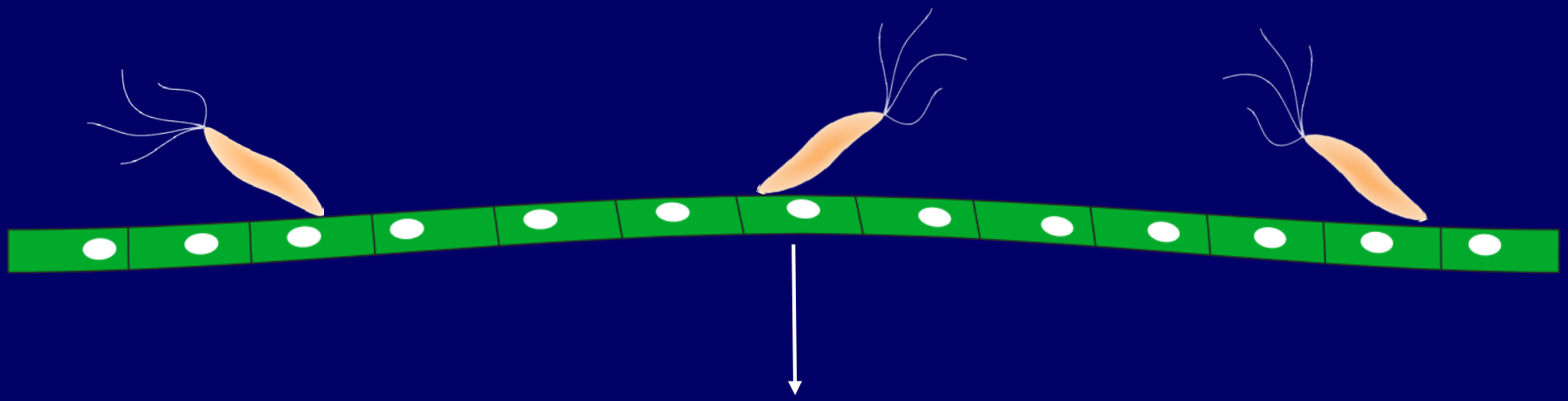
Vanderbilt University Medical Center

Disruptive and Enabling Relationships That Promote *Helicobacter pylori*-Induced Gastric Cancer

Disclosures:

None

Host responses to *H. pylori* virulence constituents influence carcinogenesis



Gastric inflammation

Decades

Distal gastric adenocarcinoma

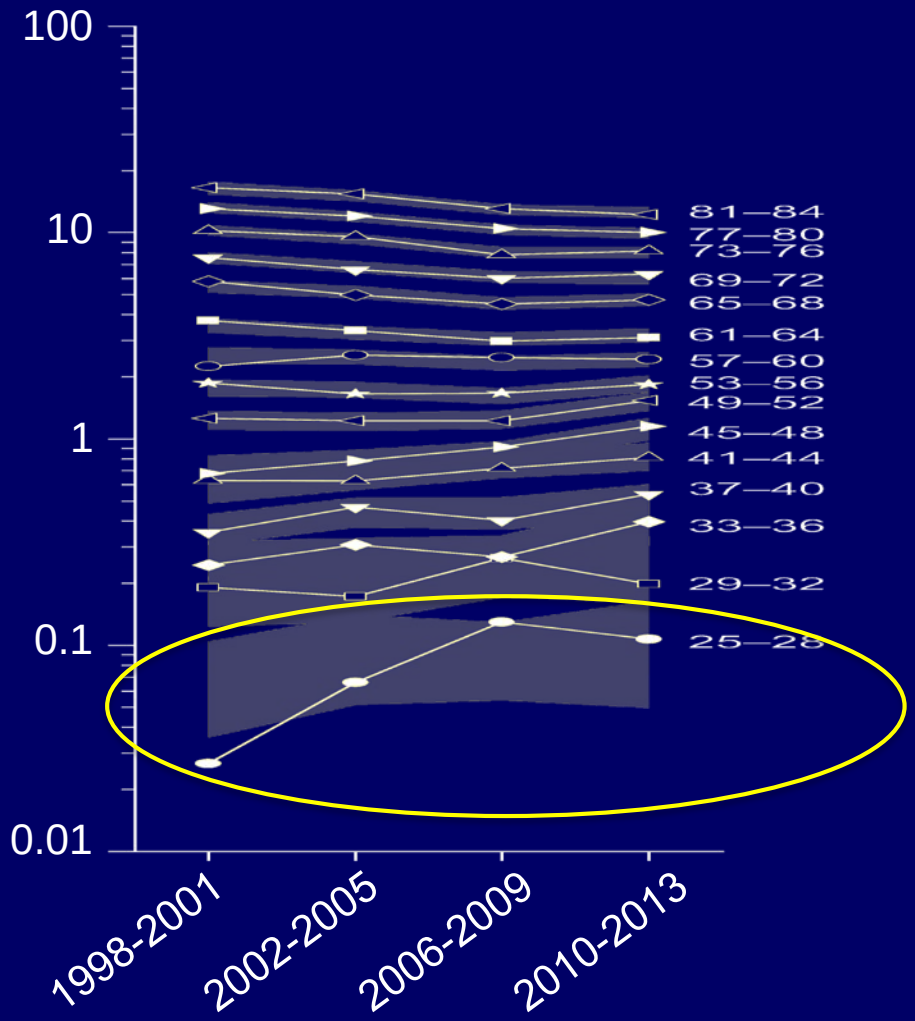
Adenocarcinoma of the Stomach

Third leading cause of cancer-related death worldwide

Estimated 800,000 deaths/year

Age-specific incidence trends of noncardia gastric cancer among non-Hispanic white women

Rate per 100,000 person-years



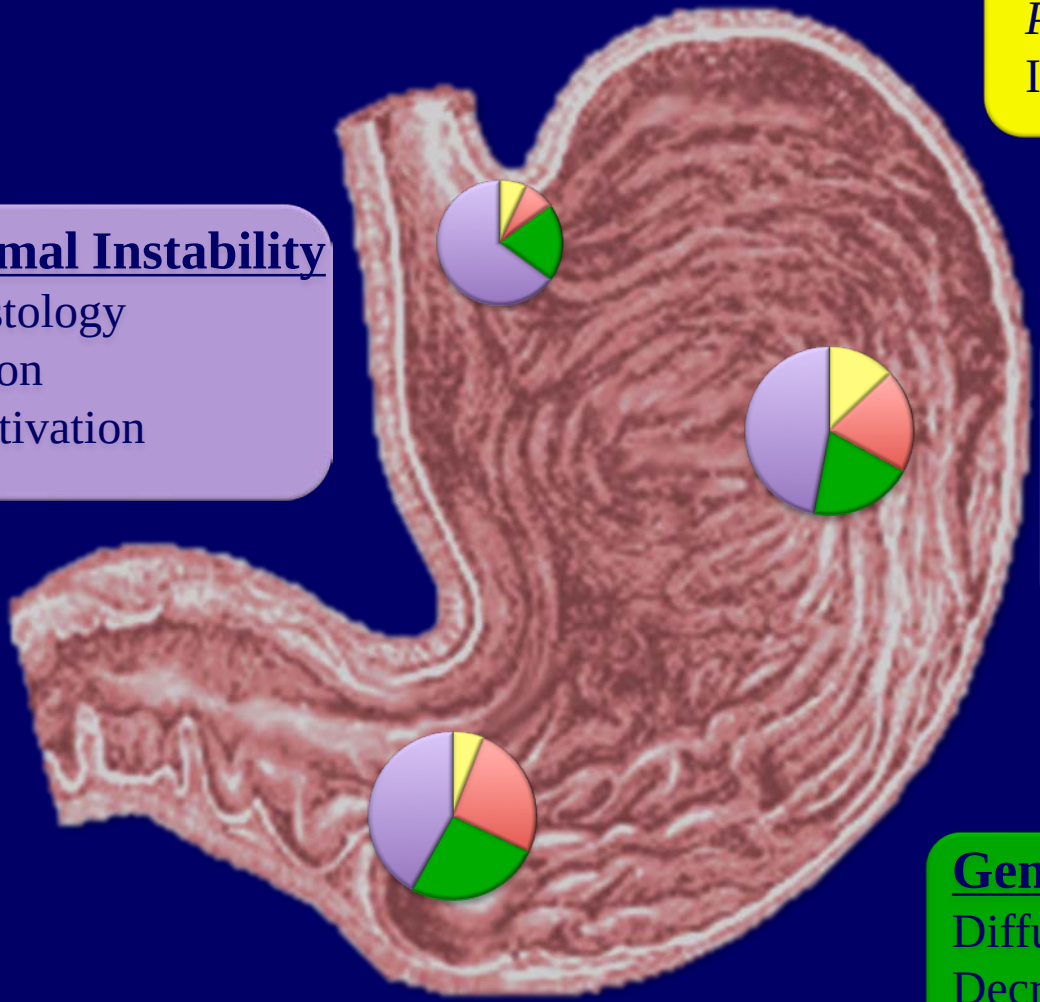
Year of diagnosis

Anderson et al., *JNCI*, 2017

Key molecular features of gastric cancer subtypes

EBV
PI3KCA mutation
Immune cell signaling

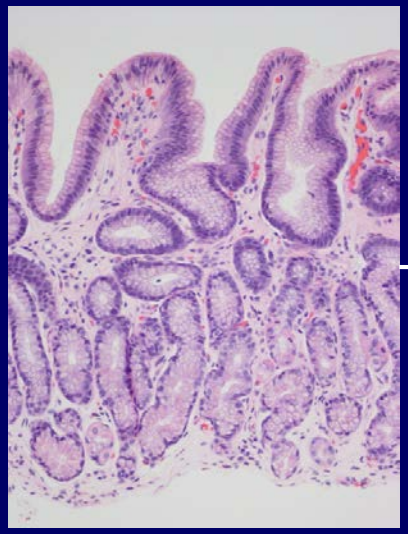
Chromosomal Instability
Intestinal histology
TP53 mutation
RTK-RAS activation



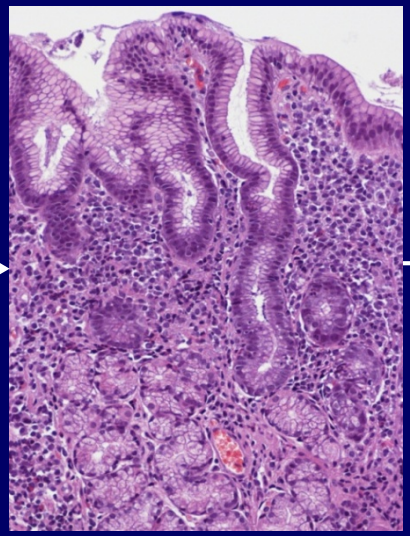
Microsatellite Instability
Hypermutation
Gastric-CpG island methylator phenotype
MLH1 silencing

Genomically Stable
Diffuse histology
Decreased cell adhesion

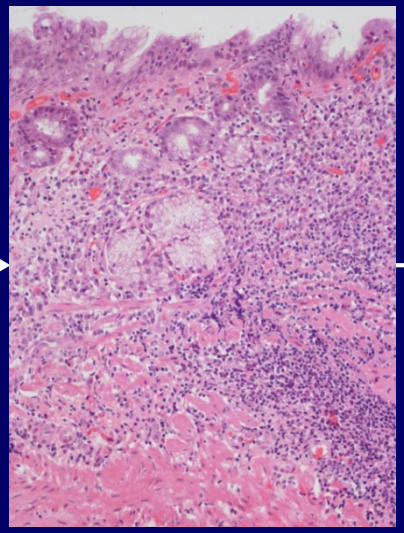
The Cancer Genome Atlas Network, *Nature*, 2014



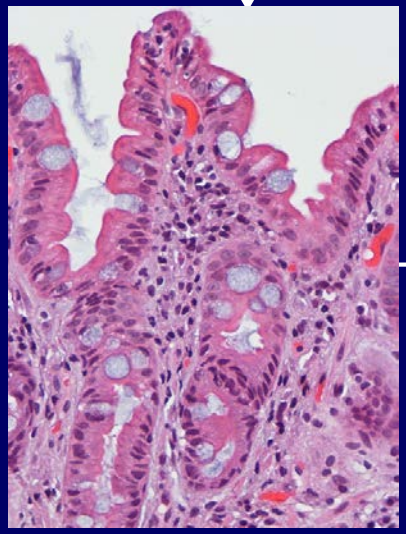
Normal



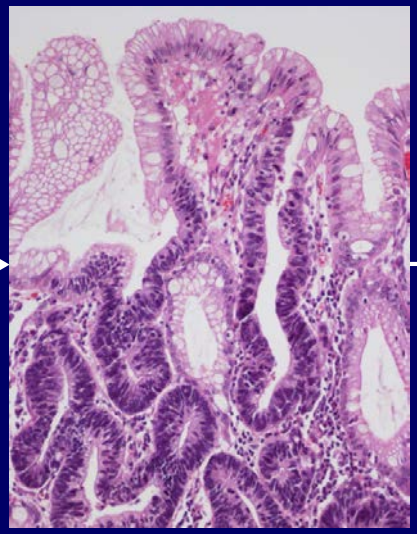
Non-atrophic gastritis



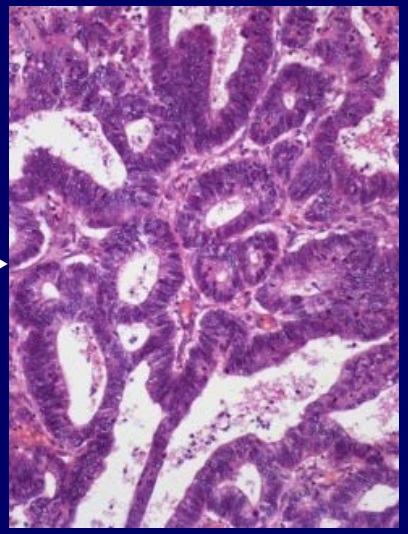
Atrophic gastritis



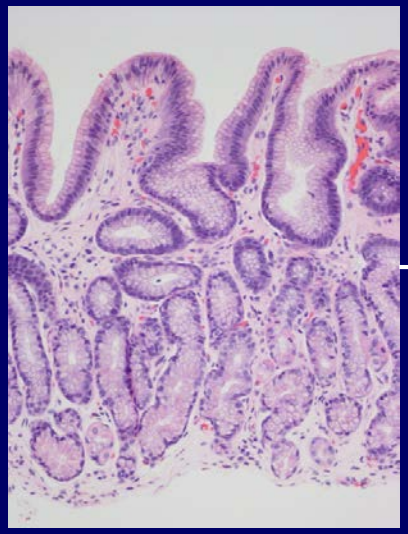
SPEM/Intestinal metaplasia



Dysplasia

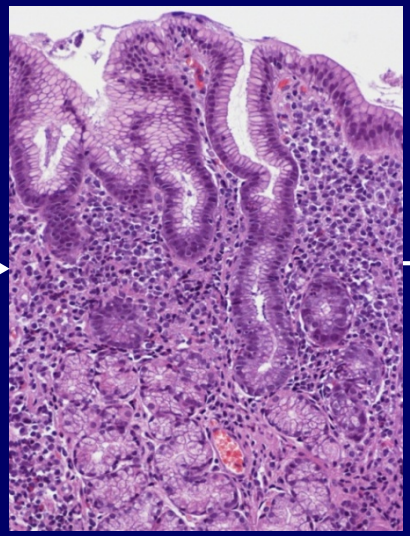


Cancer



Normal

H. pylori



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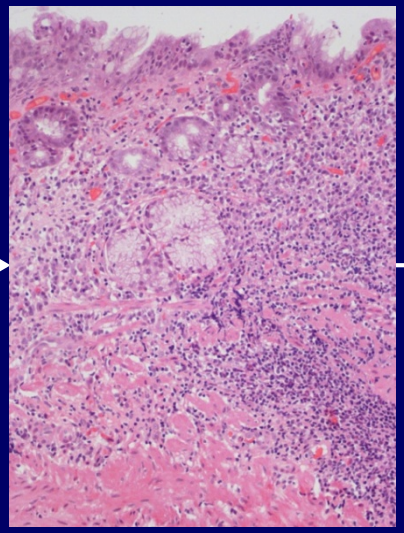
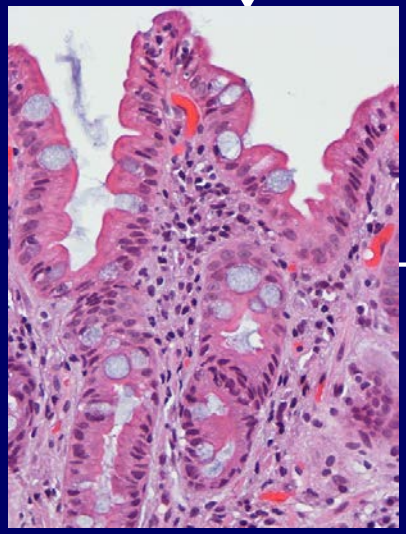
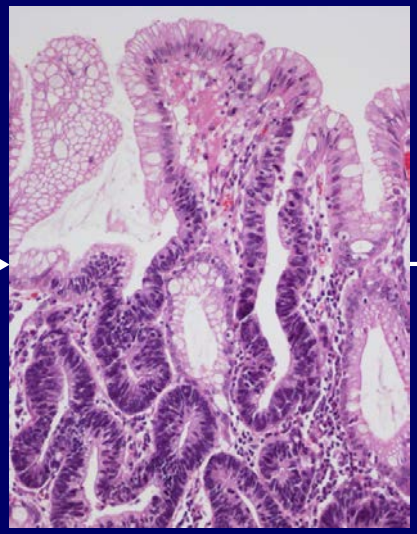


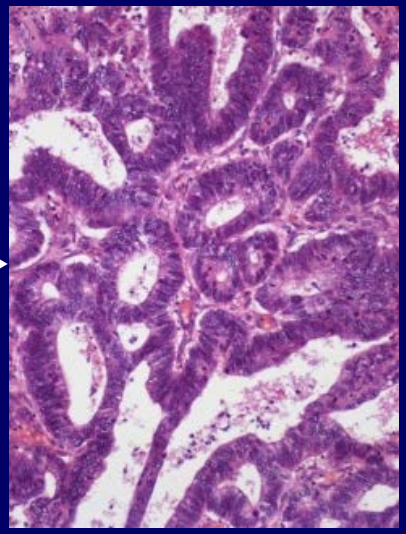
Atrophic gastritis



SPEM/Intestinal metaplasia



Dysplasia



Cancer

The NEW ENGLAND JOURNAL of MEDICINE

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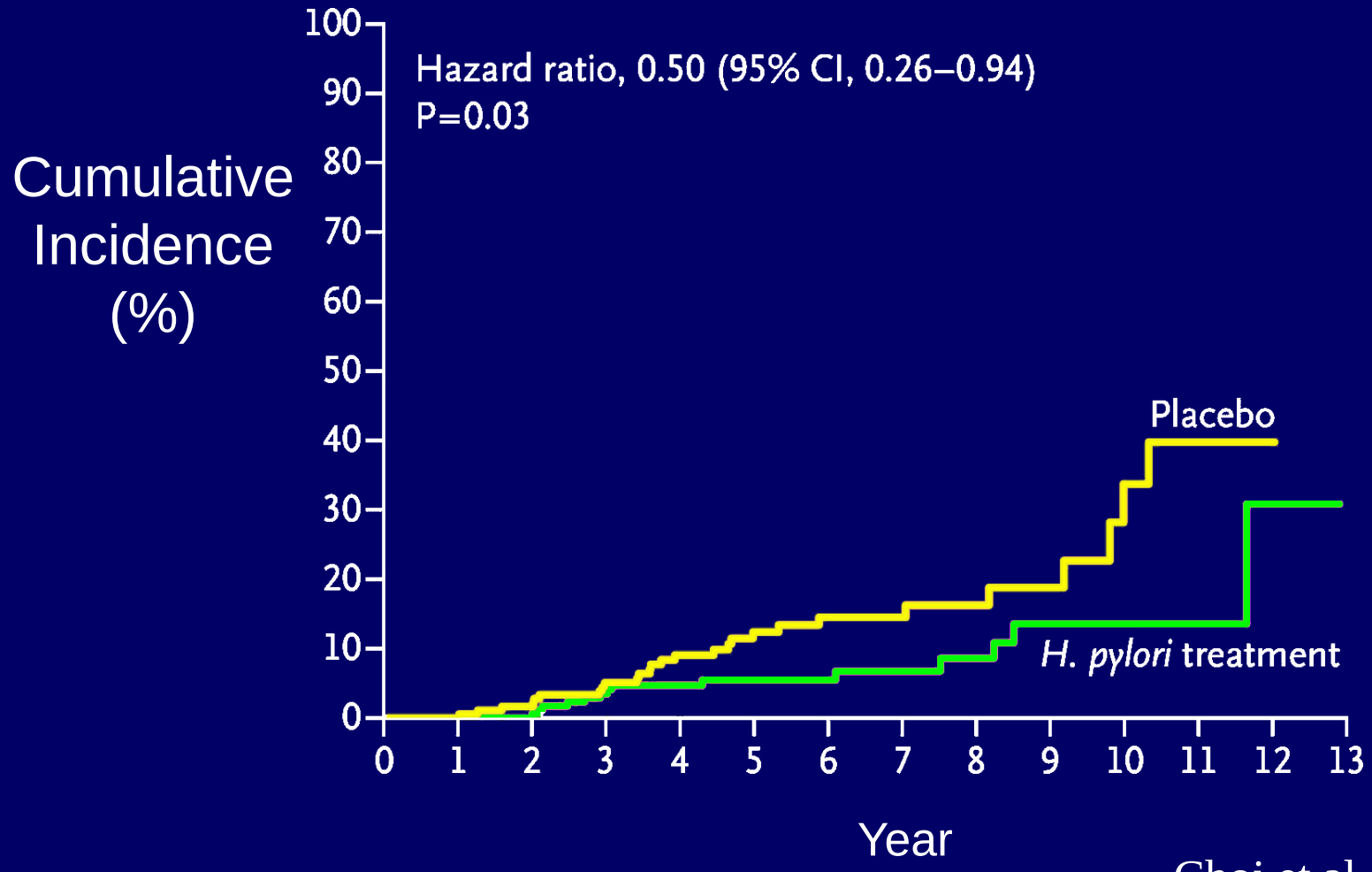
Helicobacter pylori Therapy for the Prevention of Metachronous Gastric Cancer

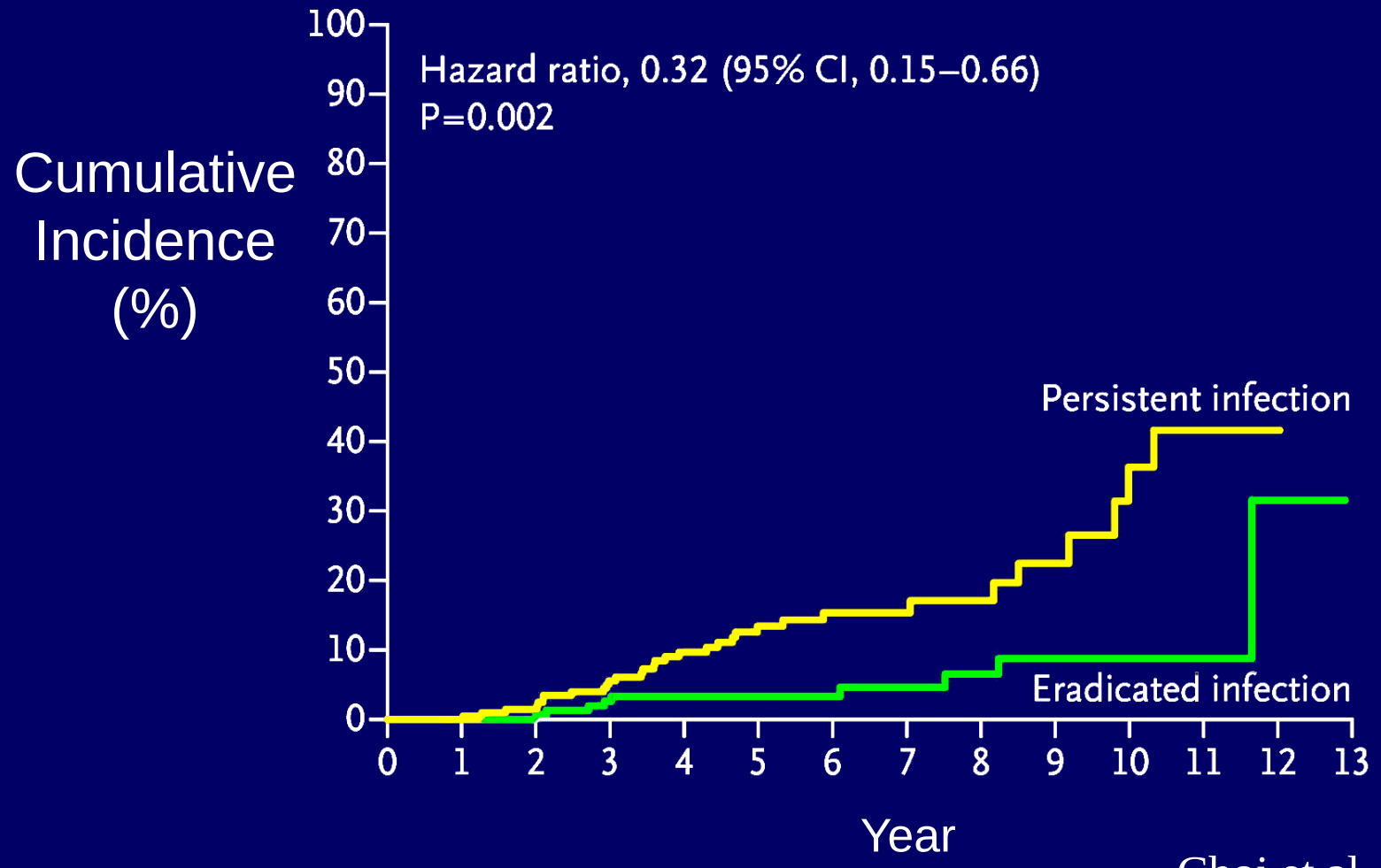
Il Ju Choi, M.D., Ph.D., Myeong-Cherl Kook, M.D., Ph.D., Young-Il Kim, M.D., Soo-Jeong Cho, M.D., Ph.D., Jong Yeul Lee, M.D., Chan Gyoo Kim, M.D., Ph.D., Boram Park, M.S., and Byung-Ho Nam, Ph.D.

Analysis of the incidence of metachronous gastric cancer



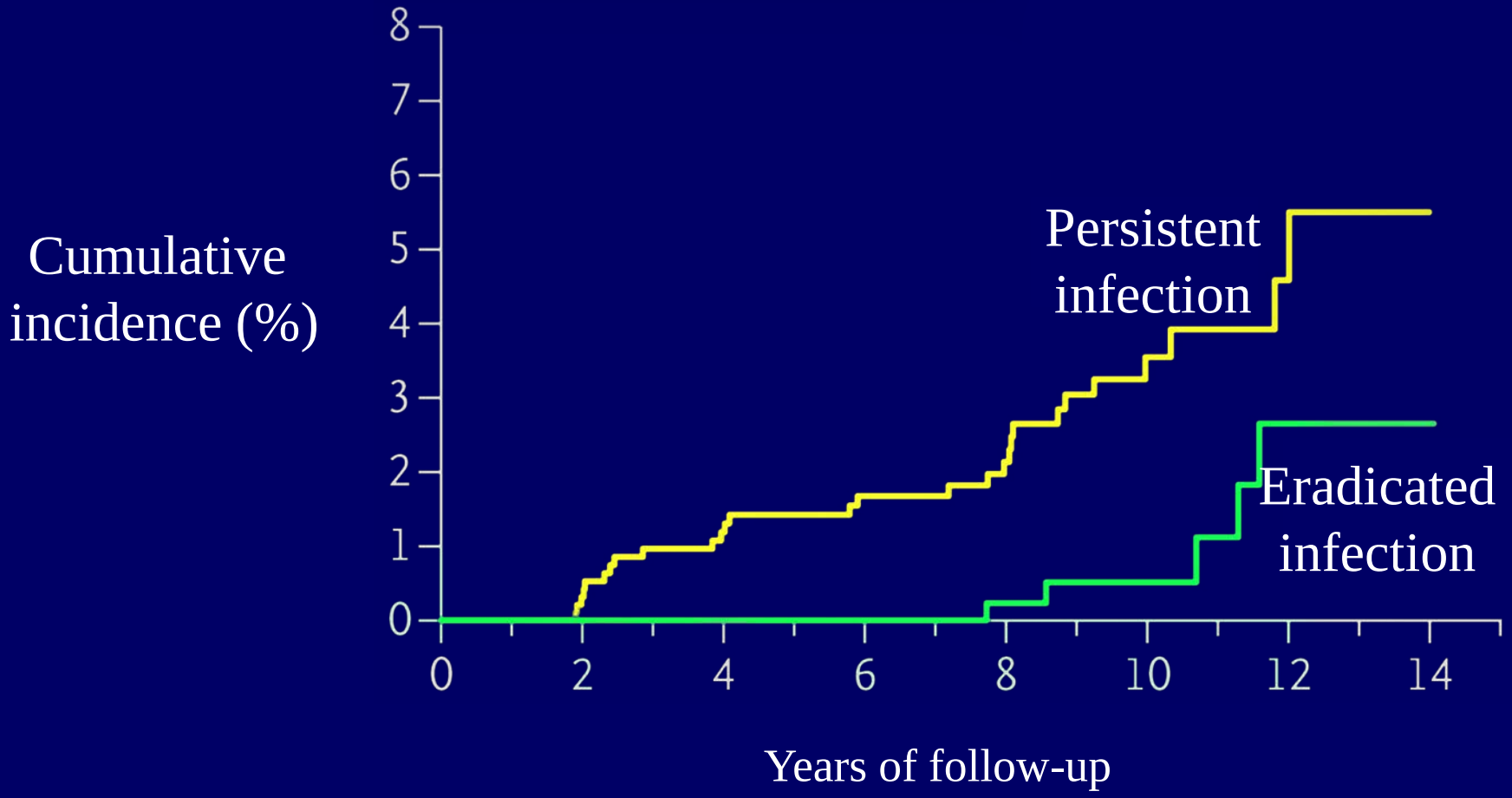
Choi et al., *NEJM*, 2018

Analysis of the incidence of metachronous gastric cancer, according to *H. pylori* status after trial medication



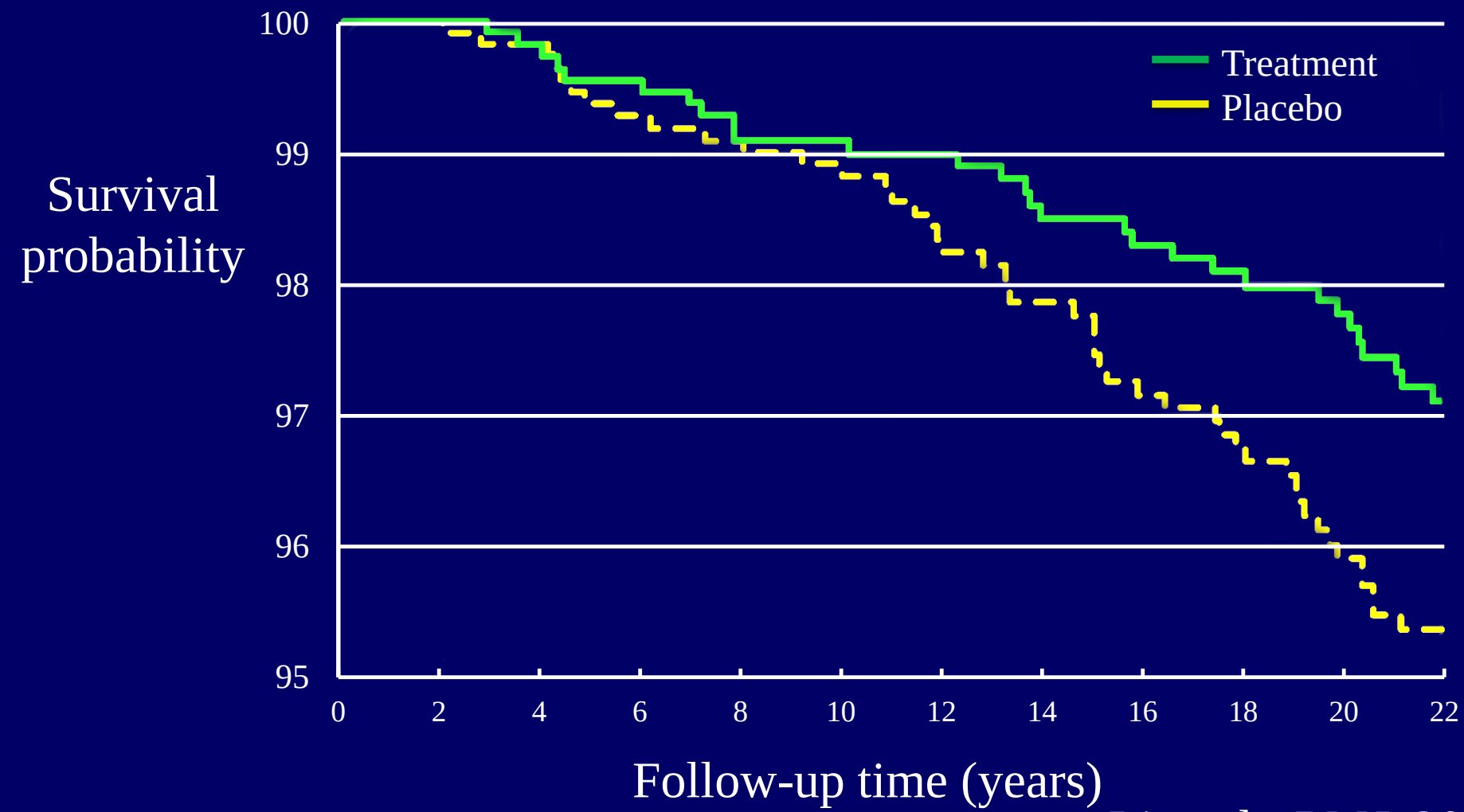
Choi et al., *NEJM*, 2018

Incidence of Gastric Cancer in First Degree Relatives Stratified by Eradication Status



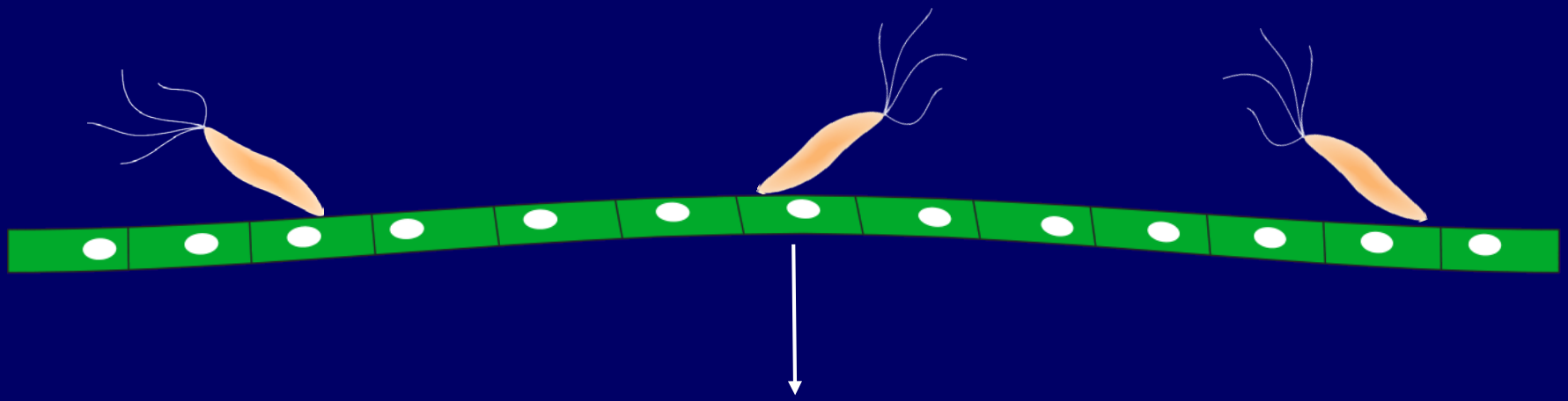
Choi et al., *NEJM*, 2020

Survival estimates for gastric cancer mortality by *H. pylori* treatment in China



Li et al., *BMJ*, 2019

Host responses to *H. pylori* virulence constituents influence carcinogenesis

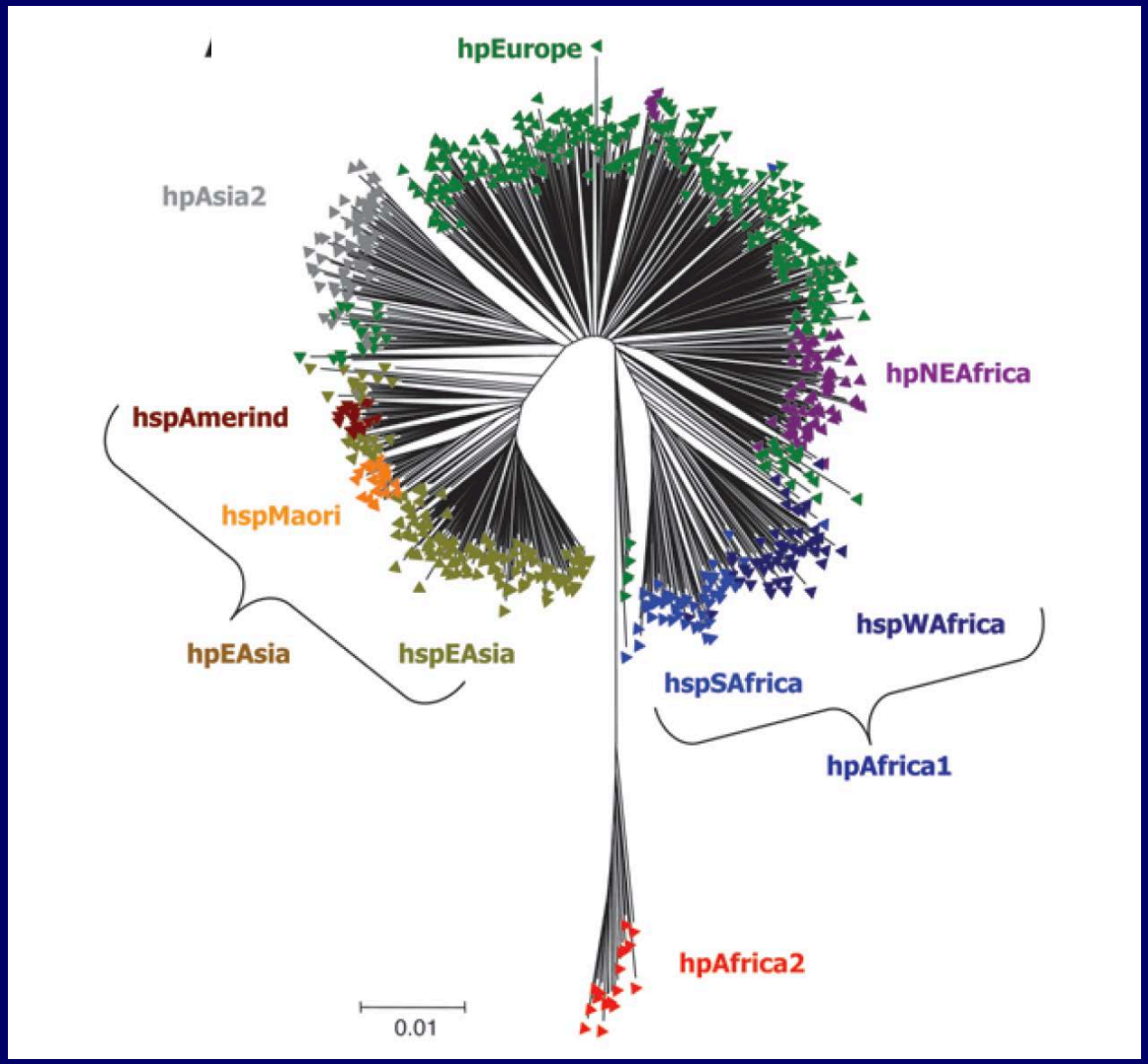


Gastric inflammation

Decades

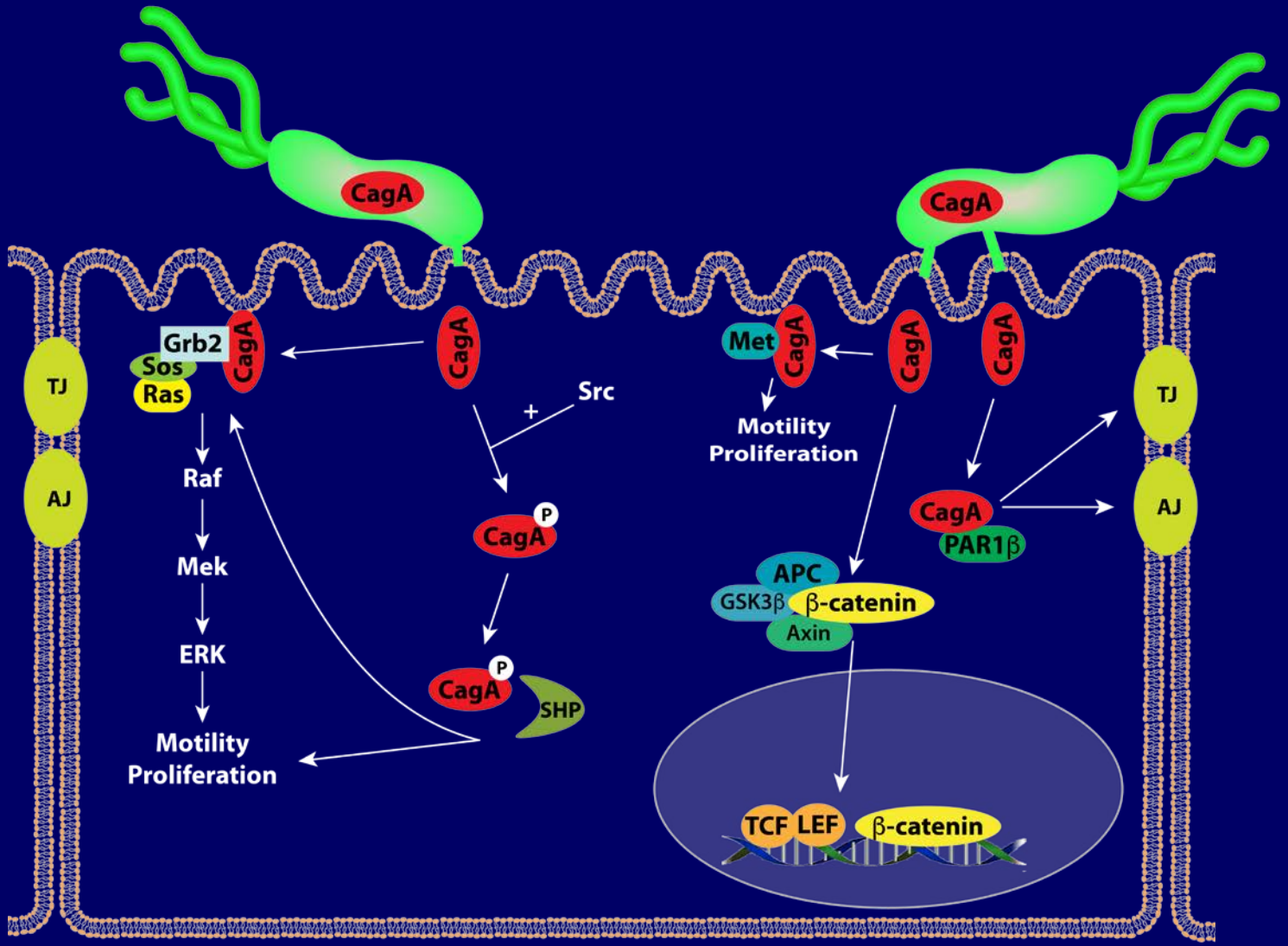
Distal gastric adenocarcinoma (1-3%)

Phylogeography of *H. pylori*

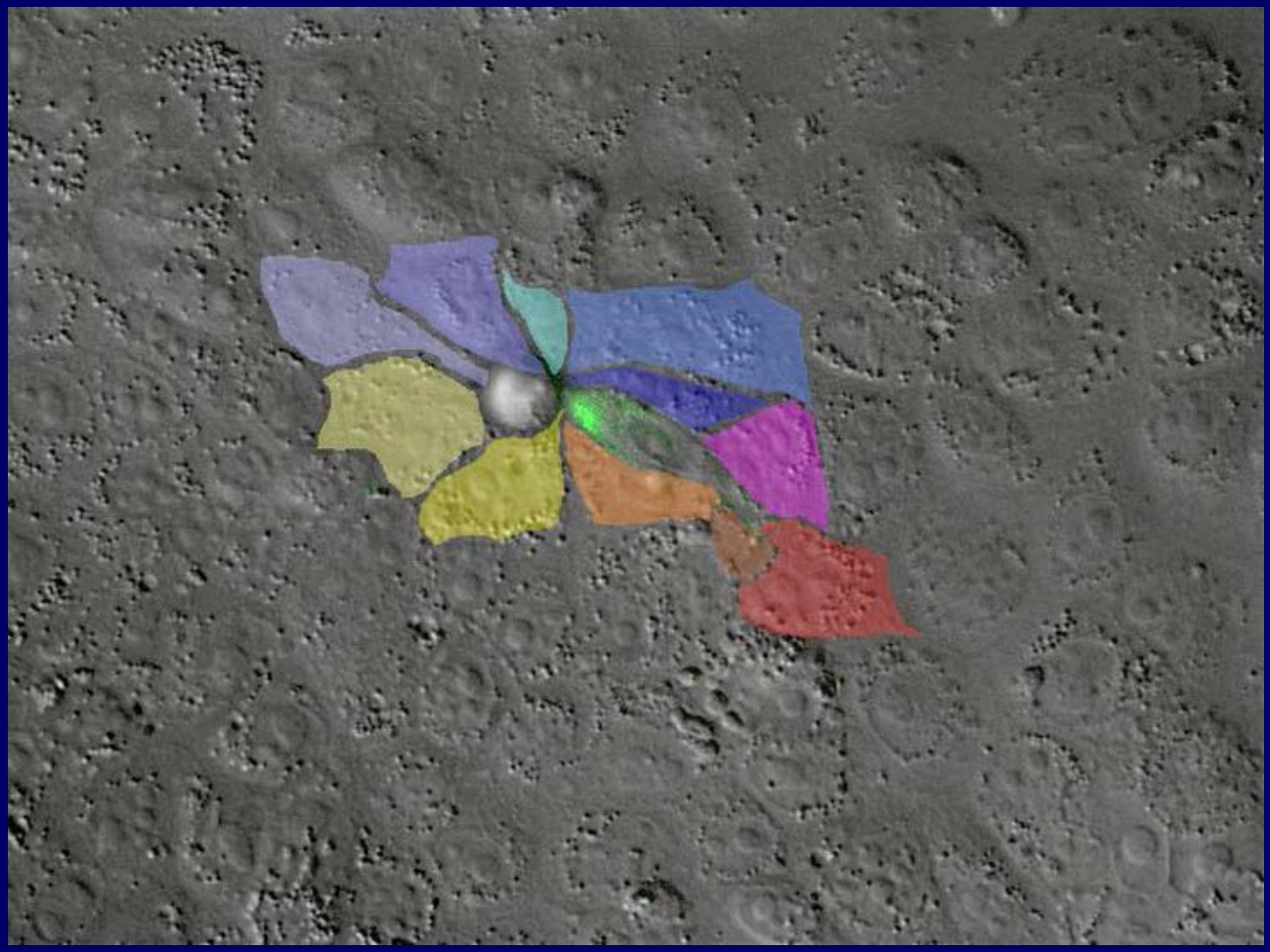


Linz et al., *Nature*

Molecular signaling alterations induced by *cag* T4SS-mediated translocation of CagA



CagA expressing cells acquire a migratory and invasive phenotype



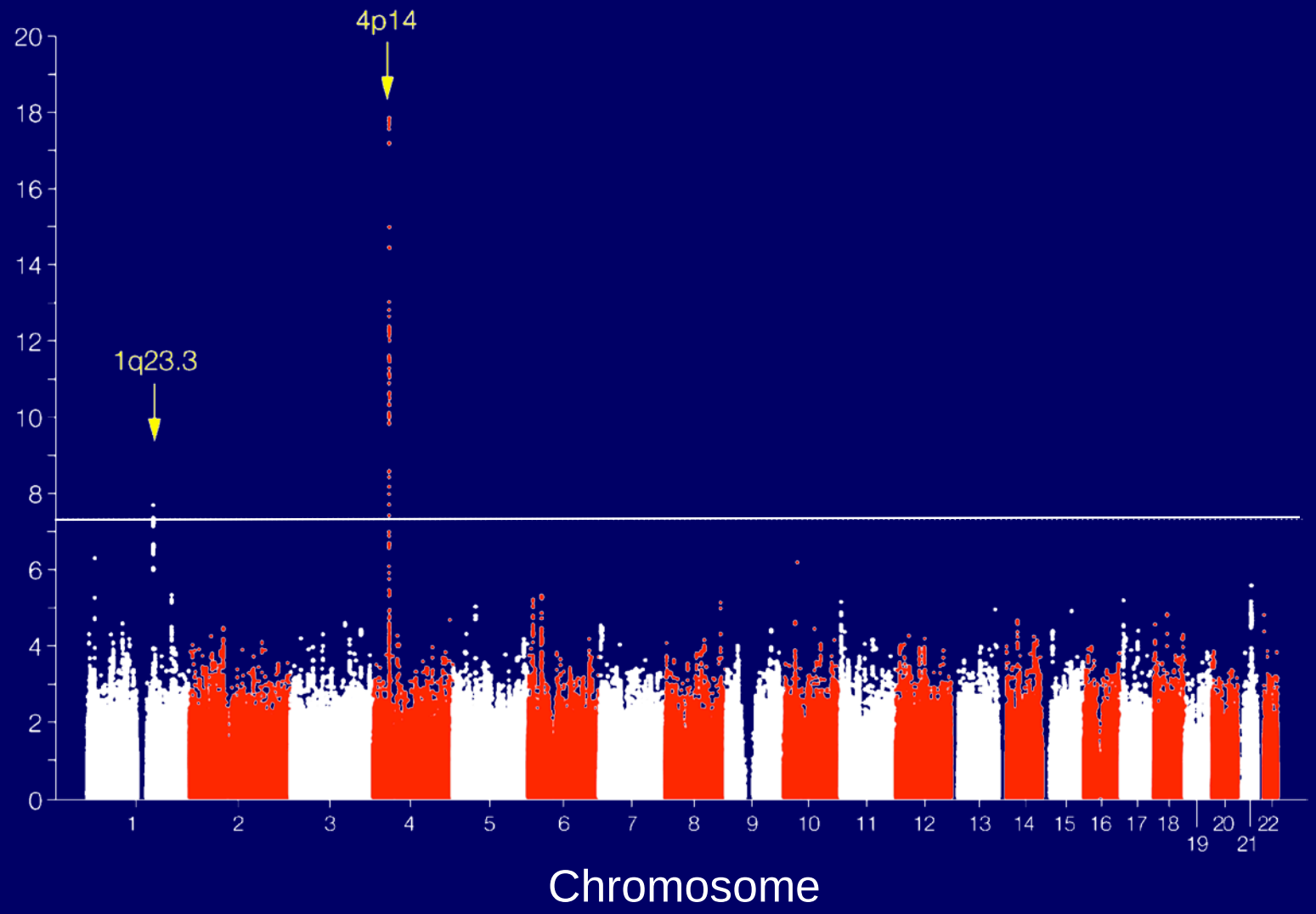
Helicobacter pylori VacA Toxin

Strain-specific alleles associated with gastric cancer

Cancer-associated alleles recently shown to facilitate *H. pylori* host evasion via creation of an intracellular niche

Capurro M *et al.*, *Nature Microbiology*, 2019

Significance of association for SNPs and anti-*H. pylori* seropositivity

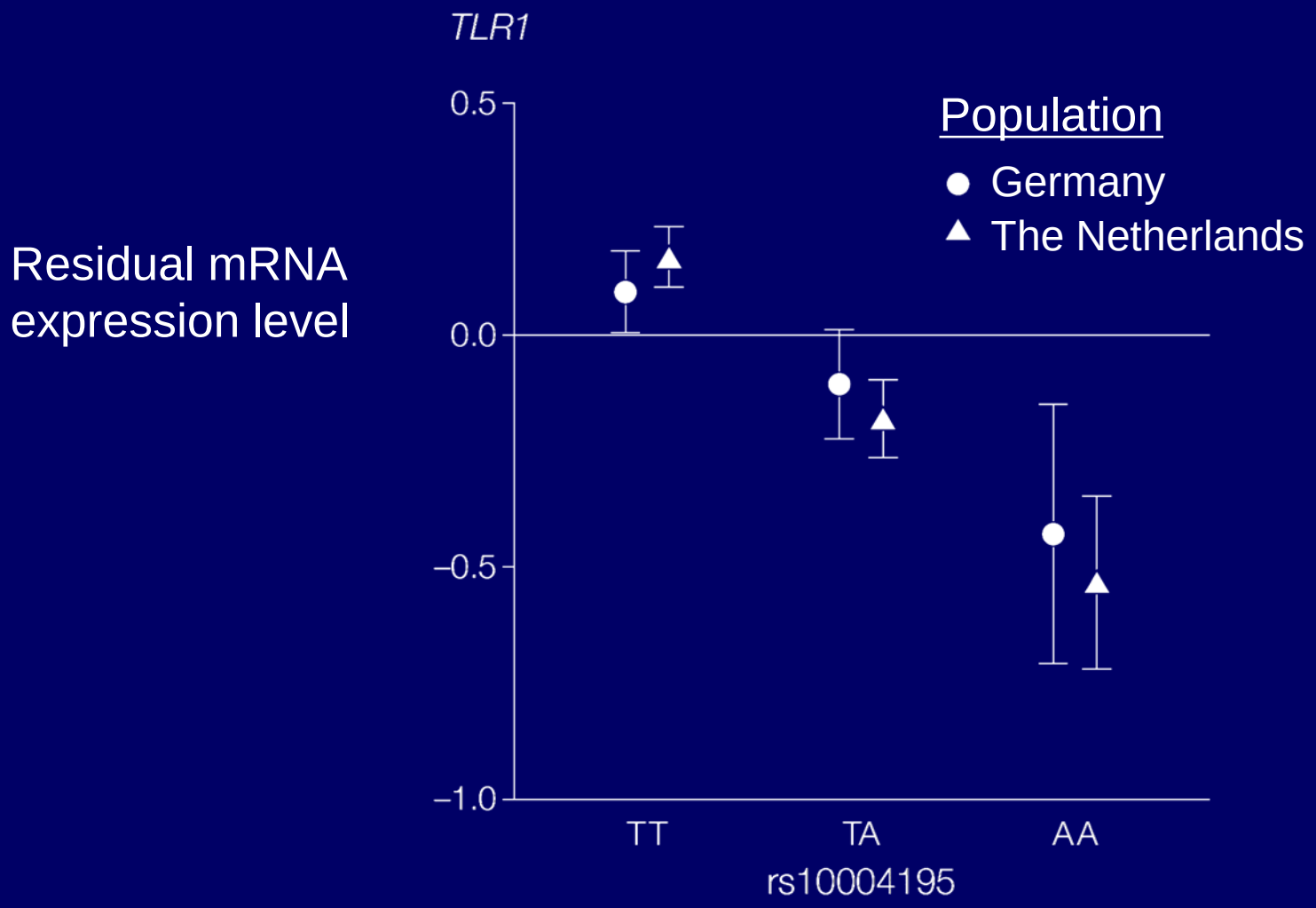


$-\log_{10}$ (*P* value)

Chromosome

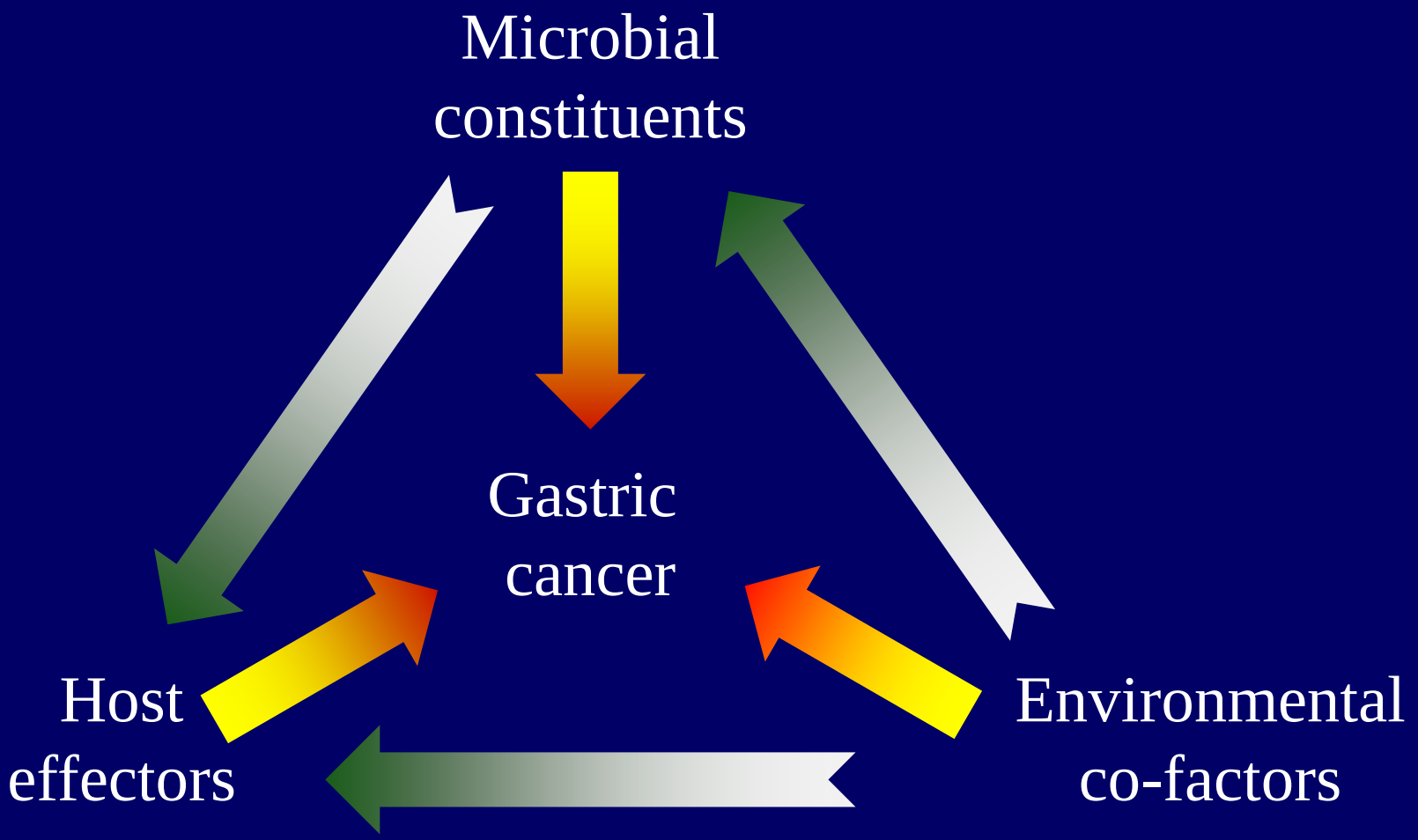
Mayerle *et al*., *JAMA*

TLR1 expression levels corresponding tors10004195 *TLR1* SNP



Mayerle *et al*., *JAMA*

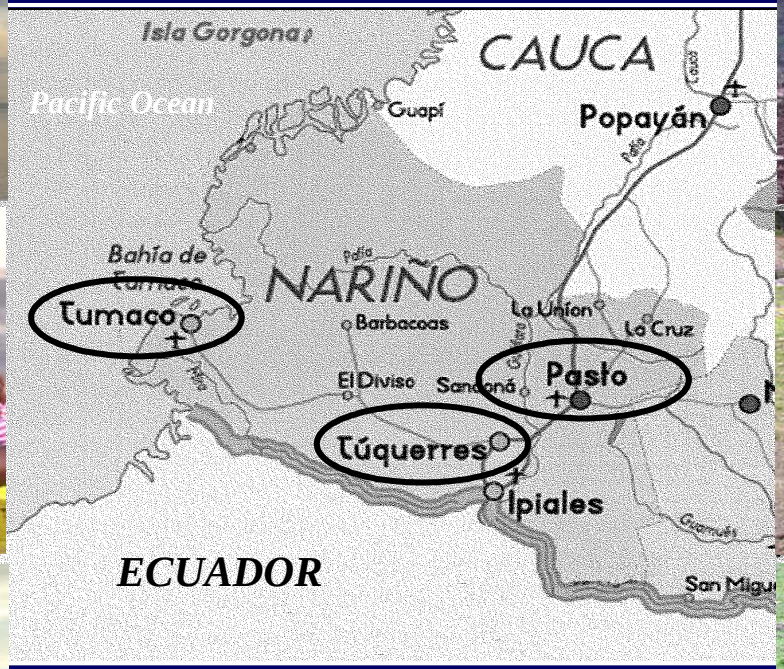
H. pylori-induced gastric cancer: an axis of evil



Nariño, Colombia

Low-risk area

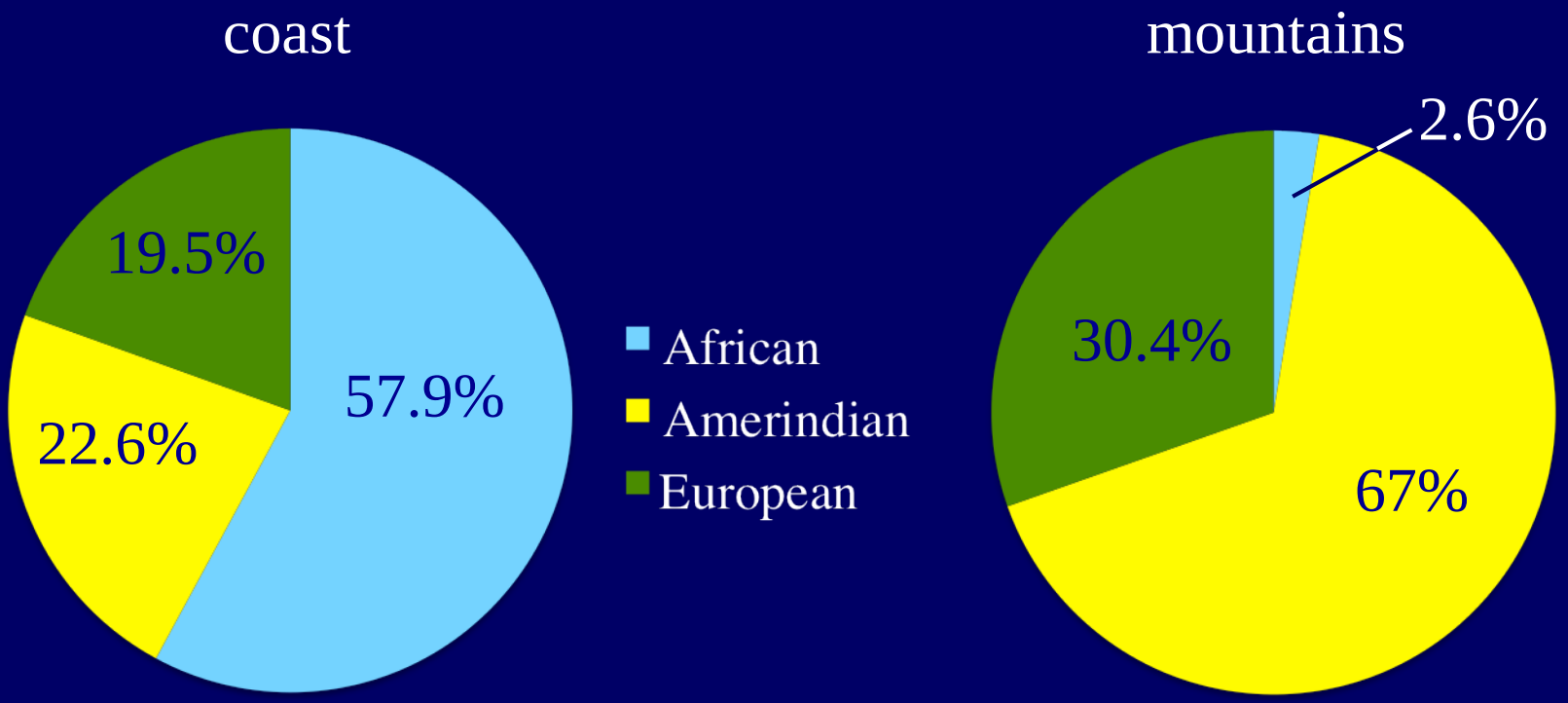
(6/100,000)



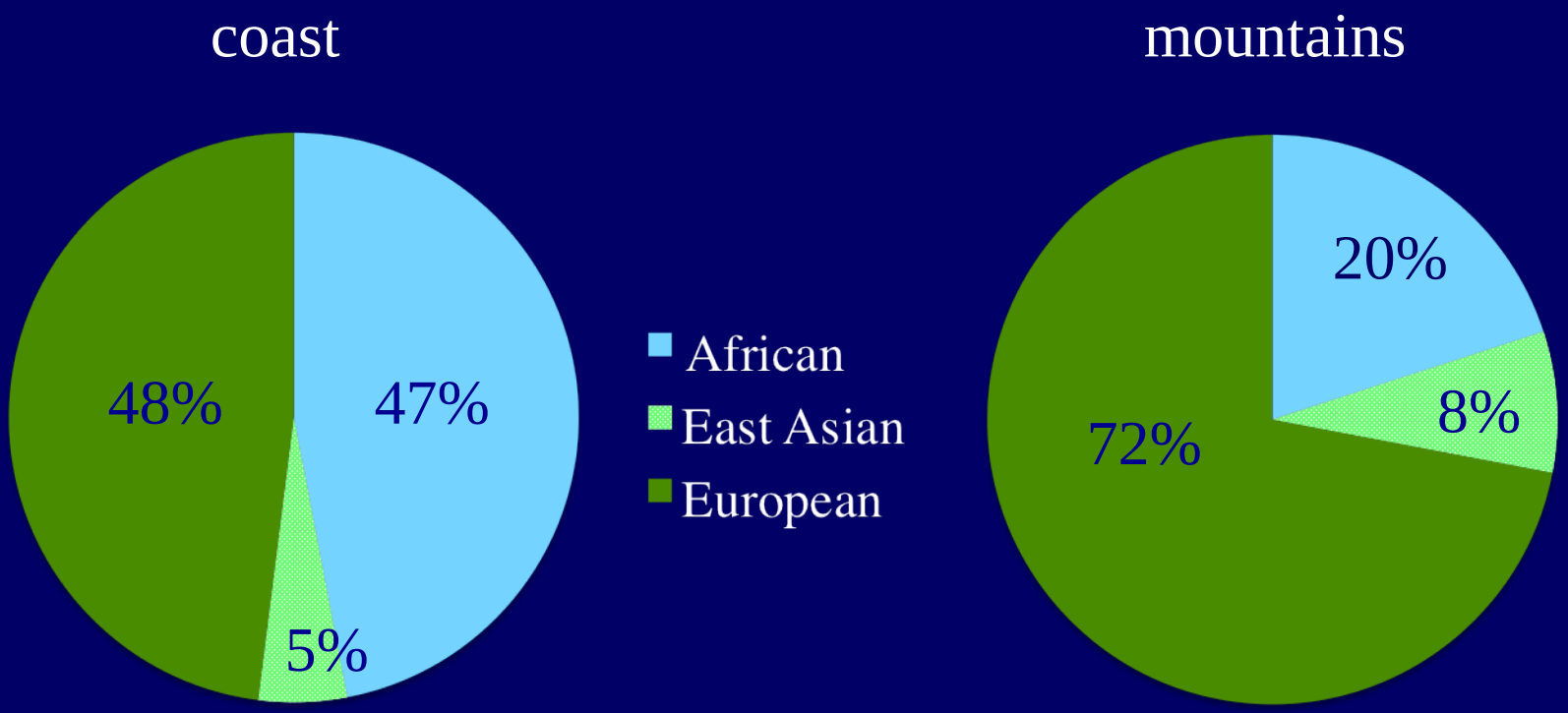
High-risk area

(150/100,000)

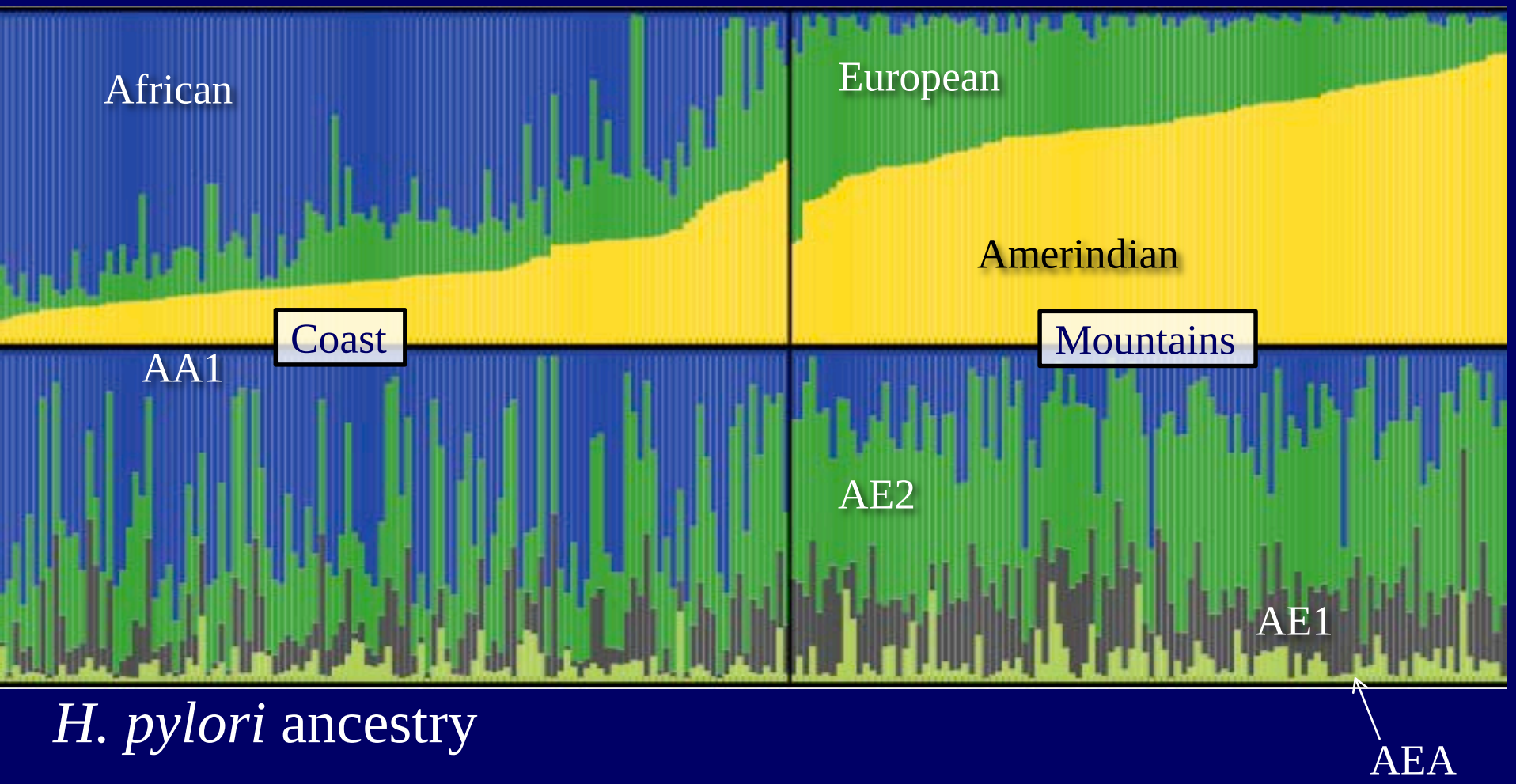
Mean ancestry of two Colombian populations



H. pylori ancestry distributions of participants from the coastal and mountain regions

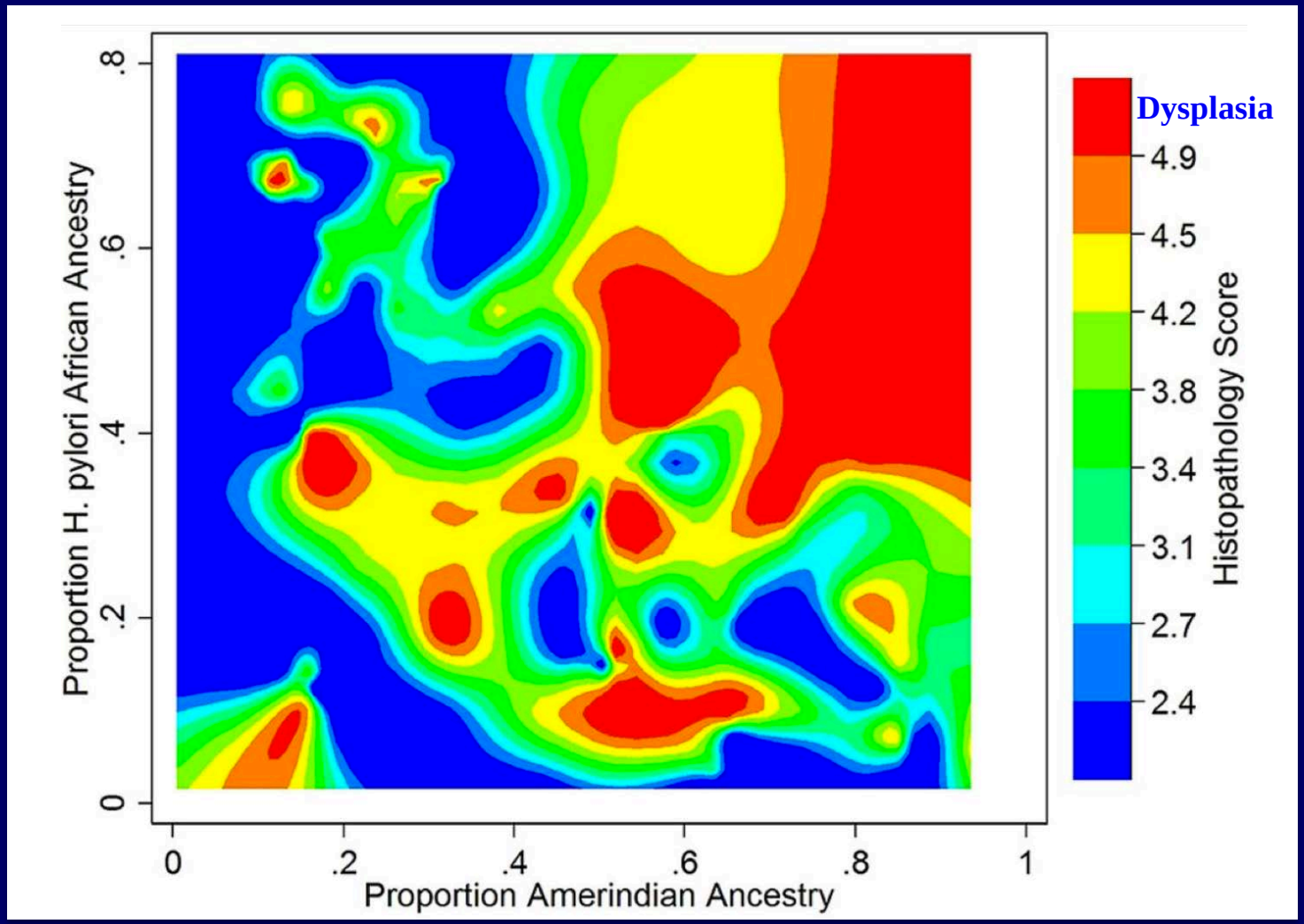


Admixture proportions of human and corresponding *H. pylori* ancestry



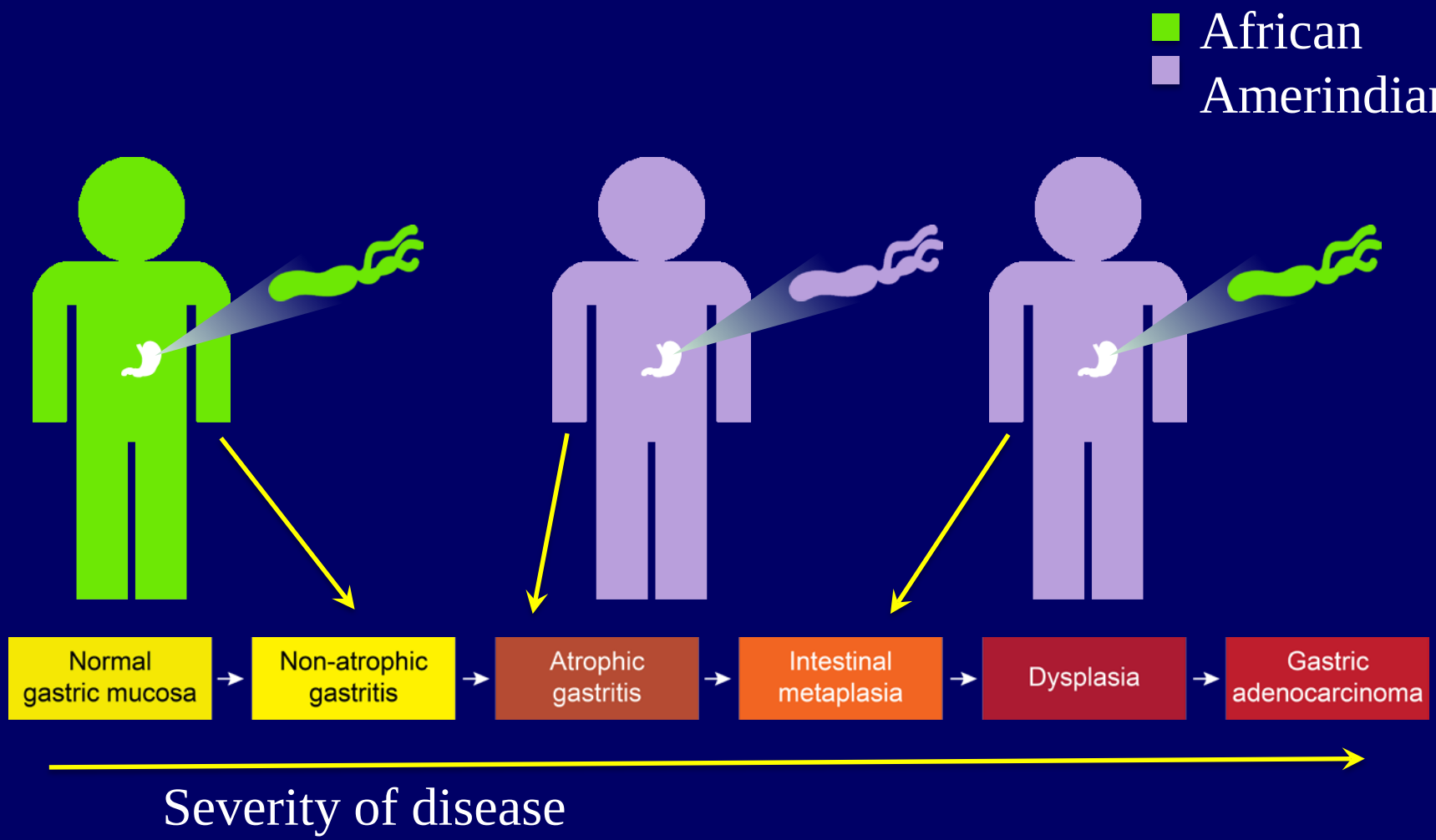
Kodaman *et al.*, *PNAS*

Gastric damage as a function of Amerindian human and African *H. pylori* ancestry interactions in a Colombian population



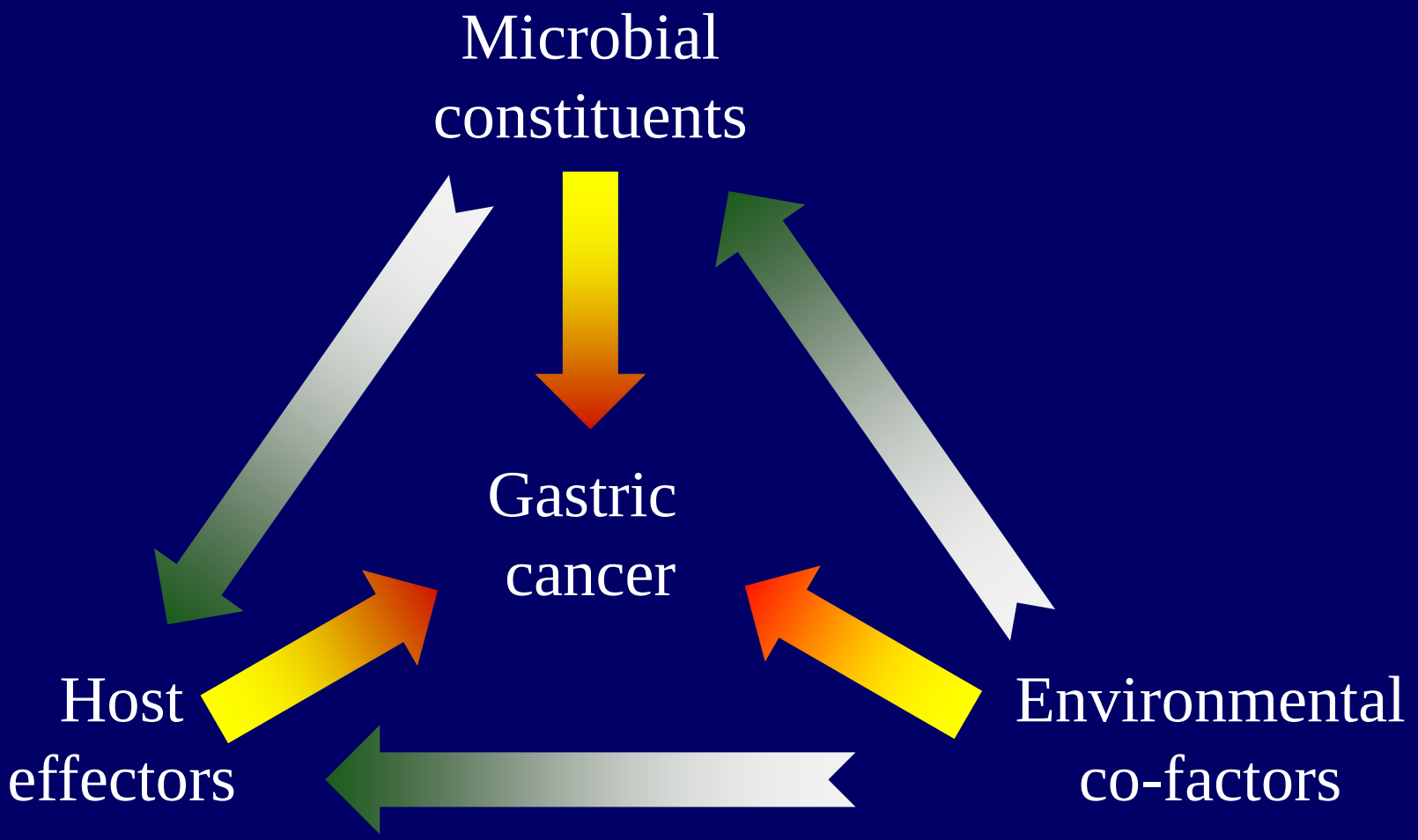
Kodaman, *et al.*, *Front Genet*

Interactions between *H. pylori* and human host genetic ancestry and histologic progression to gastric cancer



Amieva and Peek, *Gastroenterology*

H. pylori-induced gastric cancer: an axis of evil



Can dietary components change the balance between *H. pylori*'s activity as a commensal or a pathogen via direct modification of microbial virulence?

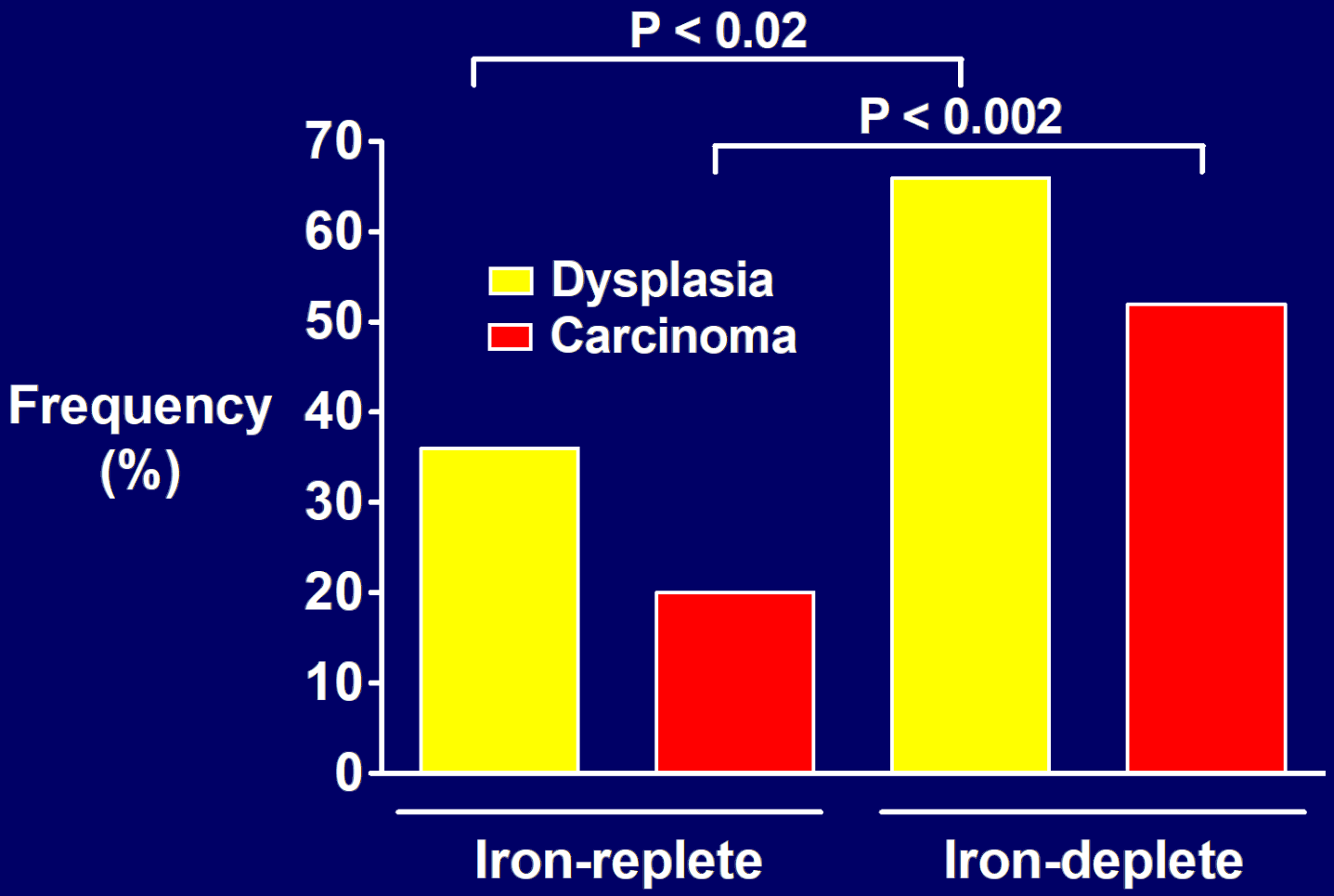
Iron deficiency increases the risk for gastric cancer

H. pylori infection is associated with iron deficiency, which affects 30% of the world's population

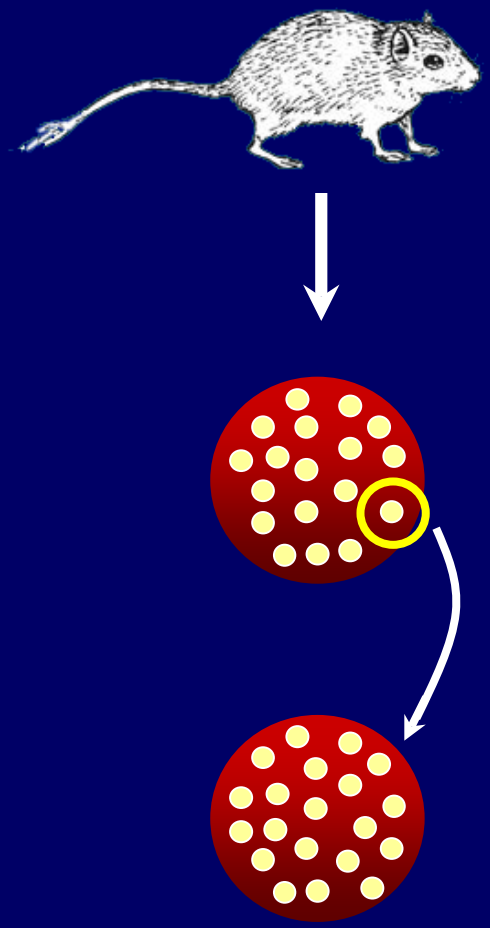
Iron deficiency is associated with a high incidence of

- Preneoplastic gastric lesions
- Gastric adenocarcinoma

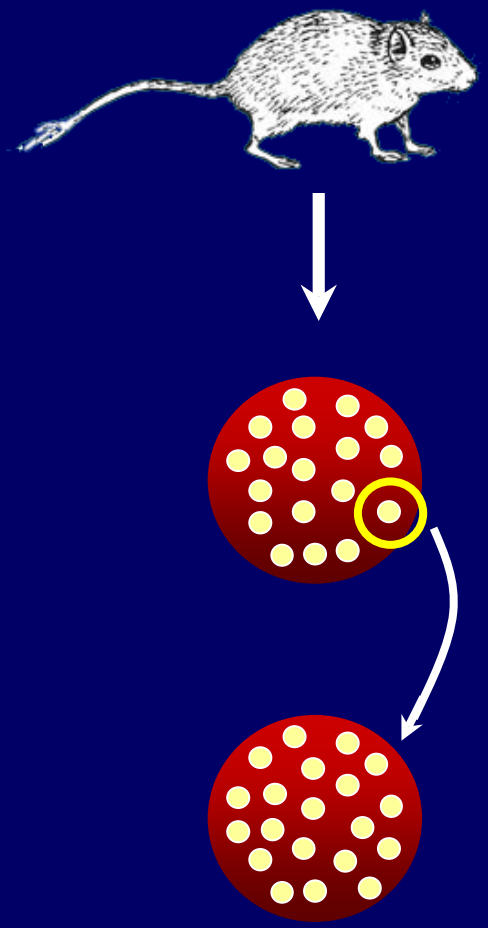
Dietary iron depletion increases gastric dysplasia and cancer in rodents



Isolation of *in vivo*-adapted *H. pylori* strains



In vivo-adapted strains
Iron-replete gerbils



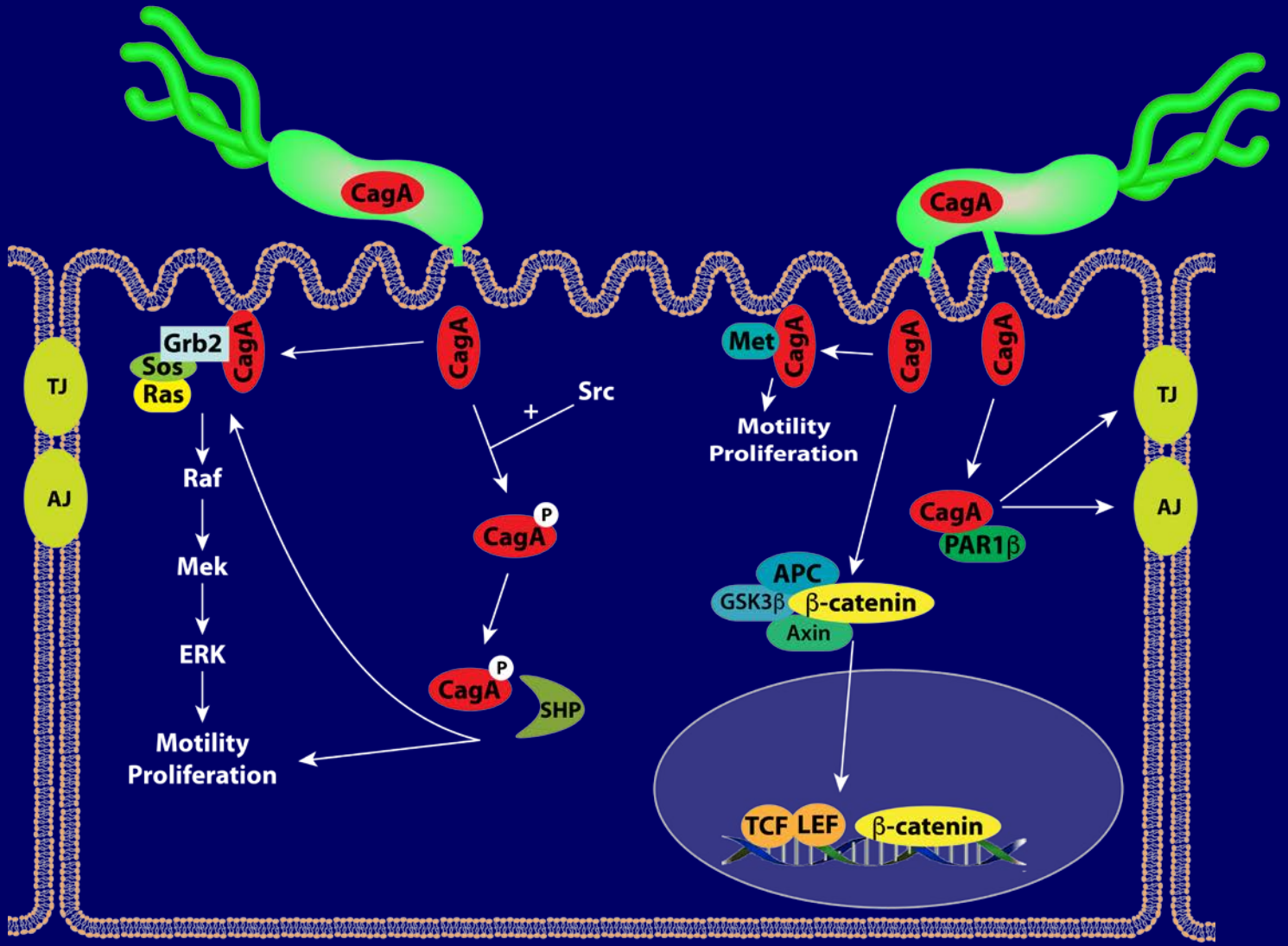
In vivo-adapted strains
Iron-deplete gerbils

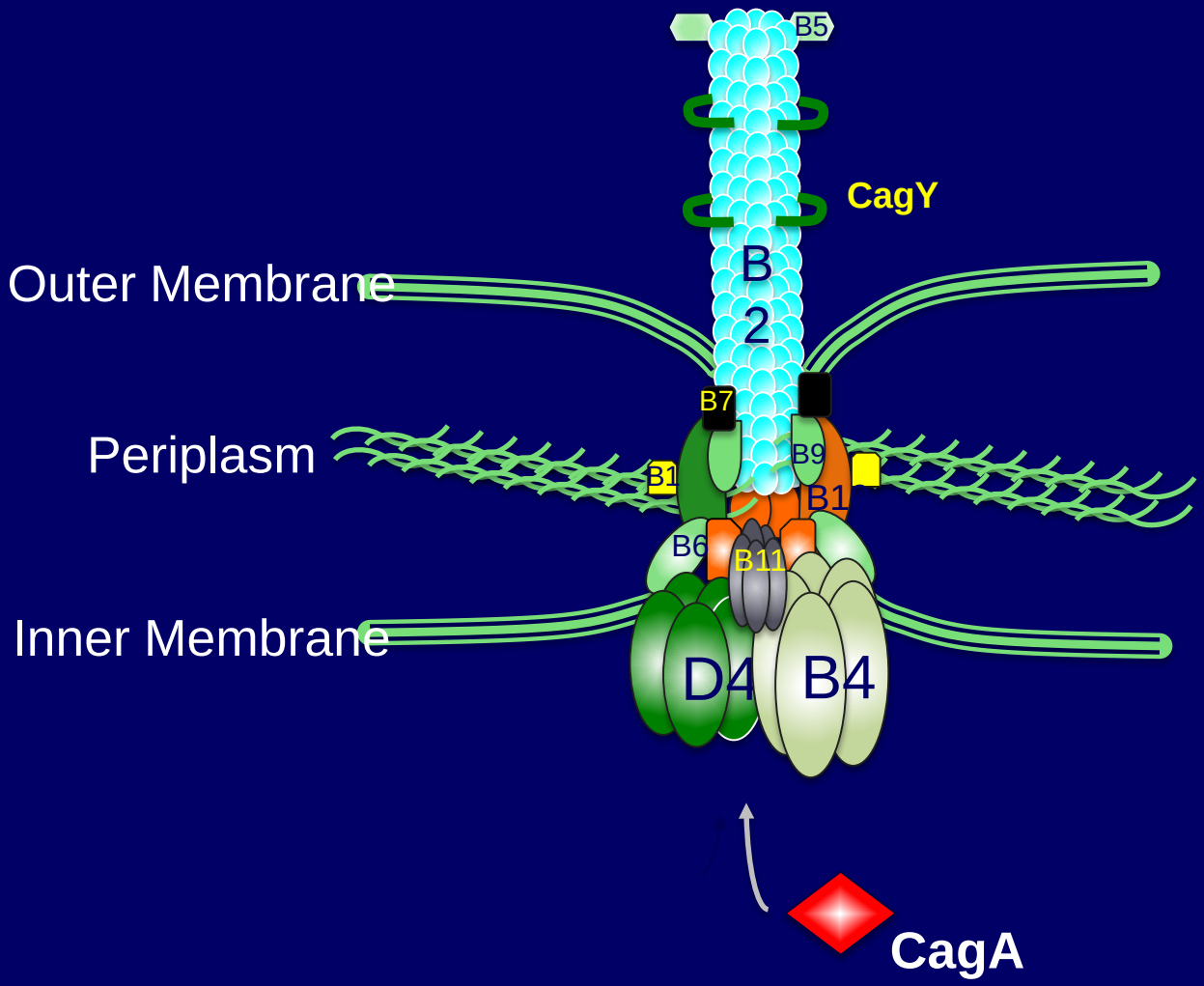
SNPs identified following *in vivo*-adaptation to conditions of iron deficiency

Gene	Function	HPB8 locus
Putative OMP	Outer membrane protein	593
Putative OMP	Outer membrane protein	626
cagY	Type IV secretion system	716
oipA	Outer inflammatory protein	838
Putative OMP	Outer membrane protein	1104
Putative OMP	Outer membrane protein	1139
fur	Ferric uptake regulator	1145

Noto et al., *Gut*

Molecular signaling alterations induced by *cag* T4SS-mediated translocation of CagA




B5
CagY
Outer Membrane
B
2
B7
Periplasm
B1
B9
B1
B6
B11
Inner Membrane
D4
B4
CagA

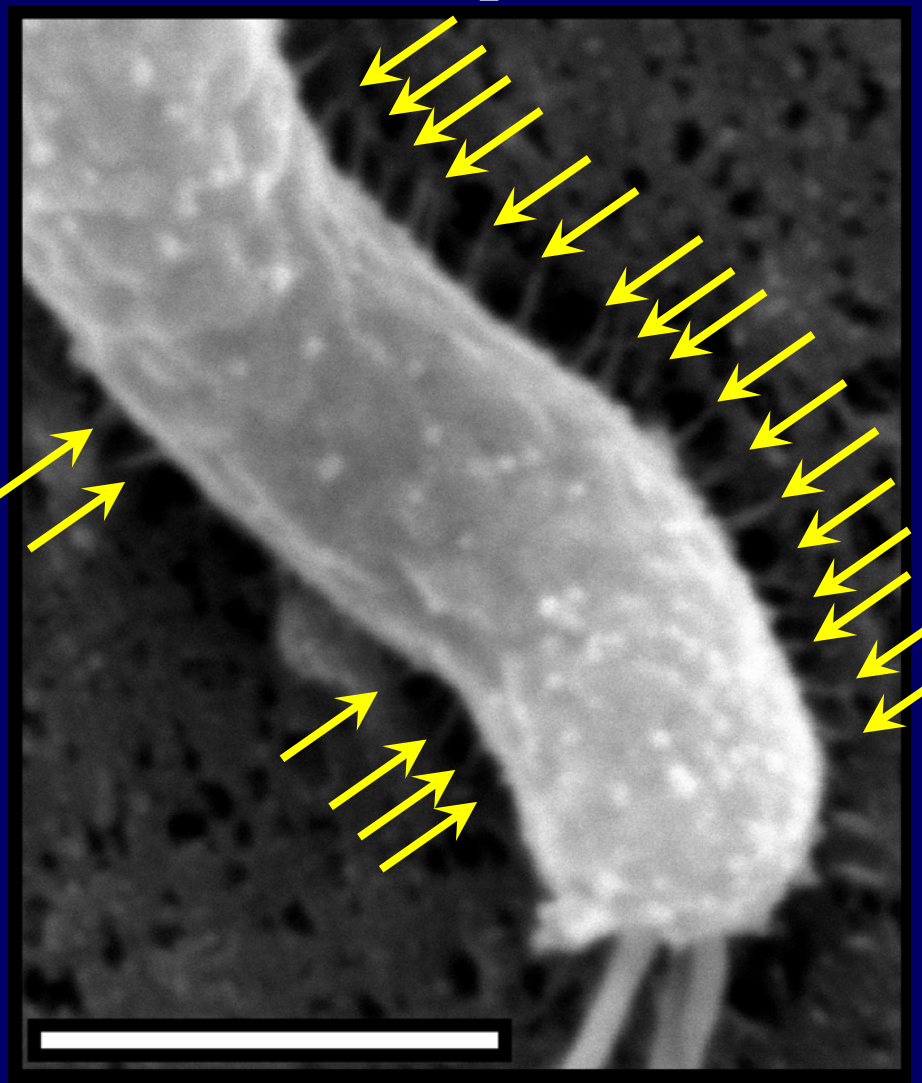
Iron depletion augments assembly of the *cag* type IV secretion system

Iron-replete

Iron depletion augments assembly of the *cag* type IV secretion system

Iron-replete

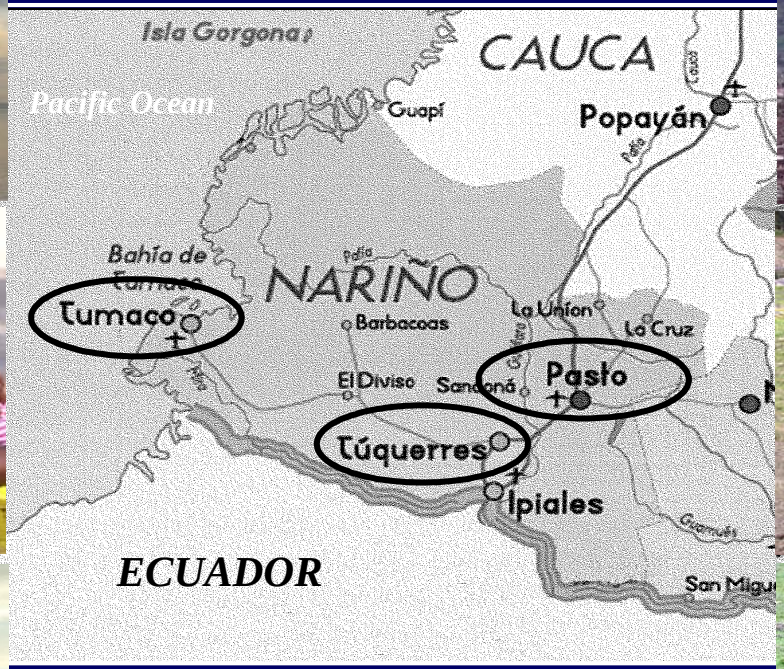
Iron-depleted



Nariño, Colombia

Low-risk area

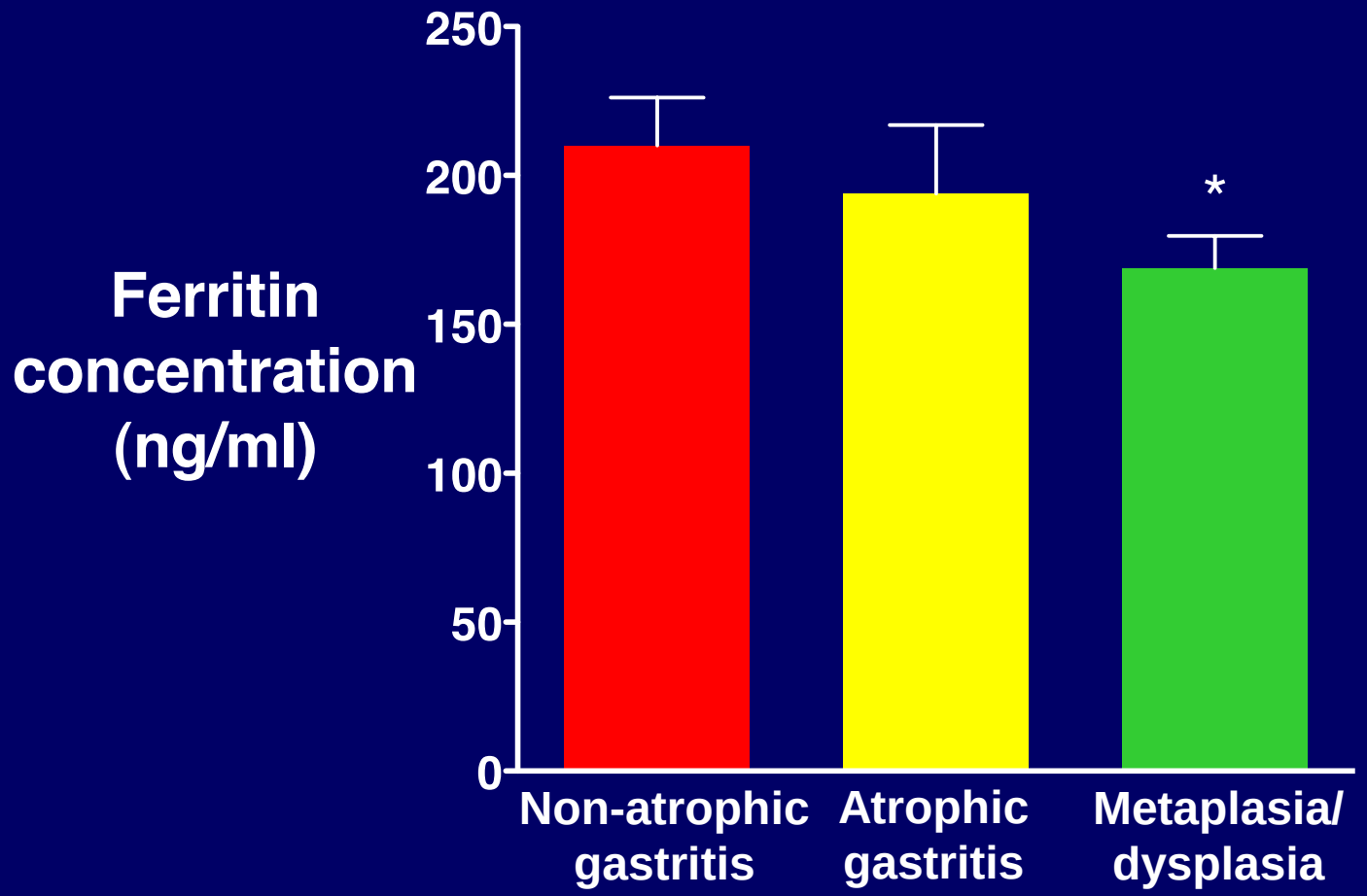
(6/100,000)



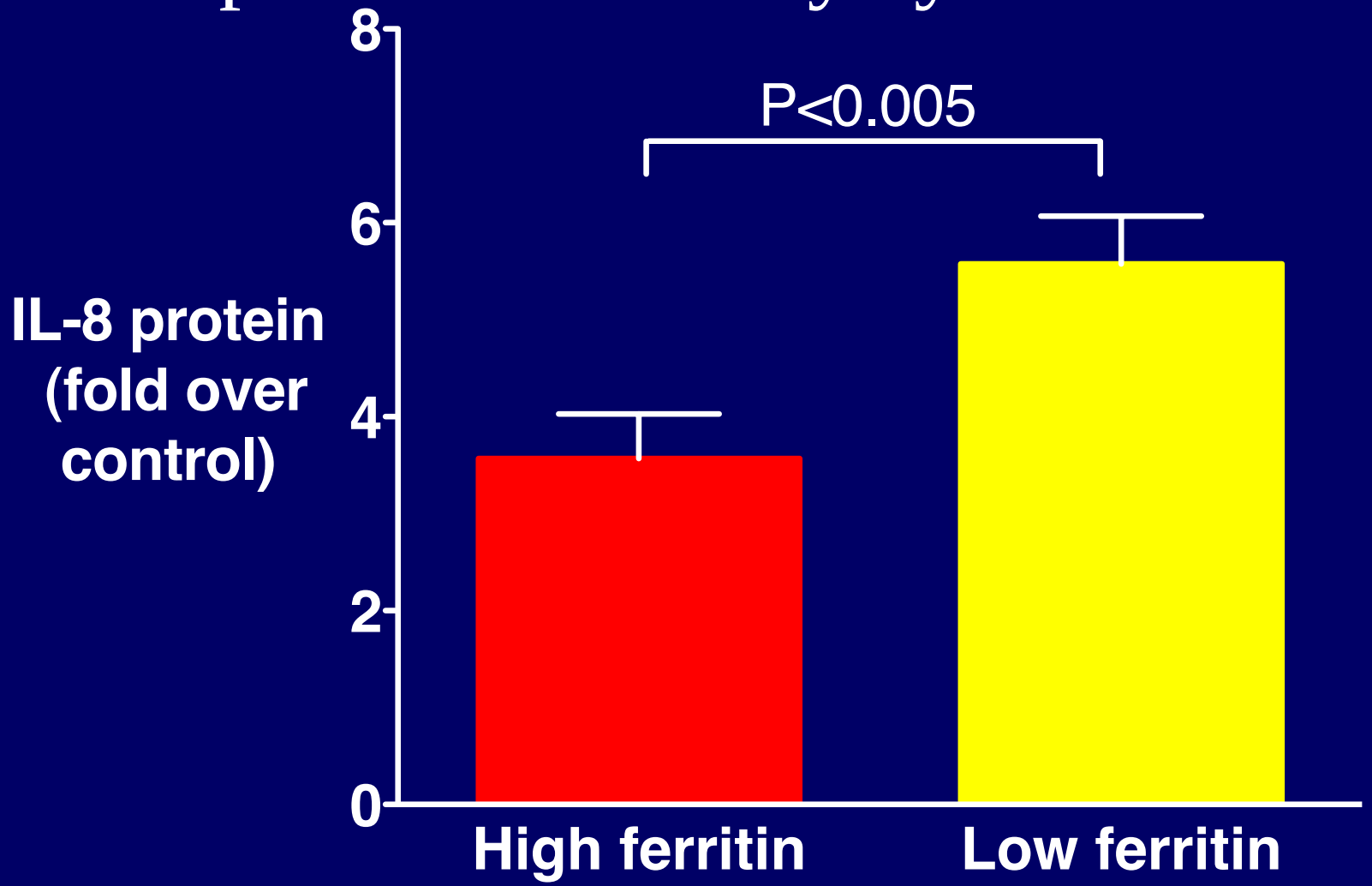
High-risk area

(150/100,000)

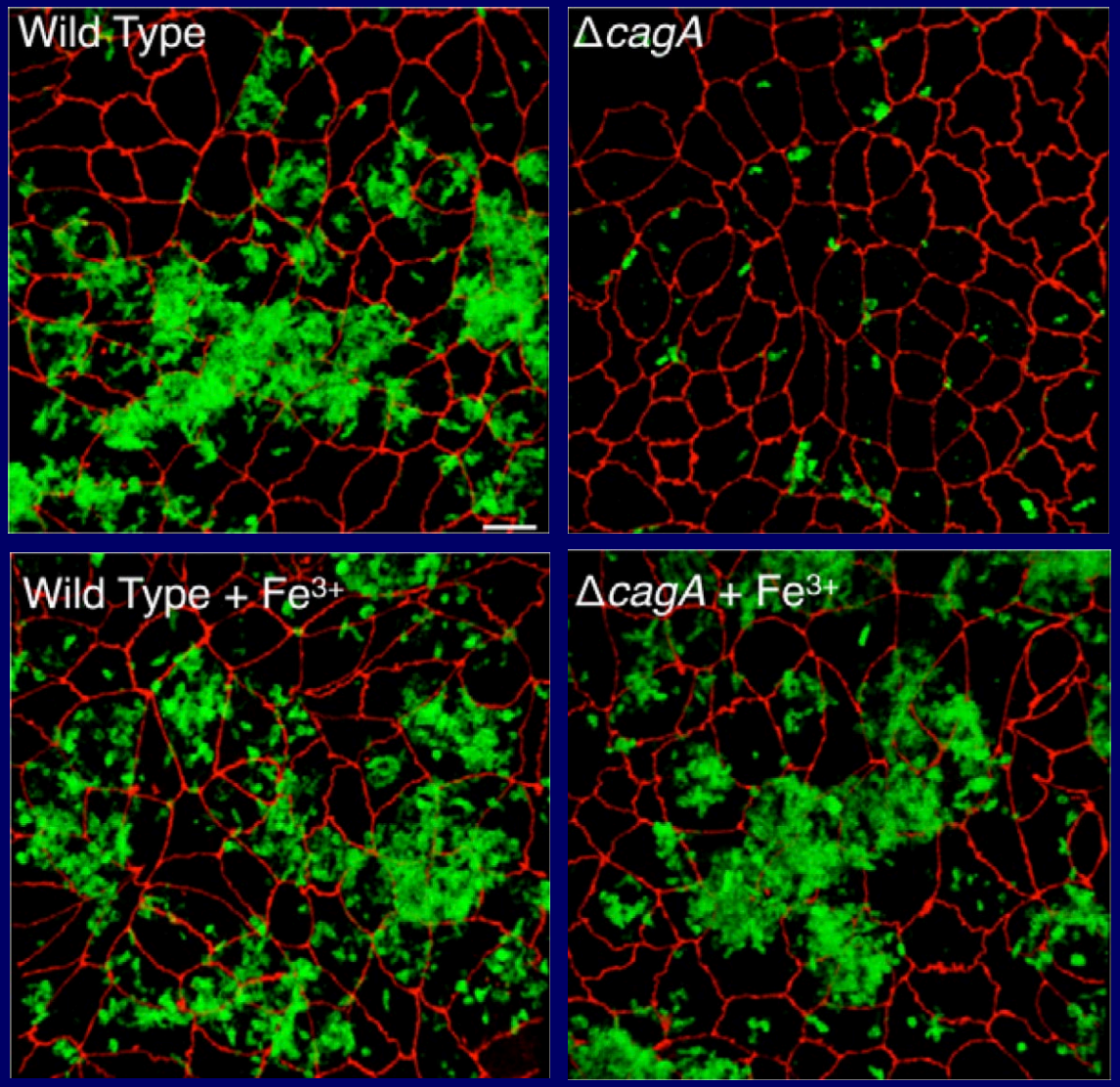
Iron deficiency parallels the severity of *H. pylori*-induced premalignant lesions in human populations



H. pylori isolated from patients with low ferritin levels induce increased levels of pro-inflammatory cytokines

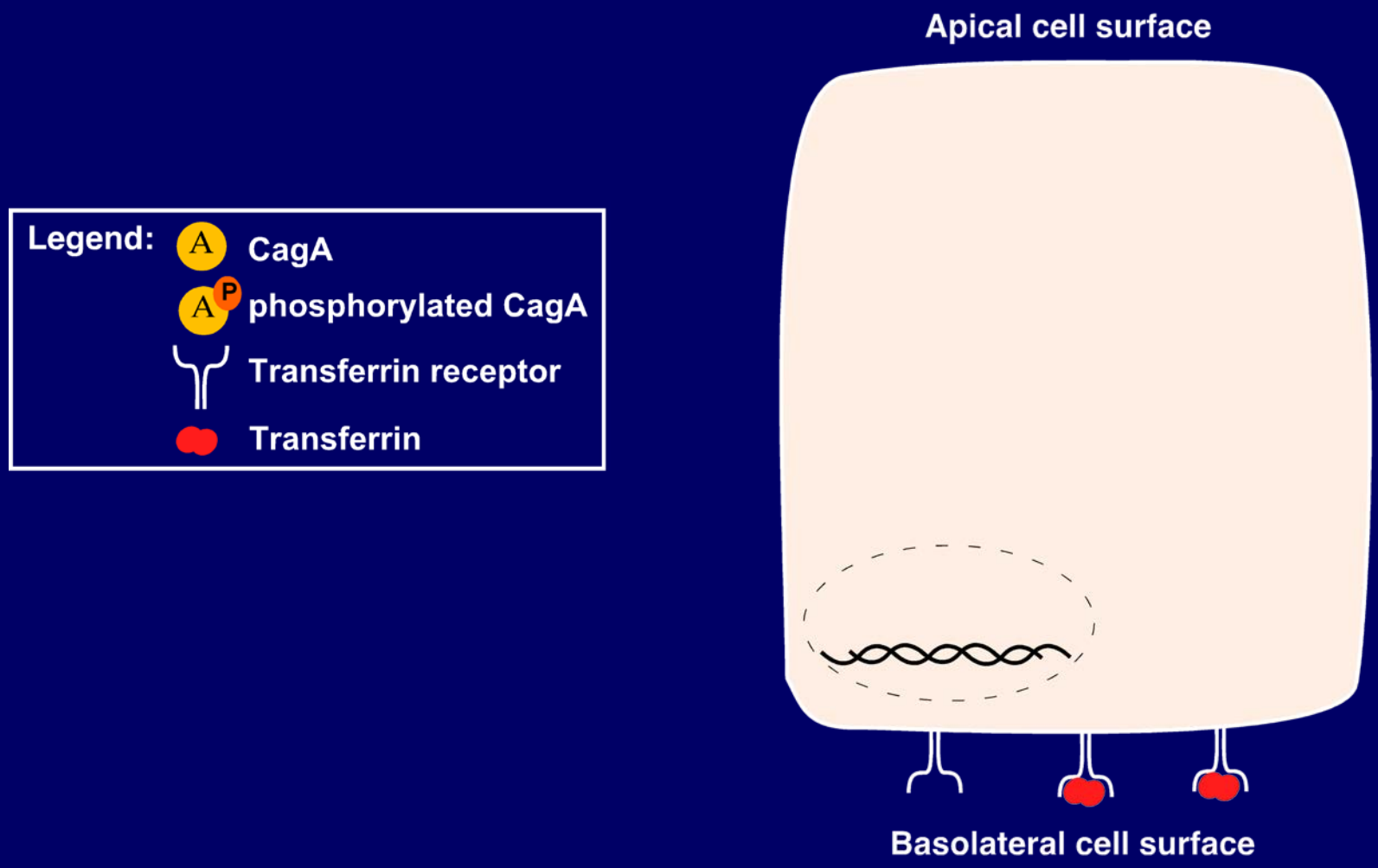


H. pylori colonization of polarized epithelium



Tan et al.,
PLoS Pathogens

Model of *H. pylori*-induced transferrin recycling under conditions of iron depletion



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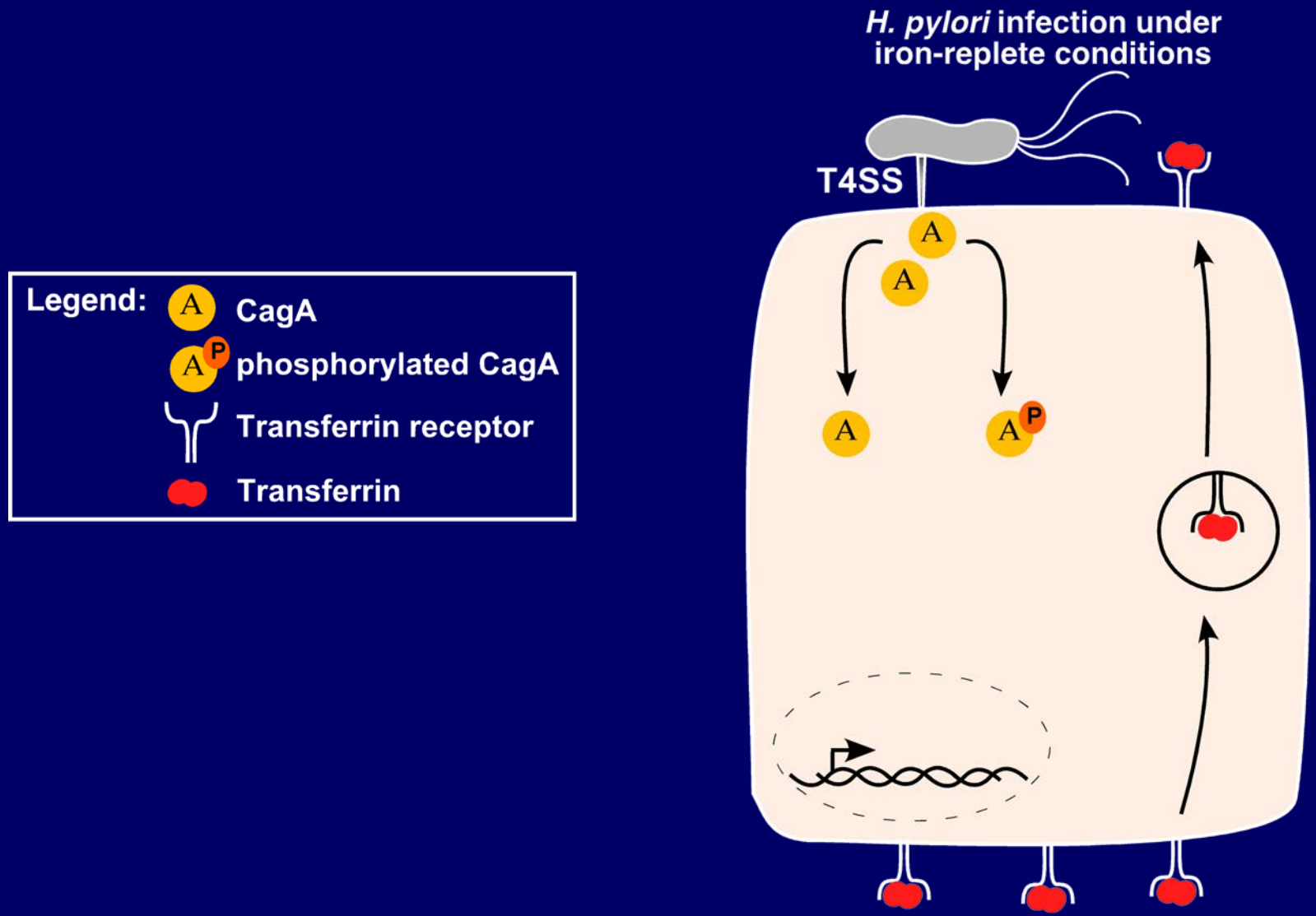
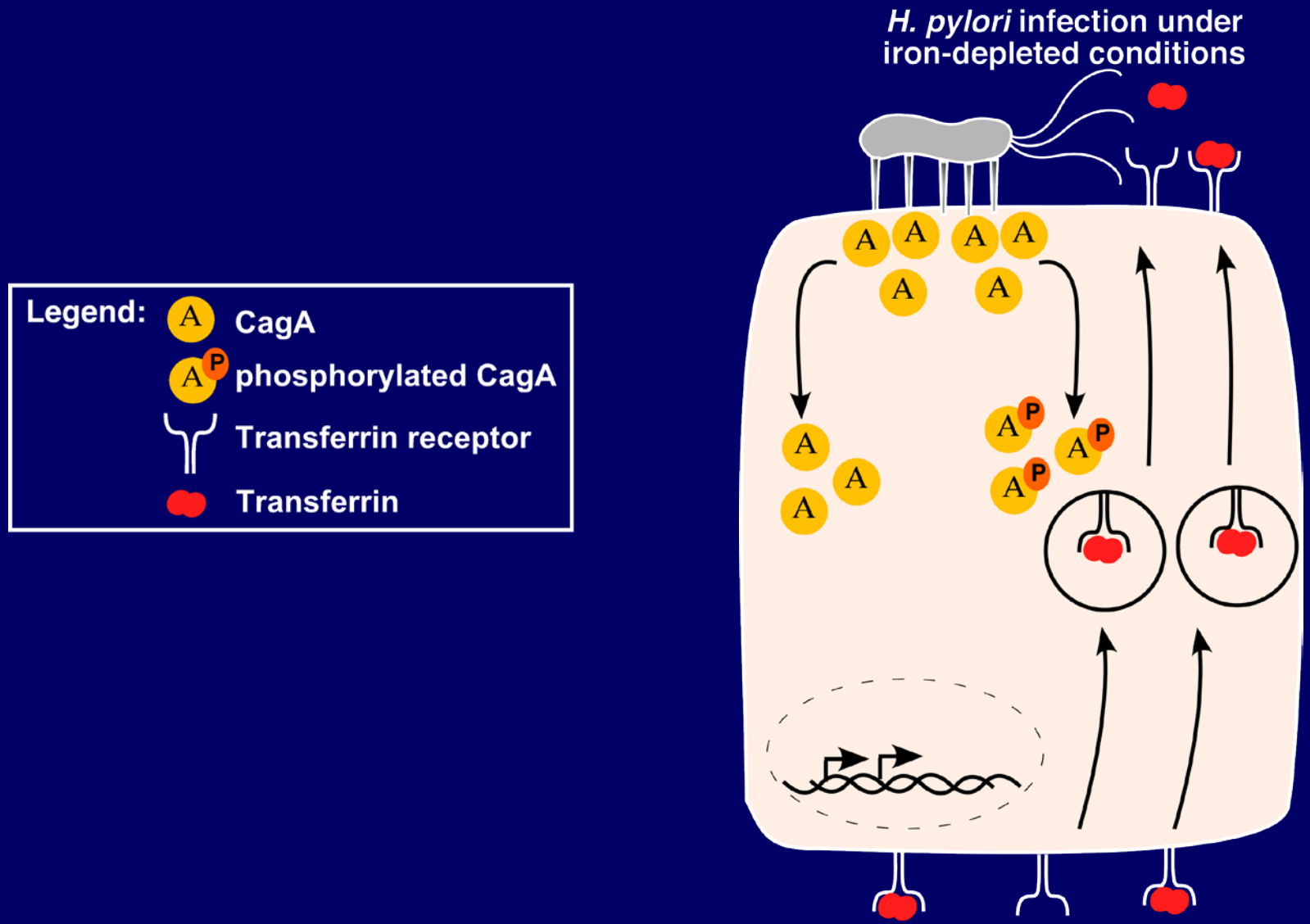


Model of *H. pylori*-induced transferrin recycling under conditions of iron depletion



Estimated odds ratios for gastric cancer incidence for *H. pylori*-, garlic-, or vitamin-treatment

	Fully adjusted	
Treatment	OR (95% CI)	*P*
H. pylori	0.61 (0.38-0.96)	0.032
Garlic	0.80 (0.53-1.20)	0.28
Vitamin	0.81 (0.54-1.22)	0.32

Ma et al., *JNCI*

Estimated odds ratios for gastric cancer incidence for *H. pylori*-, garlic-, or vitamin-treatment

	Fully adjusted	
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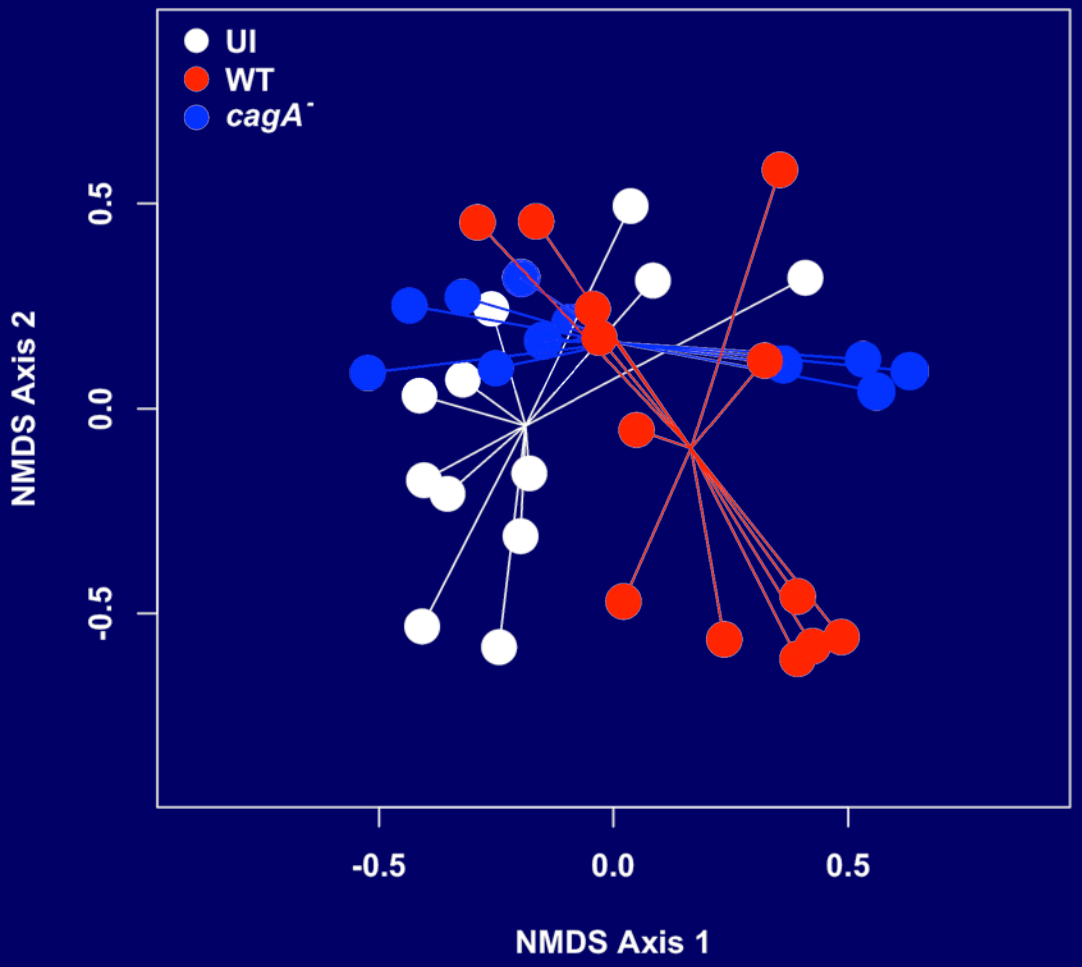
Ma et al., *JNCI*

Shandong Intervention Trial

Efficacy of *H. pylori* eradication therapy at 15 years of follow-up: 47%

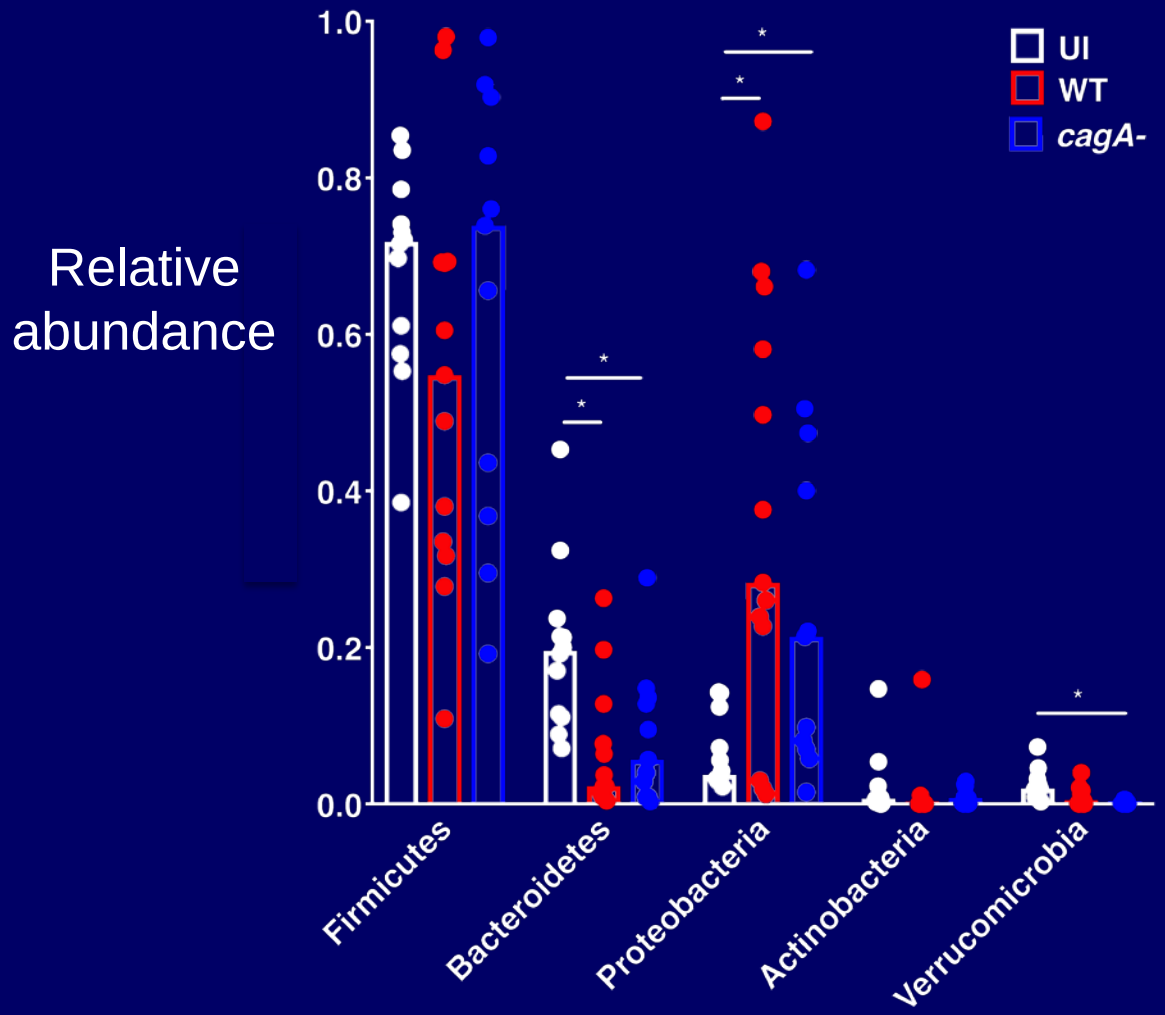
Can strain-specific *H. pylori* factors alter the structure and composition of the gastric microbiota?

H. pylori infection alters the gastric mucosal microbiota in a *cagA*-dependent manner



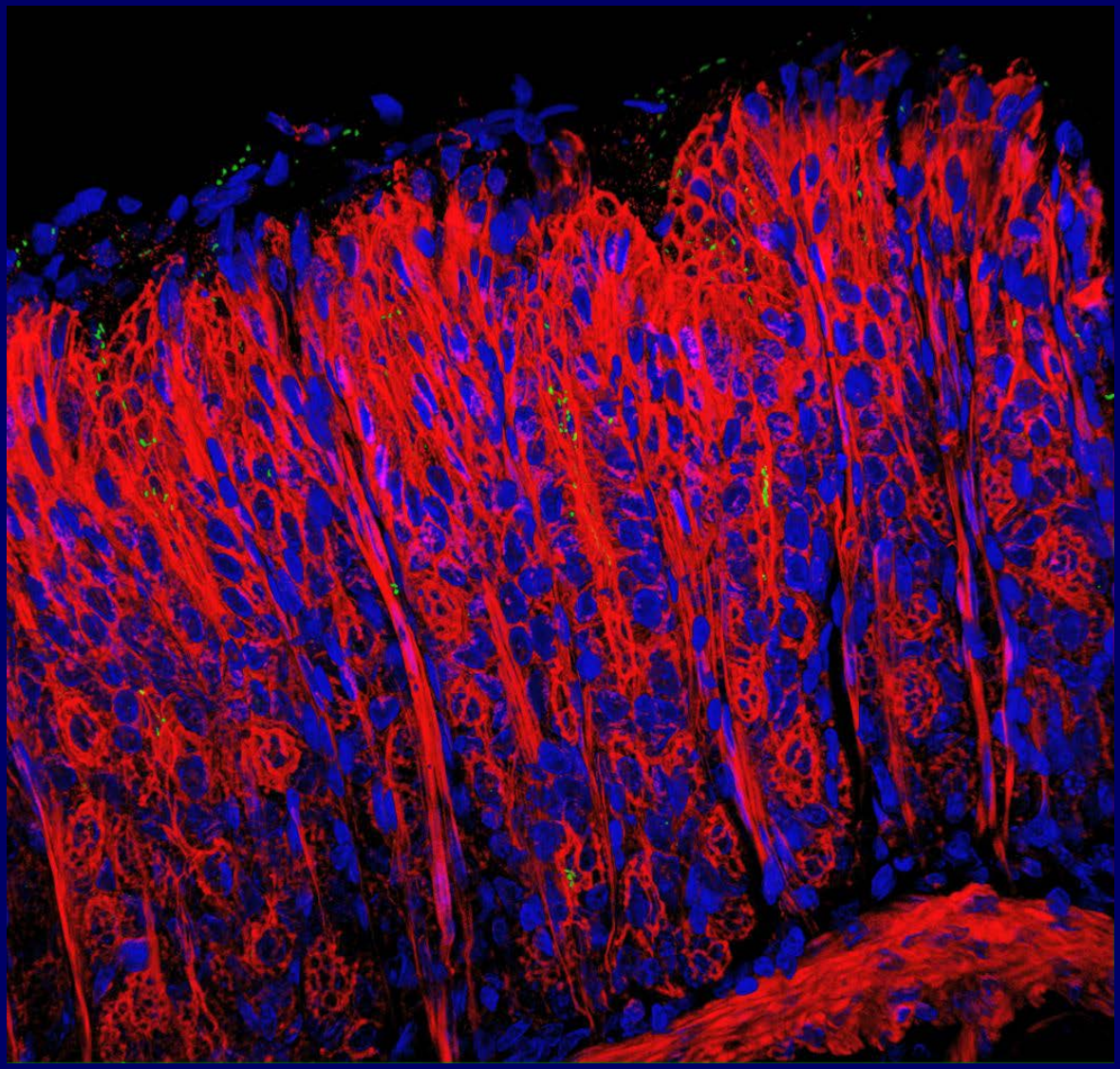
Noto et al., *mBio*

Presence of CagA alters composition of the gastric microbiota, when stratified by phyla levels, in *H. pylori*-infected gerbils

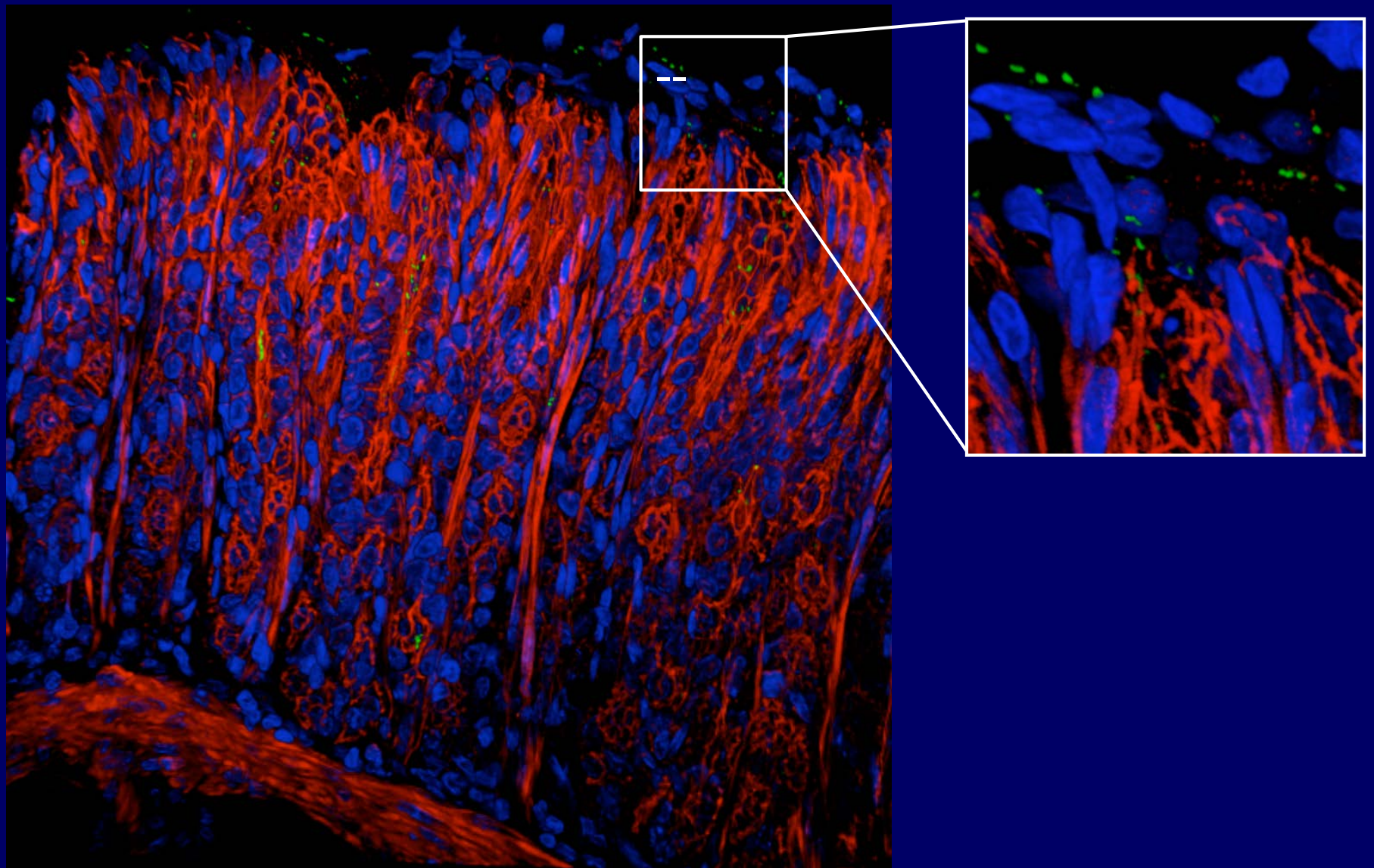


Noto et al., *mBio*

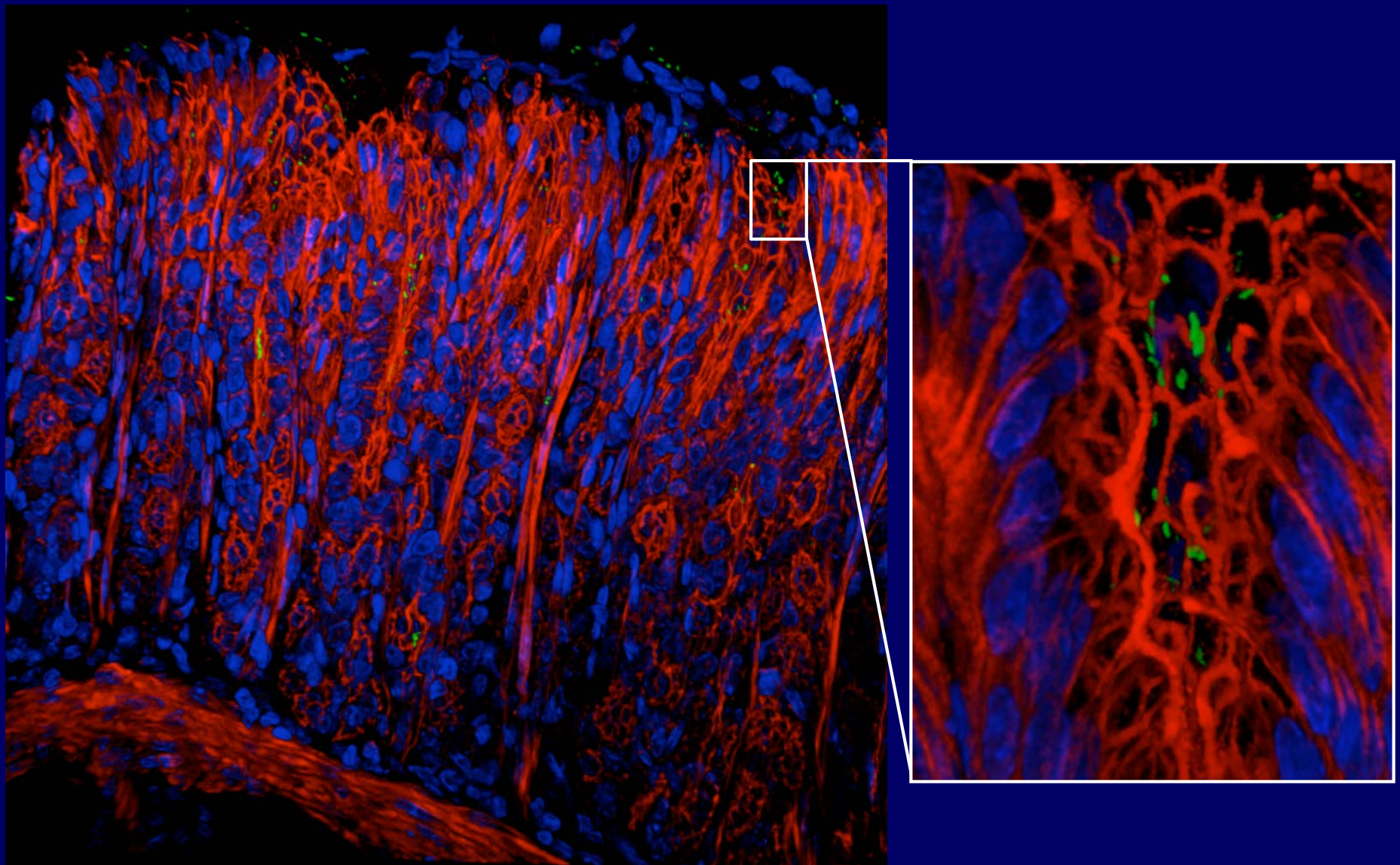
H. pylori localization within gerbil gastric mucosa



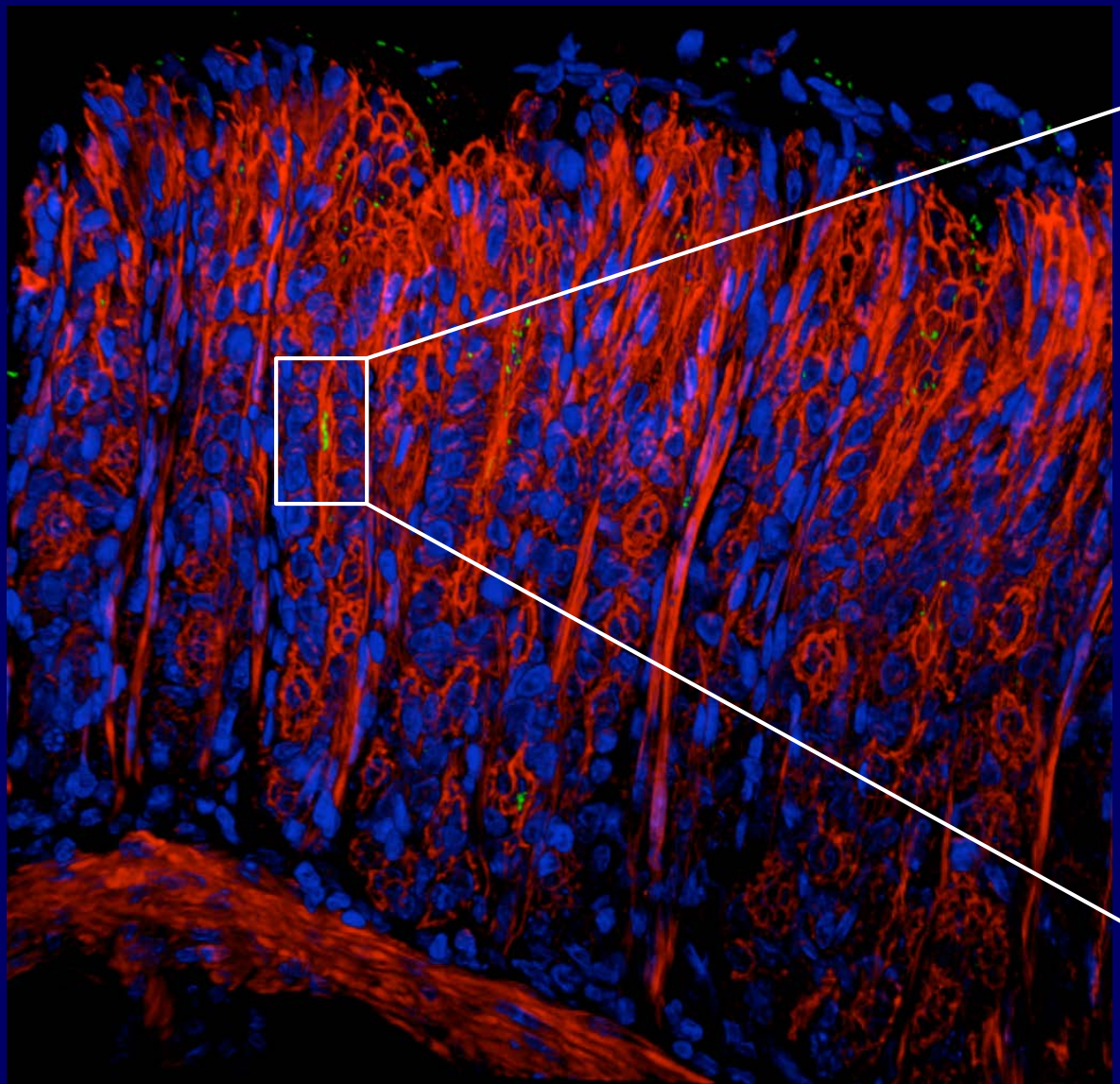
H. pylori 7.13 associates with the mucus layer under iron-replete and -deplete conditions

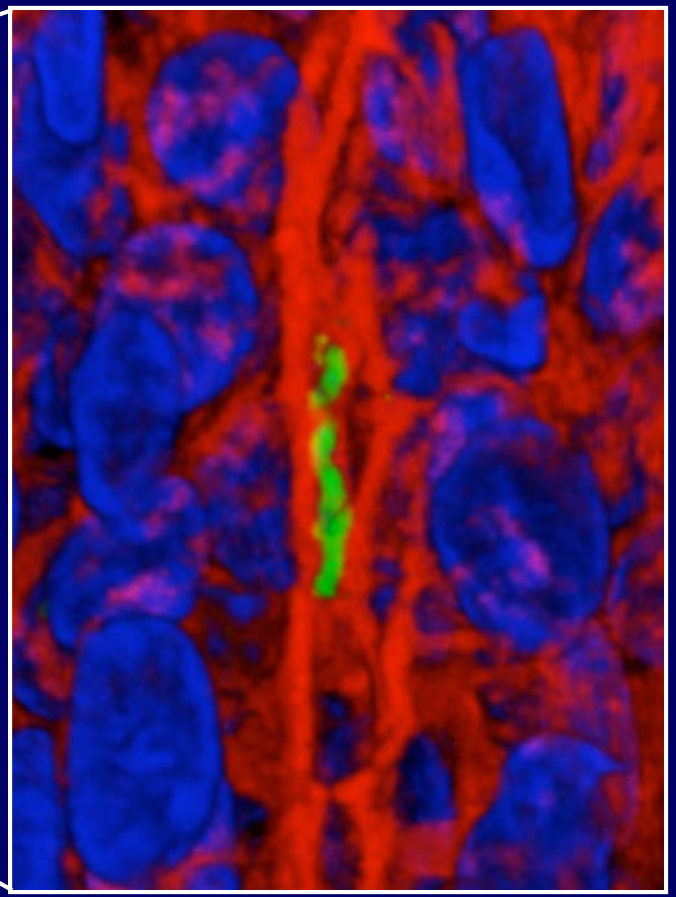


H. pylori 7.13 localizes to the pit of the gland under iron-replete and -deplete conditions

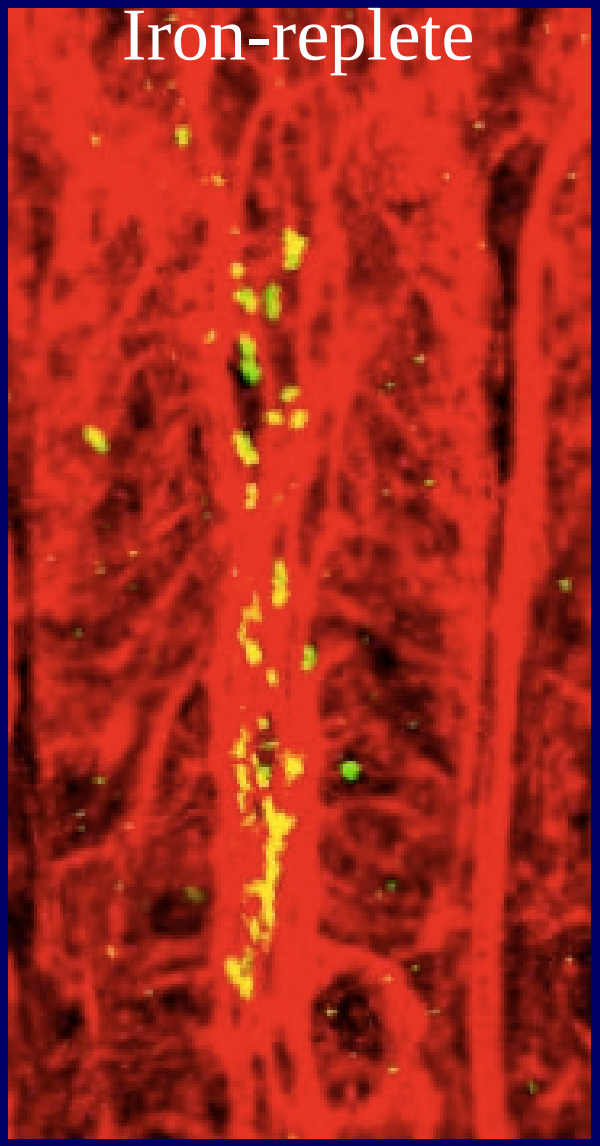


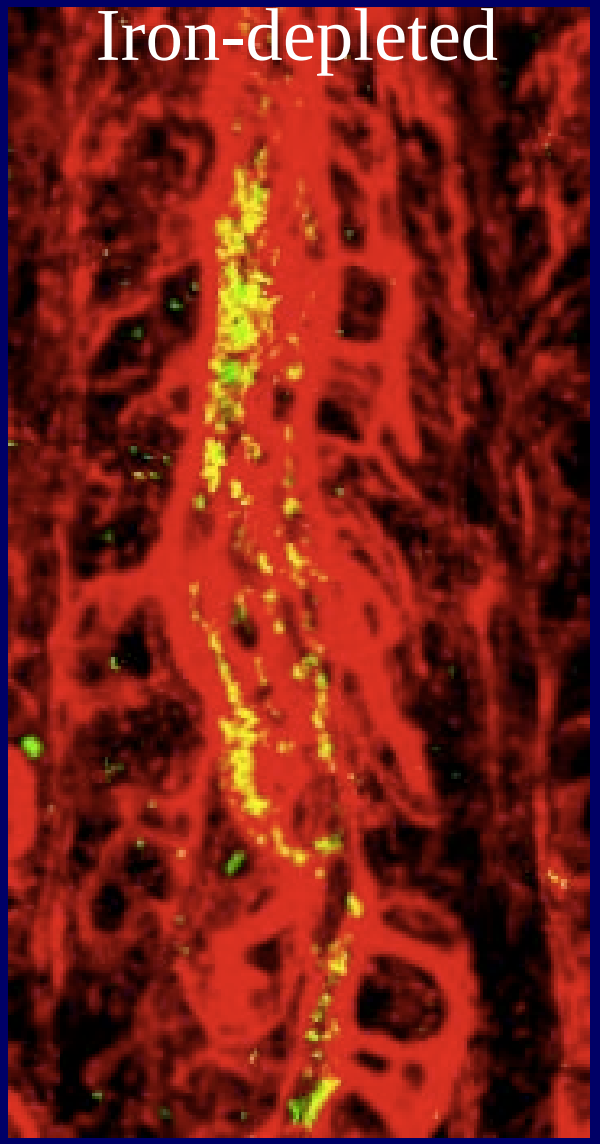
H. pylori 7.13 localizes to the neck of the gland under iron-replete and -deplete conditions





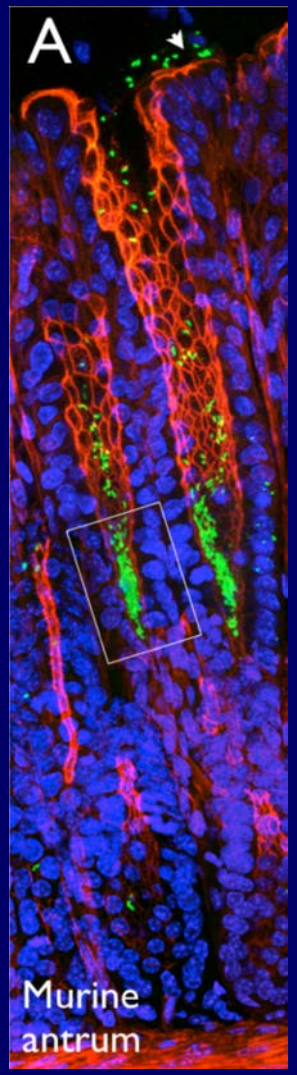
H. pylori colonizes stem cell zones at higher levels in iron-depleted conditions

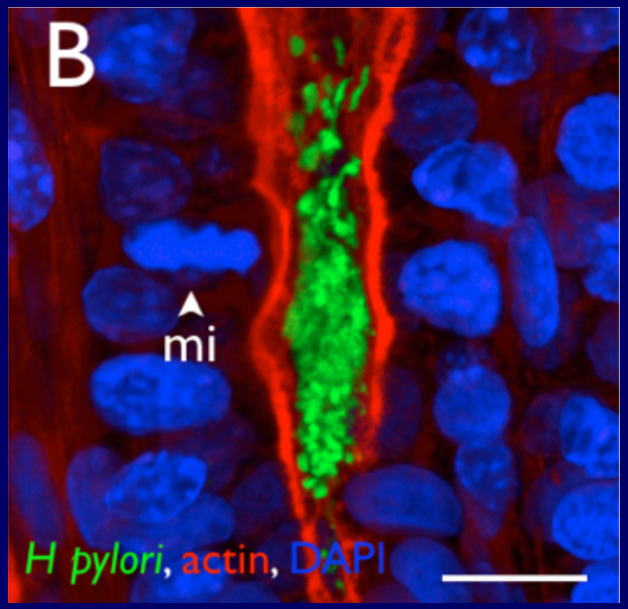




How do pathogenic *H. pylori* interact with gastric progenitor/stem cells?

H. pylori colonize the progenitor cell compartments of murine gastric glands





Sigel et al., *Gastroenterology*

Lrig1^{+} stem cells and *H. pylori*

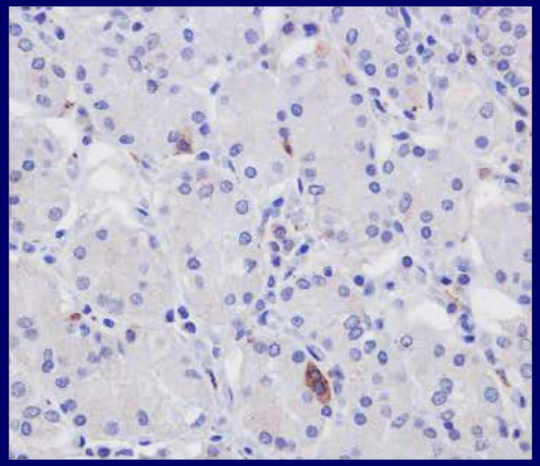
Leucine-rich repeats and immunoglobulin-like domains 1 (Lrig1) marks a population of quiescent stem cells.

Lrig1 functions as an inducible, negative feedback inhibitor of pan EGFR signaling.

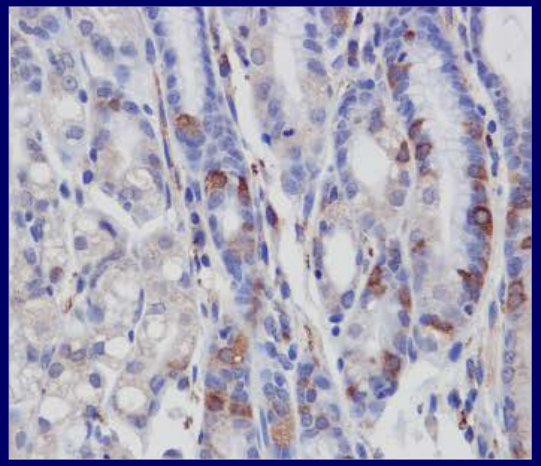
Present in both antral and corpus epithelium and expression is increased in infected mice (Noto et al.).

Loss of one *Apc* allele in Lrig1^{+} cells, thereby increasing β-catenin activation, uniformly leads to gastric hyperproliferation, hyperplasia, and dysplasia.

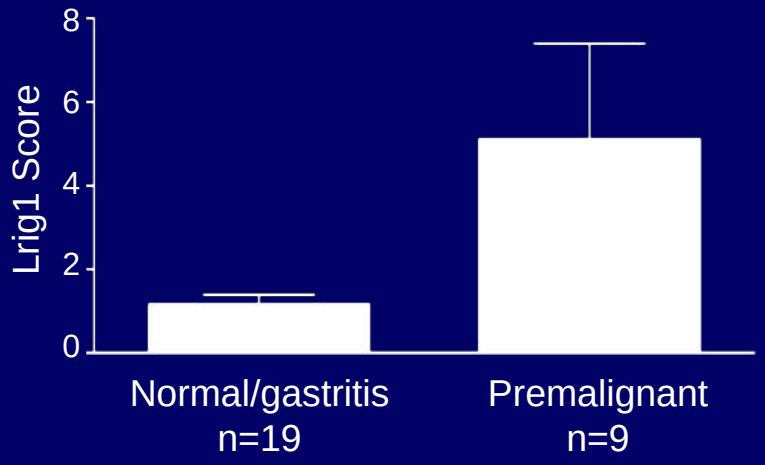
Lrig1 expression increases in gastric premalignant lesions in humans



Gastritis alone

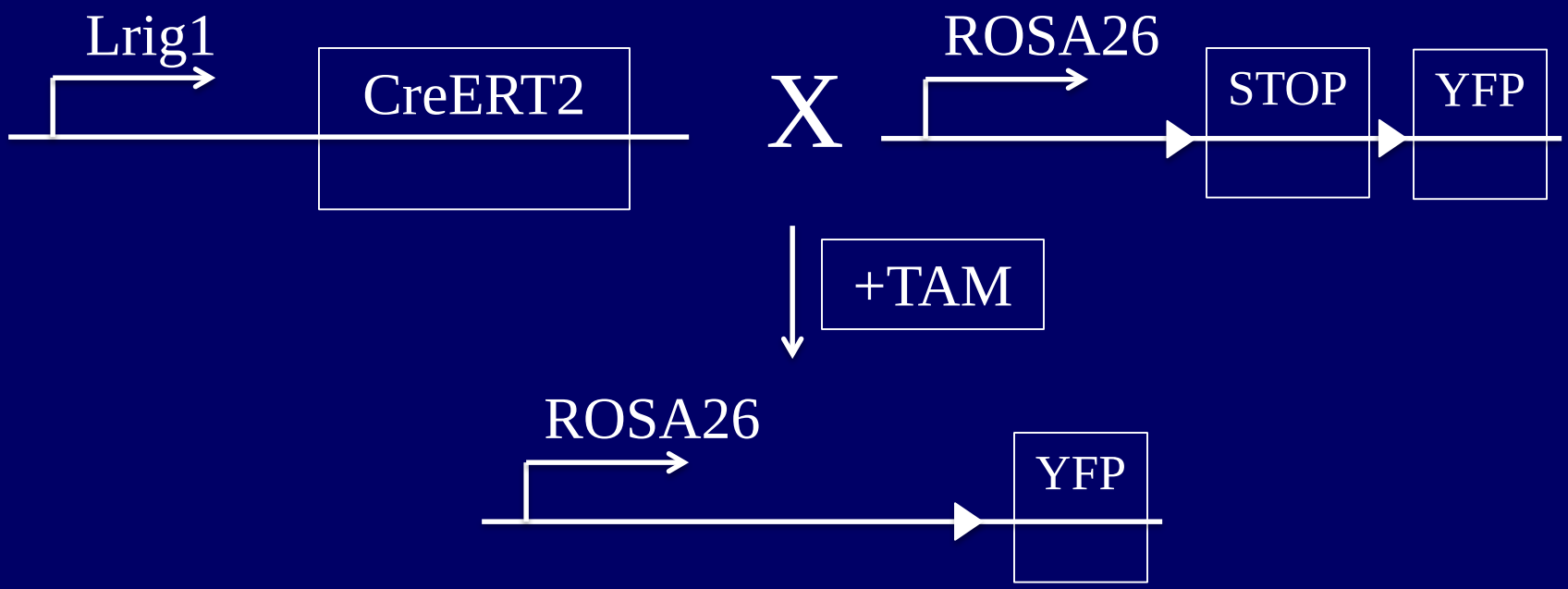


Atrophic gastritis



Wroblewski et al., *PNAS*

Lrig1 lineage tracing mouse model



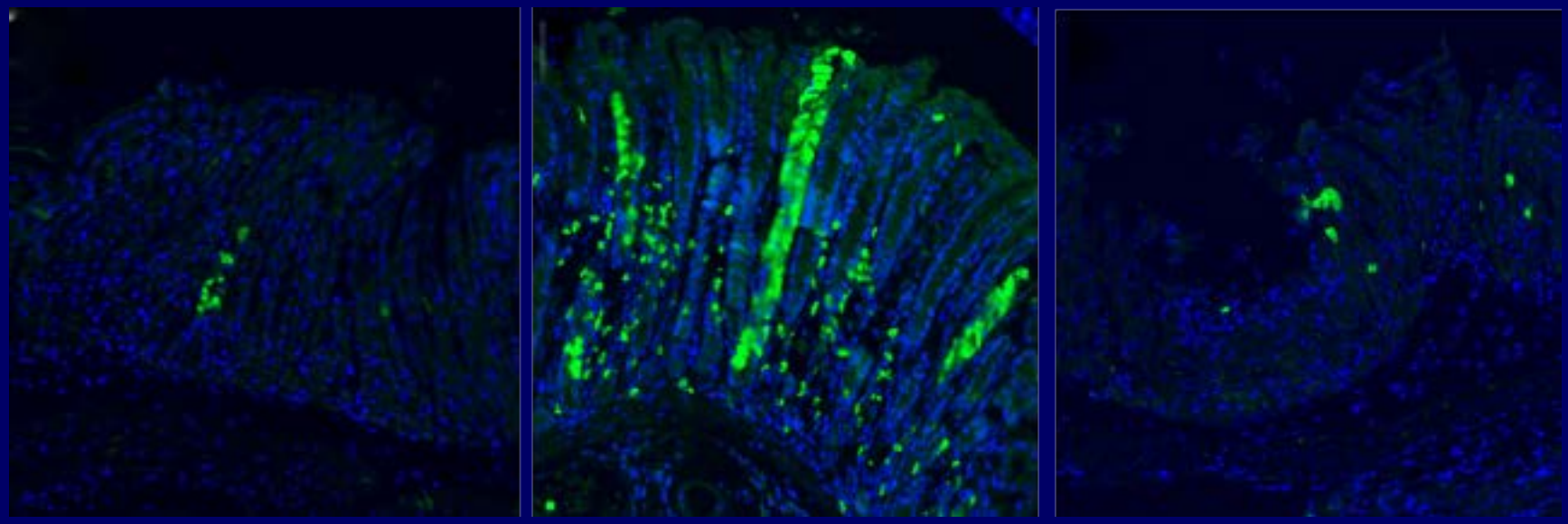
2mg tamoxifen i.p.

Infect with *H. pylori* wild-type *cag*$^{+}$ strain or

H. pylori isogenic *cag*$^{-}$ mutant

2 week and 8 week infection

H. pylori increases Lrig1 progenitor activity in a *cag*-dependent manner



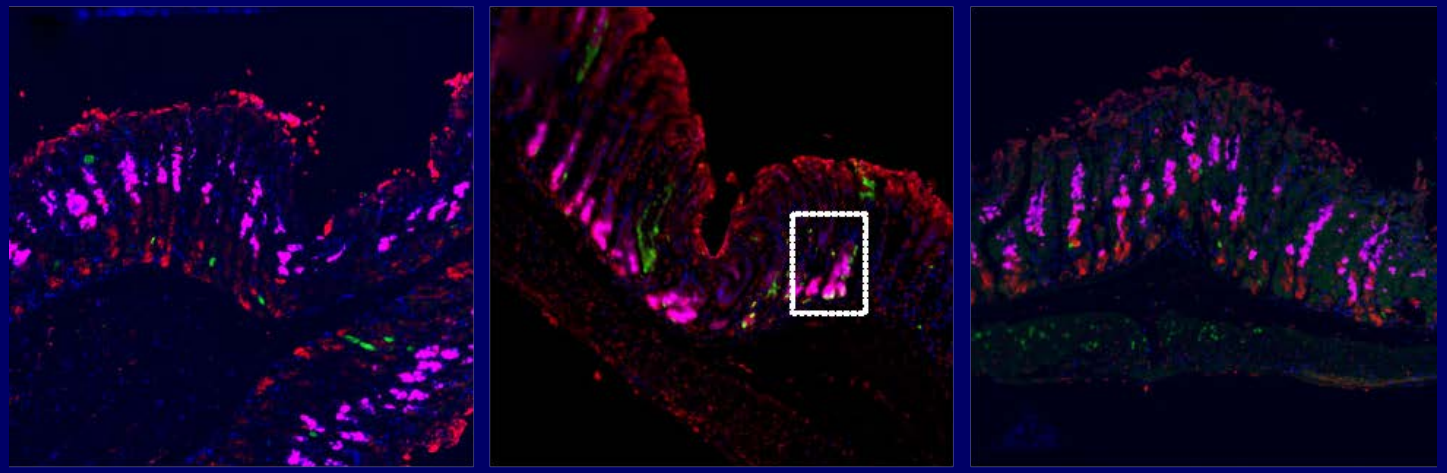
Uninfected | Wild type | *cag*$^{-}$

H. pylori

Wroblewski et al., *PNAS*

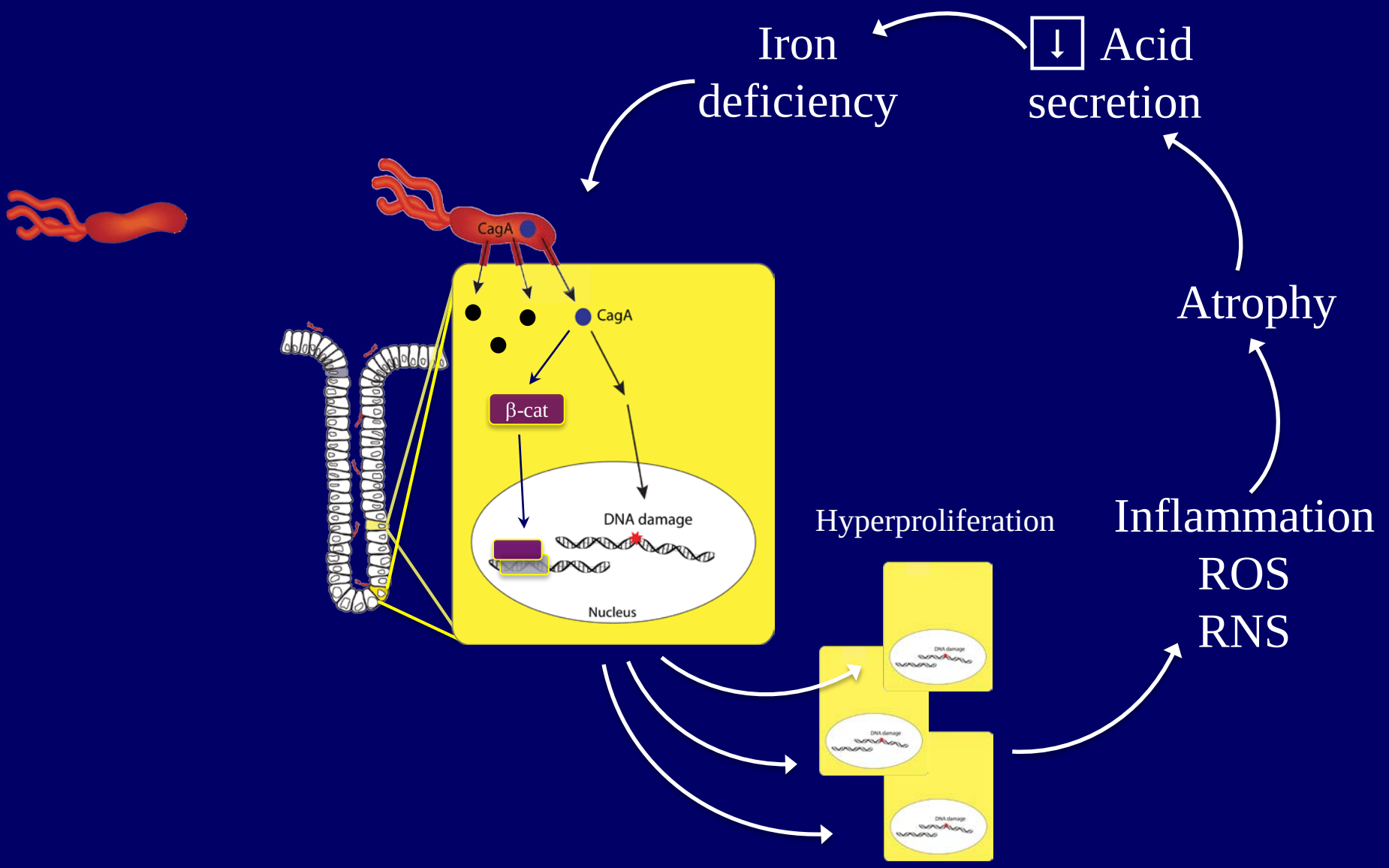
Lrig1 lineage traced cells co-localize with chief cells and SPEM cells in response to *cag*$^{+}$ *H. pylori*

Uninfected | *H. pylori* WT | *H. pylori cag*$^{-}$



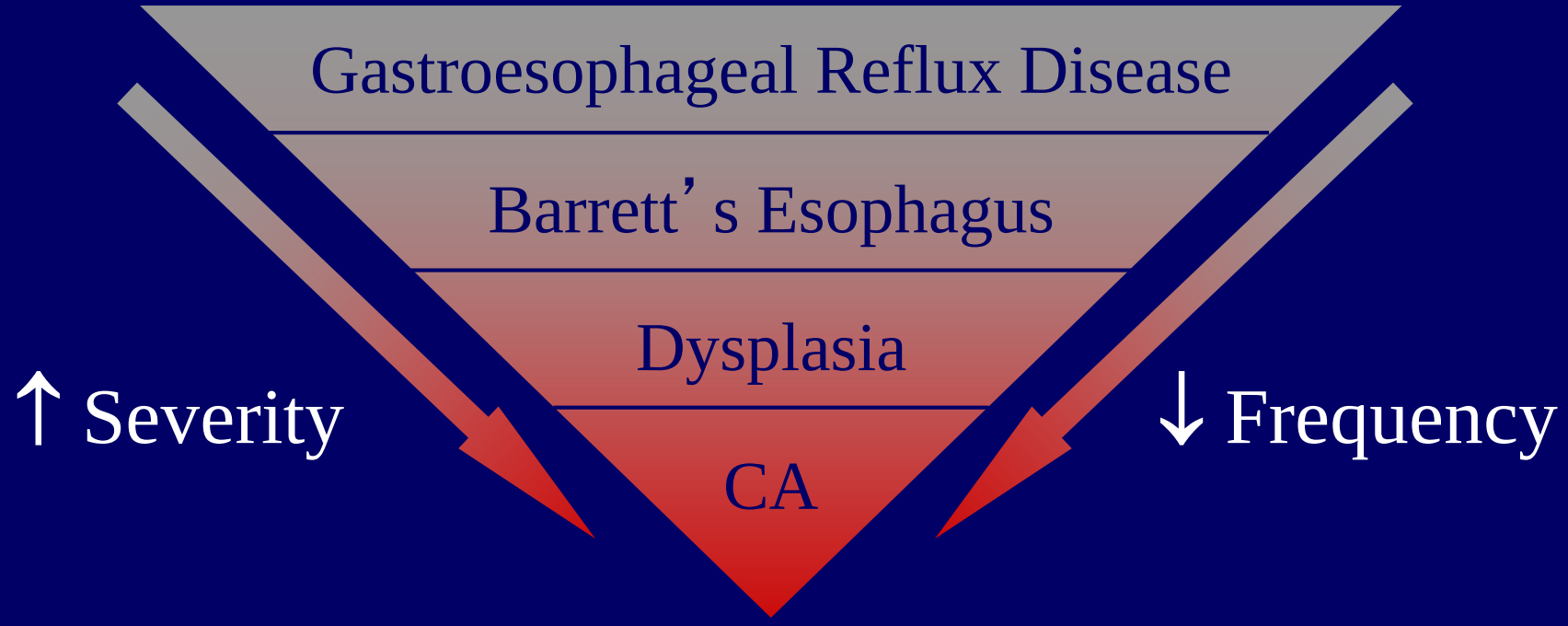
YFP (Lrig1)
GSII lectin (SPEM)
Intrinsic factor

Wroblewski et al., *PNAS*


Iron deficiency
↓ Acid secretion
Atrophy
Inflammation
ROS
RNS
Hyperproliferation
CagA
CagA
β-cat
DNA damage
Nucleus

Are there additional reasons that mitigate against widespread test and treat strategies for *H. pylori*?

Complications of Gastroesophageal Reflux Disease



Association of Barrett's metaplasia with *H. pylori* status and associated conditions

	Barrett's			
	-	+	OR	95% CI
Total	76,475	2510	-	-
H. pylori (-)	67,119	2366	1	-
H. pylori (+)	9356	144	0.42	0.35-0.49
Gastritis (-)	65,521	2317	1	-
Gastritis (+)	10,954	193	0.47	0.41-0.55

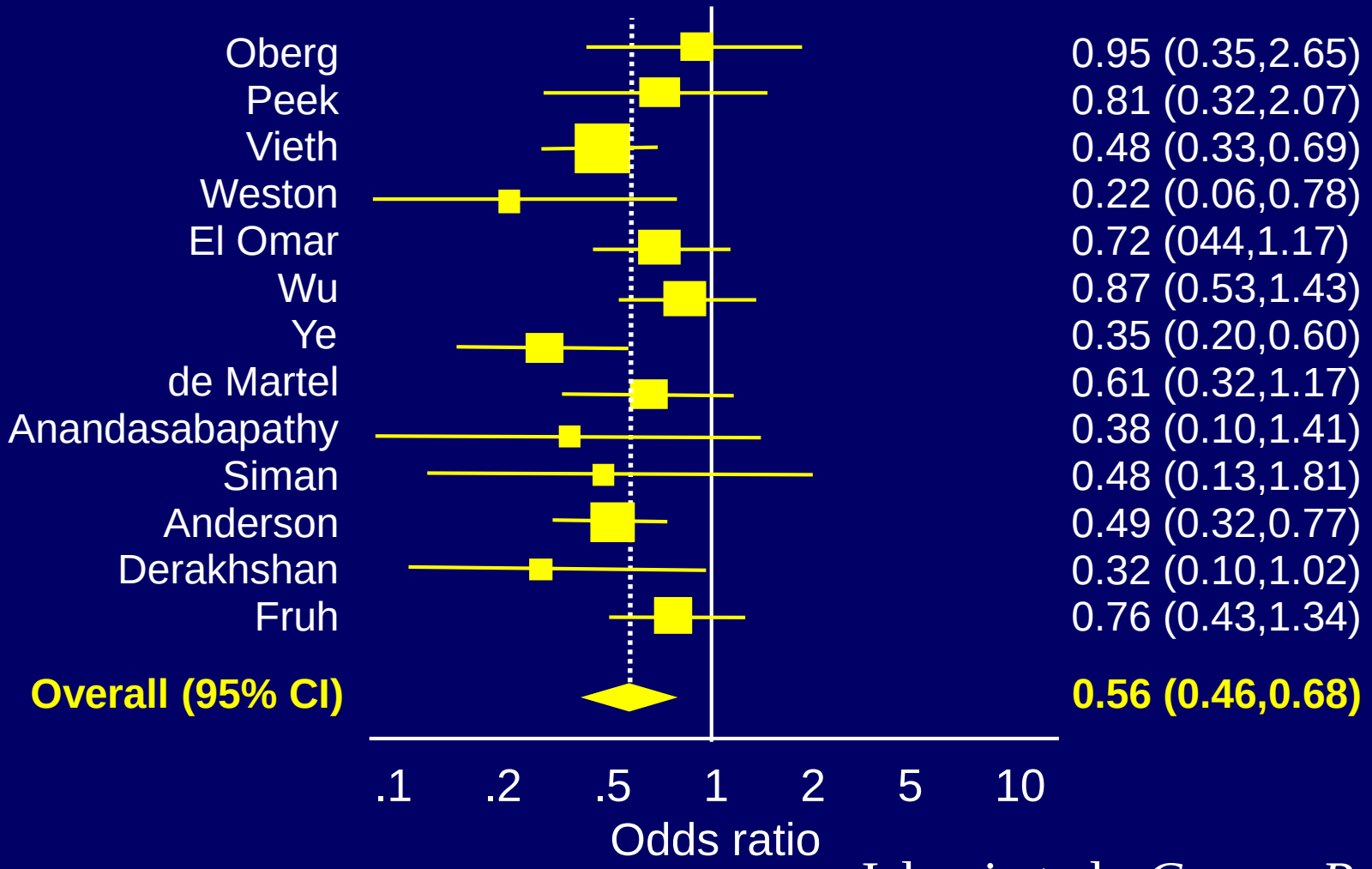
Sonnenberg, et al., *Gastroenterology*

Association of esophageal adenocarcinoma with carriage of *H. pylori*, by *cagA* status

Subject status		Number of controls	Number of cancer cases	Odds ratio	95% CI
H. pylori	*cagA*				
-	-	138	91	1.0	-
+	-	40	26	1.1	0.6-2.1
+	+	46	12	0.4	0.2-0.9

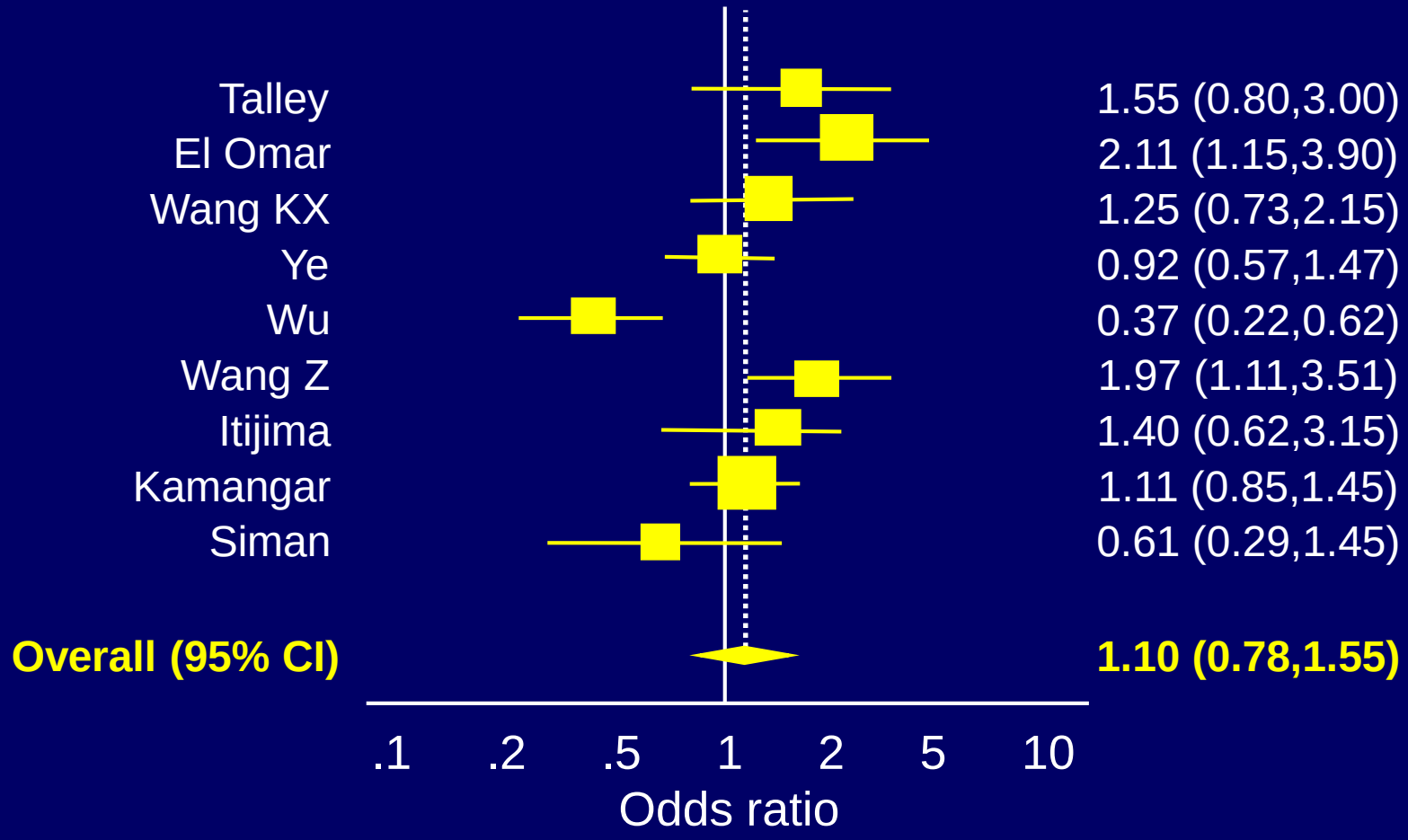
Chow et al., *JNCI*

Association between *H. pylori* and esophageal adenocarcinoma



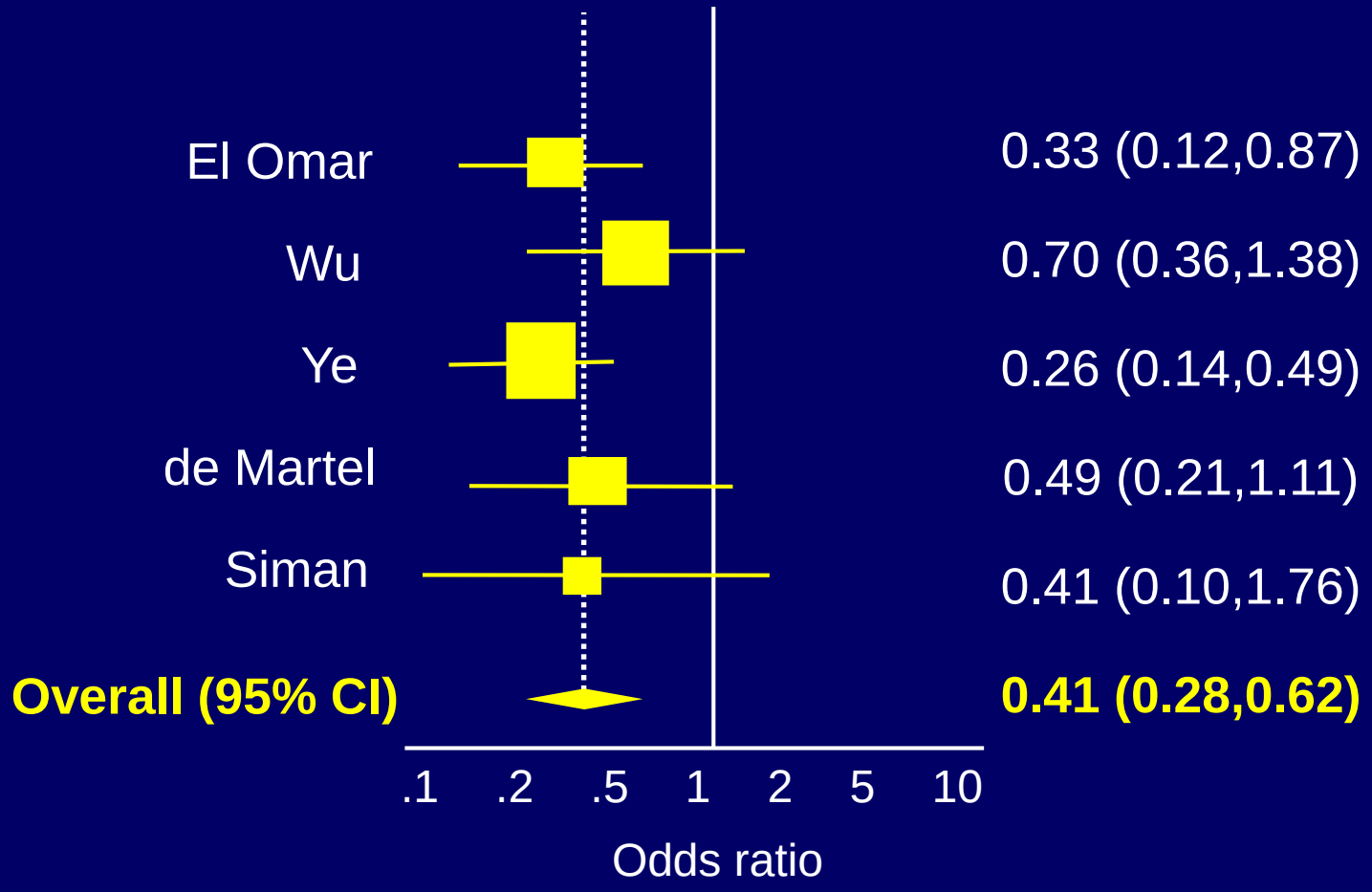
Islami et al., *Cancer Prev Res*

Association between *H. pylori* and esophageal squamous cell carcinoma



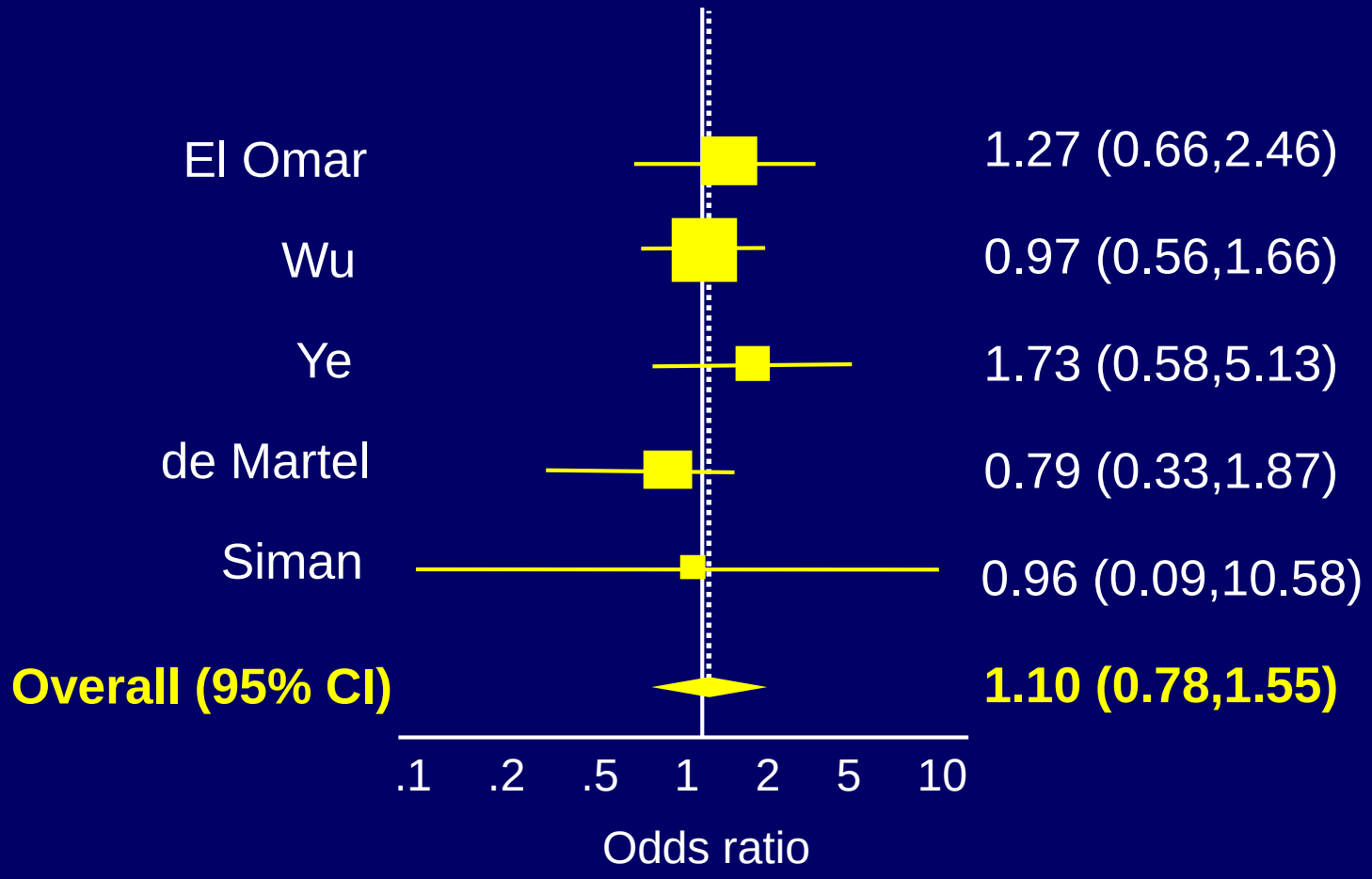
Islami et al., *Cancer Prev Res*

Association between CagA^{+} *H. pylori* and esophageal adenocarcinoma



Islami et al., *Cancer Prev Res*

Association between CagA$^-$ *H. pylori* and esophageal adenocarcinoma



Islami et al., *Cancer Prev Res*

Reciprocity between *H. pylori* colonization and disease states

Asthma

Inflammatory bowel disease

Childhood diarrheal diseases

Tuberculosis

Obesity

Stroke mortality

Who should be tested and treated for *H. pylori*?

Indications among *H. pylori*-infected persons for antimicrobial therapy

- Peptic ulcer disease
- Gastric MALToma
- Family history of gastric cancer
- Hypertrophic gastritis (Menetrier's)
- Prior to long-term NSAID use
- Non-ulcer dyspepsia
- Prior to long-term PPI use
- Atrophy/intestinal metaplasia/dysplasia

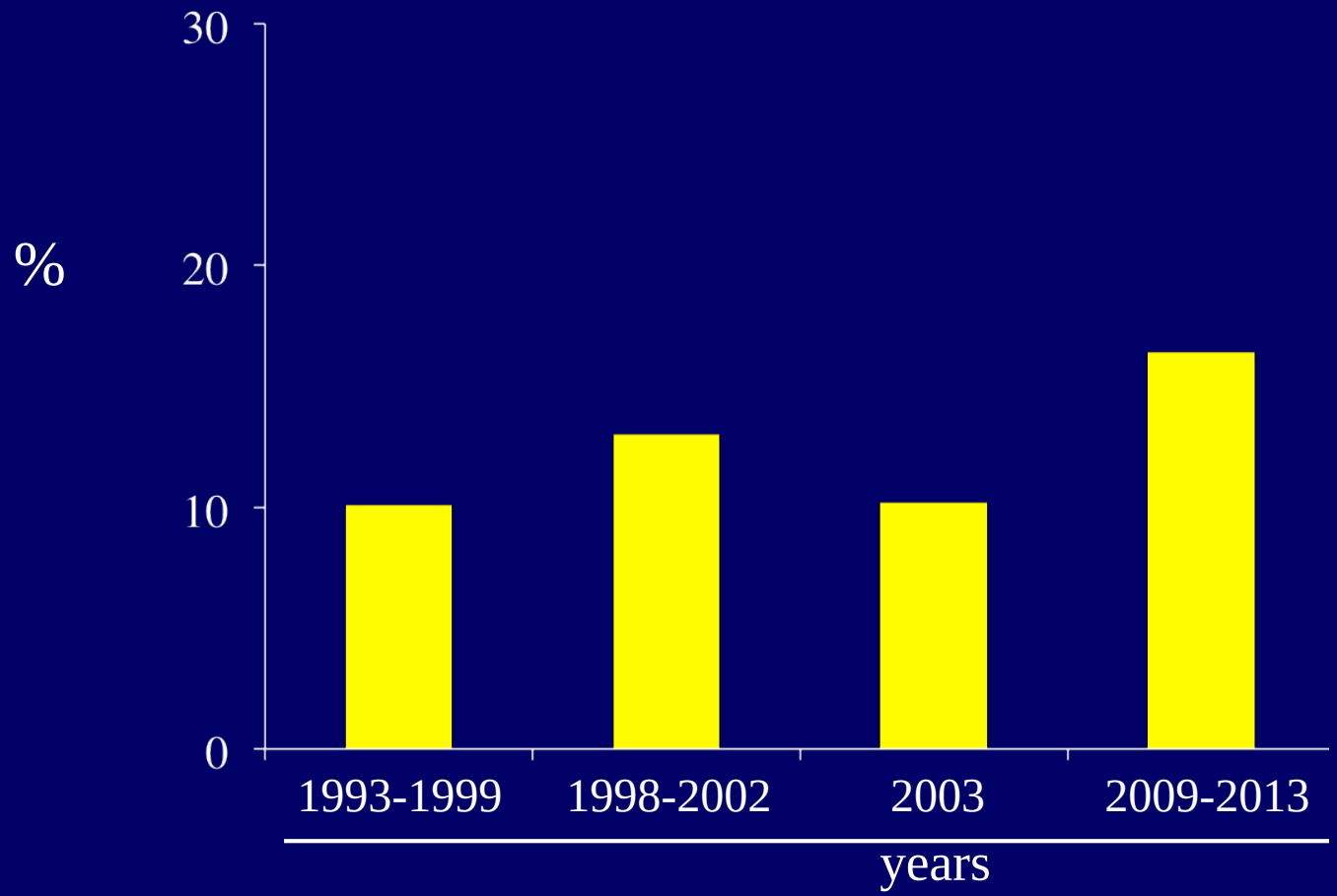
General principles of anti-*H. pylori* therapy

Target efficacy is 90% eradication rate

Level of clarithromycin resistance (15%) is decision inflection point

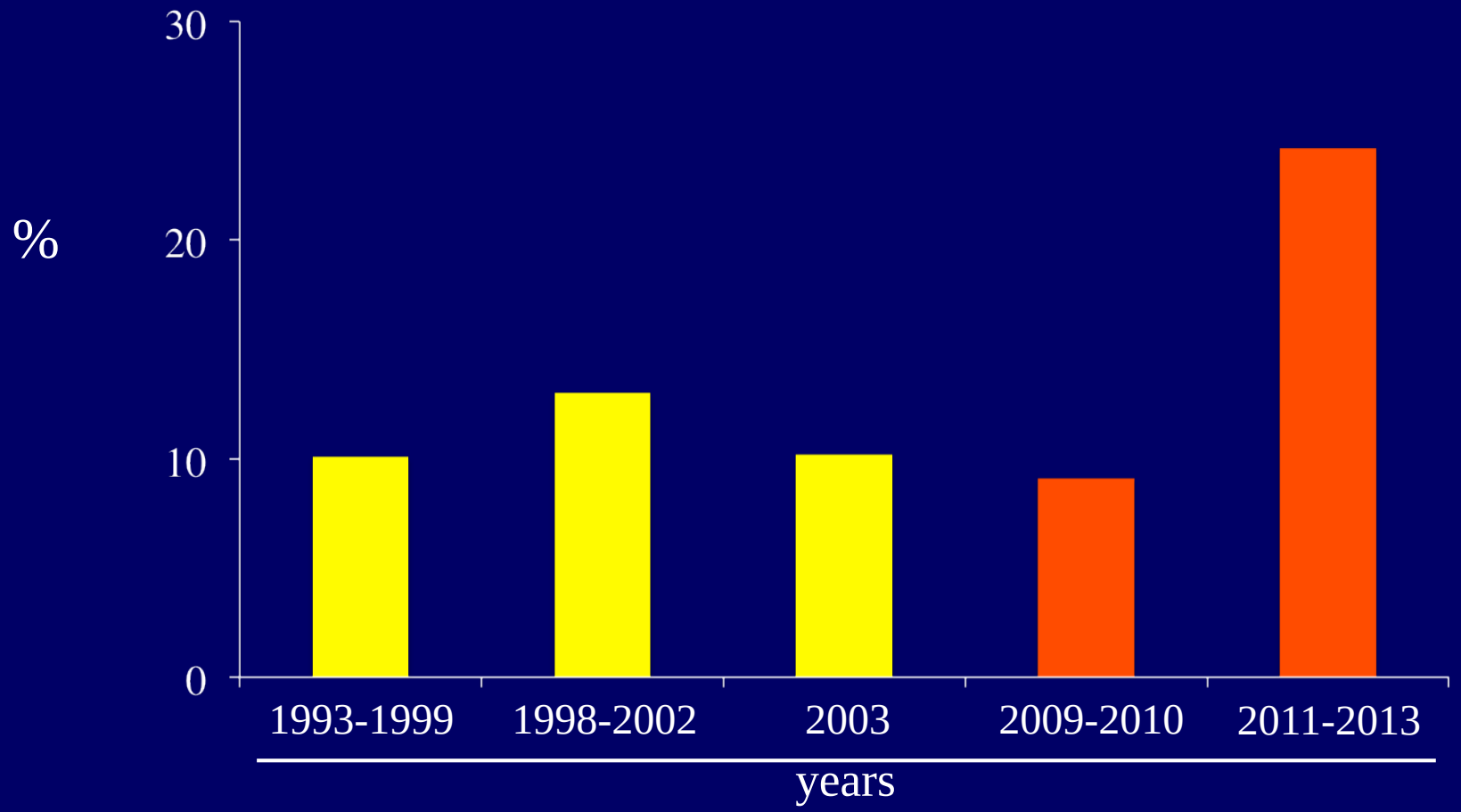
Extending duration to 14 days improves efficacy

H. pylori resistance rates to Clarithromycin in the United States



Shiota *et al.*, *CGH*, 2015

H. pylori resistance rates to Clarithromycin in the United States

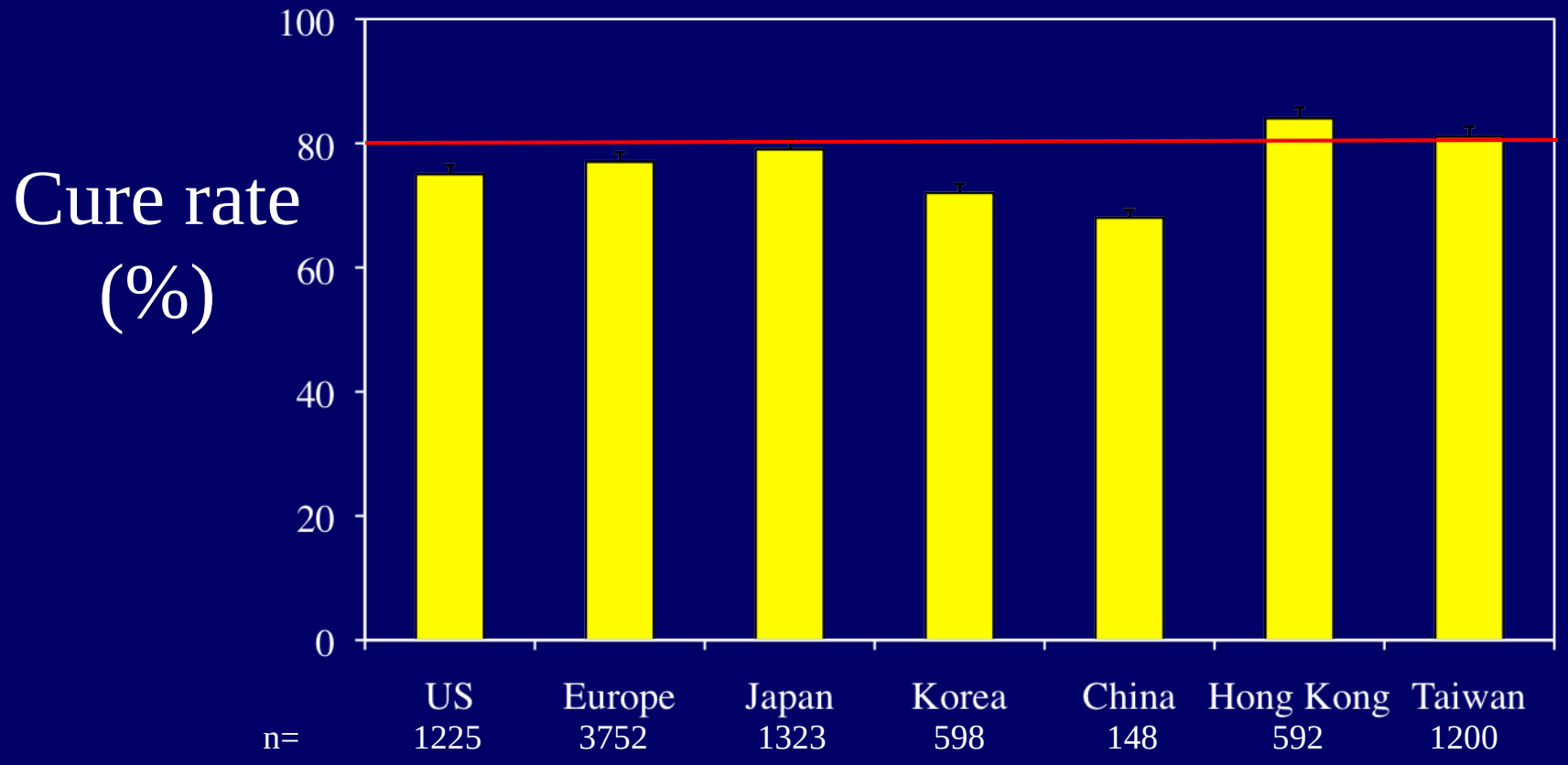


Shiota *et al.*, *CGH*, 2015

Triple therapy

A PPI plus clarithromycin 500 mg twice daily and either amoxicillin 1 g twice daily OR metronidazole 500 mg twice daily

Cure rates with standard triple therapy



Bismuth-containing quadruple therapy

A PPI plus bismuth, tetracycline and metronidazole

Non-bismuth quadruple therapy: Concomitant therapy

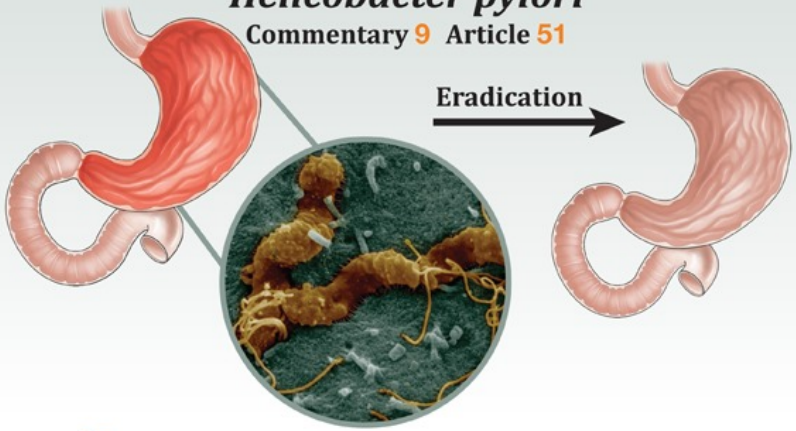
A PPI plus amoxicillin 1 g, clarithromycin 500 mg and metronidazole 500 mg twice daily

Gastroenterology

www.gastrojournal.org Volume 151 Number 1 July 2016

Optimizing Eradication of *Helicobacter pylori*

Commentary 9 Article 51



87 Relamorelin Use Improves Diabetic Gastroparesis

130 Efficacy of HCV Eradication and Portal Hypertension Stage

140 Small Bowel Crypt Genesis and Neuroendocrine Tumors

180 P53 Loss Promotes Pancreatic Carcinogenesis and Drug Resistance

ALSO:
• Introducing *Gastroenterology*'s New Board of Editors 4
• Review: Direct-Acting Antivirals and HCV Resistance 70

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Algorithm for eradication therapies

H. pylori infection

Known local patterns?

Low clarithromycin resistance or high PPI triple therapy success rates

Algorithm for eradication therapies

H. pylori infection

Known local patterns?

Low clarithromycin resistance or high PPI triple therapy success rates

What is the recommended management and surveillance for patients with pre-malignant lesions?

Gastric Intestinal Metaplasia

Present in 5-20% of patients undergoing EGD

Annual risk of gastric cancer: 0.13-0.25% per year

Management of epithelial precancerous conditions and lesions in the stomach (MAPS II)

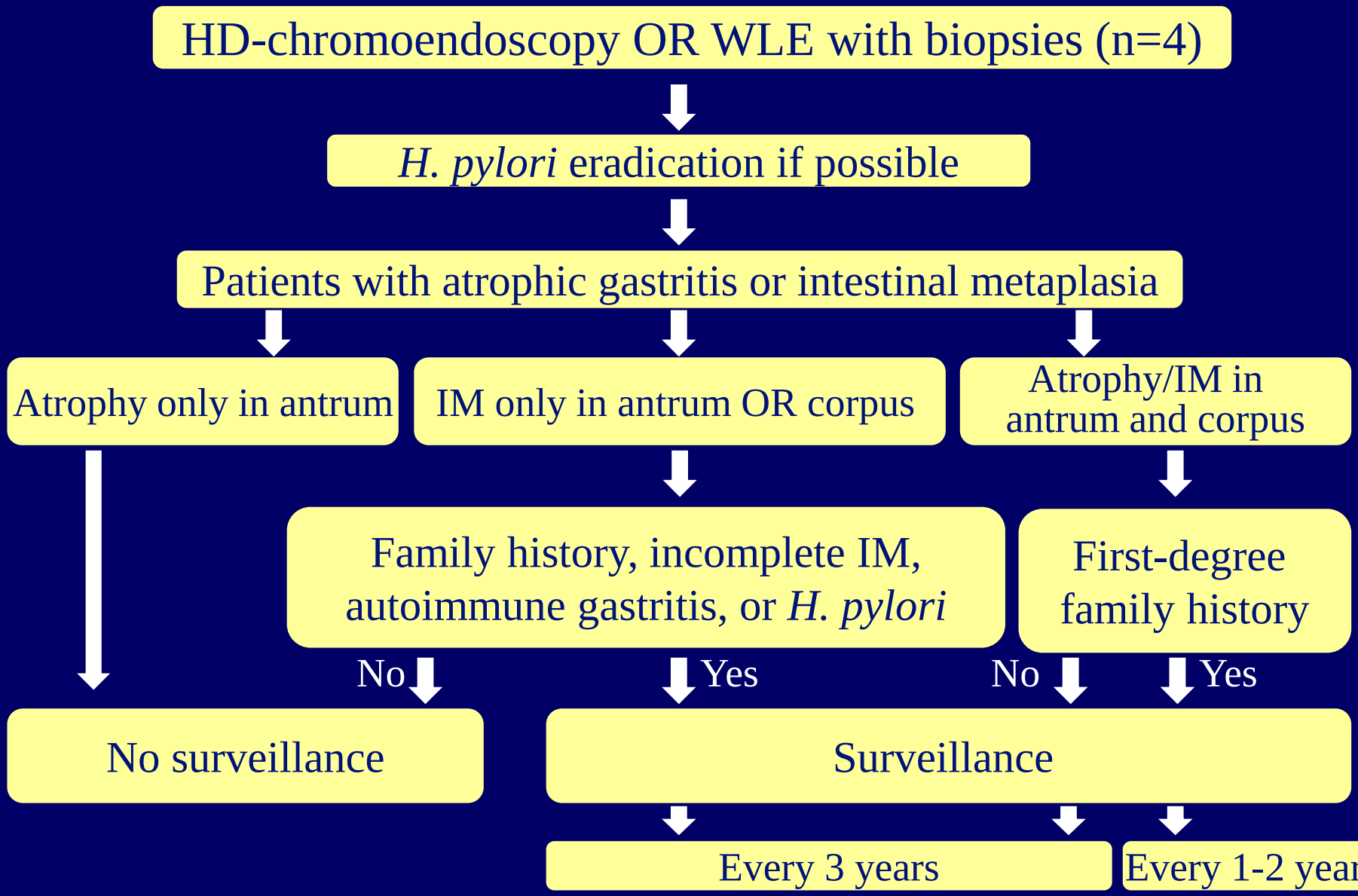
Utilized Delphi method for expert consensus

MAPS II 2019 guidelines updated 2012 MAPS I guidelines with a focus on articles post-2010

Low quality evidence drove several recommendations

Endoscopy, 2019

MAPS II proposed management for GIM



Pimentel-Nunes, et al., *MAPS II*, 2019

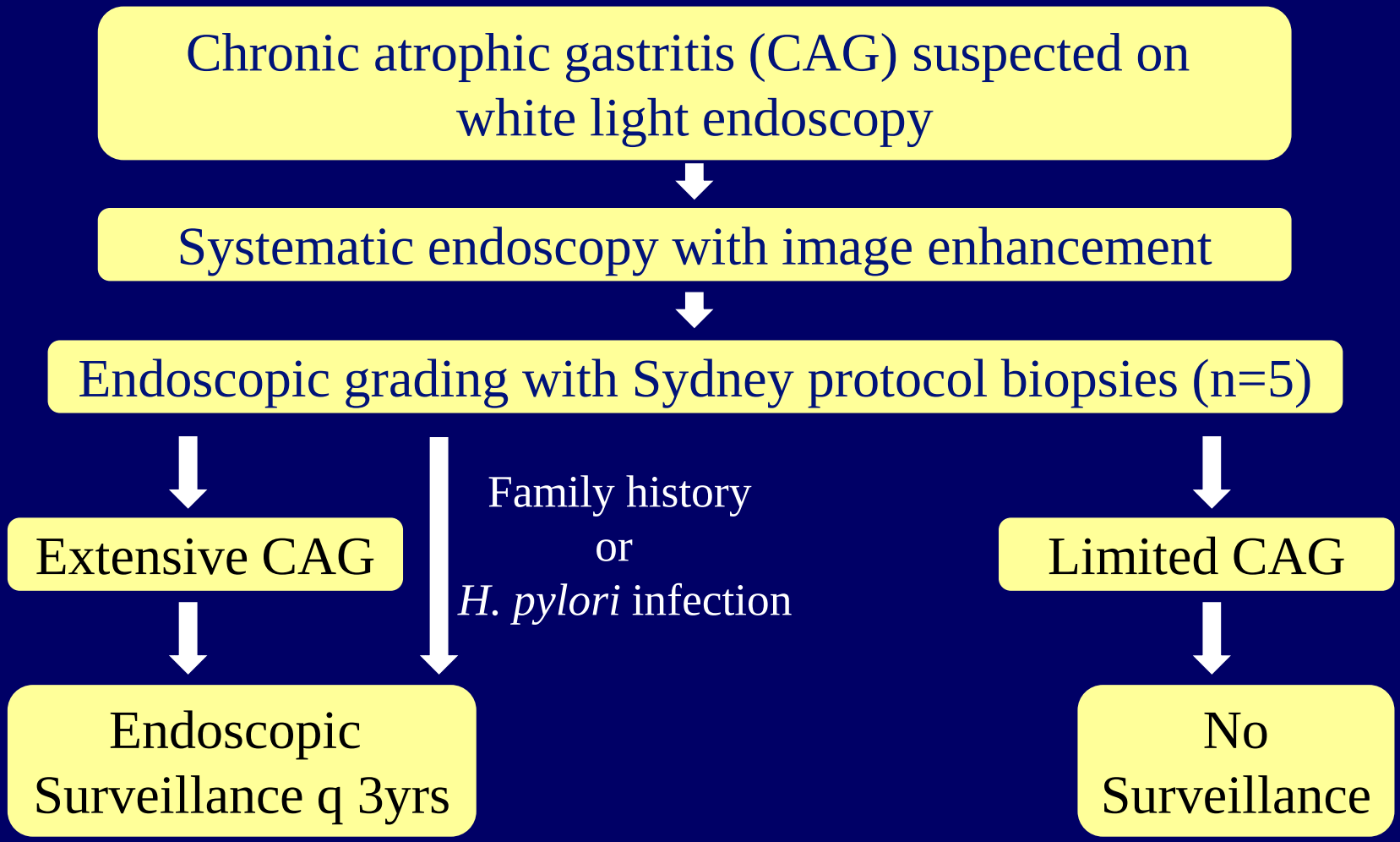
British Society of Gastroenterology Guidelines

Intended for UK populations

Chronic atrophic gastritis (CAG) includes GIM and gastric atrophy

Gut, 2019

British Society of Gastroenterology guidelines



Banks, et al., *Gut*, 2019

AGA Recommendation for Patients with GIM

In patients with GIM, the AGA suggests against *routine* use of endoscopic surveillance

Gastroenterology, 2020

AGA Recommendation for Patients with GIM

In patients with GIM, the AGA suggests against *routine* use of endoscopic surveillance

Conditional recommendation: very low quality of evidence

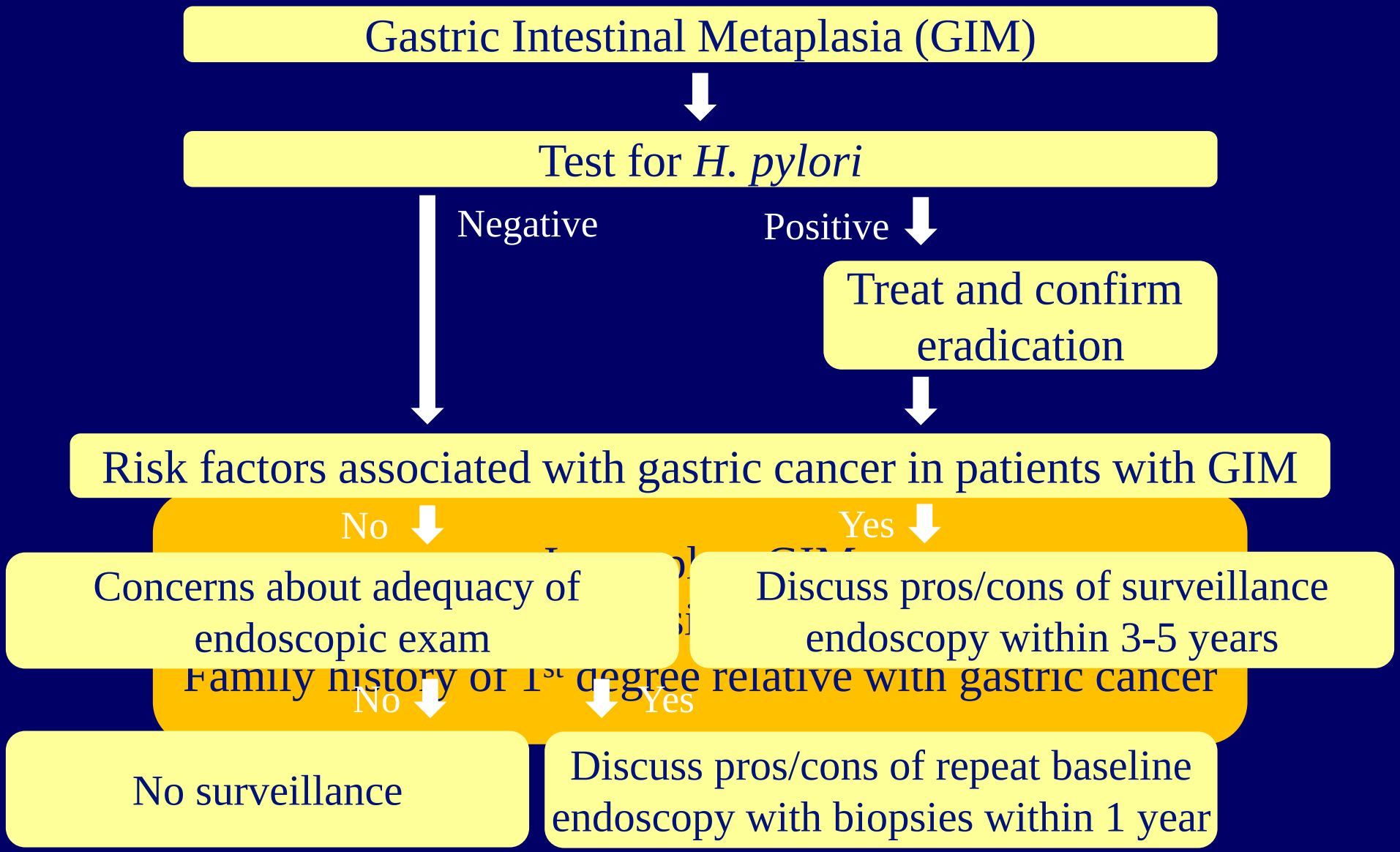
Nuances of AGA Clinical Guidelines on Management of Gastric Intestinal Metaplasia

Utilized GRADE methodology

Patients with incidentally diagnosed GIM and North American populations

More emphasis on shared decision making between providers and patients

AGA Clinical Guidelines for GIM



Shah, *Gastroenterology*, 2020

Future Research Needs

Randomized trials on surveillance impact

Importance of routine characterization of incomplete versus complete GIM

Lack of informative natural history studies to evaluate importance of race, ethnicity or country of origin on GIM progression

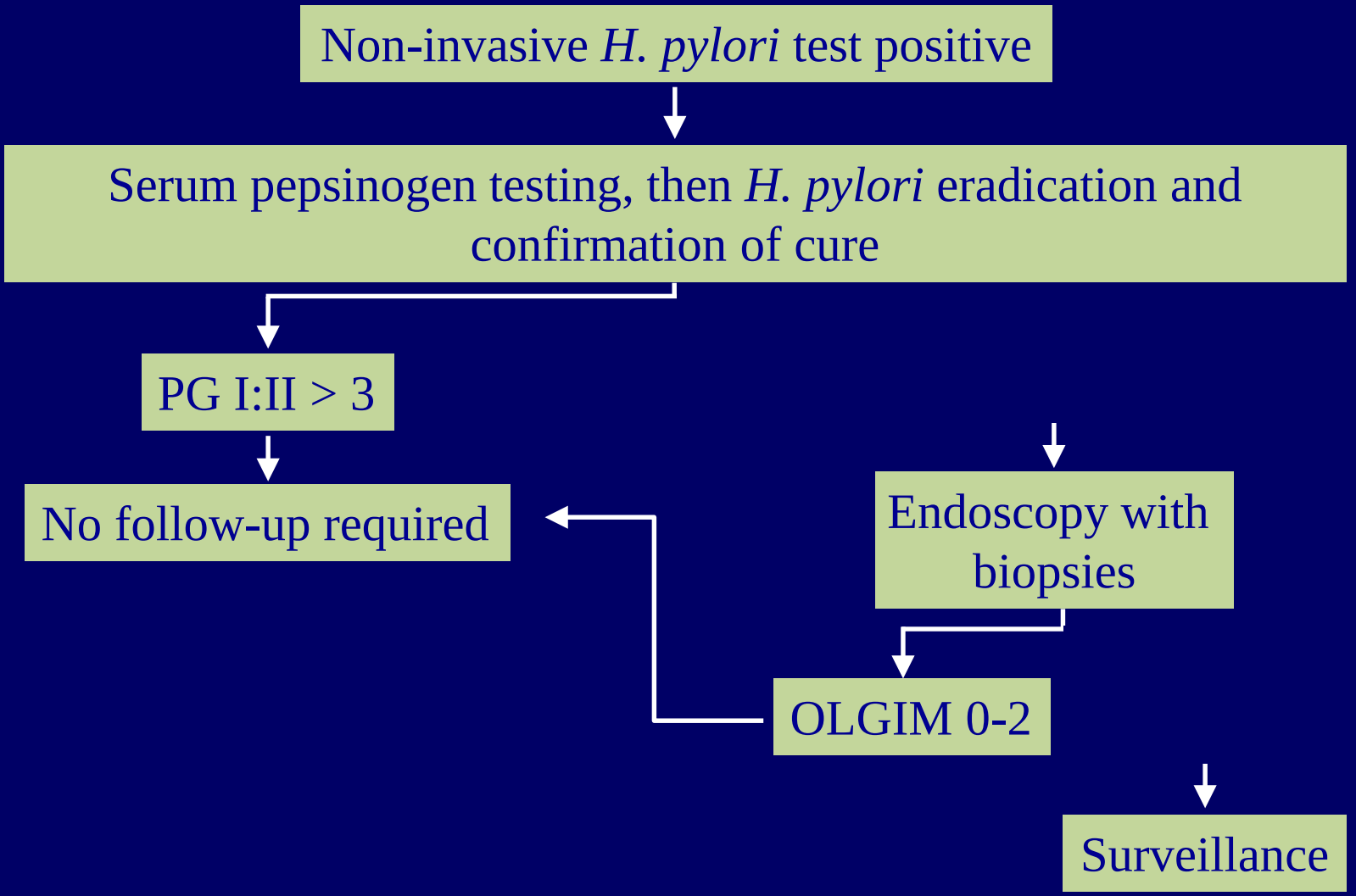
Future Research Needs

Does GIM progress after *H. pylori* therapy?

What is the optimal biopsy protocol to increase the yield of GIM detection?

What is the role of noninvasive biomarkers in North American populations?

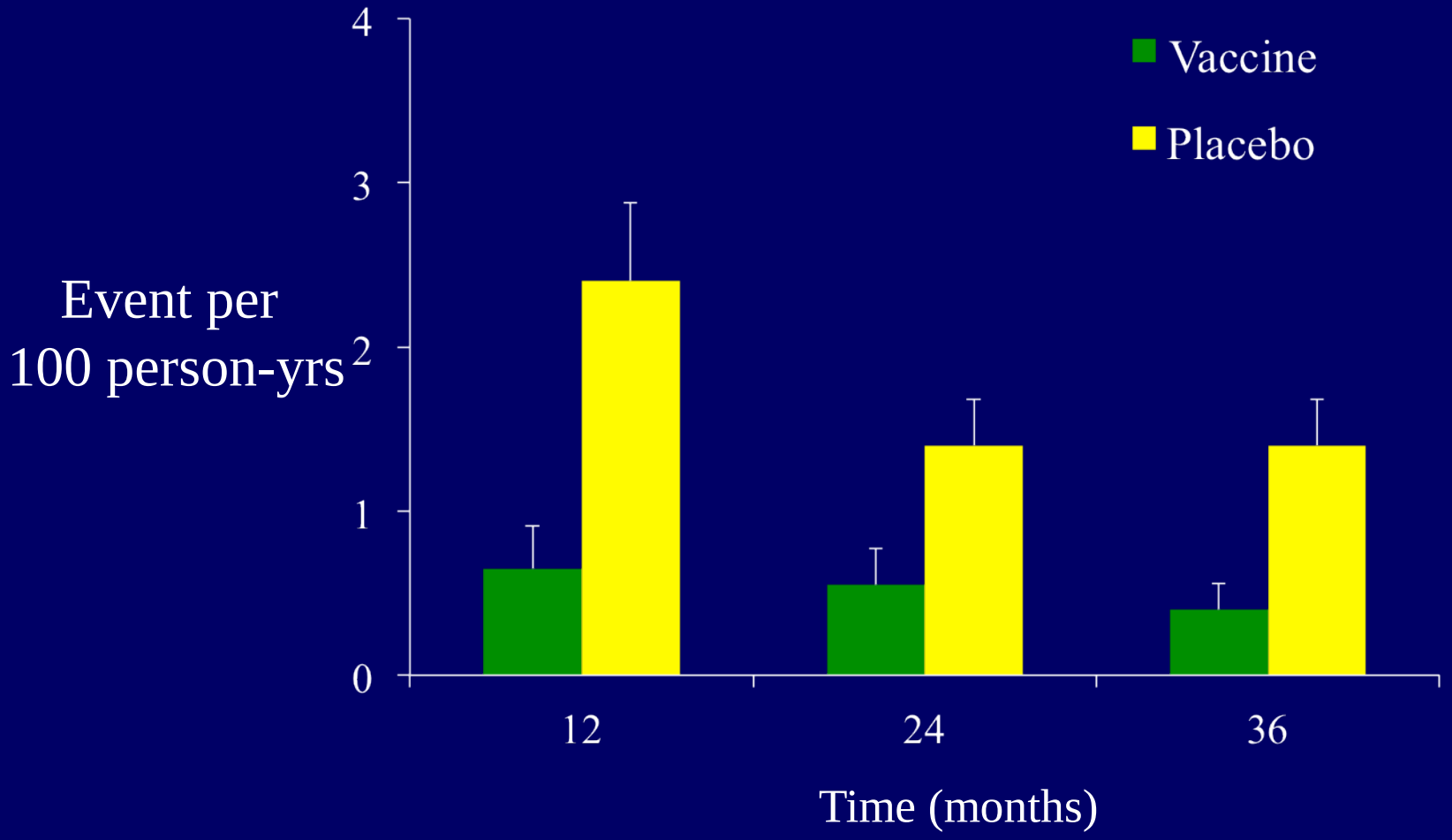
Future *H. pylori* screening and follow-up approaches



Graham, *Gastroenterology*, 2015

What is the prospect for developing an effective vaccine targeting *H. pylori*?

Risk of developing new *H. pylori* infections



Zeng *et al.*, *Lancet*, 2015

Conclusions

Complex human diseases such as gastric cancer are multifactorial, and their pathogenesis combines effects of microbial, host and environmental factors

Conclusions

- Test and treat strategies for the indiscriminant elimination of *H. pylori* are not supported by current data unless a defined risk factor is present

Conclusions

Based on low-quality evidence, patients who have GIM in conjunction with additional risk factors should be considered for surveillance but, at a minimum, be fully informed by their providers regarding the benefits and risks of surveillance

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