Gastric Cancer Epidemiology and Prevention in the Low Resource Settings

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IOM Workshop in Cancer Care in Low Resource Areas

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Gastric Cancer Prevention in Low Resource Areas

Gastric cancer epidemiology

- The altitude enigma in Latin America

The biology of *H. pylori* and gastric cancer

- The role of the microbiome

Context: Central America

Opportunities for prevention

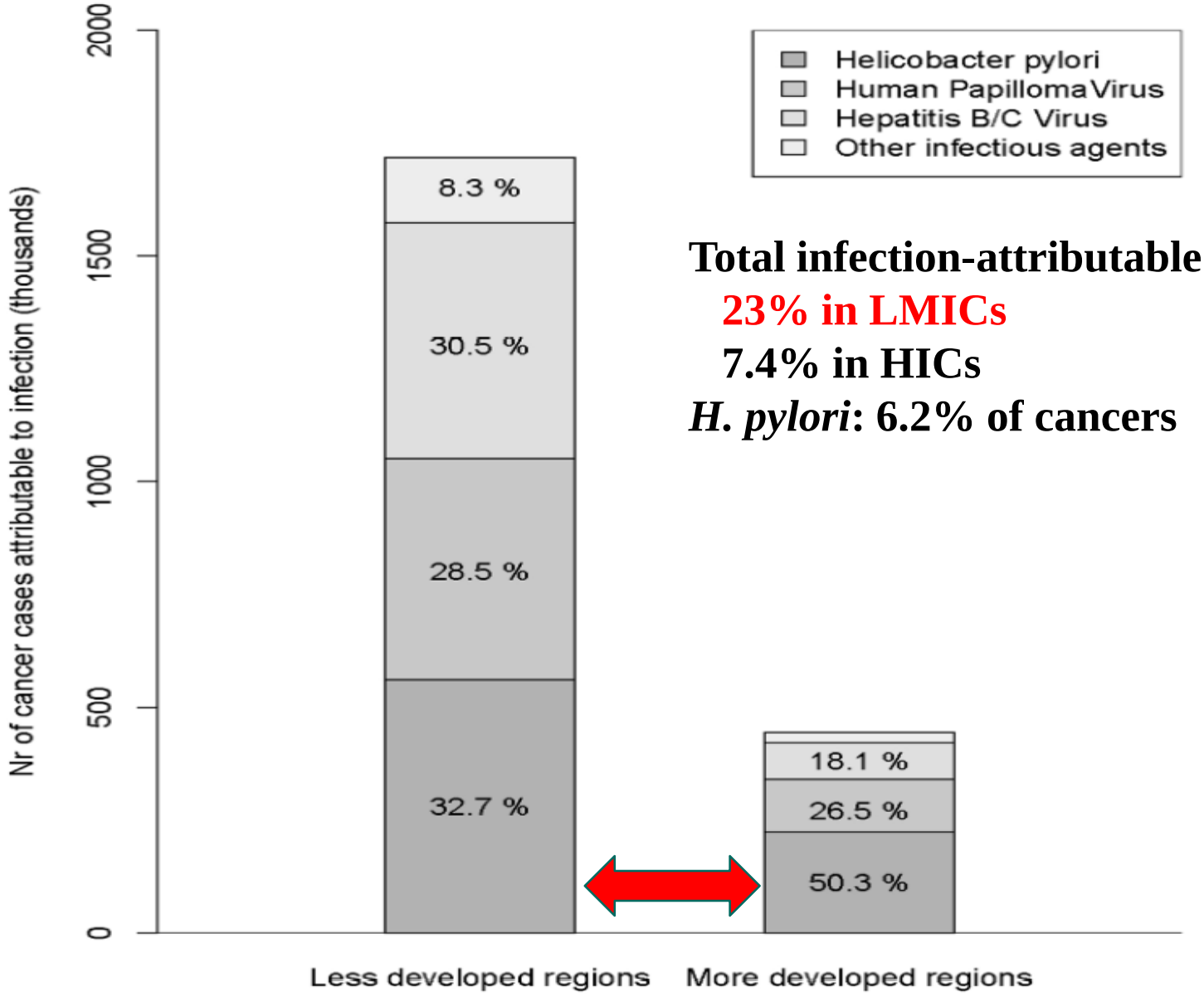
- Biomarker development
- *H. pylori* eradication
- Chemoprevention
- Novel endoscopy technologies

Gastric Cancer: Provocative Themes

- **The “other” infection-associated cancer**
  - Chronic *bacterial* infection, *H. pylori*
- ***H. pylori* eradication (antibiotics) to prevent cancer**
- **Geography as a “biomarker” for risk**
  - Implications for immigrant populations
- **Role of the human microbiome**
  - Carcinogenesis and homeostasis
- **Partnering of cancer screening programs**

New Cancer Cases Attributable to Infection

Plummer M, Int J Cancer 2014; deMartel C, Lancet Onc 2012



Total infection-attributable in 2008:

23% in LMICs

7.4% in HICs

***H. pylori*: 6.2% of cancers**

Gastric cancer: Epidemiology Summary 2015

The third leading cause of cancer mortality
- Annual incidence over one million

Leading cause of infection-associated cancer mortality
- *H. pylori* is a WHO Class I Carcinogen

All-cause mortality worldwide: 14th
- Will rise to 10th, given growing & aging populations
- Consistent 2:1 male to female ratio

Significant geographic variability offers the opportunity for scientific discovery & focused prevention
- High incidence regions include:
  - Latin America, Eastern Asia, Eastern Europe

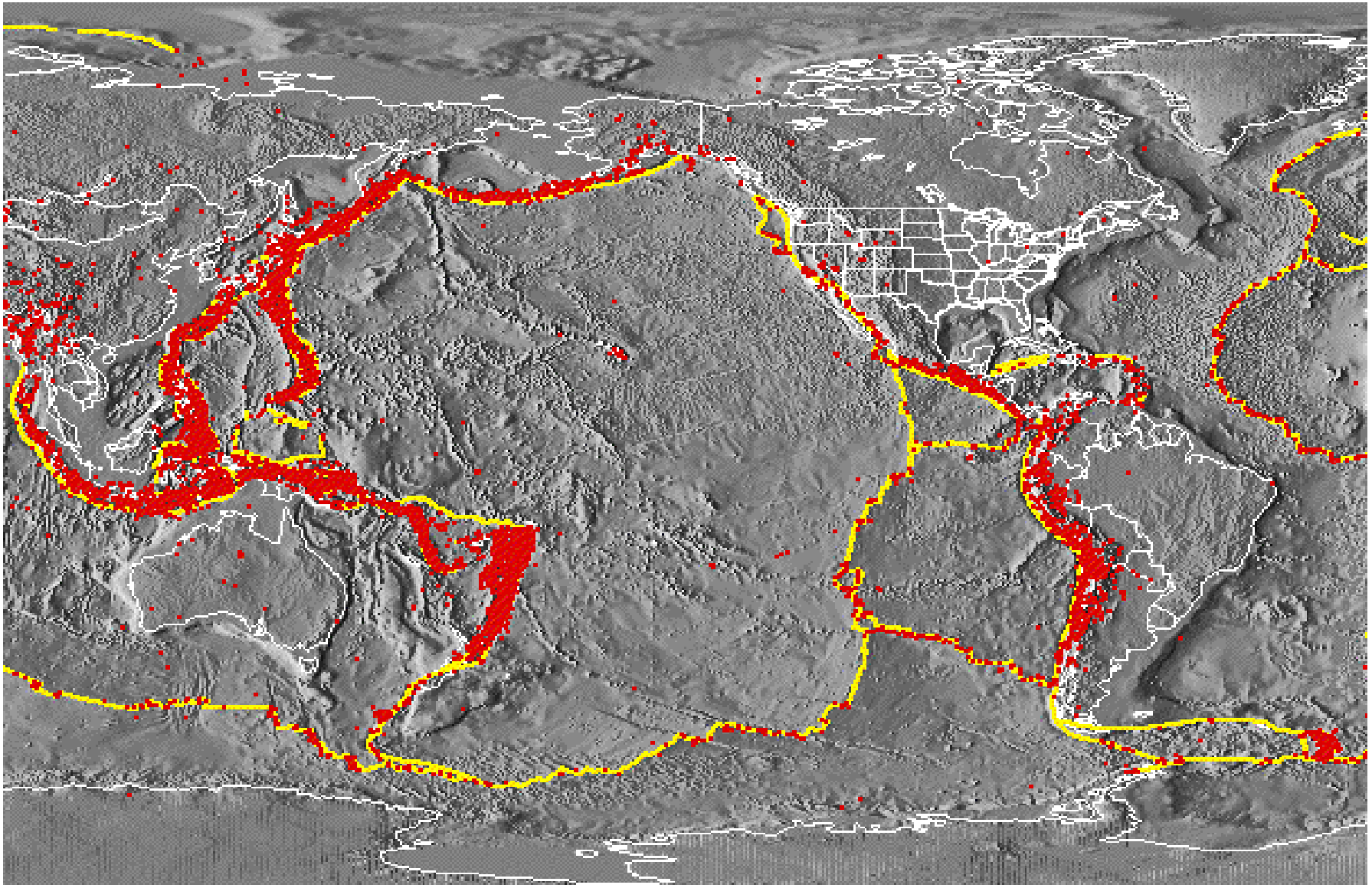
In the U.S., incidence rates are double in minorities

Risk Factors for Gastric Cancer by Subsite
Worldwide Data

Level of evidence	Risk factor	DISTAL	Cardia
Convincing	Chronic *H. pylori* infection[1, 2]	↑	↓ or null
	Smoking[3]	↑	↑
Probable	High consumption of fruits and vegetables[4-6]	↓	↓
	Excessive salt consumption[7,8]	↑	↑
	High consumption of processed meat[9]	↑	↑
	Excess weight[10]	null	↑
	Reflux[11]	?	↑
	Epstein-Barr virus infection[12]	↑	↑
Suggestive	High consumption of fiber[13]	↓	↓
	High consumption of alcohol[14]	↑	↑
	Estrogens[15]	↓	?
	Some genetic variants[16, 17]	↑	↑

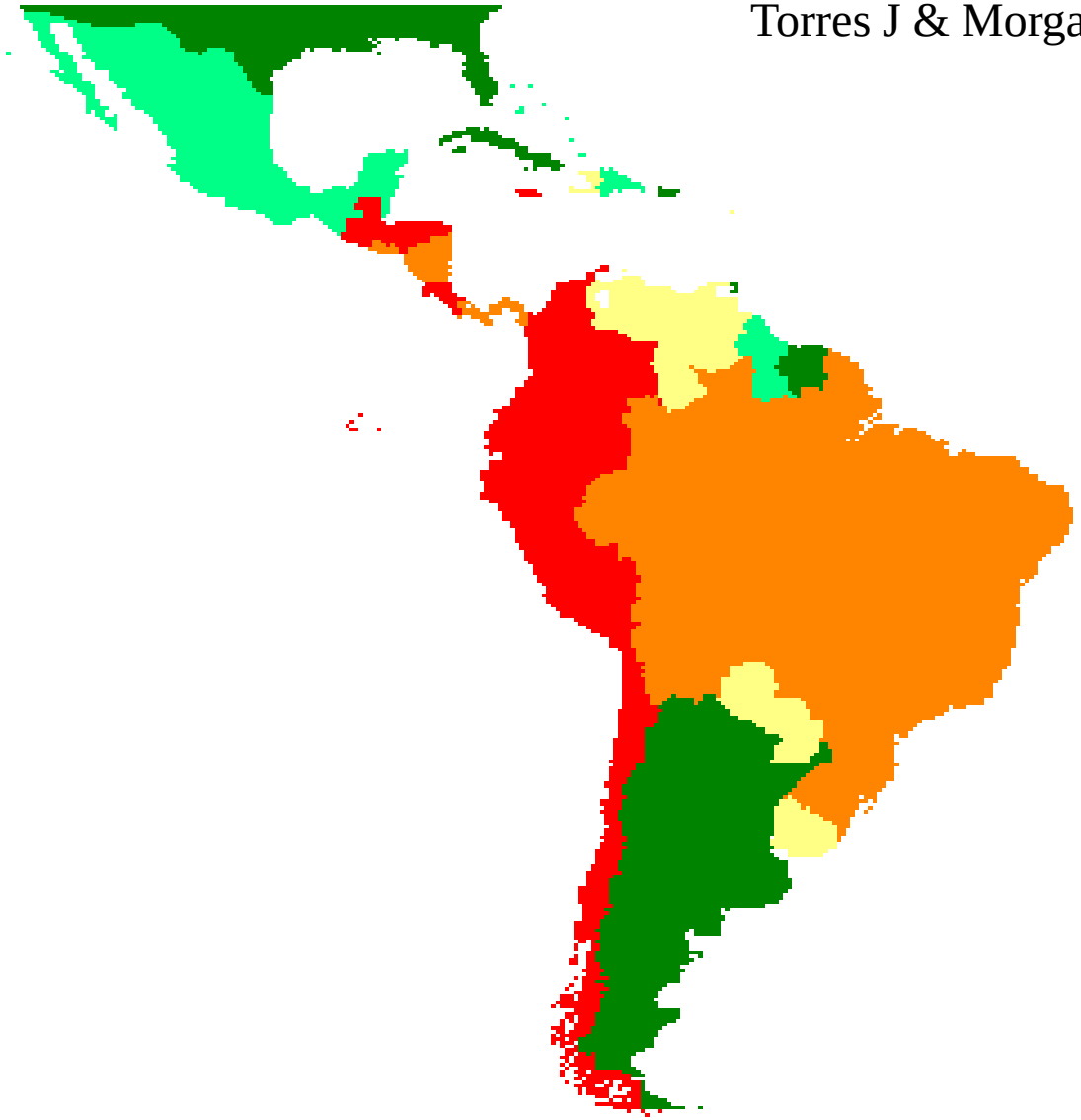
[1]IARC, 1994; [2]Helicobacter and Cancer Collaborative Group, Gut 2001; [3]Ladeiras-Lopez, Cancer Causes Control 2008; [4]Lunet, Eur J Cancer Prev 2007; [5]Lunet , Nutr Cancer 2005; [6]WCRF/AICR, 2006; [7]Tsugane, Gastric Cancer 2007; [8]D'Elia, Clin Nutr 2012; [9]Larsson, JNCI 2006; [10]Yang, Eur J Cancer 2009; [11]Forman, Aliment Pharmacol Ther 2004; [12]Murphy, Gastroenterol 2009; [13]Jacobs, Nutr Cancer 1998, [14]Tramacere, Ann Oncol 2012; [15]Camargo, CEBP 2012; [16]Gonzalez, Int J Cancer 2002; [17]Abnet, Nat Genet 2010.

Gastric cancer “Rim of Fire” ?



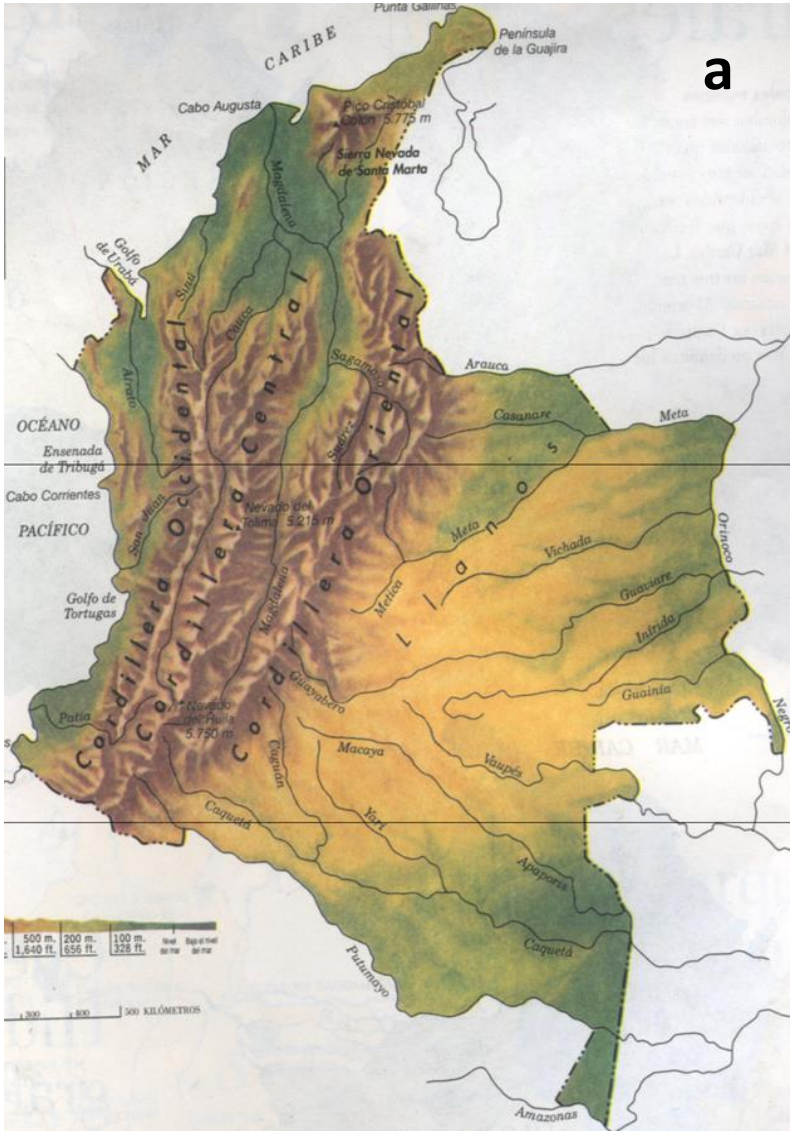
Gastric Cancer Mortality in the Americas

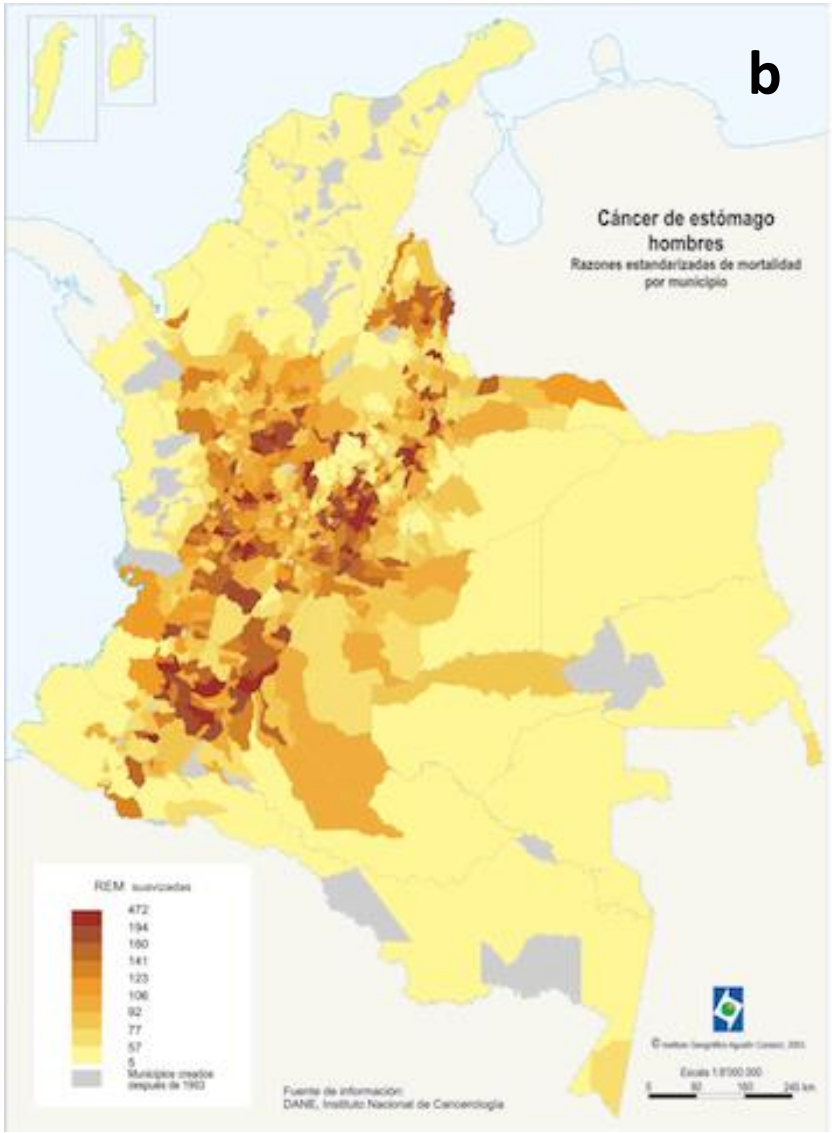
Torres J & Morgan DR, Cancer Causes Control 2013
IARC 2010, GLOBOCAN 2010



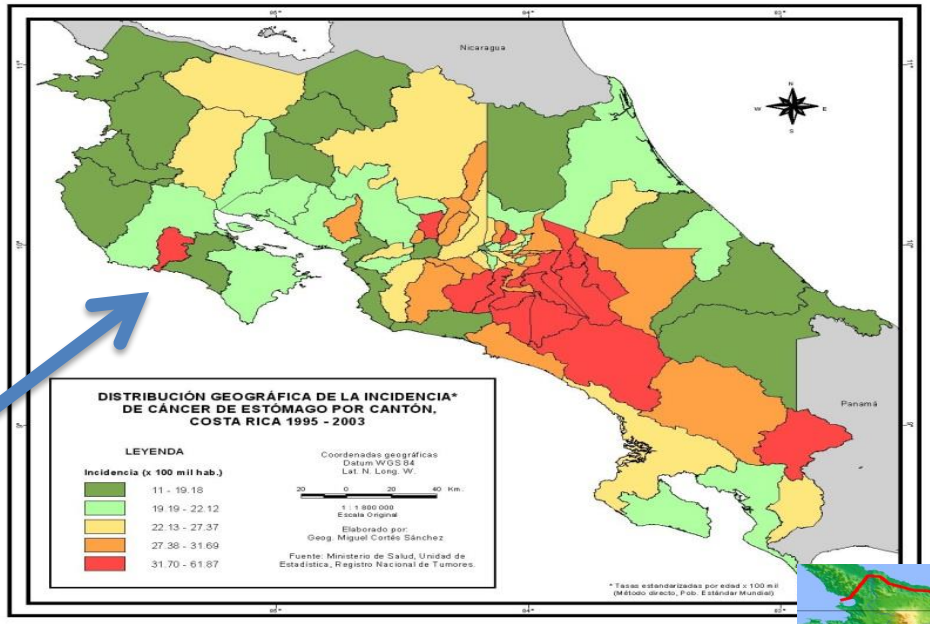
< 7.5 < 8.9 < 12.4 < 22.3

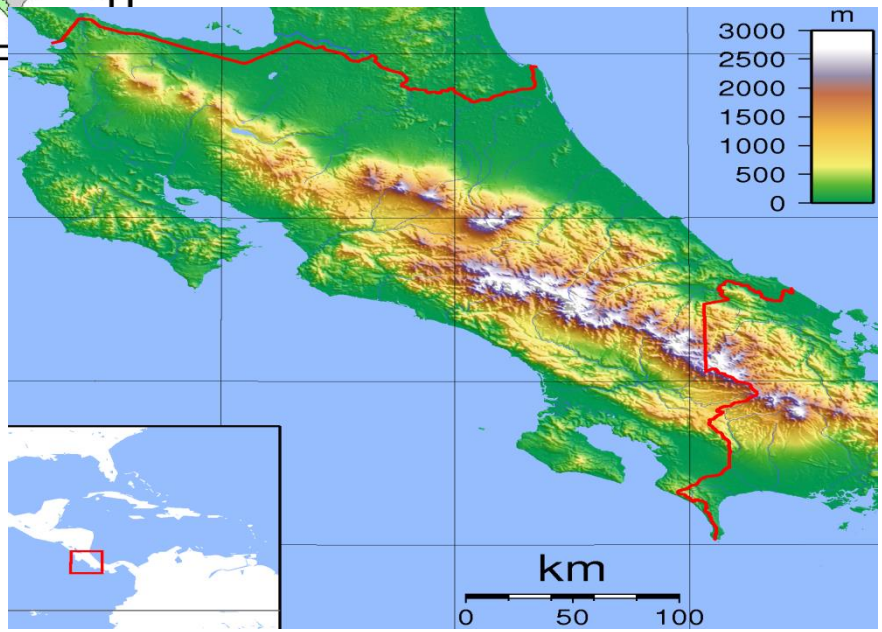
Colombia GC mortality variation by municipio

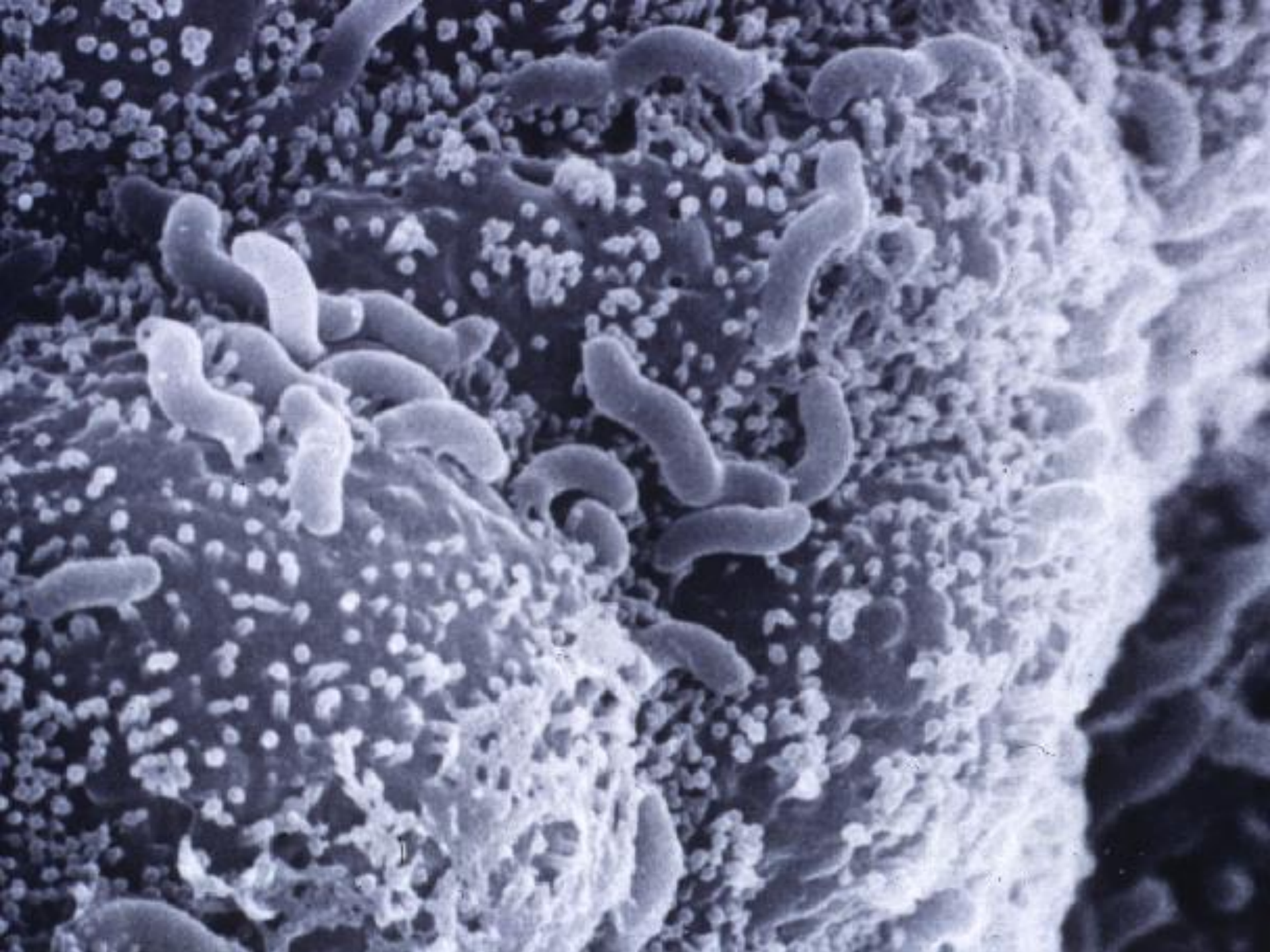




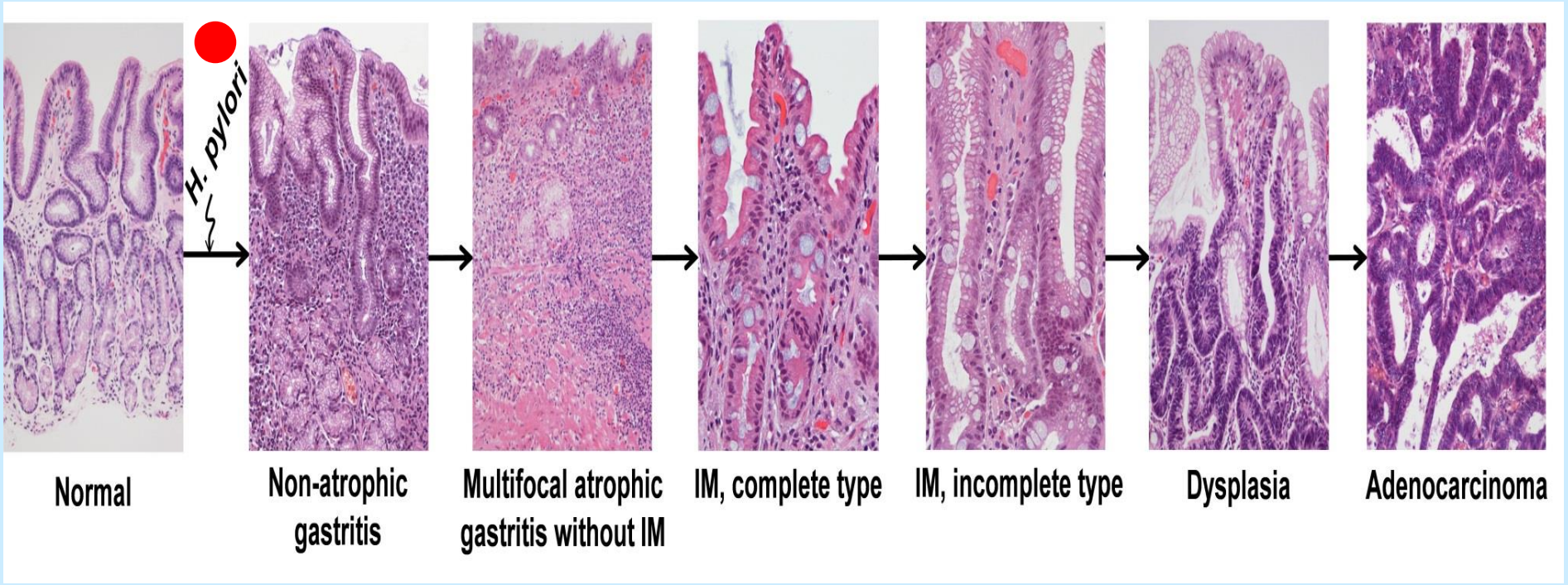
Costa Rica GC incidence variation by canton







Gastric Cancer “Correa” Cascade

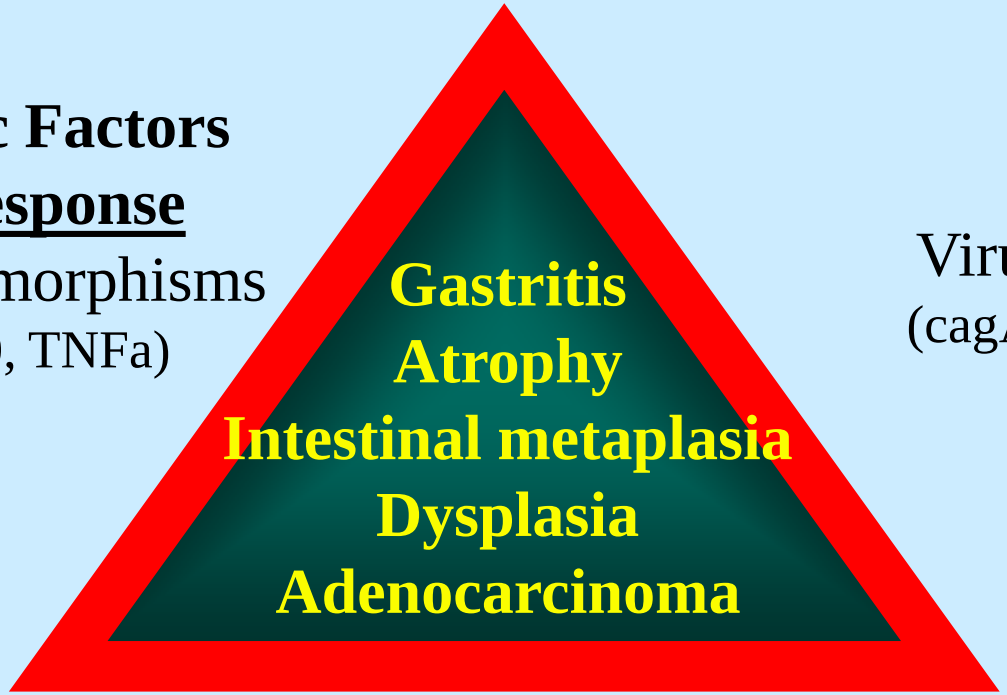


Premalignant lesions

Polk DB, Nature Rev Cancer 2010;
Correa P, Gastro 2007
Correa P, Cancer Res 1992

Pathogenesis Triangle for Gastric Cancer

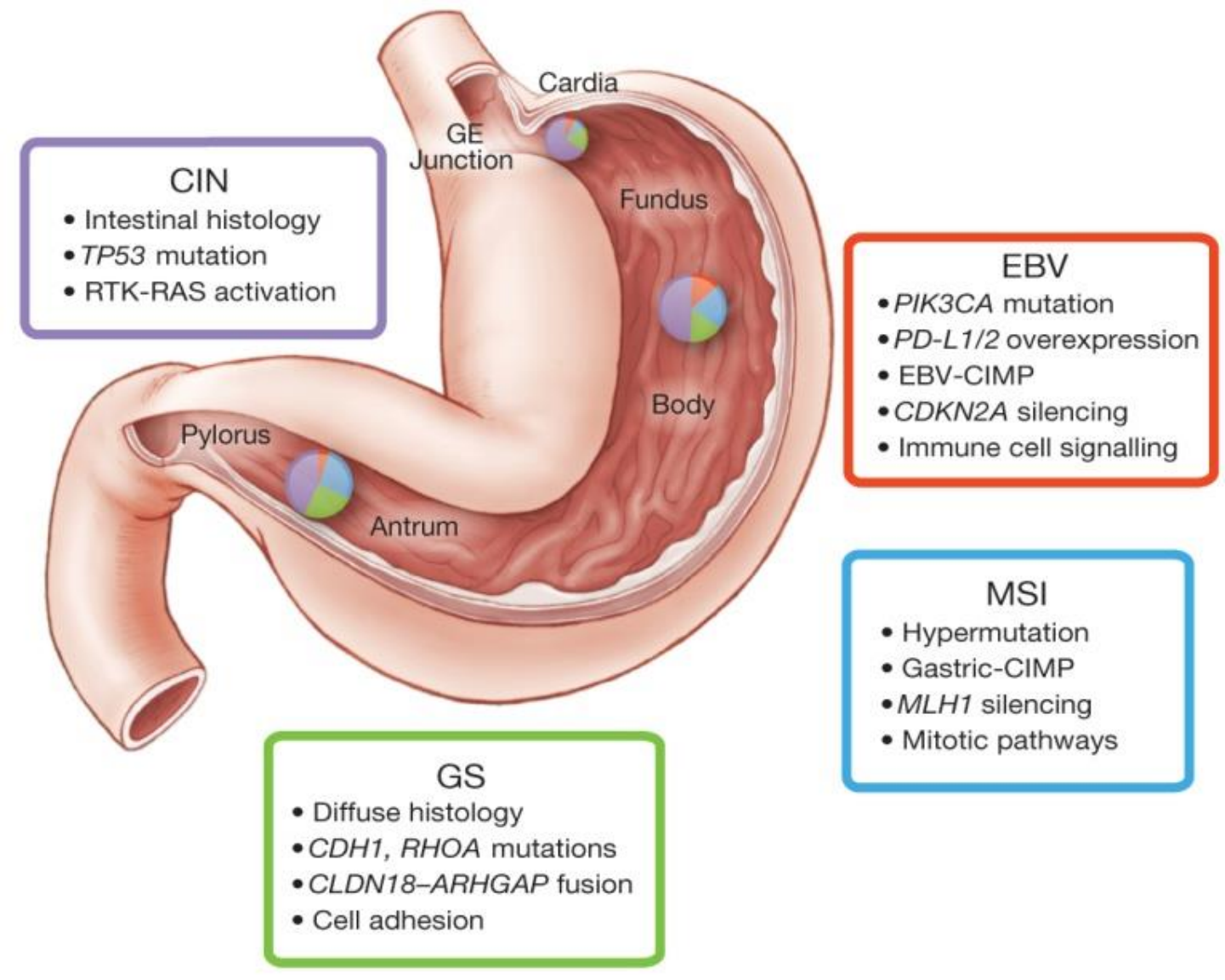
Host Genetic Factors
& Host Response
Cytokine polymorphisms
(IL1B, 1L-10, TNFa)



H. Pylori
Virulence factors
(cagA, vacA, babA2)

Dietary & Environmental Factors
Diet: Antioxidants & Insults
Co-infection: EBV
Other: Tobacco, Alcohol, Fogón

Four Molecular Subtypes of Gastric Adenocarcinoma



Bass AJ for TCGA, *Nature* July 23, 2014

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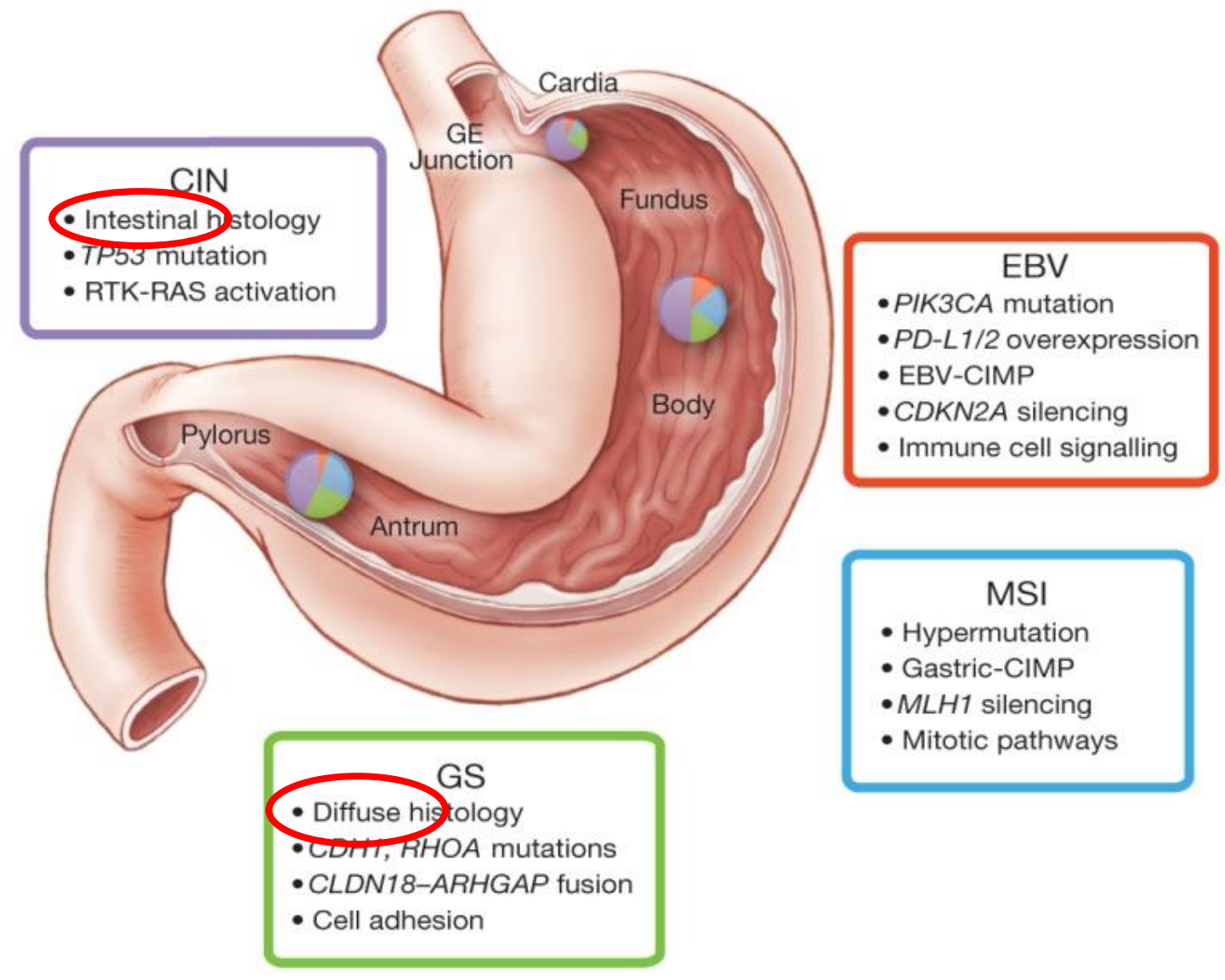

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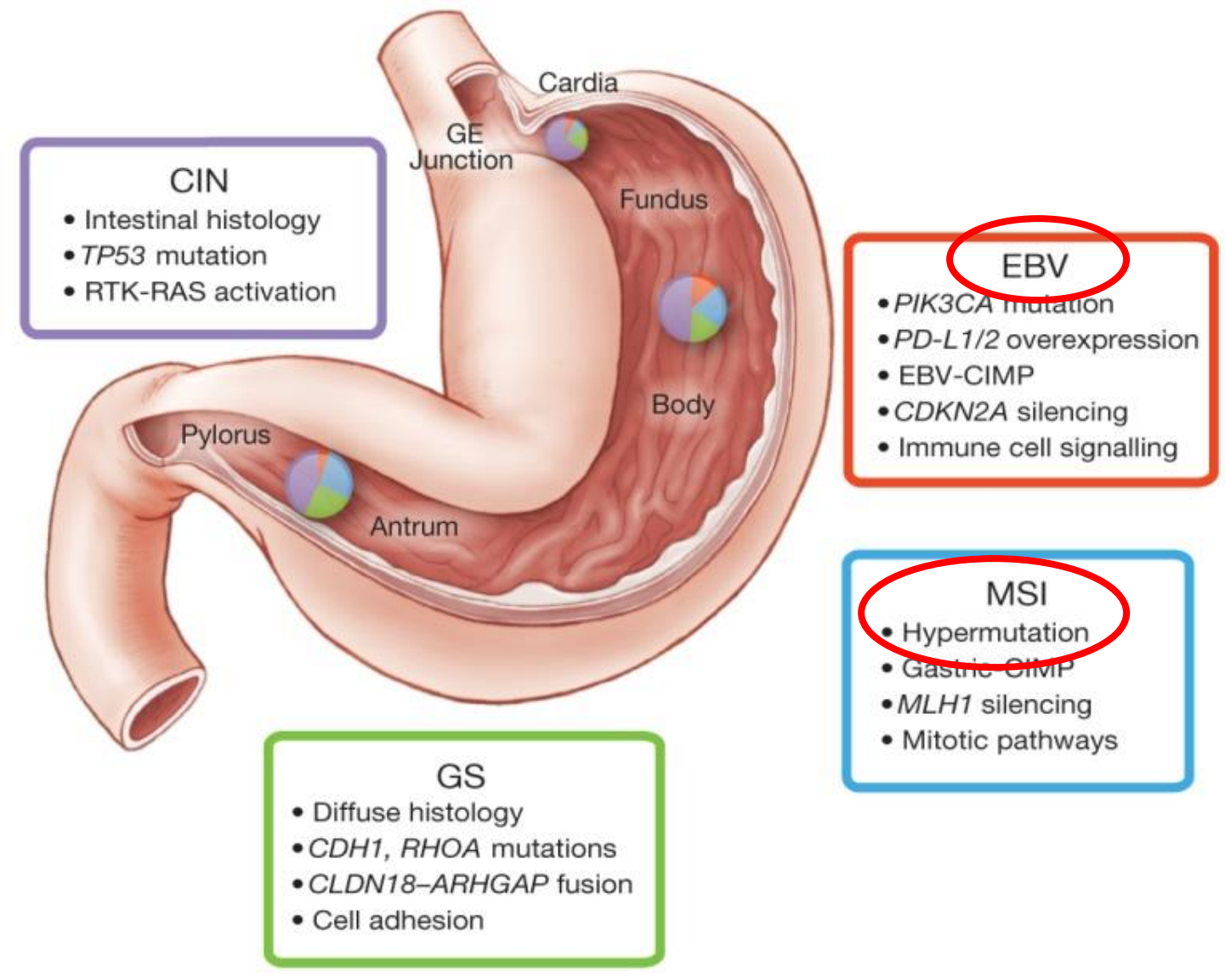

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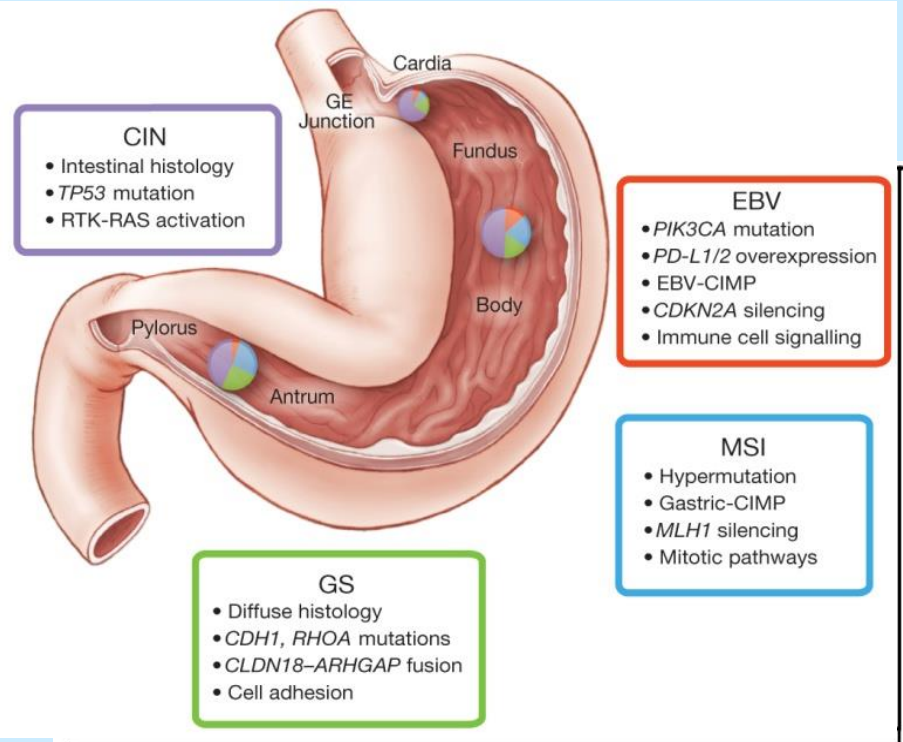
Four Molecular Subtypes of Gastric Adenocarcinoma



Key Features of Four Molecular Classes of Gastric Cancer

Epstein-Barr virus positive (9% of cancers)
- -High levels of EBV genome
- -*PIK3CA* mutation in 82%, cell survival and growth
- -*MET* mutation in 32%, growth factor signalling
- -*ERBB2* mutation in 18%, growth factor signalling

Microsatellite instability (22% of cancers)
- -hypermutation (> 11.4 mutations/ Mb)
- -*PIK3CA* mutation in 64%, cell survival and growth
- -*ERBB3 mutation in 55%,* growth factor signalling
- -*B2M* mutation in 36%, HLA class 1 antigen presentation

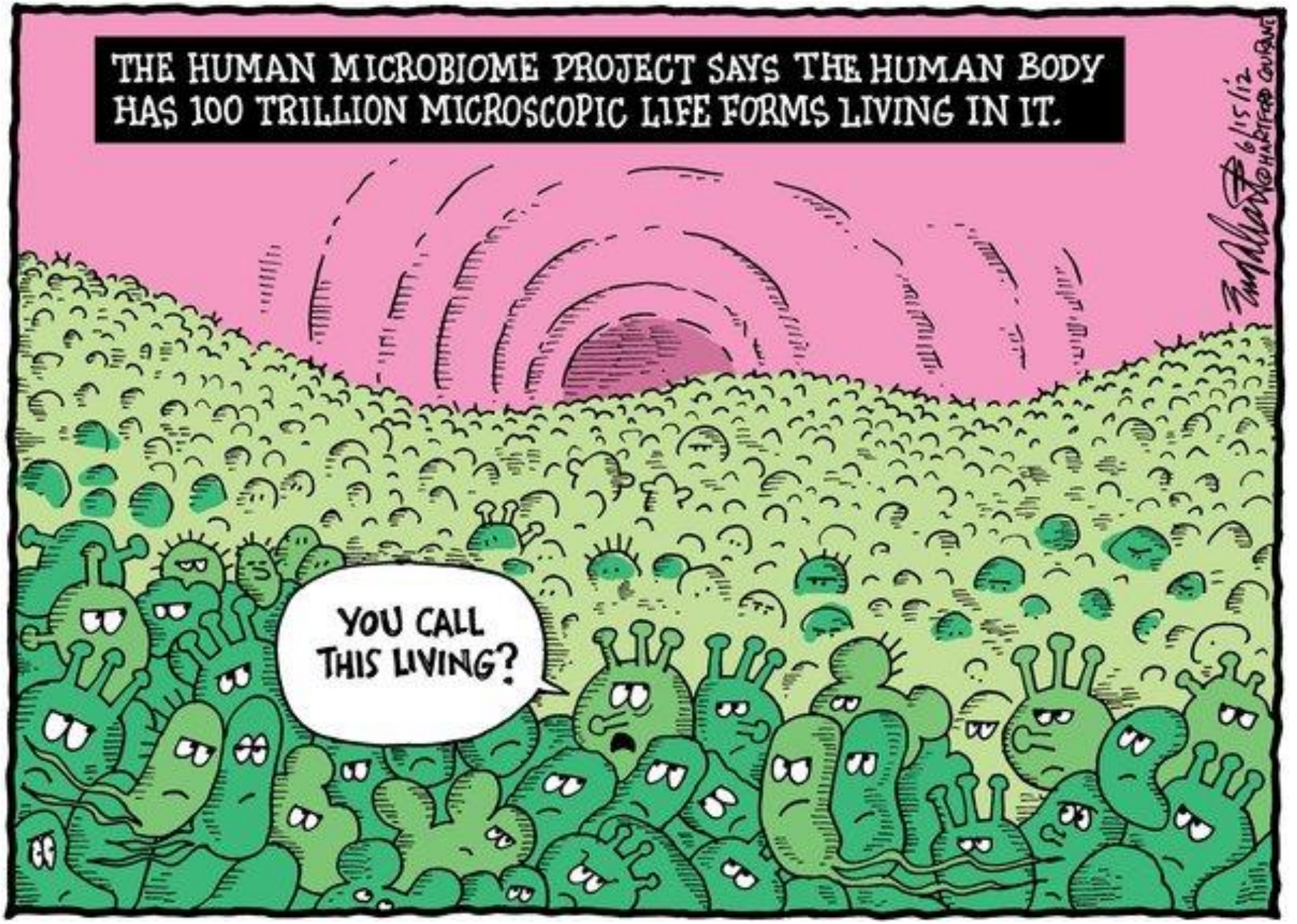
Genomically stable (20% of cancers)
- -*CDH1* mutation in 38%, cell adhesion defects
- -*MET* mutation in 29%, growth factor signalling
- -*RHOA* mutation in 15%, GTP-ase activity
- -diffuse +/- signet ring cell histology

Chromosome instability (50% of cancers)
- -*TP53* mutation in 71%, DNA repair
- -*ERBB2 mutation in 38%,* growth factor signalling
- -*CDKN2A* mutation in 29%, cell cycle regulation
- -*PIK3CA* mutation in 26%, cell survival and growth

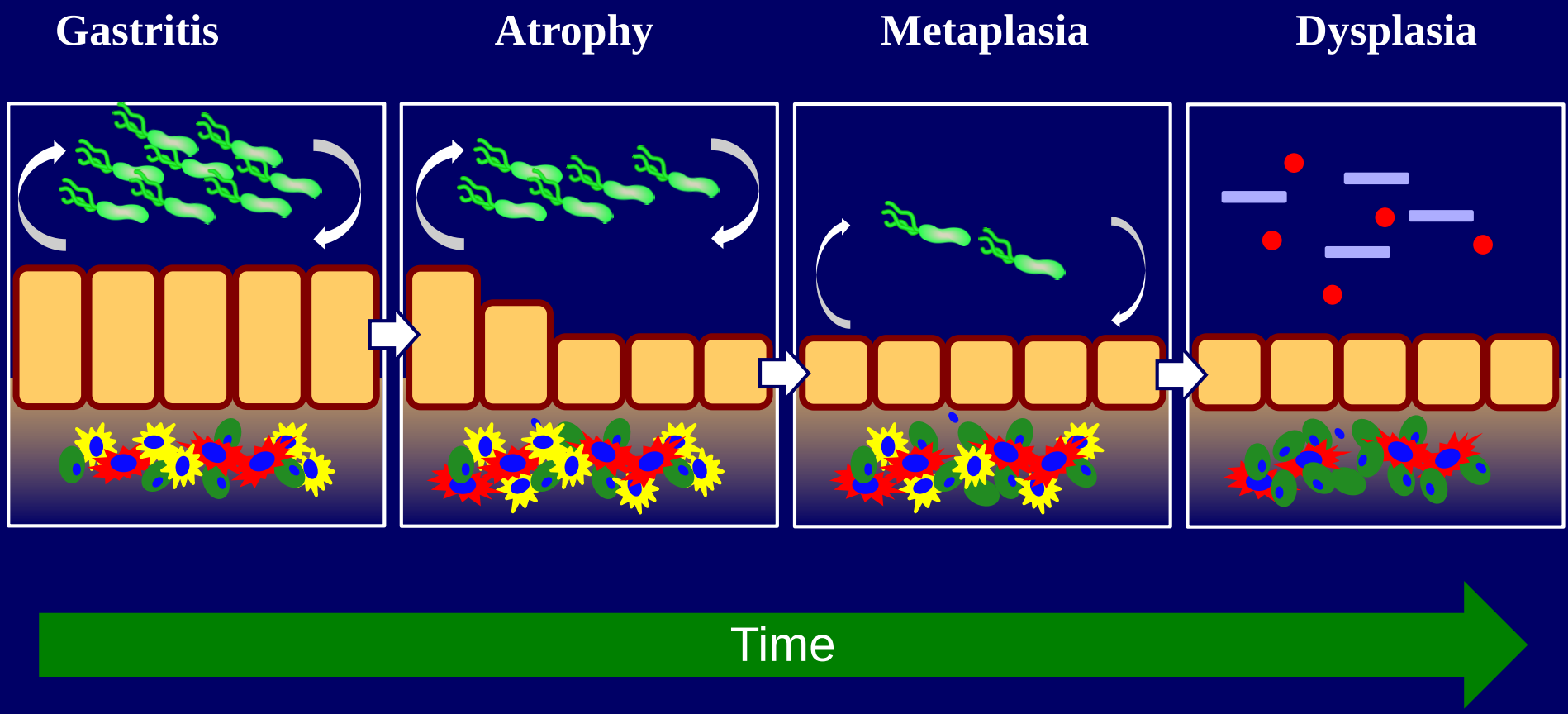
Genes commonly mutated (any molecular class)

TP53	*KRAS*	*RNF43*	*RASA1*	*PTPRC*
CDH1	*MUC6*	*ABCA10*	*FAM46D*	
SMAD4	*APC*	*CTNNB1*	*PLB1*	
PIK3CA	*BCOR*	*MACF1*	*CNGA4*	
RHOA	*EYA4*	*SMAD2*	*EIF2C4*	
ARID1A	*BNC2*	*SOHLH2*	*ERBB2 (HER2)*	

Bass AJ for TCGA, *Nature* July 23, 2014


THE HUMAN MICROBIOME PROJECT SAYS THE HUMAN BODY HAS 100 TRILLION MICROSCOPIC LIFE FORMS LIVING IN IT.
YOU CALL THIS LIVING?
©HABTFORD COURANT 6/15/12

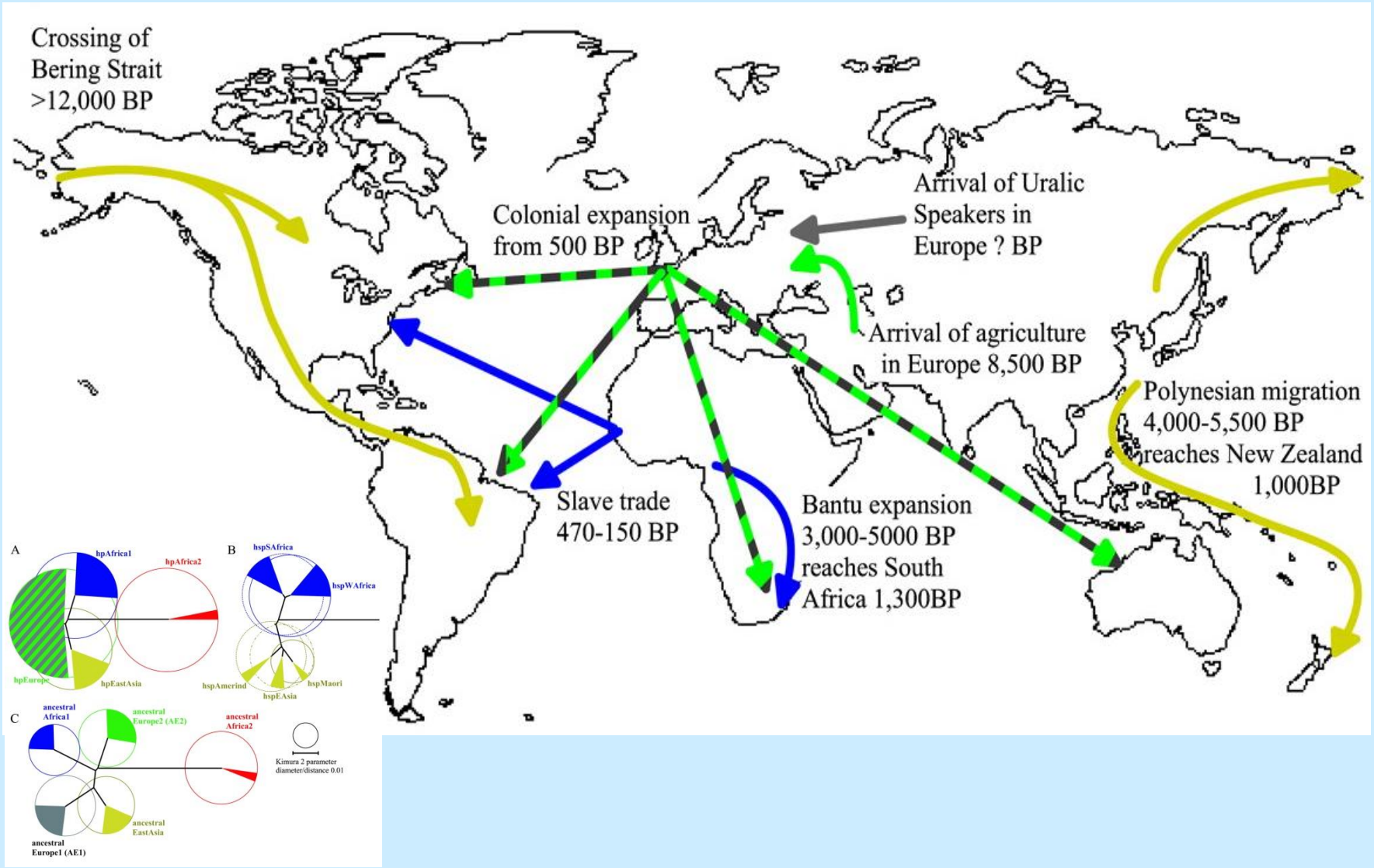
Gastric Cancer Cascade and the Microbiome



Plottel and Blaser, *Cell Host and Microbe*

H. Pylori: Phylogenetics

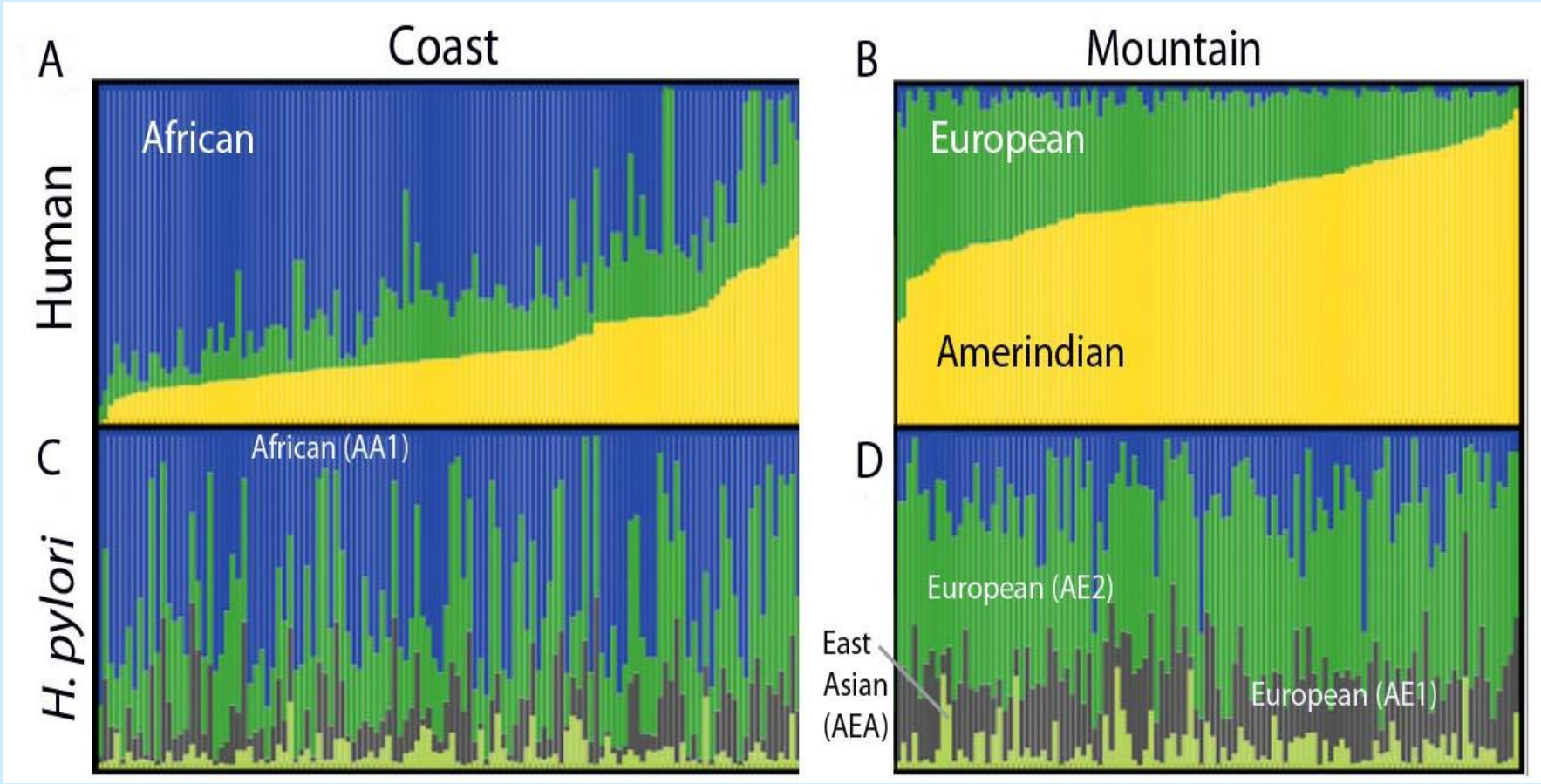
Falush D, Science 2003



Nariño, Colombia

Human and *H. pylori* co-evolution

Kodaman N, PNAS 2014



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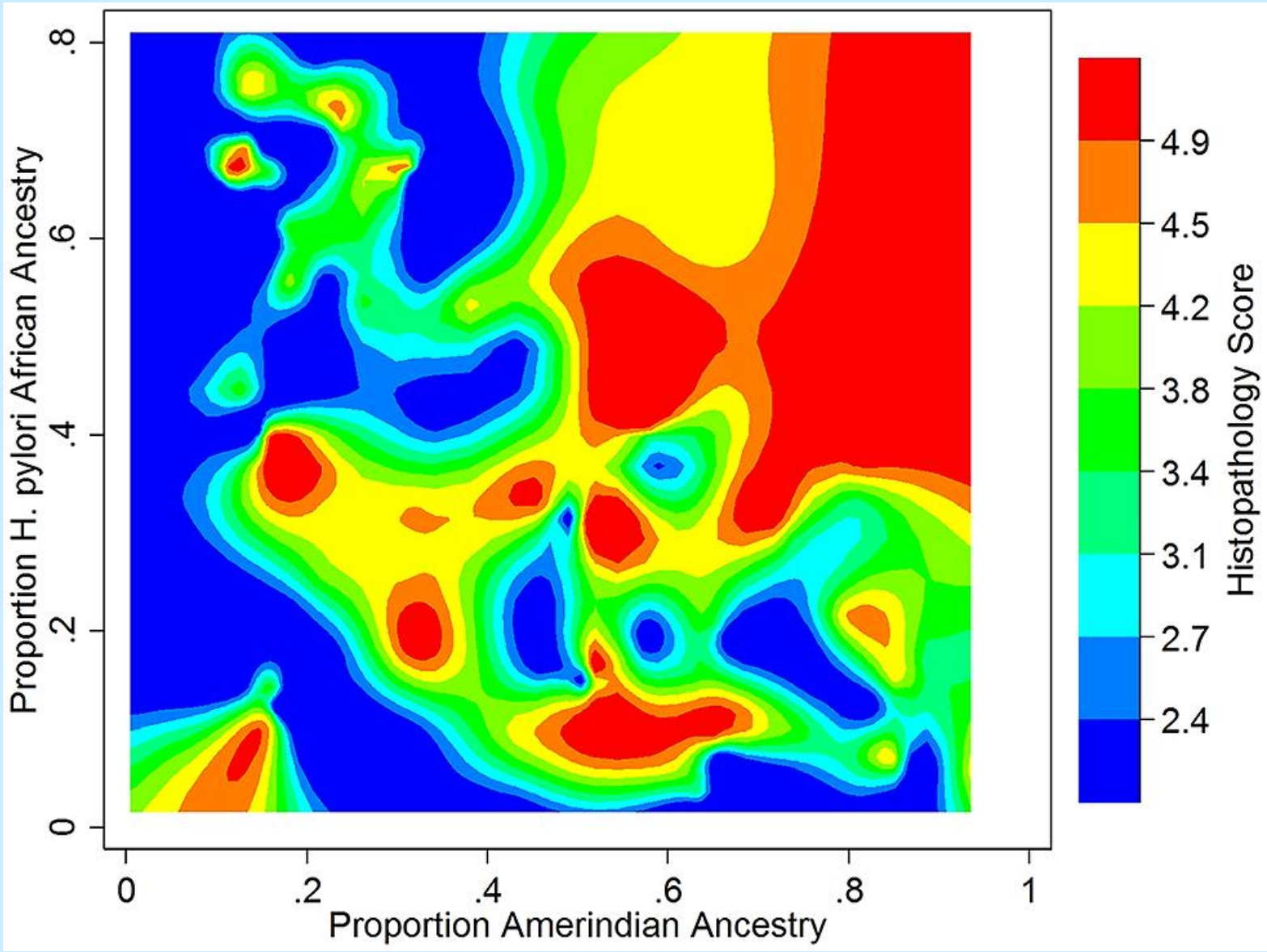
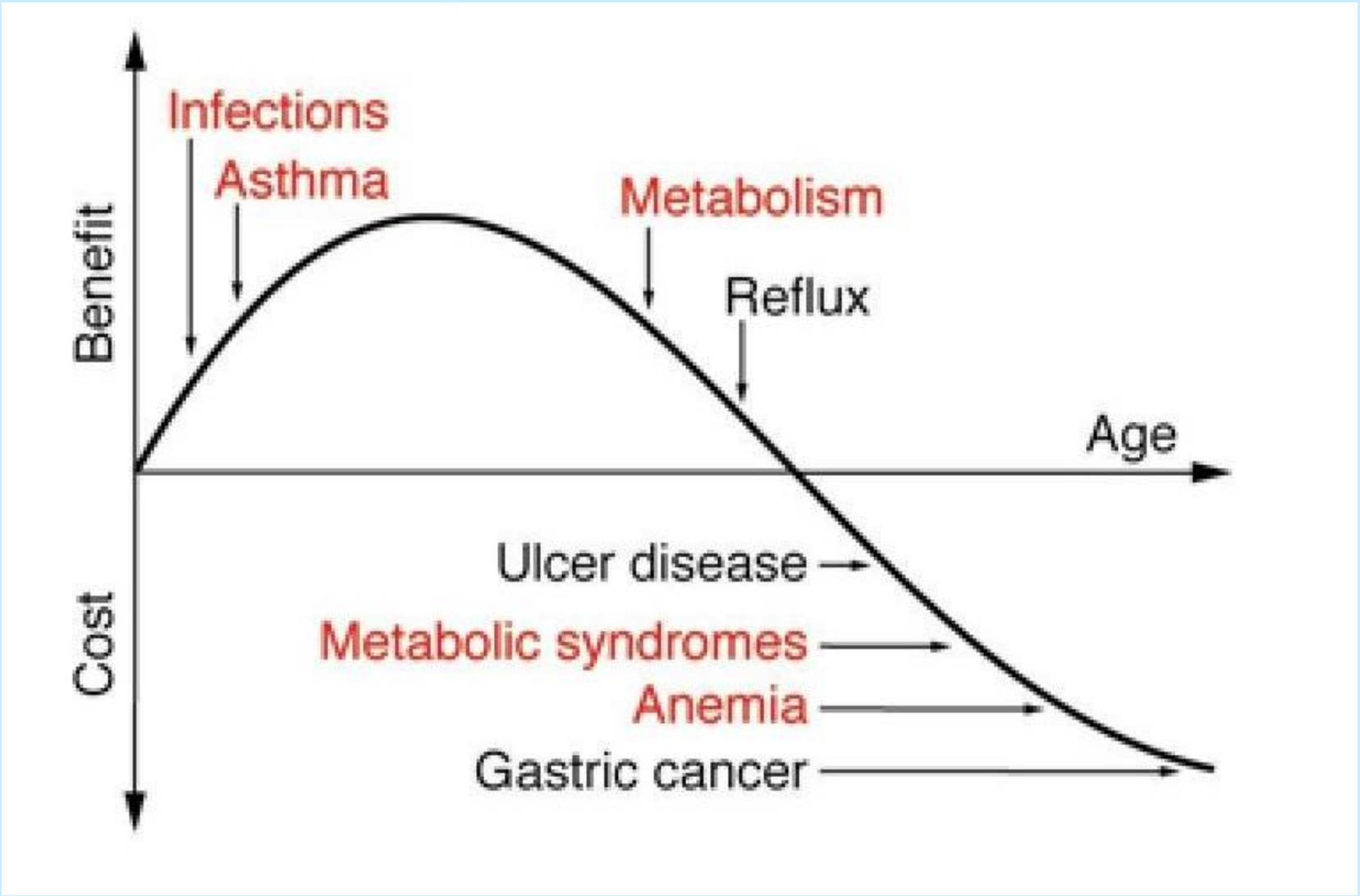
Kodaman N, PNAS 2014; Kodaman N, Front Genetics 2014





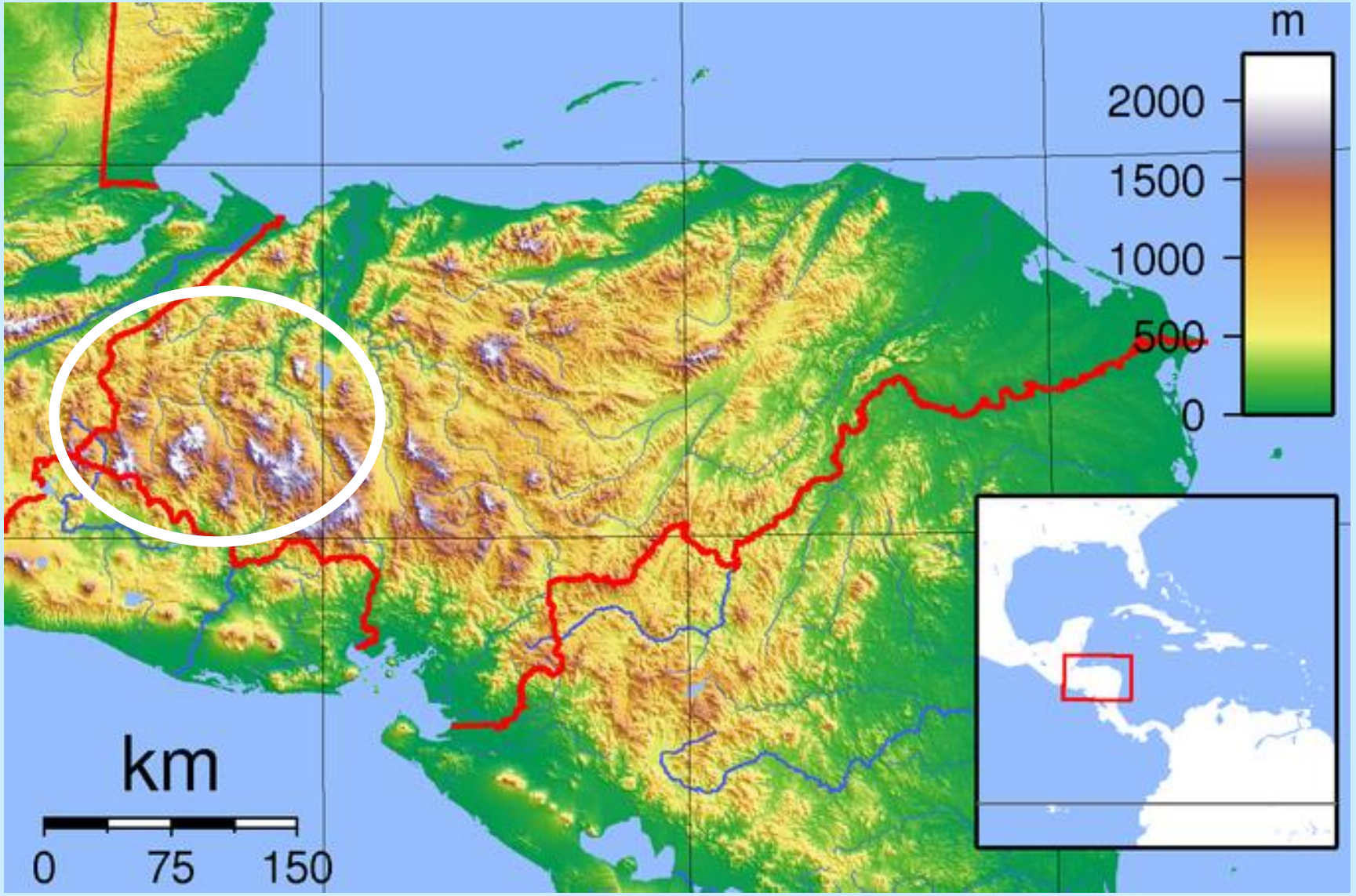
Atherton JC, J Clin Invest 2009

The Central America Four region (CA-4)

Central America Four (CA-4)

- Region united by history, politics, language, culture, and poverty
- Regional integration with open borders in 2006, affecting health and economic systems, is in process (~European Union)
- Core LMIC region of Latin America with a population of 35 million
  - Account for a significant U.S. Hispanic immigrant population (4M)
  - Total at-risk population: **>40 million**
- **Conclusion**: A regional approach to global health and cancer control is efficient and imperative

Western Honduras Gastric Cancer Initiative



Western Honduras Gastric Cancer Initiative

<u>Western Honduras</u>

- Mountainous coffee region
- Hispanic Mestizo (Mayan)

<u>Hospital de Occidente</u>:

- District Hospital for region
- Referral population: ~1M
- Significant clinical & research infrastructure improvements
- "Watershed" (cuenca) for epidemiology research

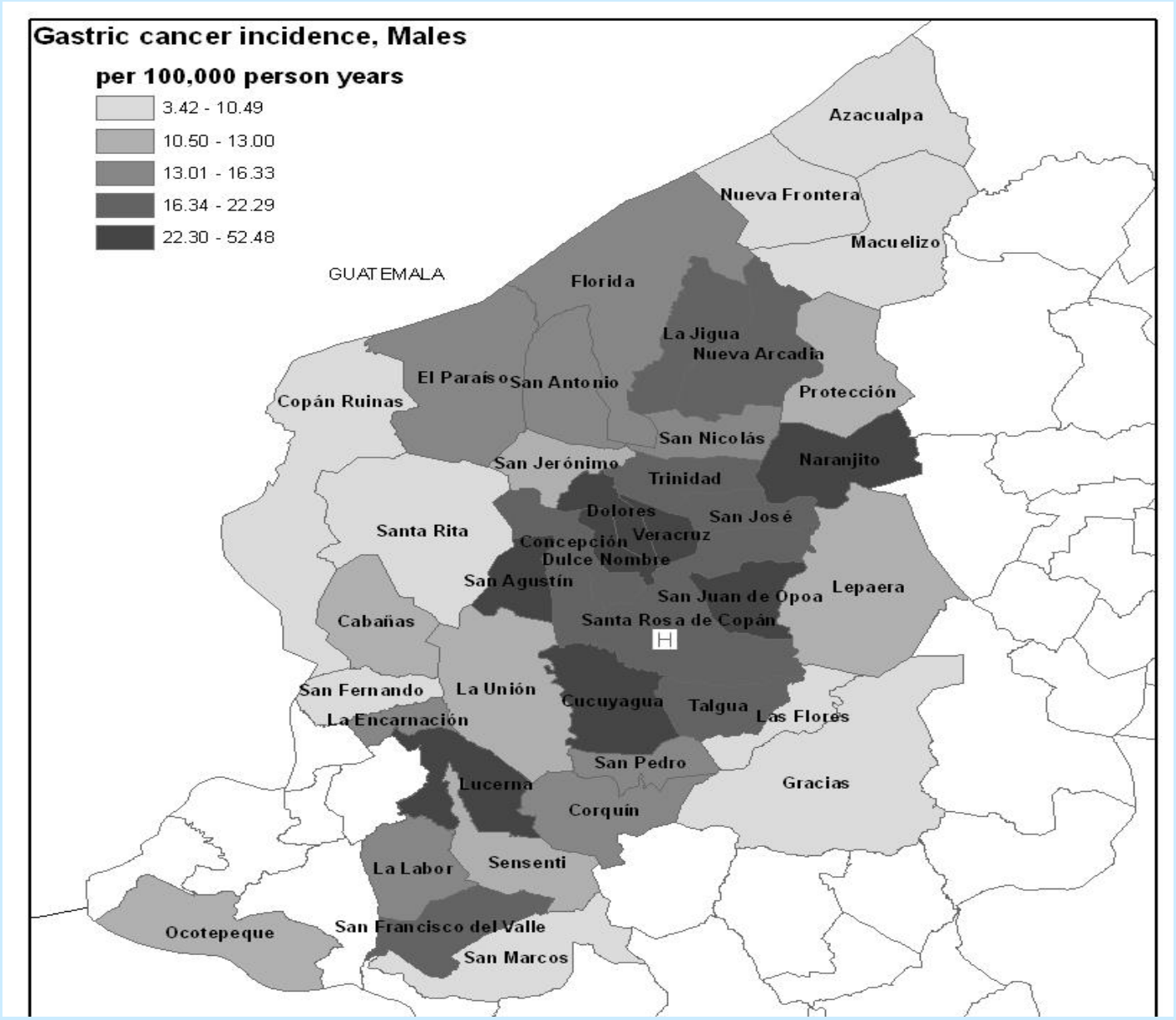
Gastric cancer incidence estimation in a resource-limited nation: use of endoscopy registry methodology

Ricardo L. Dominguez · Seth D. Crockett · Jennifer L. Lund · Lia P. Suazo · Paris Heidt · Christopher Martin · Douglas R. Morgan

Cancer Causes Control (2013)

- Incidence 2000-09, mean ASRs :
  - Males 36 (29-43), Females 14.5 (11-20)
- Patient population
  - Male : Female ratio, 2.1 : 1
  - Median age: 58 (youngest patient, 17)
  - Age distribution: <25 <35 <49
    5% 12% 25%
- Endoscopy yield: 1 cancer / 7-10 endoscopies
  - Pyloric obstruction: 30-40% with high mortality
- Pathology: 60% poor, 30% moderate, <10% well

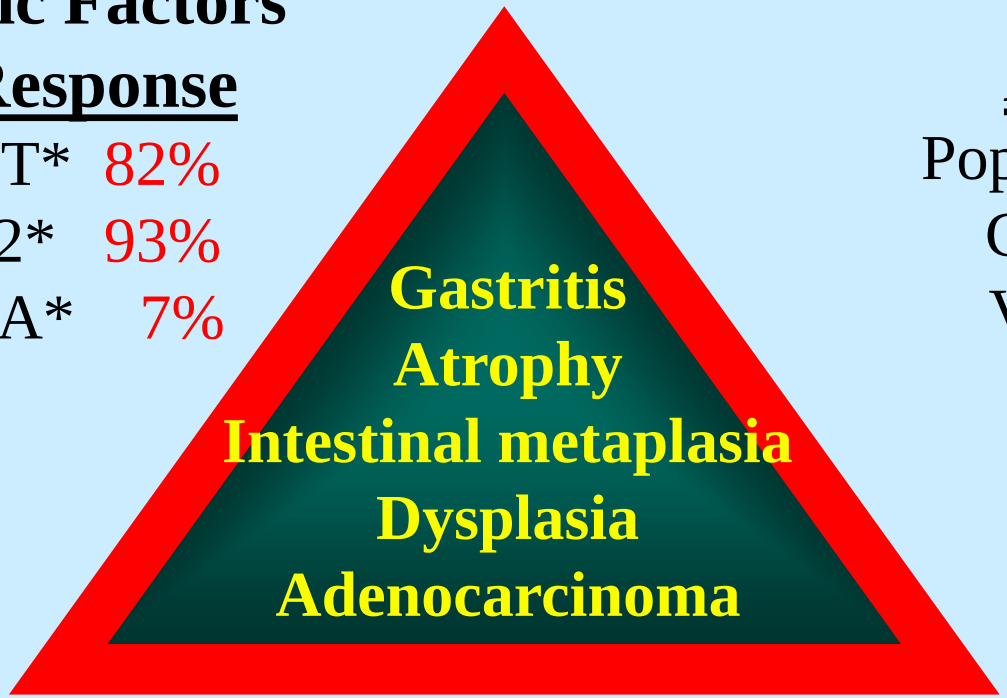
Western Honduras Gastric Cancer Initiative



Gastric Carcinogenesis Triangle: Honduras

Host Genetic Factors & Host Response

IL-1B-511T* 82%
IL-10-1082* 93%
TNFα-308A* 7%



H. Pylori

Population: 87%
CagA: 71%
VacA: 71%

Dietary & Environmental Factors

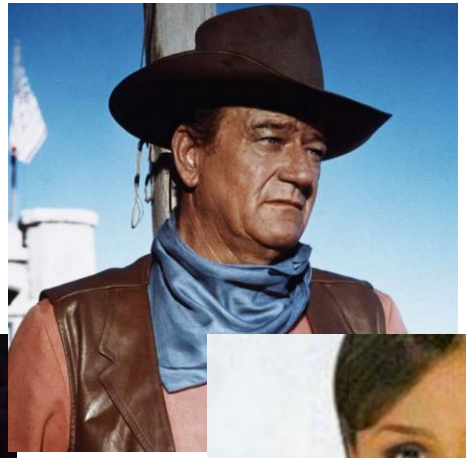
Diet: +Salt, -Selenium
Co-infections: EBV
Other: Fogón

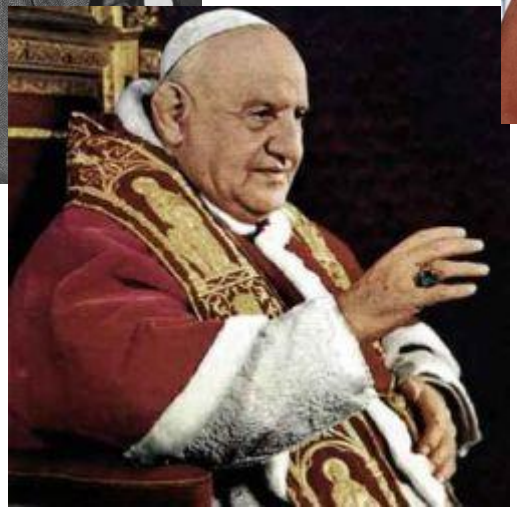
Wood stove (fogón) association with gastric cancer

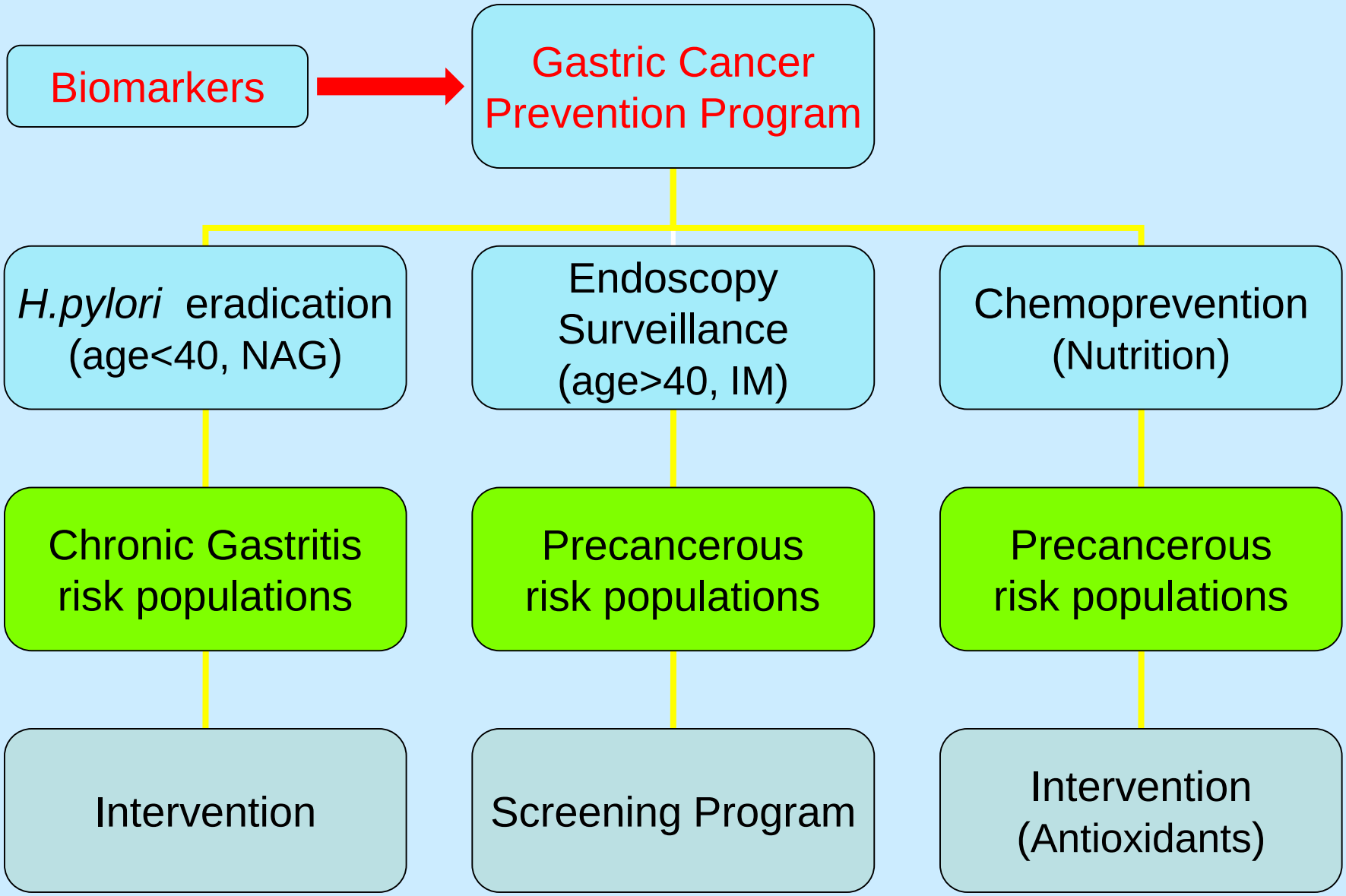
Rifkin S, Digestive Disease Week 2015









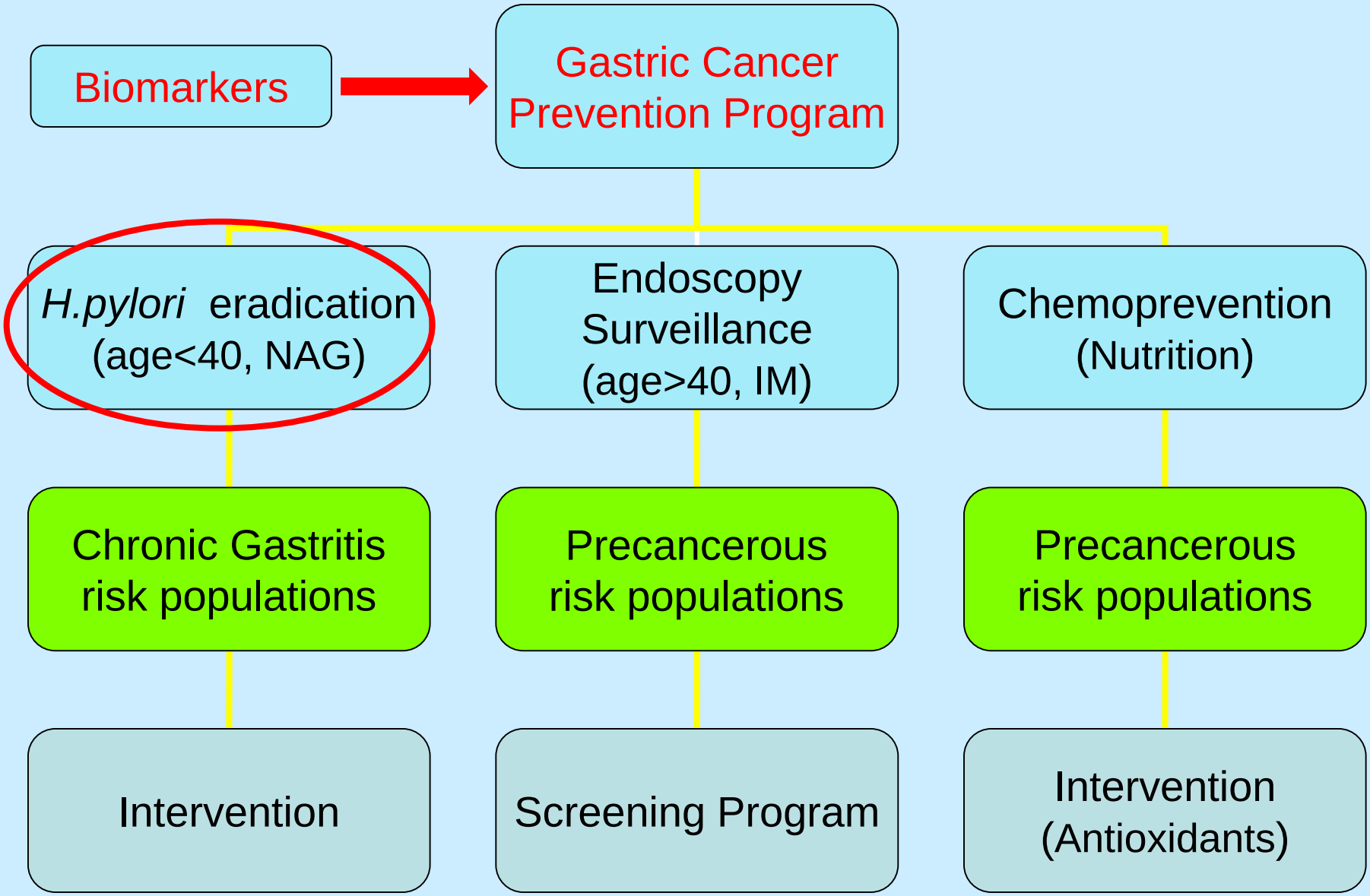

Biomarkers
Gastric Cancer Prevention Program
H.pylori eradication (age<40, NAG)
Endoscopy Surveillance (age>40, IM)
Chemoprevention (Nutrition)
Chronic Gastritis risk populations
Precancerous risk populations
Precancerous risk populations
Intervention
Screening Program
Intervention (Antioxidants)

Gastric cancer prevention: Needed research

Biomarkers: There are no proven serum biomarkers for gastric cancer, gastric premalignant lesions, nor for the risk of progression of premalignant lesions. *H. pylori,* CagA and/or pepsinogen testing lack sensitivity and specificity

Chemoprevention: There are no existing agents for patients with precancerous lesions. *H. pylori* eradication may be helpful in patients with chronic gastritis, but is insufficient for atrophy or IM

Endoscopy technology. Endoscopy screening programs have a significant impact (Japan, Korea). Needed: Novel imaging & cost-effective strategies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Precancerous risk populations
Intervention
Screening Program
Intervention (Antioxidants)

VIEWPOINT

Prevention of Gastric Cancer

Rolando Herrero, MD, PhD
Section of Early Detection and Prevention, International Agency for Research on Cancer, Lyon, France.

Julie Parsonnet, MD
Department of Medicine, Stanford University Medical Center, Stanford, California.

Edwin Robert Greenberg, MD
Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington.

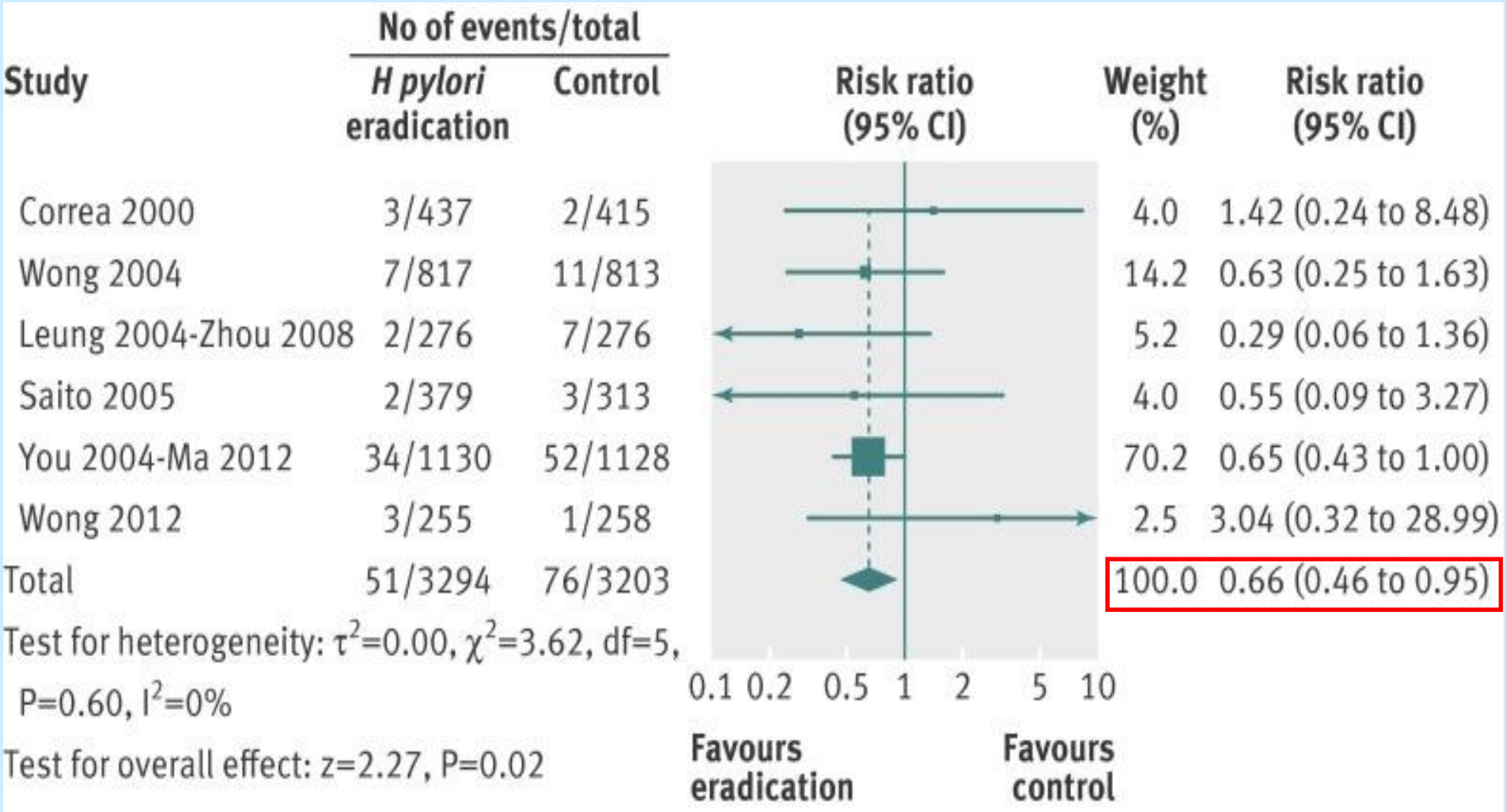
This year, it is estimated that more than 700 000 people will die of gastric cancer, making this disease the third most common cause of cancer death globally.[1] Although gastric cancer rates have been declining by approximately 2% per year, the numbers of cases and deaths are expected to increase in coming years, reflecting increasing numbers of older (and thus, higher-risk) individuals in the world. Despite its importance, gastric cancer receives little attention from research funding agencies or public health organizations. For example, the National Cancer Institute annually spends approximately $12 million on programs directly related to gastric cancer, just 0.2% of its budget, and only 10% of this amount is allocated for prevention research.[2] In contrast, the annual cost of treating gastric cancer in the United States, a lower-risk country, is estimated at approximately $2 billion.[3]

Of the 989 000 gastric cancer cases in the world in 2008, an estimated 770 000 could be attributed to Population-based *H pylori* treatment could select for antibiotic-resistant pathogens in the community, although in many countries, such an effect might be overshadowed by indiscriminate use of antibiotics for other human and veterinary purposes. Treating *H pylori* will alter the overall composition of the intestinal flora; the health consequences are unknown.

Screening and treatment for *H pylori* is generally acceptable and affordable. An inexpensive serological test can determine who may be infected, with a sensitivity and specificity that could be sufficient for population-based prevention programs. Low-cost treatment regimens using 2 or 3 generic antibiotics plus a proton pump inhibitor for 7 to 14 days can eradicate the infection in more than 80% of cases, depending on the antibiotic resistance patterns of *H pylori* within the population.[8] Economic modeling studies indicate that *H pylori* screening and treatment strategies are cost-effective under a large range of assumptions about effectiveness and

Randomised controlled trials of *H pylori* eradication therapy

Ford AC, BMJ 2014; Ford AC, Cochrane Database Syst Rev 2015



JAMA September 24, 2014 Volume 312, Number 12

VIEWPOINT

Prevention of Gastric Cancer

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Section of Early Detection and Prevention, International Agency for Research on Cancer, Lyon, France.

Julie Parsonnet, MD
Department of Medicine, Stanford University Medical Center, Stanford, California.

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Potential risks

- Side effects of drugs
- Induction of antimicrobial resistance
- Antibiotic-induced alterations in microbial flora
- Esophageal adenocarcinoma
- Gastroesophageal reflux disease
- Obesity
- Childhood asthma and allergic rhinitis

Latin America *H. pylori* and Gastric Cancer Consortium

México, northern & southern

Ciudad Obregón, Sonora

Tapachula, Chiapas

Honduras, Copán

Western Regional Hospital

Nicaragua, León

University of Nicaragua, León

Costa Rica, Guanacaste

INCIENSA Fundación

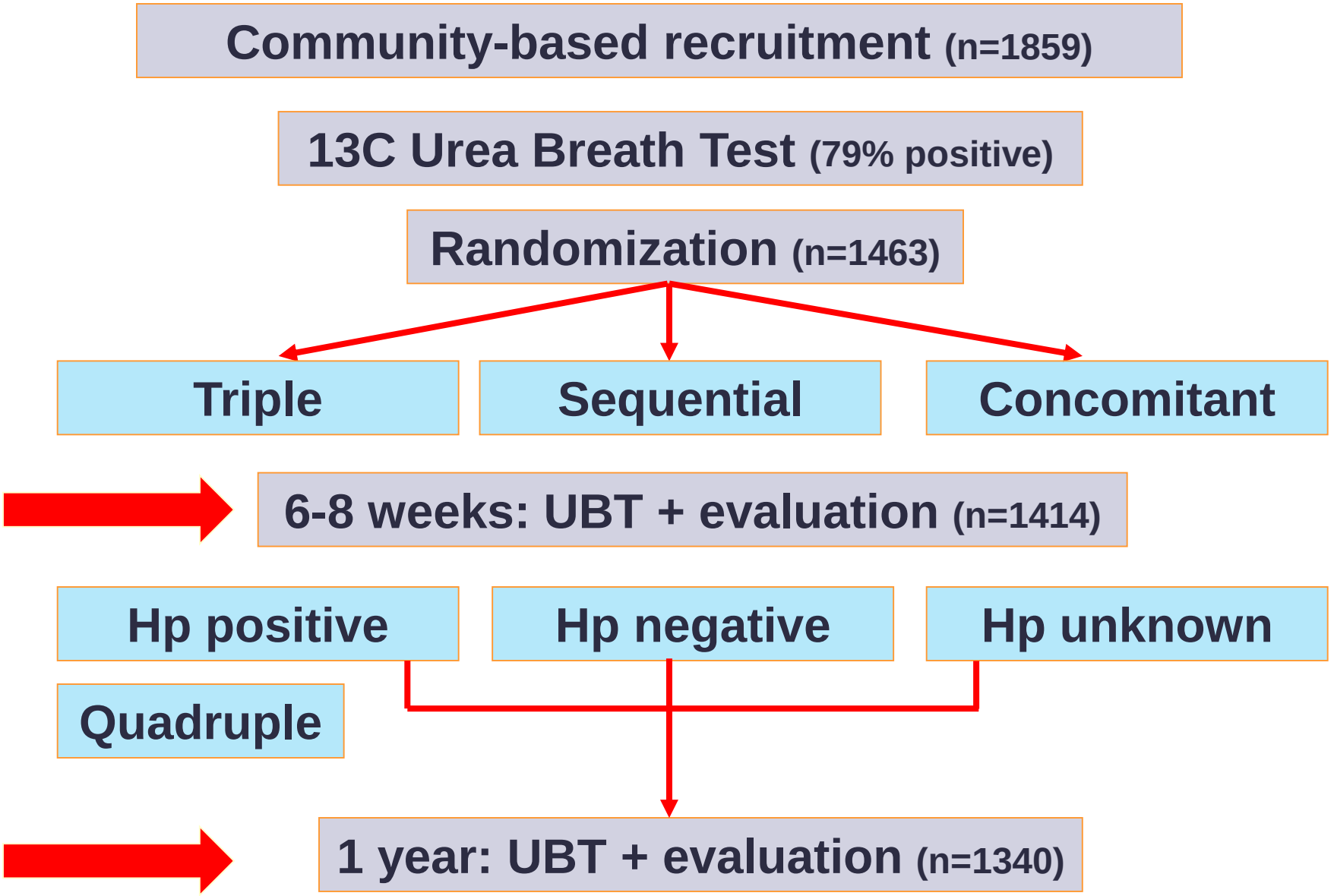
Colombia, Pasto

Universidad de Valle

Chile, Santiago

Pontificia Universidad Católica

Study Schema



Risk of Recurrent *Helicobacter pylori* Infection 1 Year After Initial Eradication Therapy in 7 Latin American Communities

Douglas R. Morgan, MD, MPH
Javier Torres, PhD
Rachael Sexton, MS

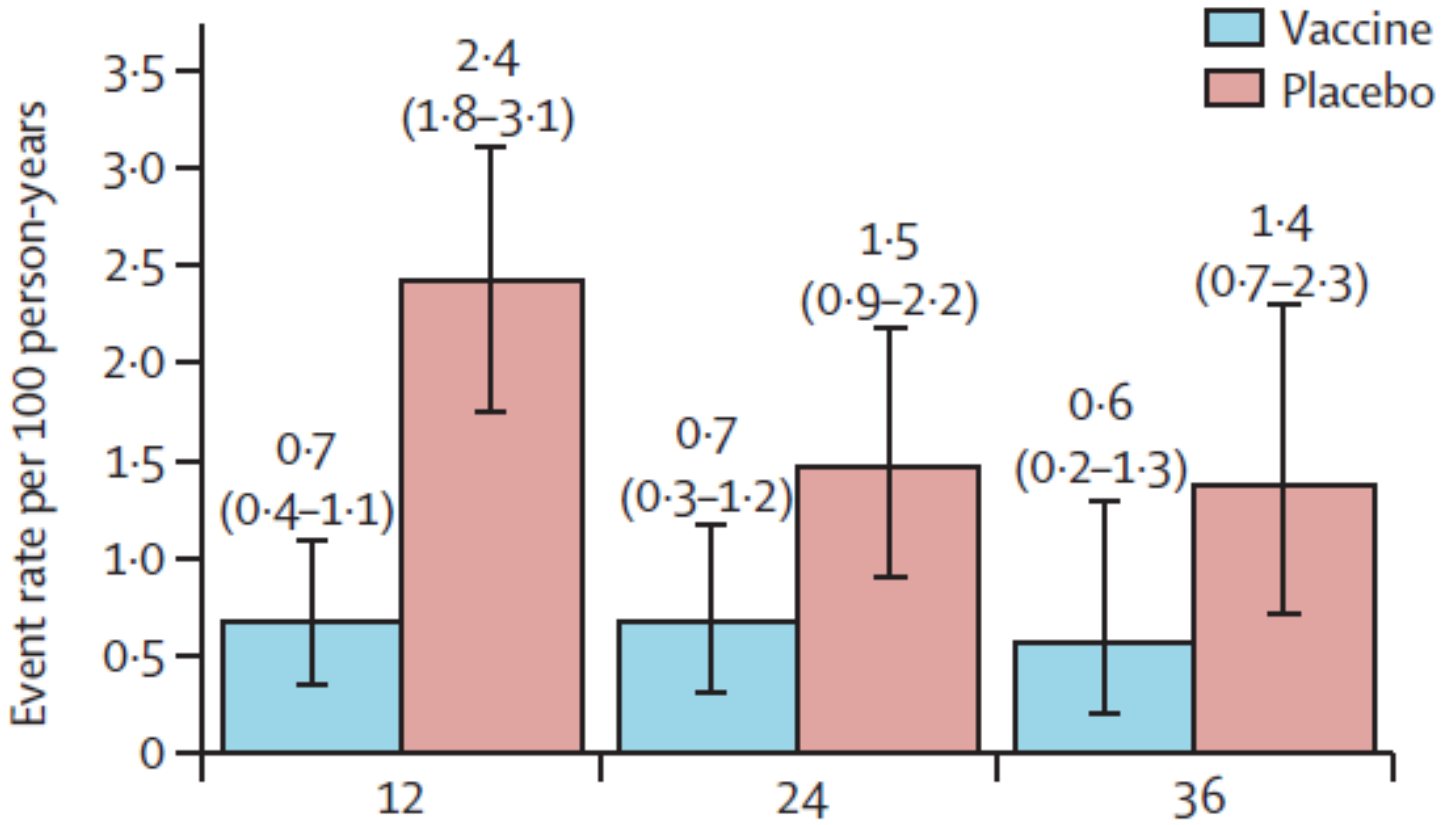
Importance The long-term effectiveness of *Helicobacter pylori* eradication programs for preventing gastric cancer will depend on recurrence risk and individual and community factors.

JAMA. 2013;309(6):578-586

	Total Subjects (n / N)	Recurrence Rate (%)	95% Confidence Interval (%)
Overall	125 / 1091	**11.5**	9.9 – 13.3
Antibiotic regimens p-value			0.62
Triple, 14 days	47 / 389	12.1	8.8 – 15.3
Sequential, 10 days	36 / 356	10.1	7.0 – 13.2
Concomitant, 5 days	42 / 346	12.1	8.7 – 15.6

Efficacy, safety, and immunogenicity of an oral recombinant *Helicobacter pylori* vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial

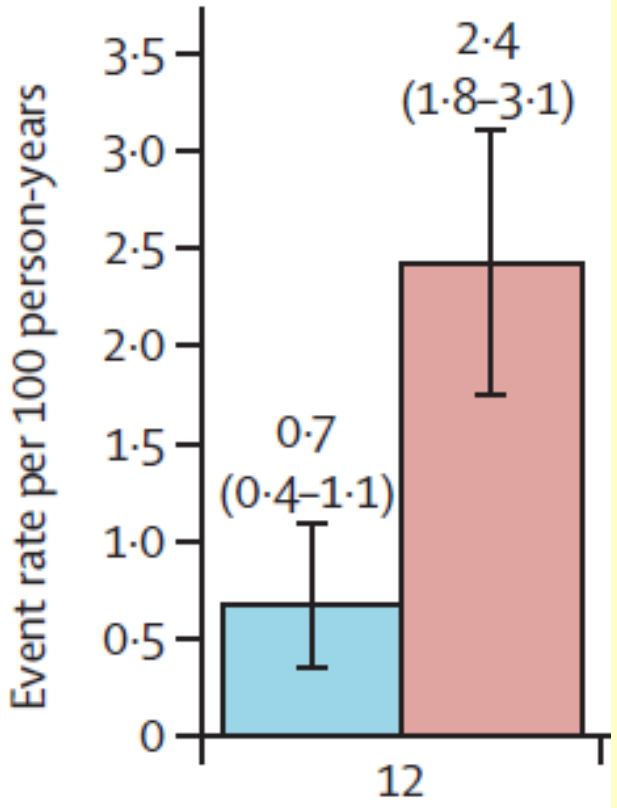
Ming Zeng, Xu-Hu Mao*, Jing-Xin Li, Wen-De Tong, Bin Wang, Yi-Ju Zhang, Gang Guo, Zhi-Jing Zhao, Liang Li, De-Lin Wu, Dong-Shui Lu, Zhong-Ming Tan, Hao-Yu Liang, Chao Wu, Da-Han Li, Ping Luo, Hao Zeng, Wei-Jun Zhang, Jin-Yu Zhang, Bo-Tao Guo, Feng-Cai Zhu, Quan-Ming Zou*



Ming Z, Lancet 2015

Efficacy, safety, and immunogenicity of an oral recombinant *Helicobacter pylori* vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial

Ming Zeng, Xu-Hu Mao*, Jing-Xin Li, Wen-De Tong, Bin Wang, Yi-Ju Zhang, Gang Guo, Zhi-Jing Zhao, Liang Li, De-Lin Wu, Dong-Shui Lu, Zhong-Ming Tan, Hao-Yu Liang, Chao Wu, Da-Han Li, Ping Luo, Hao Zeng, Wei-Jun Zhang, Jin-Yu Zhang, Bo-Tao Guo, Feng-Cai Zhu, Quan-Ming Zou*



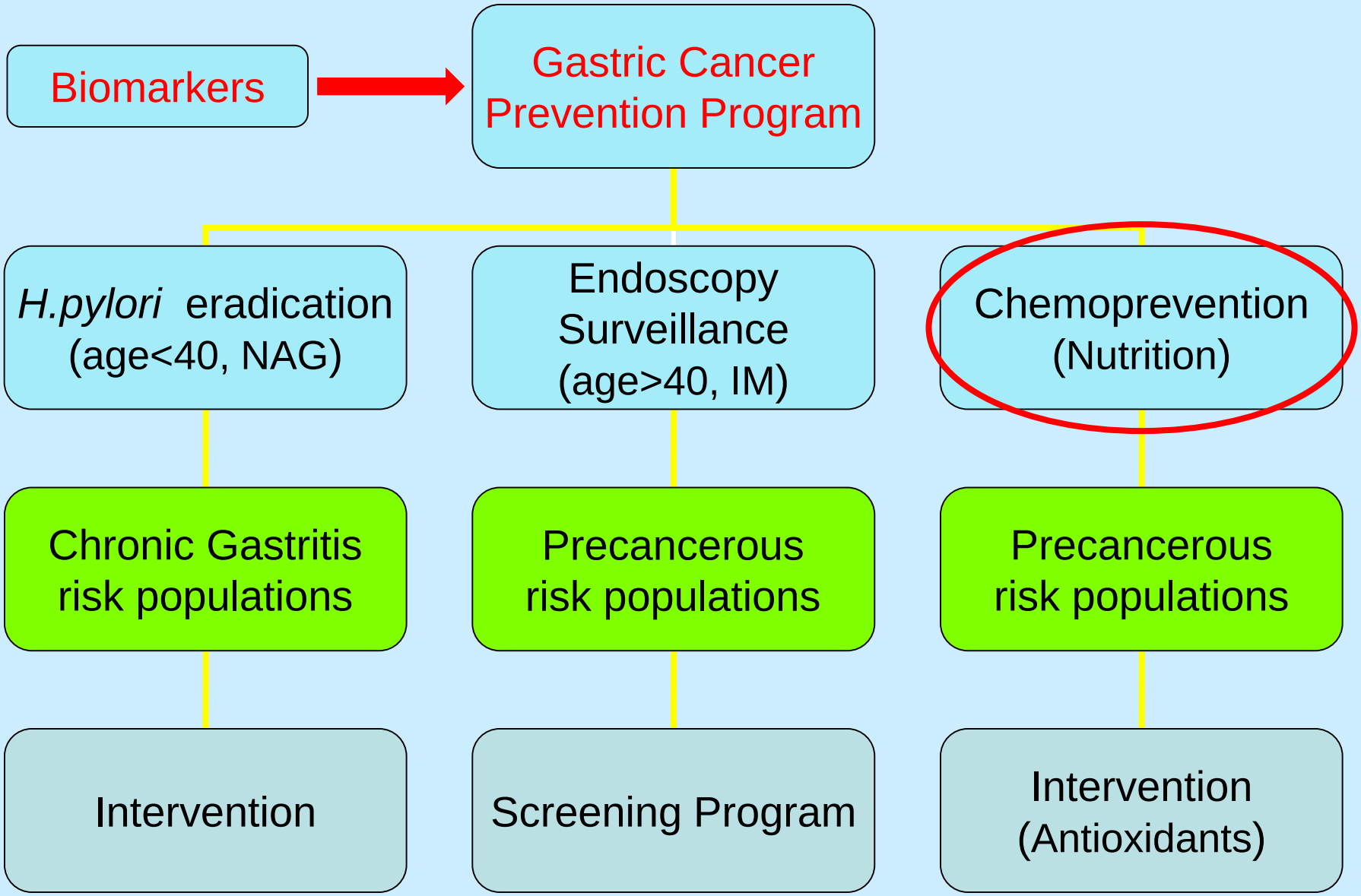
Overview

- Large phase III trial (n= 4464)
- Performed in children (ages 6-15)
- Follow-up, 1-3 years
- Outcome, natural infection
- Efficacy 71.8%

Challenges

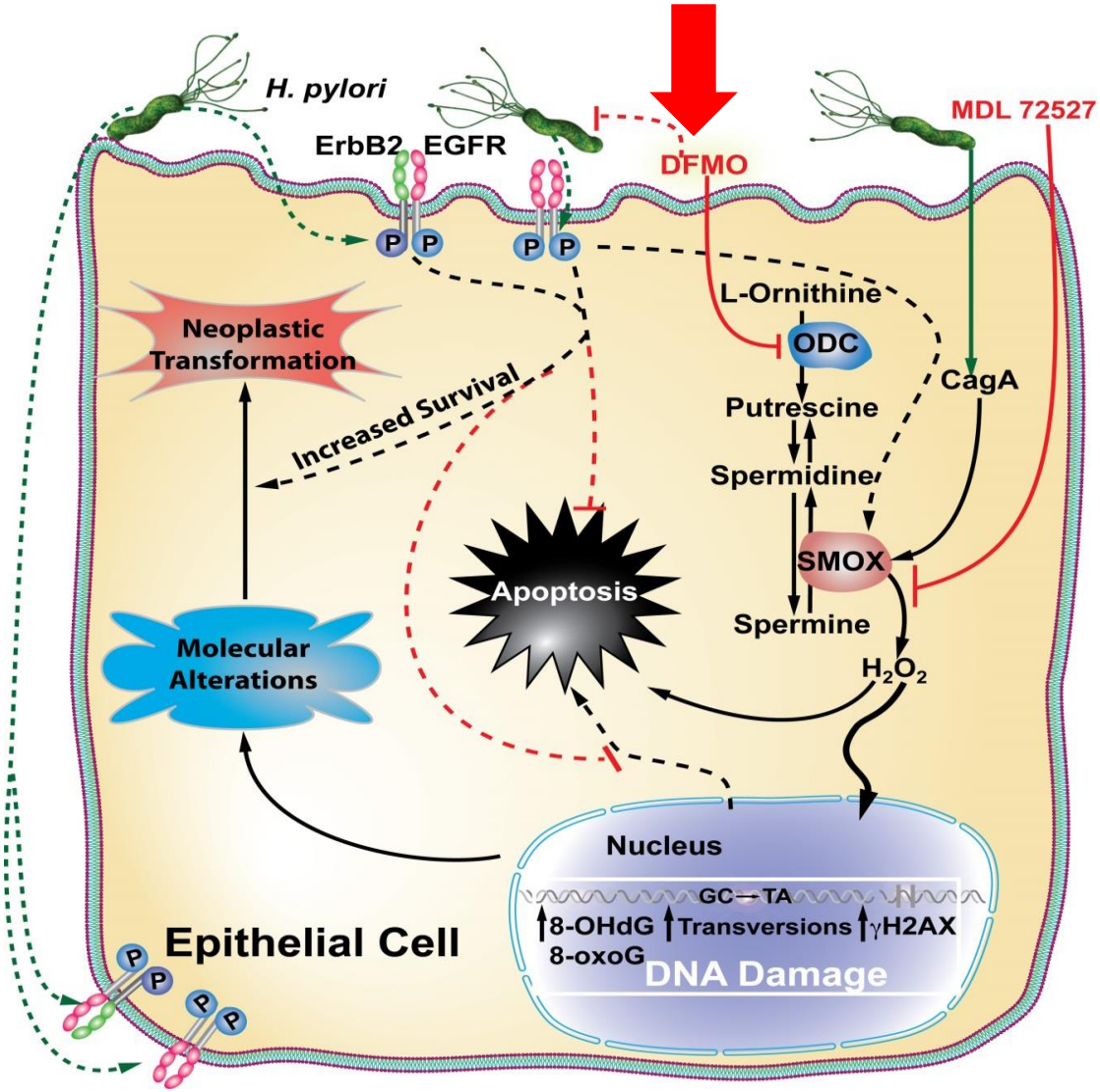
- Administration, 2hr fast & bicarbonate
- Fusion protein with E.coli LTB (Bell's)
- Waning efficacy at 3 years
- Therapeutic vaccine?

Ming Z, Lancet 2015

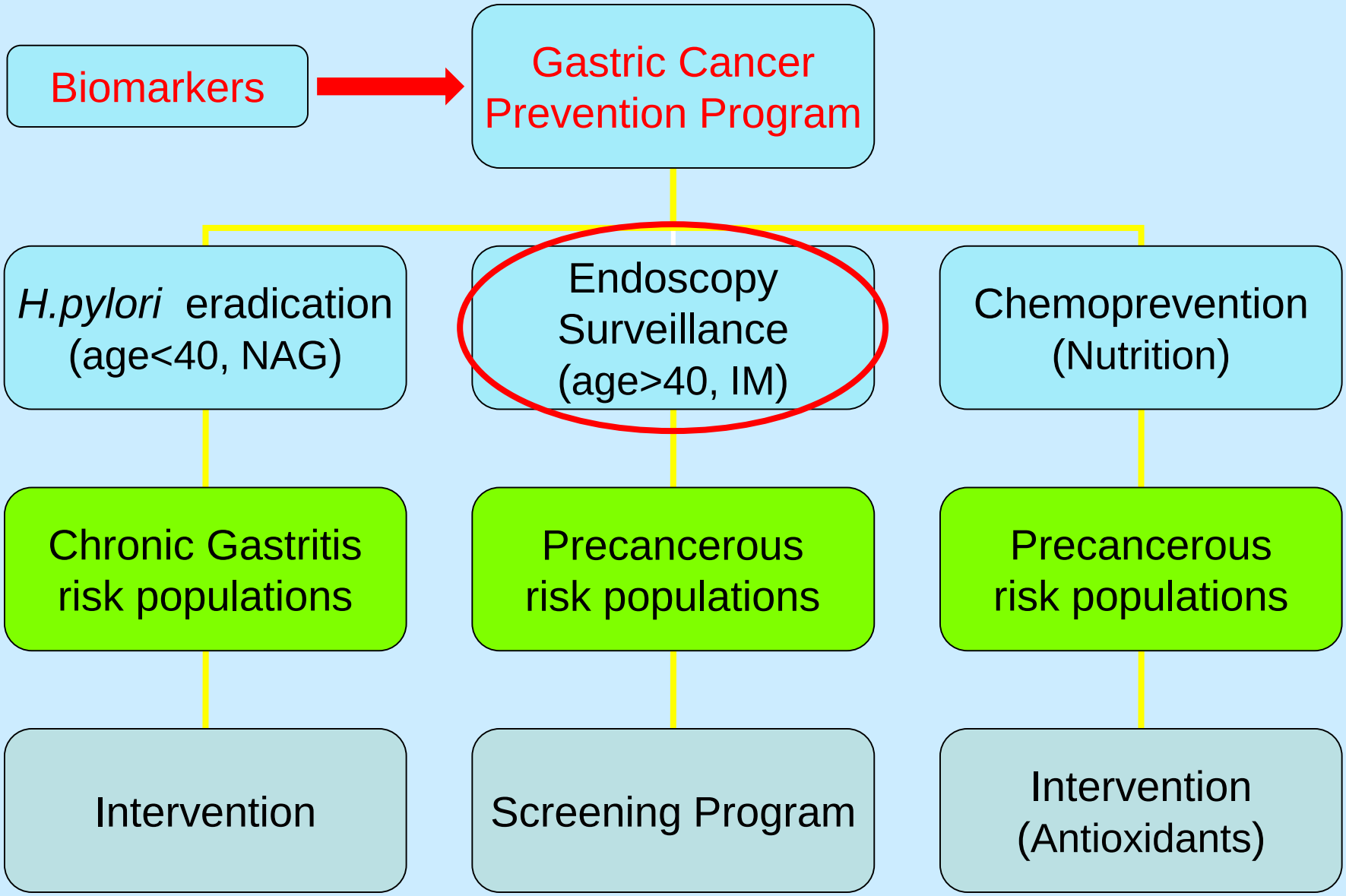

Biomarkers
Gastric Cancer Prevention Program
H.pylori eradication (age<40, NAG)
Endoscopy Surveillance (age>40, IM)
Chemoprevention (Nutrition)
Chronic Gastritis risk populations
Precancerous risk populations
Precancerous risk populations
Intervention
Screening Program
Intervention (Antioxidants)

Eflornithine (DFMO) in chemoprevention

R Chaturvedi and KT Wilson, Oncogene 2015



- ***H. pylori*** infection results in increased levels of polyamines, natural polycations, synthesized by the enzyme ornithine decarboxylase (**ODC**)
- Infection also increases the level of spermine oxidase (**SMOX**), which catabolizes spermine and produces hydrogen peroxide (H2O2), and leads to DNA damage in gastric epithelial cells
- **DFMO** has been shown to inhibit ODC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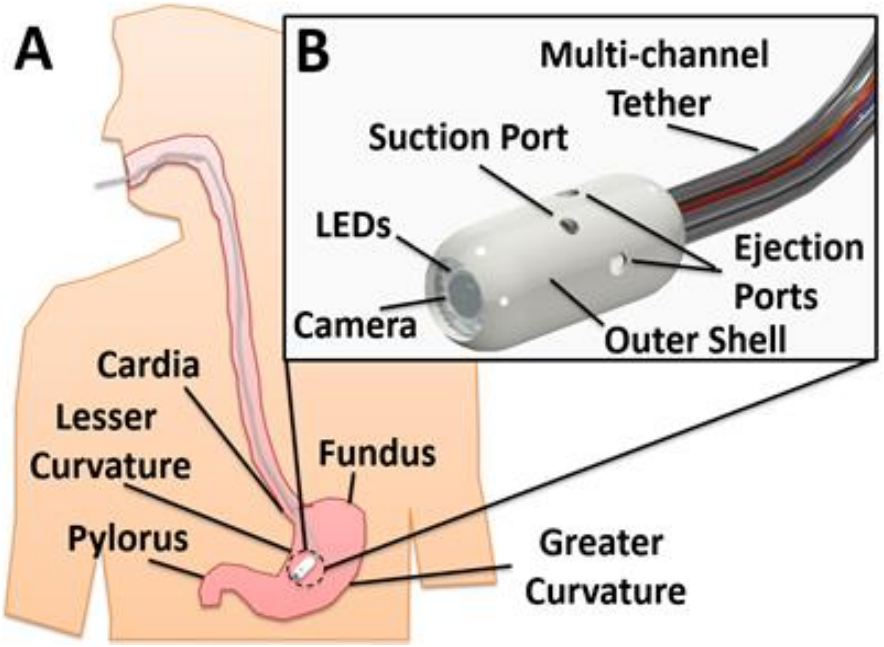
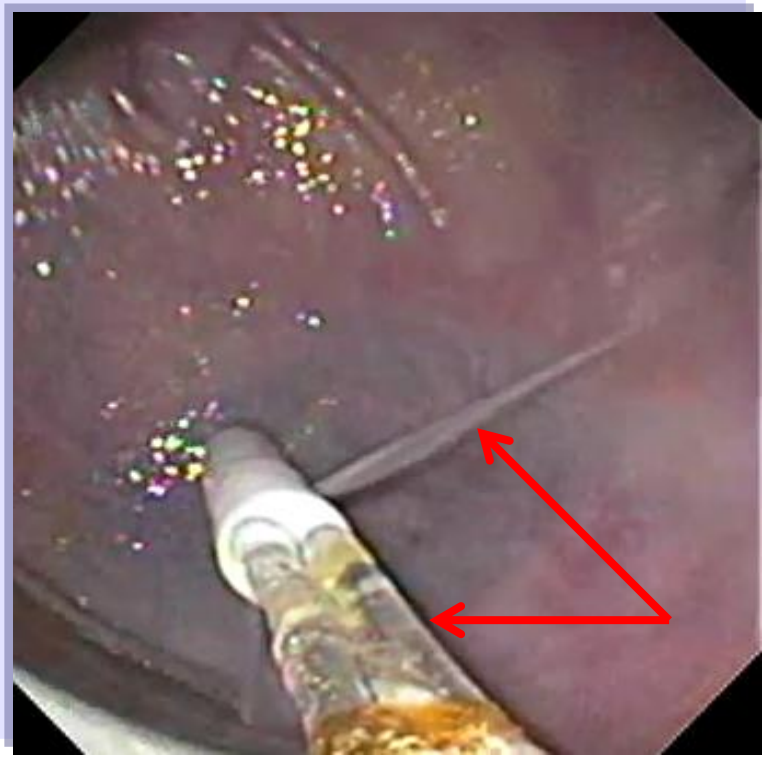
Ultra low-cost endoscopy for UGI and gastric cancer screening in low resource settings

Caprara R, IEEE BME 2015





Gastric Cancer: LMIC Case Study in Prevention

Gastric cancer is a common cancer affecting LMICs

- A marked health disparity in the U.S.

The marked geographic variability permits scientific discovery and focused prevention & PBCRs

Opportunities for prevention

- Biomarker development
- *H. pylori* eradication
- Role of diet and environment
- Chemoprevention
- Novel endoscopy technologies

¡Mil Gracias!