Updates in the Diagnosis and Management of Gastric Intestinal Metaplasia

American Foregut Society Annual Meeting

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Disclosures

- Consultant fees, Phathom Pharmaceuticals

Outline

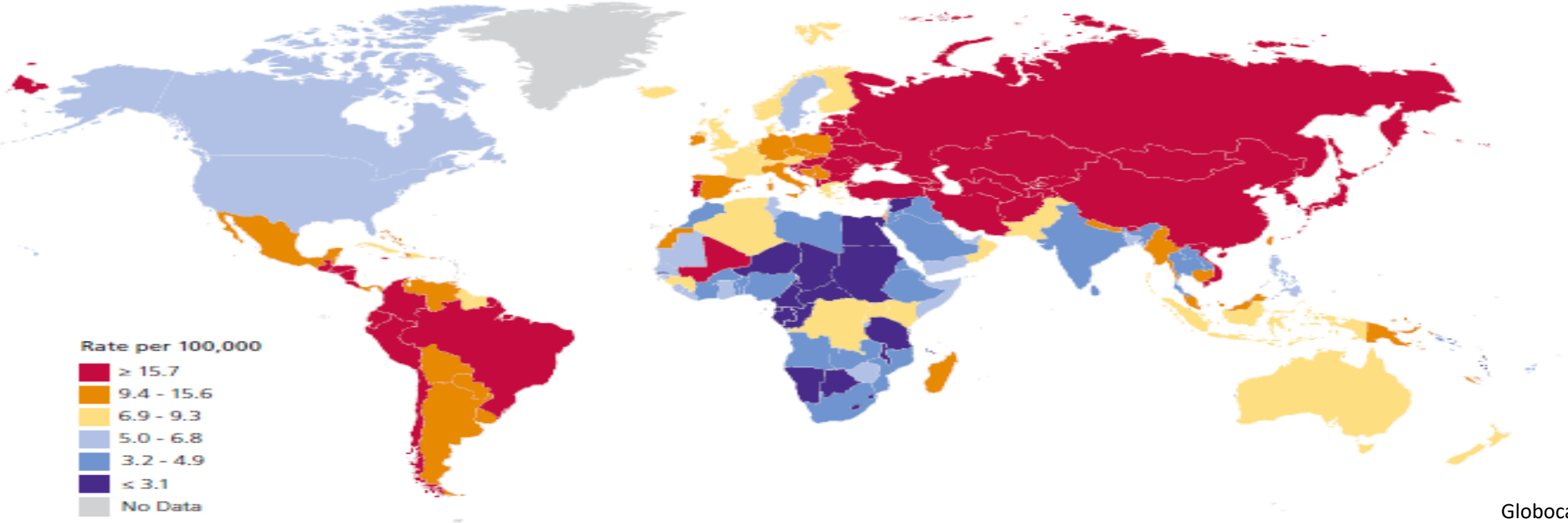
- **Gastric cancer**
  - Epidemiology
  - Risk factors
  - Pathogenesis

- ***Gastric preneoplasia***
  - **Gastric intestinal metaplasia**
    - **Diagnosis and management (surveillance)**
  - Atrophic gastritis

Worldwide Variation in Gastric Cancer

Third leading cause of cancer mortality and the **fifth most common cancer** worldwide.

- **<u>>1 million new cases / year</u>** and **<u>>780,000 related deaths</u>**
- Marked global variation
  - SE Asia (>**50%** of new cases); Central/Latin America; Eastern Europe
- Also, significant within country variation

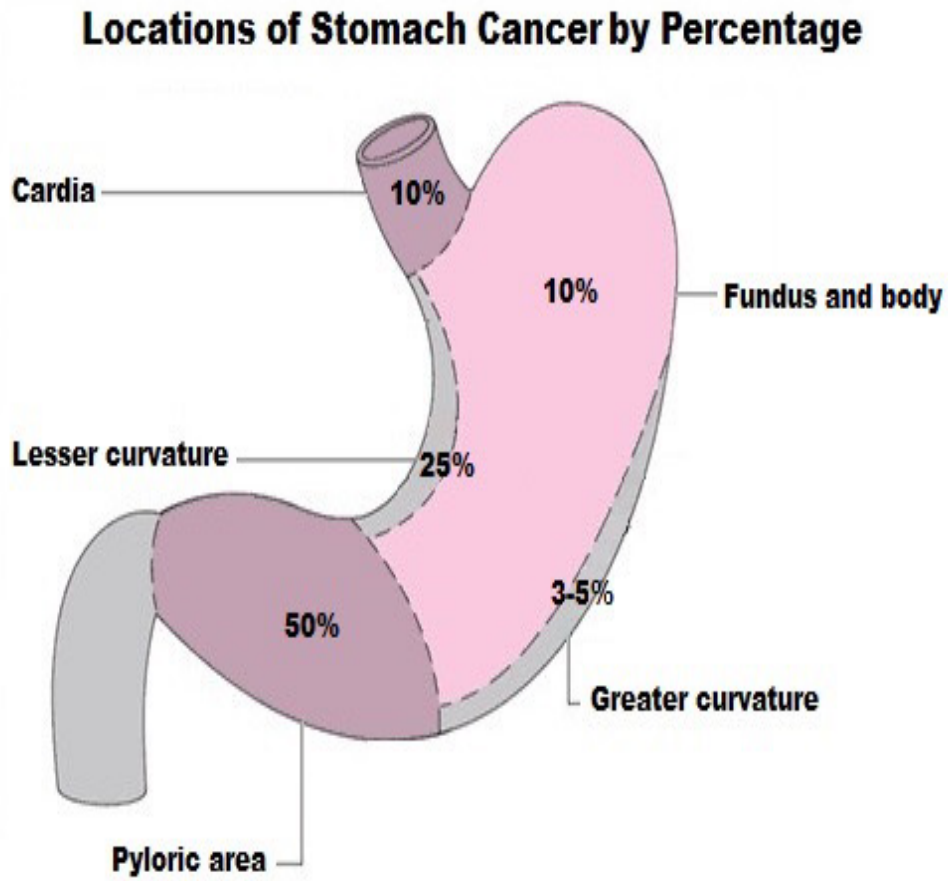


Globocan 2018

Burden of Gastric Cancer in the USA

NATIONAL CANCER INSTITUTE
Surveillance, Epidemiology, and End Results Program

	Common Types of Cancer	Estimated New Cases 2019	Estimated Deaths 2019
1.	Breast Cancer (Female)	268,600	41,760
2.	Lung and Bronchus Cancer	228,150	142,670
3.	Prostate Cancer	174,650	31,620
4.	Colorectal Cancer	145,600	51,020
5.	Melanoma of the Skin	96,480	7,230
6.	Bladder Cancer	80,470	17,670
7.	Non-Hodgkin Lymphoma	74,200	19,970
8.	Kidney and Renal Pelvis Cancer	73,820	14,770
9.	Uterine Cancer	61,880	12,160
10.	Leukemia	61,780	22,840
	-	-	-
15.	Stomach Cancer	27,510	11,140
	-	-	-
18.	Esophageal Cancer	17,650	16,080

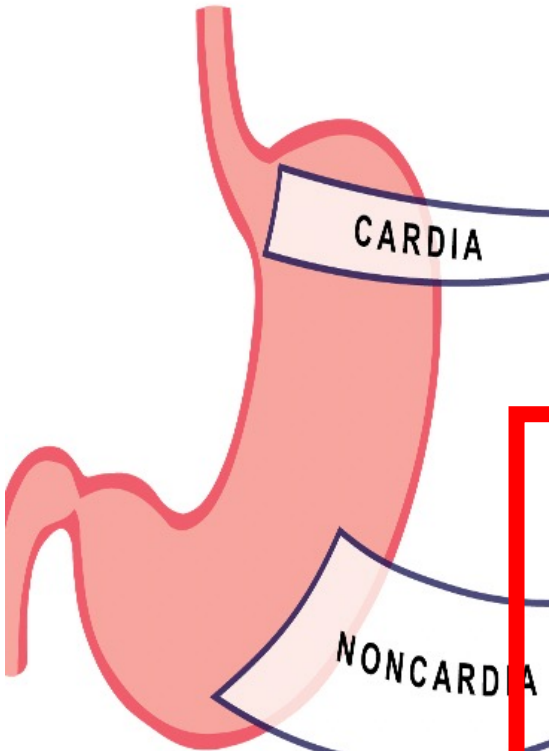


NONCARDIA = 90%

CARDIA = 10%

SEER 2019

Population-Based Analysis of Differences in Gastric Cancer Incidence Among Races and Ethnicities in Individuals Age 50 Years and Older



Age- and sex-adjusted incidence rate ratios for individuals ≥50 years

Vietnamese	0.50
South Asian	0.56
Non-Hispanic Black	0.56
Filipino	0.57
Chinese	0.59
Hispanic	0.66
Korean	0.70*
Japanese	0.97*
Non-Hispanic White	1.00 (reference)

All non-white race and ethnic groups, except Japanese and Korean Americans, had a ***lower risk of*** **CARDIA** gastric adenocarcinoma compared to non-Hispanic white individuals.

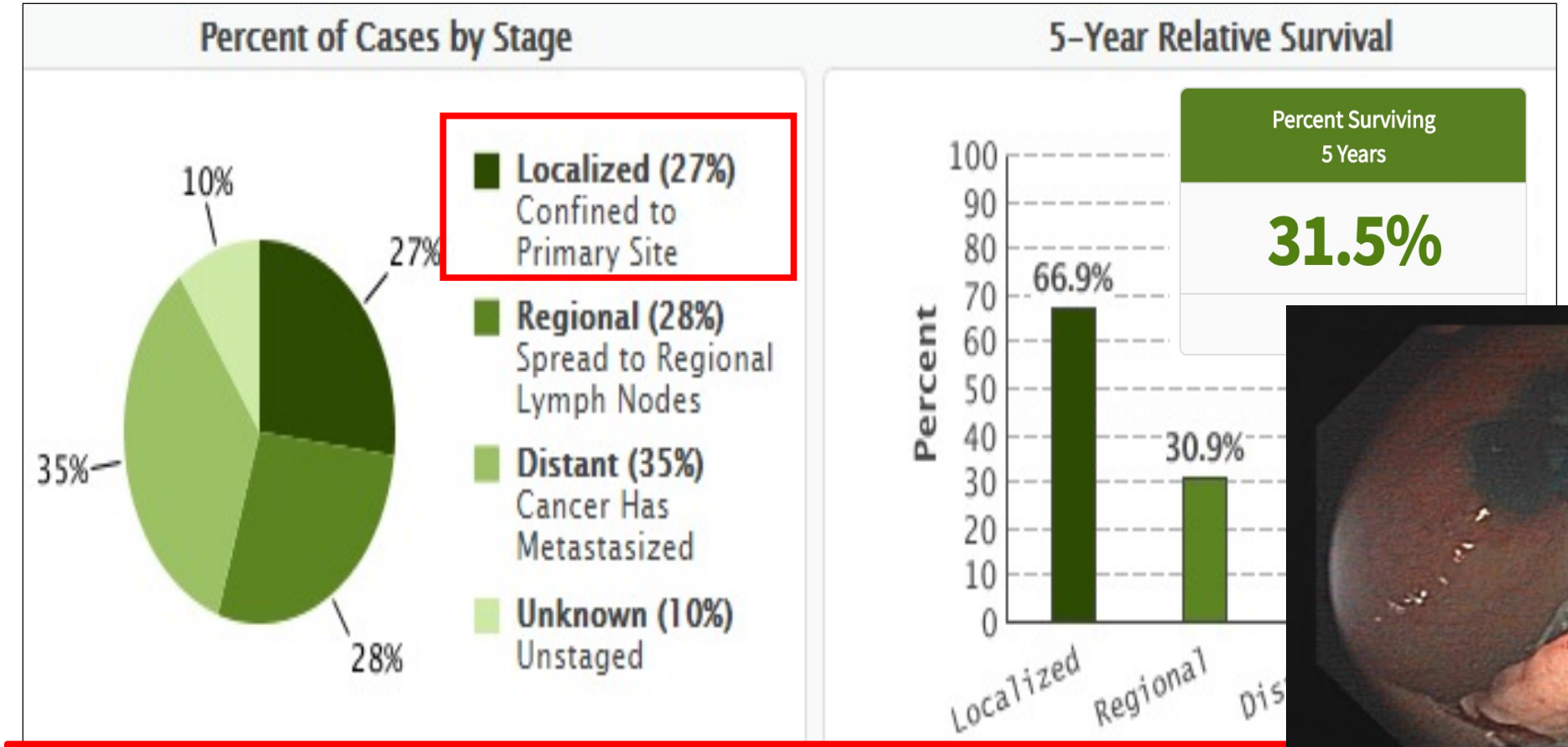
Korean	13.25
Vietnamese	6.46
Southeast Asian	5.71
Japanese	5.18
Chinese	4.77
Hispanic	3.79
Non-Hispanic Black	3.03
South Asian	2.09
Filipino	1.81
Non-Hispanic White	1.00 (reference)

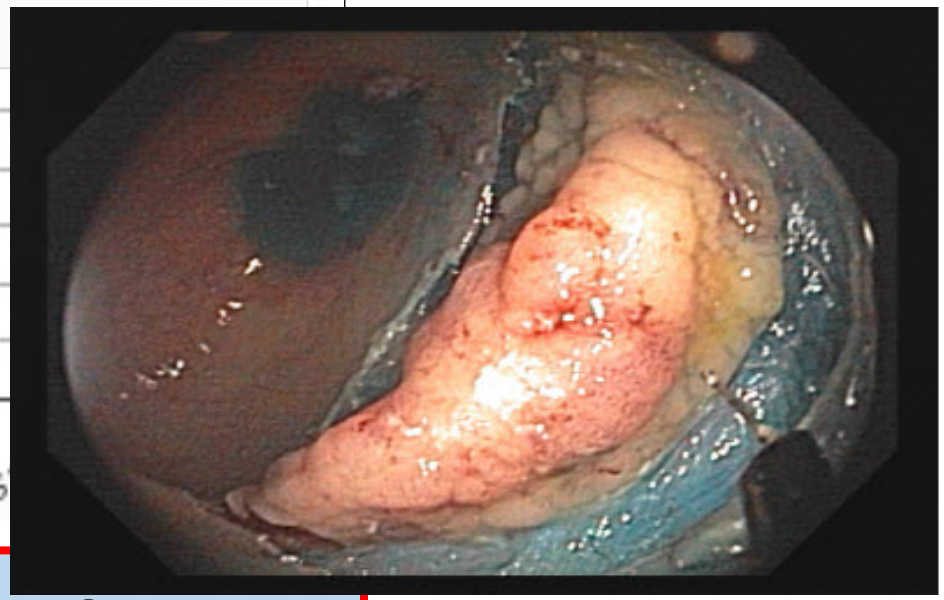
All non-white race and ethnic groups, especially Korean Americans, had a ***higher risk of*** **NONCARDIA** gastric adenocarcinoma compared to non-Hispanic white individuals

*Statistically non-significant
Data from California Cancer Registry (2011-2015)

Shah SC et al. Gastroenterology 2020

Survival data - US



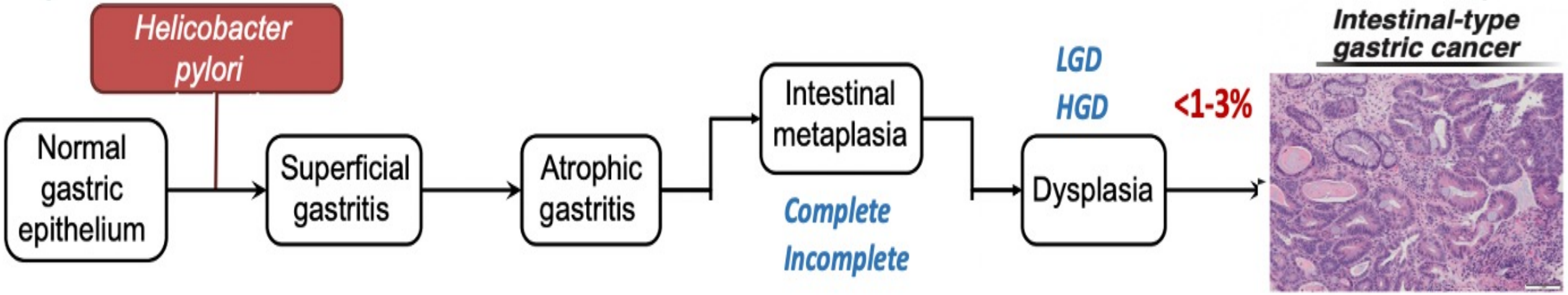


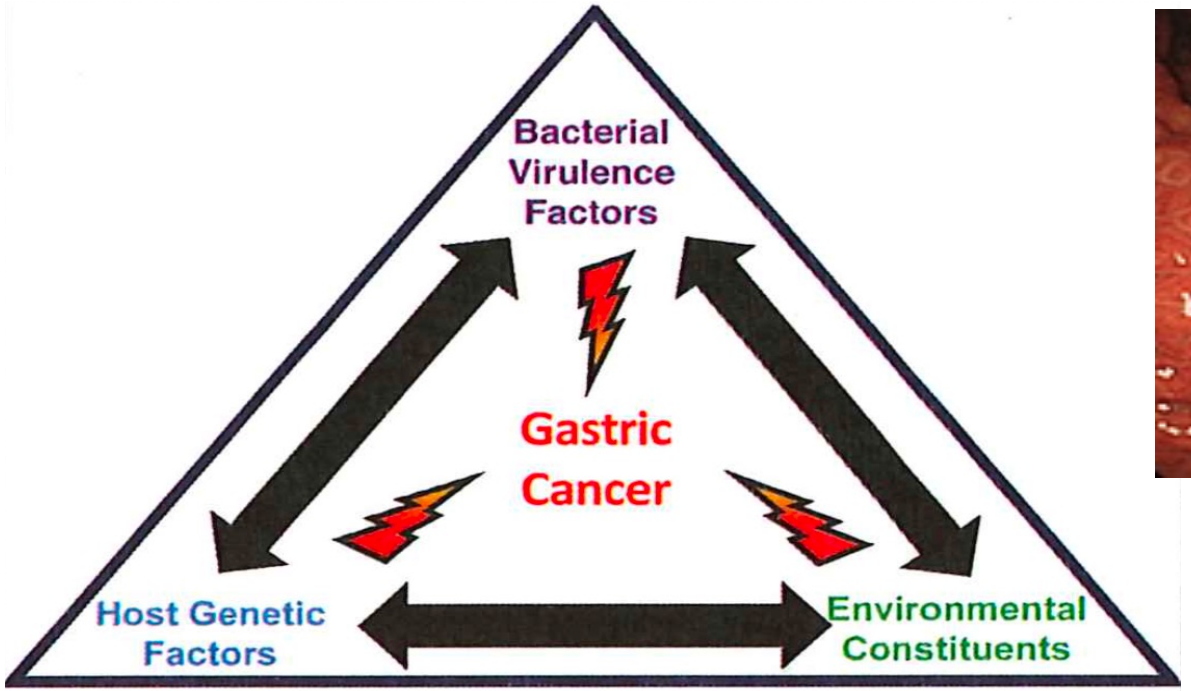
Vs. Asian countries w/ screening programs → now ~50-60% of GCs are diagnosed in early stage

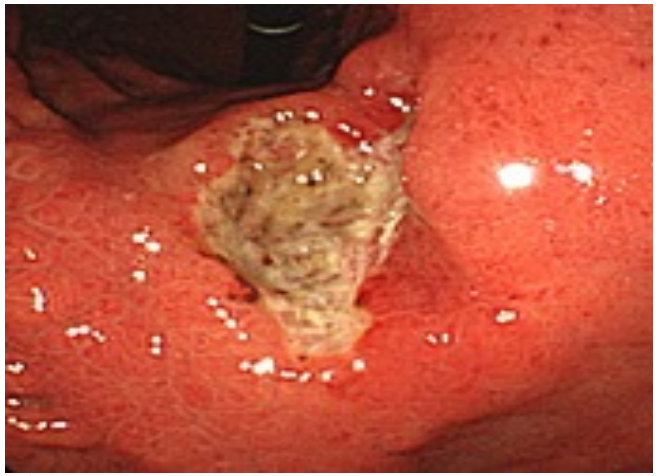
- ***5-year overall survival = 69% (and >95% for early gastric cancer)***

Jung 2014
SEER 2019
Nashimoto 2013

Stepwise progression to intestinal-type noncardia GA

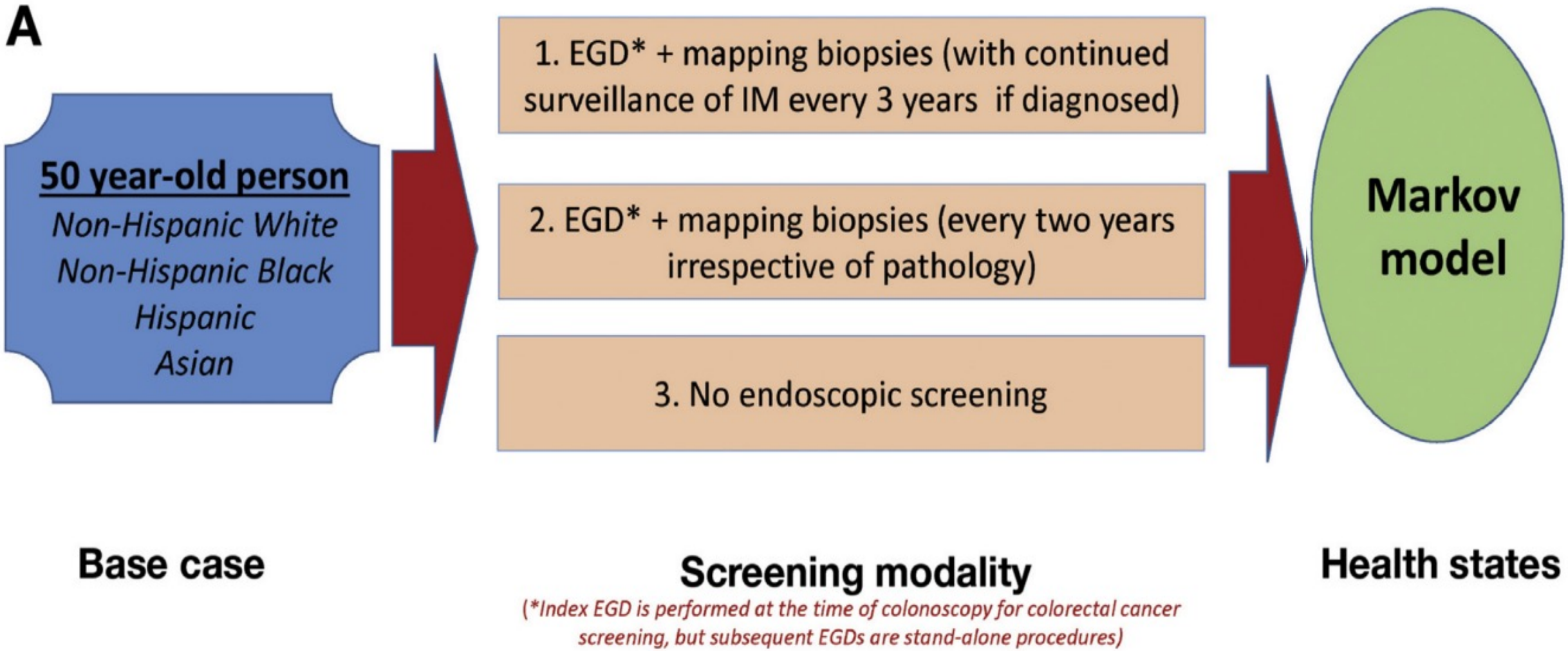






Burkitt, et al. 2017

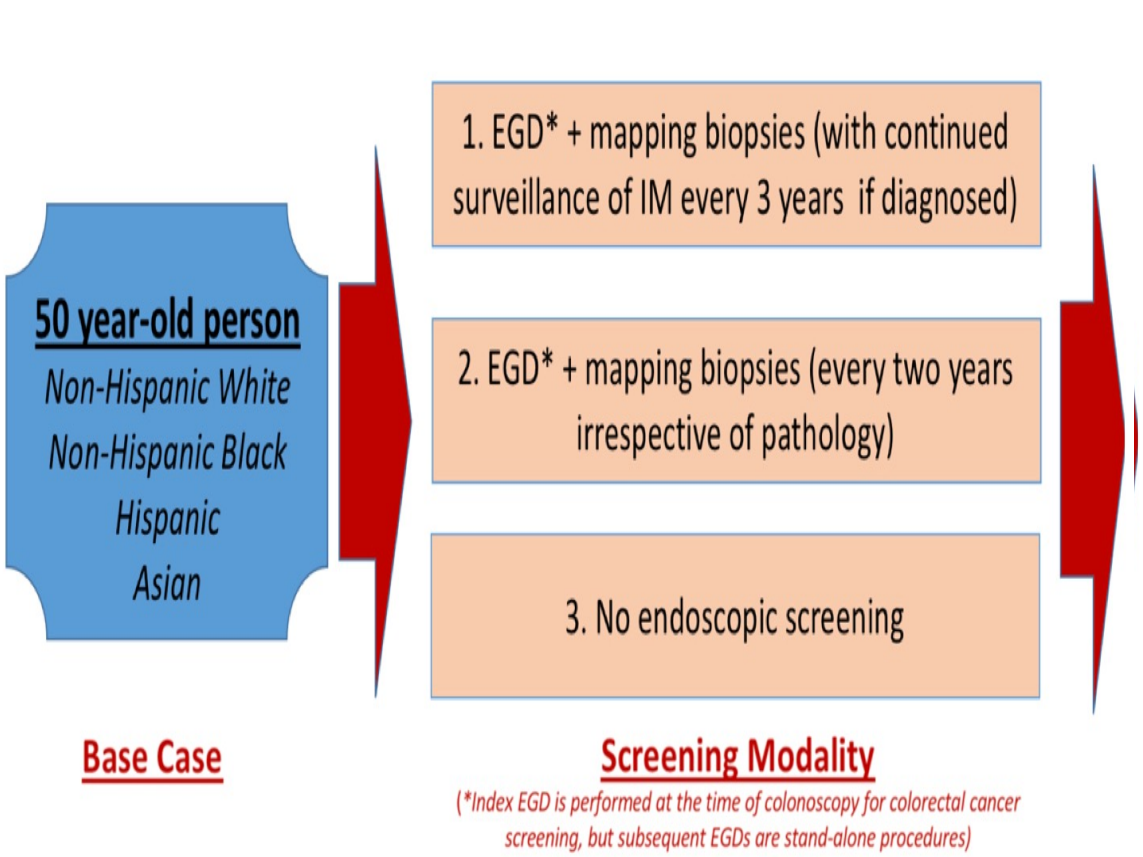
Gastric Cancer Screening and Surveillance in the US

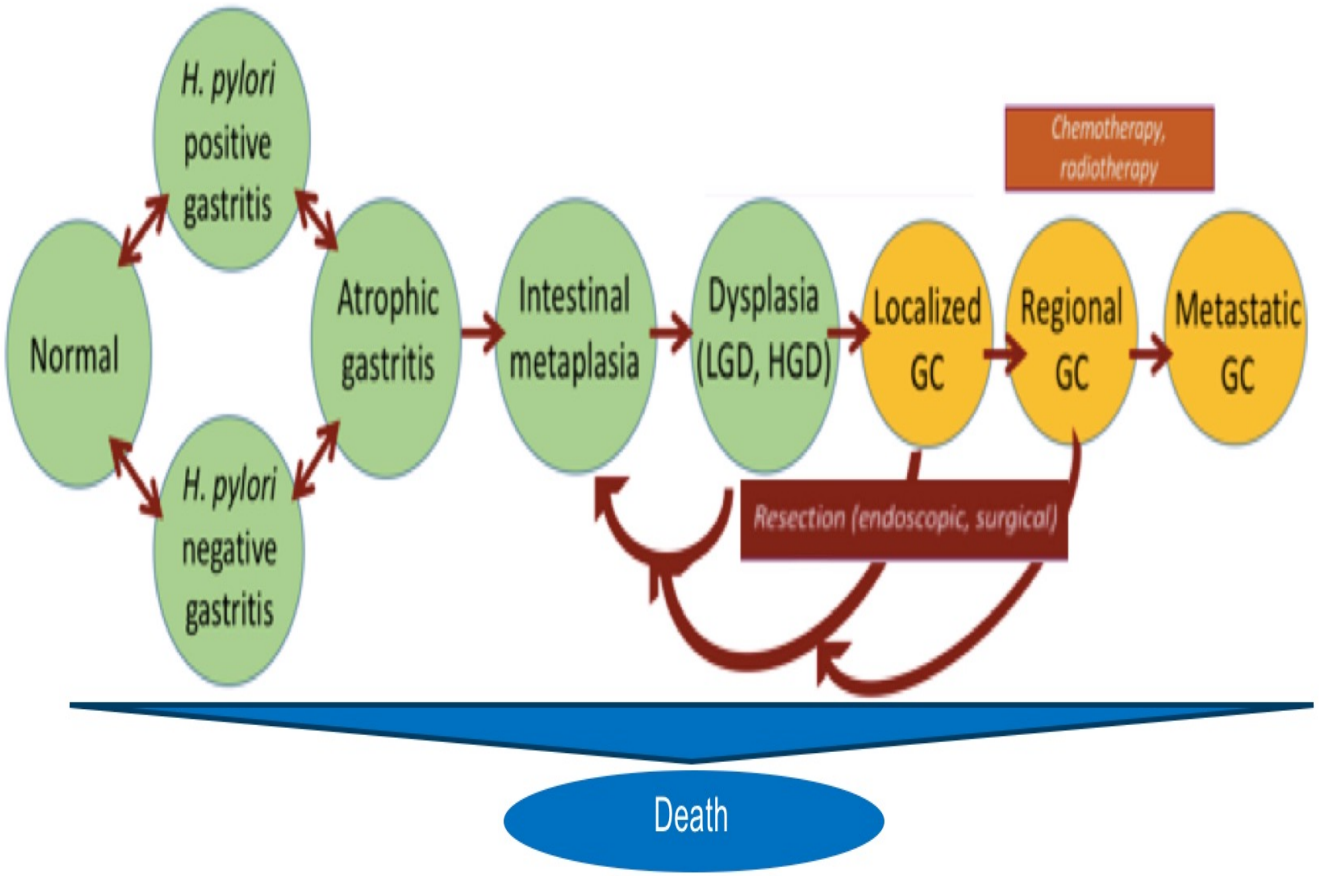


IM = (gastric) intestinal metaplasia

Saumoy and Shah et al. *Gastroenterology* 2018

Gastric Cancer Screening and Surveillance in the US

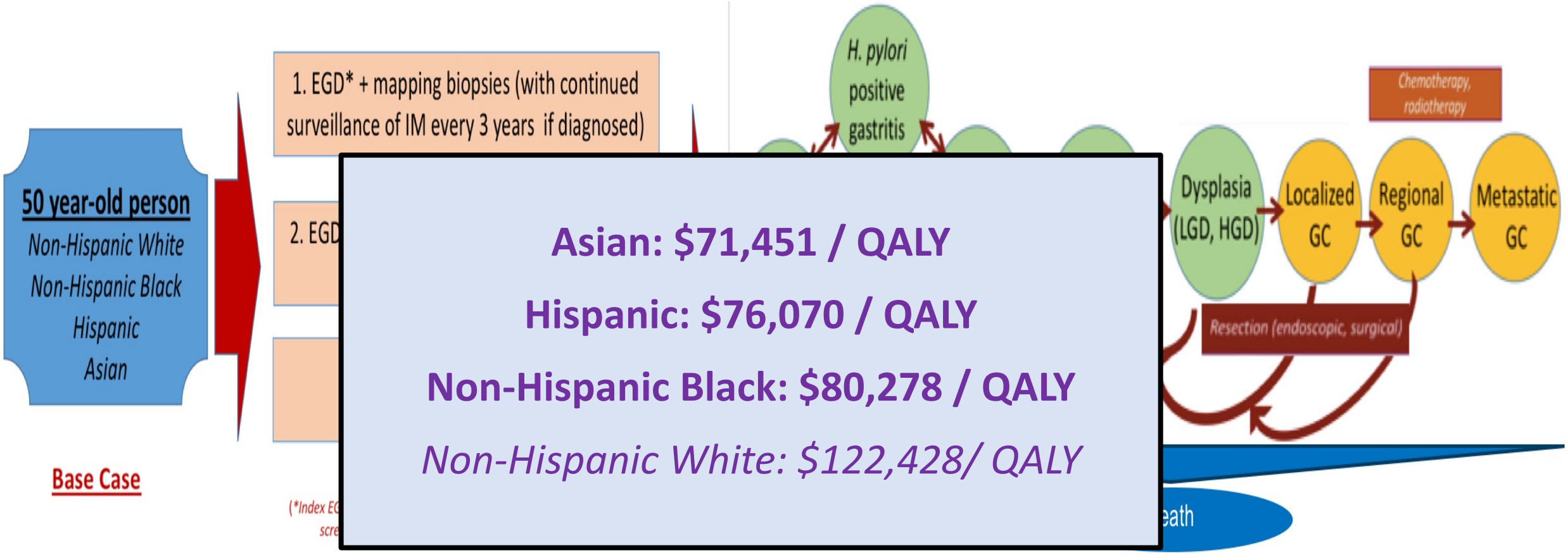




*Gastric cancer screening with <u>EGD + mapping biopsies at the time of colonoscopic CRC screening</u> with ongoing surveillance if indicated might be cost-effective for **Asians, Hispanics, and non-Hispanic blacks** <u>compared to either biennial EGD (irrespective of normal findings) or compared to no screening</u>*

Saumoy and Shah et al. *Gastroenterology* 2018

Gastric Cancer Screening and Surveillance in the US

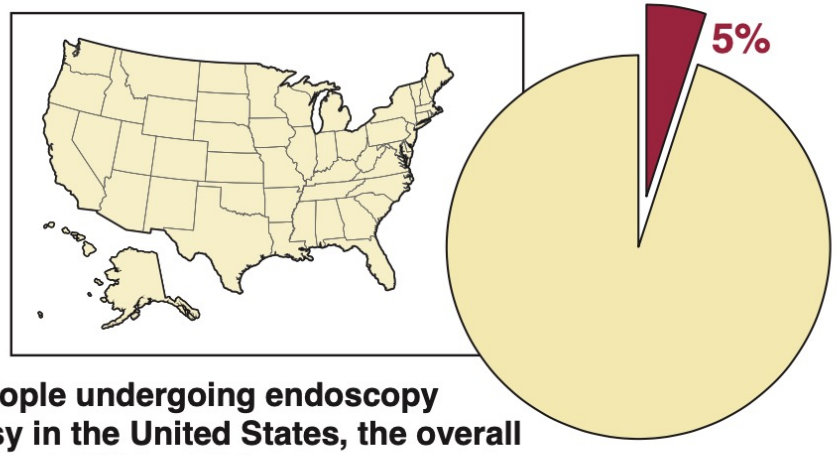


Gastric cancer screening with EGD + mapping biopsies at the time of colonoscopic CRC screening with ongoing surveillance if indicated might be cost-effective for ***Asians, Hispanics, and non-Hispanic blacks*** *compared to either biennial EGD (irrespective of normal findings) or compared to no screening*

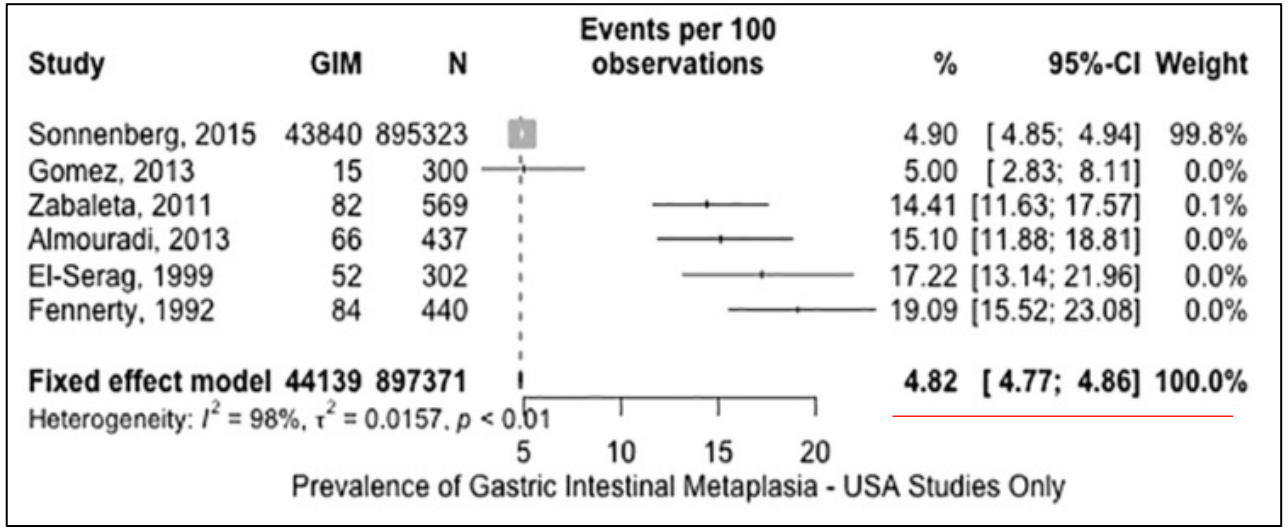
Saumoy and Shah et al. *Gastroenterology* 2018

Epidemiology of GIM in the United States

How common is GIM?



- **Among people undergoing endoscopy with biopsy in the United States, the overall prevalence of GIM is ~5%[2]**



US national pathology database: all EGDs with gastric biopsies 2008-2013 (N=895,323 unique patients)

- ***4.9% GIM prevalence**, but did not state limited/focal vs extensive*

But might be higher among some subgroups…

- ***Racial/ethnic minorities & immigrant groups, US Veterans***
- ***Family history of GC in 1st degree relative***
- ***Tobacco current or former use***
- ***Alcohol current or former use***
- ***Pernicious anemia***

Gawron A and Shah SC et al. *Gastroenterology* 2019

Why do we care about GIM?

Cumulative risk of GC in people diagnosed with GIM

- *0.4% at 3 years*
- *1.1% at 5 years*
- *1.6% at 10 years*

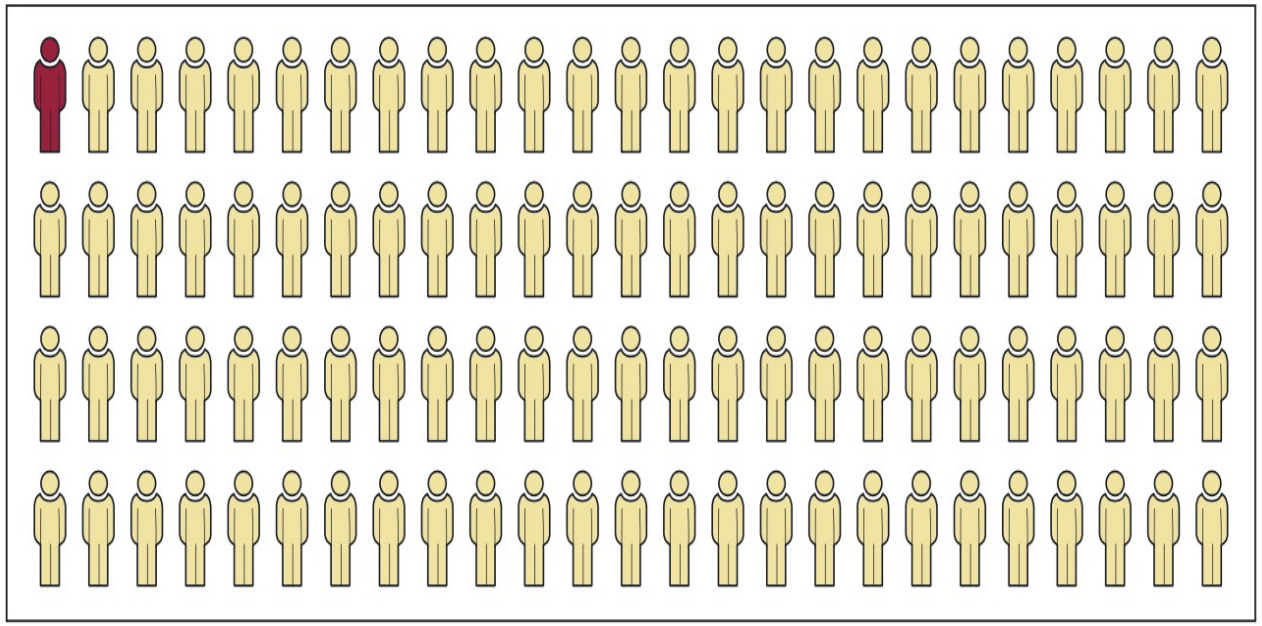
Nondysplastic Barrett's → Esophageal Ca

- ***0.1-0.3% per 1 year***

Adenoma <1cm → Colorectal Ca

- ***0.4% per 5-year surveillance***

5-year cumulative risk of incident gastric cancer in people diagnosed with GIM



Of 100 people with GIM, ~1 will develop GC within 5 years

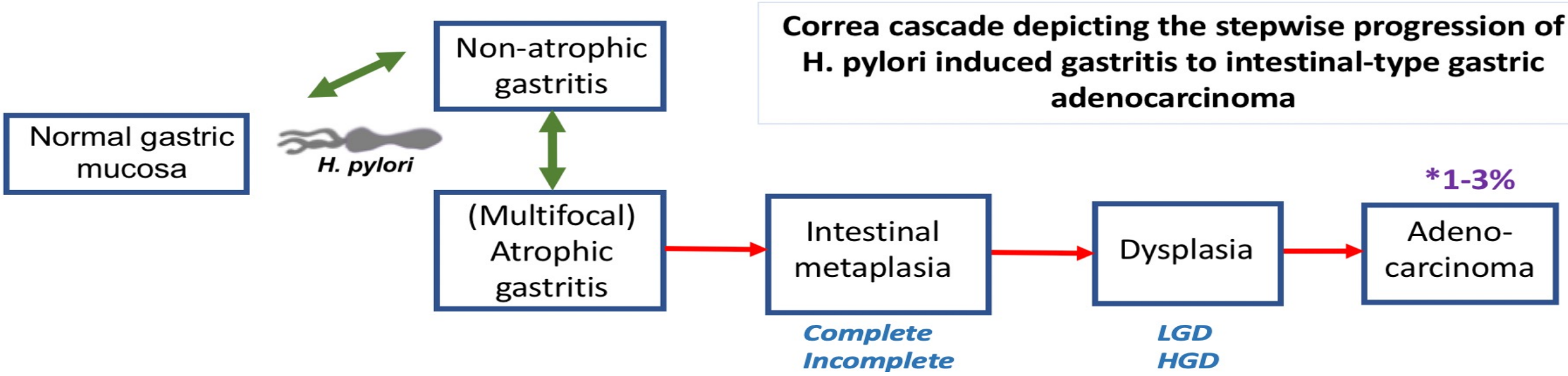
Shah SC et al. (Spotlight) *Gastroenterology* 2019

Natural history of GIM: Risk factors for GIM PROGRESSION

		Relative risk or odds ratio of incident GC
H pylori eradication (vs persistent infection)	↓	RR 0.76 (95% CI: 0.36–1.61)
Family history of gastric cancer	↑	RR 4.53 (95% CI: 1.33–15.5)
OLGIM III/IV (vs OLGIM I/II)*	↑	RR 27.7 (95% CI: 3.75–204.9) OR 3.99 (95% CI: 3.05–5.21)
Incomplete histologic subtype (vs complete)	↑	RR 3.33 (95% CI: 1.96–5.64)
Extensive GIM (vs limited)	↑	RR 2.07 (95% CI: 0.97–4.42)

Shah SC et al. (Spotlight) *Gastroenterology* 2019

Natural history of GIM: Global histological *REGRESSION*



Cumulative proportion with global histologic **regression** of GIM

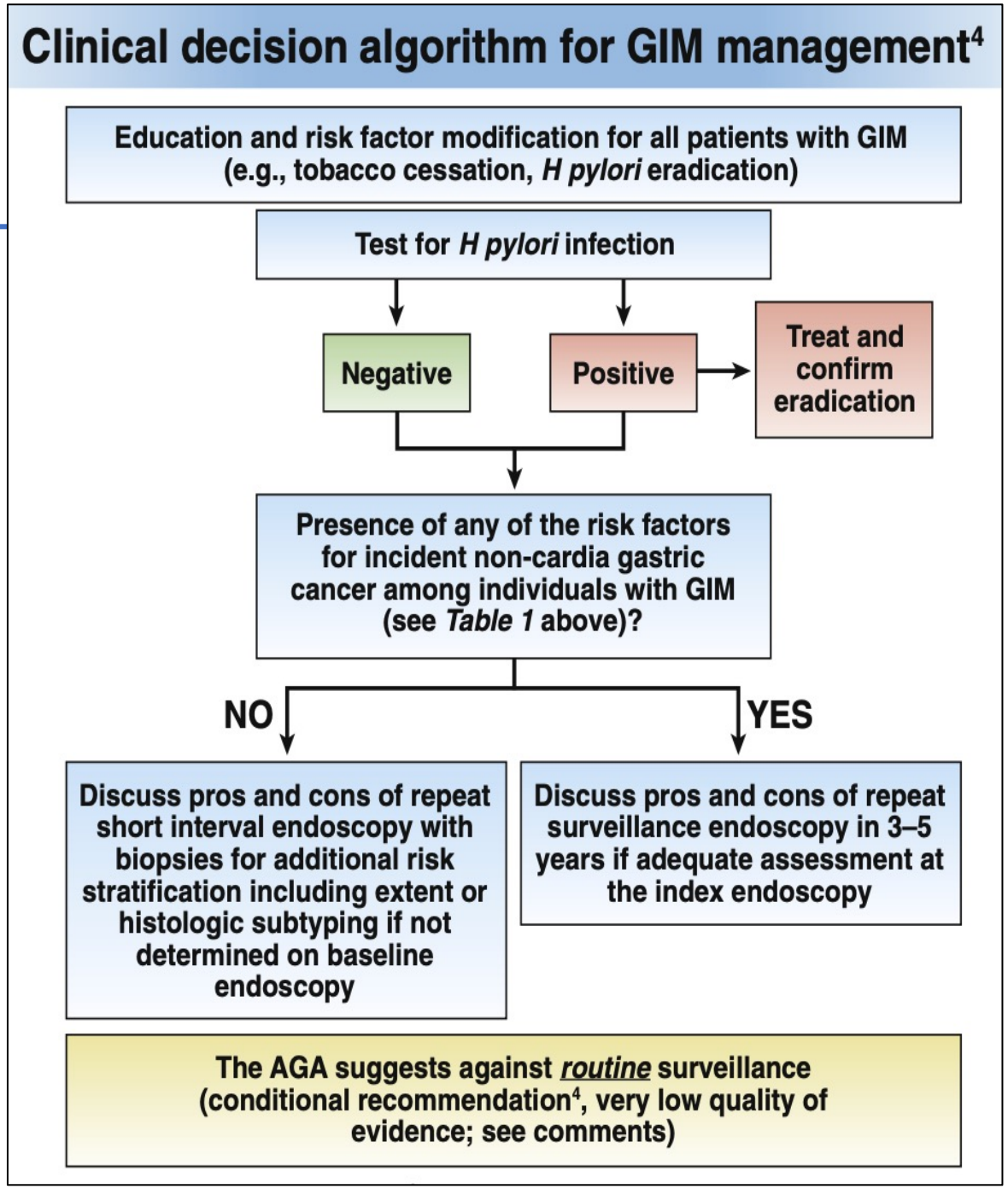
- *29.7% at 1 year*
- *19.4% at 3 years*
- *25.9% at 5 years*

Gawron A and Shah SC et al. *Gastroenterology* 2019

GIM Management, International Guidelines

- *American Gastroenterological Association (AGA), 2020*
- European Society of Gastrointestinal Endoscopy (ESGE), 2012 and updated 2019
- British Society of Gastroenterology (BSG), 2019
- Latin American Guidelines (AEG, SEED, SEAP), 2020

- American Society for Gastrointestinal Endoscopy (ASGE), 2015
- American College of Gastroenterology (ACG), coming soon 2022



Shah SC et al. (Spotlight) *Gastroenterology* 2019

AGA Clinical Practice Guidelines on Management of Gastric Intestinal Metaplasia

Samir Gupta,[1,2] Dan Li,[3,4] Hashem B. El Serag,[5] Perica Davitkov,[6,7] Osama Altayar,[8] Shahnaz Sultan,[9] Yngve Falck-Ytter,[10,11] and Reem A. Mustafa[12]

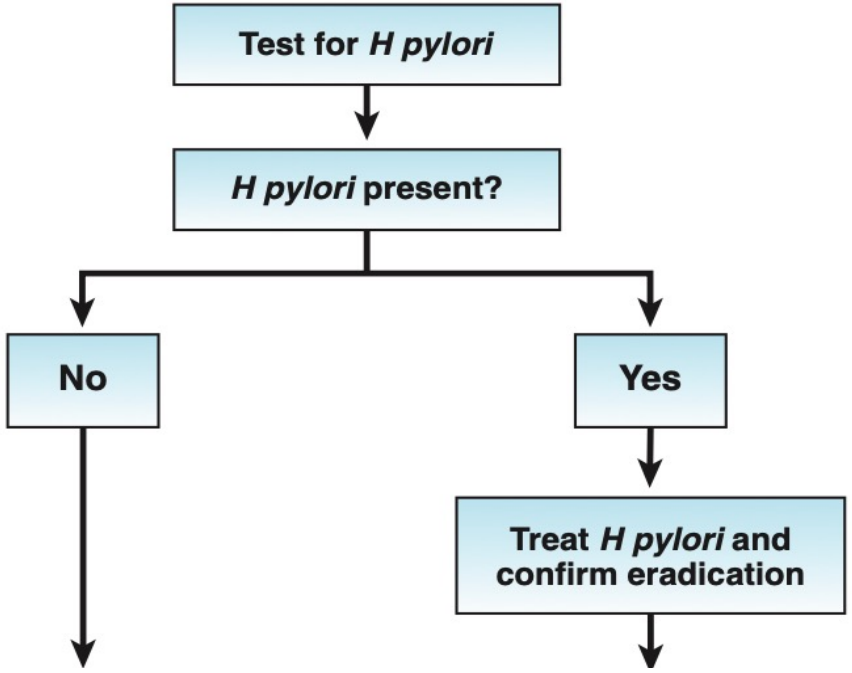
Recommendation 1

In patients with GIM, the AGA recommends testing for *H. pylori* followed by eradication over no testing and eradication.

- *Strong recommendation, moderate quality of evidence.*

Gastric Intestinal Metaplasia (GIM)

Clinical Decision Support Tool



ESGE MAPS II and BSG Guidelines

21 In patients with established IM, *H. pylori* eradication does not appear to significantly reduce the risk of gastric cancer, at least in the short term, but reduces inflammation and atrophy and, therefore, it should be considered (low quality evidence, weak recommendation)

2. *We suggest that H. pylori eradication may be of some benefit to reduce the risk of developing gastric adenocarcinoma in those who already have H. pylori-associated GIM, dysplasia or cancer* (evidence level: high quality; grade of recommendation: weak; level of agreement: 100%).

Clinical decision algorithm for GIM management[4]

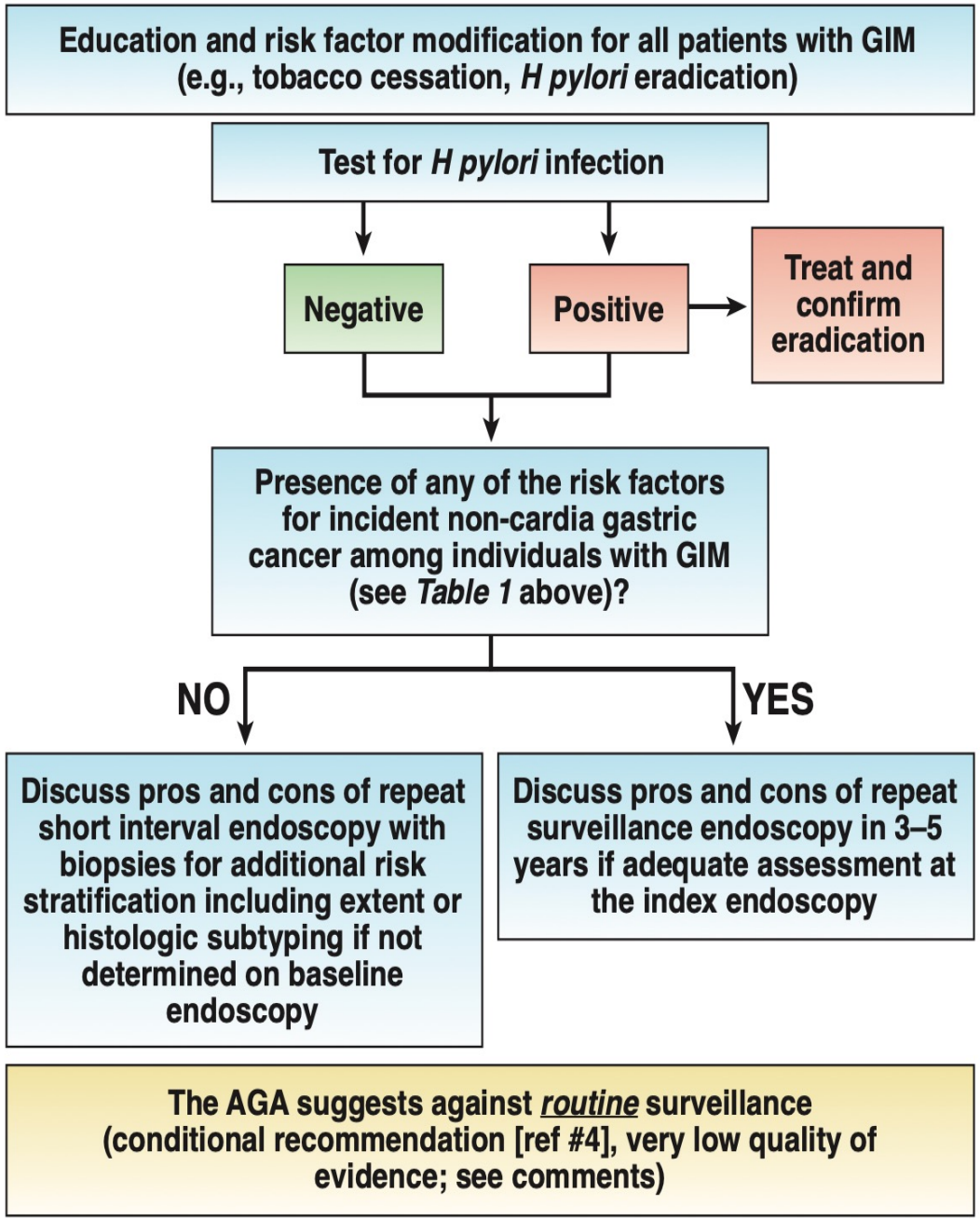


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Table 1: Factors associated with risk of incident gastric cancer in individuals with GIM

Evidence-based risk factors*		Relative risk of incident GC
H pylori eradication (vs persistent infection)	↓	RR 0.76 (95% CI: 0.36–1.61)
Family history of gastric cancer	↑	RR 4.53 (95% CI: 1.33–15.5)
Incomplete histologic subtype (vs complete)	↑	RR 3.33 (95% CI: 1.96–5.64)
Extensive GIM (vs limited)	↑	RR 2.07 (95% CI: 0.97–4.42)

AGA Clinical Practice Guidelines on Management of Gastric Intestinal Metaplasia

Gupta et al. *Gastroenterology* 2019

Recommendation 2

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

- *Conditional recommendation, very low quality of evidence*

AGA Clinical Practice Guidelines on Management of Gastric Intestinal Metaplasia

Gupta et al. *Gastroenterology* 2019

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Comment: *Patients with GIM at higher risk for gastric cancer who put a high value on potential but uncertain reduction in gastric cancer mortality, and who put a low value on potential risks of surveillance endoscopies, may reasonably elect for surveillance.*

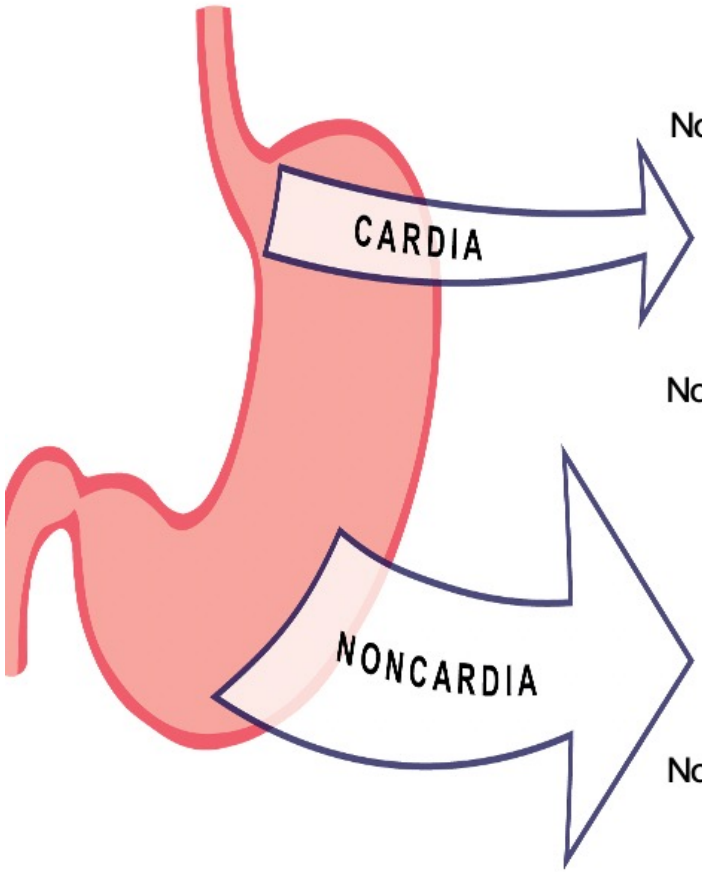
Patients with GIM specifically at higher risk of gastric cancer include those with:

- **Incomplete vs complete GIM**
- **Extensive vs limited GIM**
- **Family history of gastric cancer**

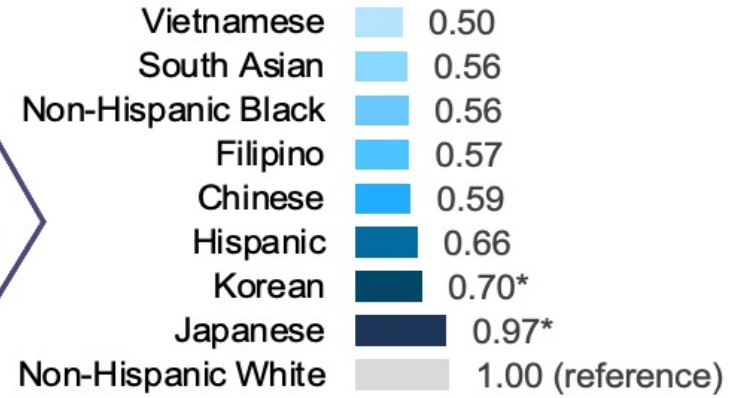
Patients at overall increased risk for gastric cancer include:

- **Racial/ethnic minorities**
- **Immigrants from high incidence regions**

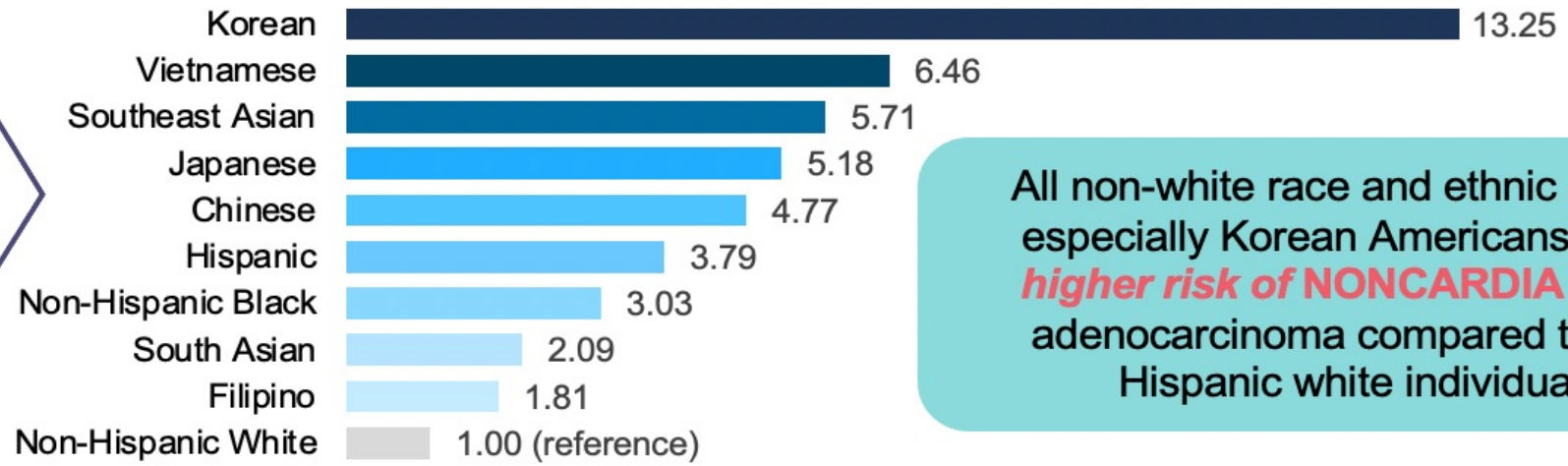
Population-Based Analysis of Differences in Gastric Cancer Incidence Among Races and Ethnicities in Individuals Age 50 Years and Older



Age- and sex-adjusted incidence rate ratios for individuals ≥50 years



All non-white race and ethnic groups, except Japanese and Korean Americans, had a ***lower risk of*** **CARDIA** gastric adenocarcinoma compared to non-Hispanic white individuals.



All non-white race and ethnic groups, especially Korean Americans, had a ***higher risk of*** **NONCARDIA** gastric adenocarcinoma compared to non-Hispanic white individuals

*Statistically non-significant
Data from California Cancer Registry (2011-2015)

Shah SC et al. Gastroenterology 2020

ESGE MAPS II Guidelines

15 Patients with IM at a single location have a higher risk of gastric cancer. However, this increased risk does not justify surveillance in most cases, particularly if a high quality endoscopy with biopsies has excluded advanced stages of atrophic gastritis (moderate quality evidence, strong recommendation)

16 In patients with IM at a single location but with a family history of gastric cancer, or with incomplete IM, or with persistent *H. pylori* gastritis, endoscopic surveillance with chromoendoscopy and guided biopsies in 3 years' time may be considered (low quality evidence, weak recommendation)

BSG Guidelines

13. *We recommend endoscopic surveillance every 3 years should be offered to patients diagnosed with extensive GA or GIM, defined as that affecting the antrum and body* (evidence level: low quality; grade of recommendation: strong; level of agreement: 100%).

14. *We do not recommend surveillance in patients with GA or GIM limited just to the gastric antrum unless there are additional risk factors, such as a strong family history of gastric cancer or persistent H. pylori infection, then we suggest 3-yearly surveillance* (evidence level: low quality; grade of recommendation: strong; level of agreement: 93%).

Surveillance of GIM: Benefit of short-interval endoscopy (<12 months)

AGA Clinical Practice Guidelines on Management of Gastric Intestinal Metaplasia

Recommendation 3

In patients with GIM, the AGA suggest against *routine* short-interval repeat endoscopy for the purpose of risk stratification

- *Conditional recommendation, very low quality of evidence*

Surveillance of GIM: Benefit of short-interval endoscopy (<12 months)

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Comment: Based on shared decision-making, patients with GIM and any of the following may reasonably elect for repeat endoscopy *within 1 year for risk stratification*

- High-risk stigmata,
- Concerns re: completeness of baseline endoscopy, and/or
- Who are at overall increased risk for gastric cancer
  - Racial/ethnic minorities,
  - Immigrants from regions with high gastric cancer incidence, or
  - Individuals with family history of first-degree relative with gastric cancer)

Surveillance of GIM: Benefit of short-interval endoscopy (<12 months)

Recommendation 3

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ESGE:

"If baseline data are incomplete or suboptimal in anyway, consider repeating the gastroscopy to provide assurance regarding missed lesions, *H pylori* status and staging of GIM in 1–3 years"

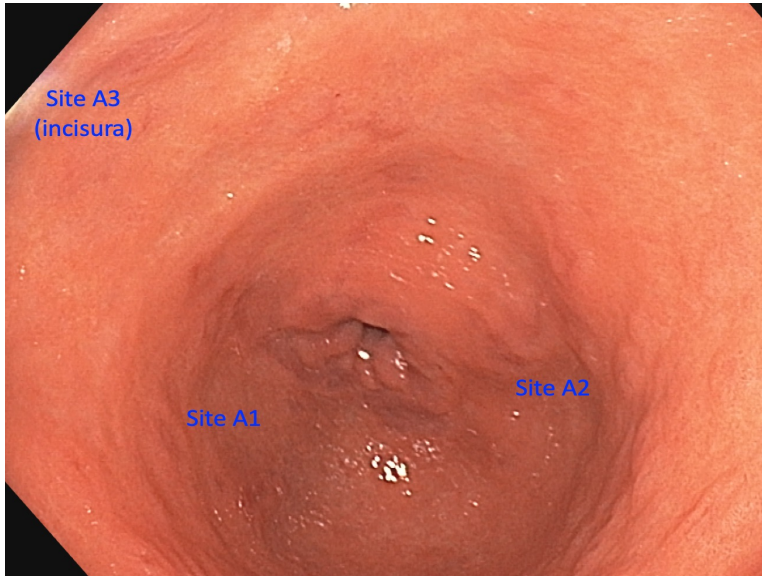
Need for quality metrics in upper endoscopy…

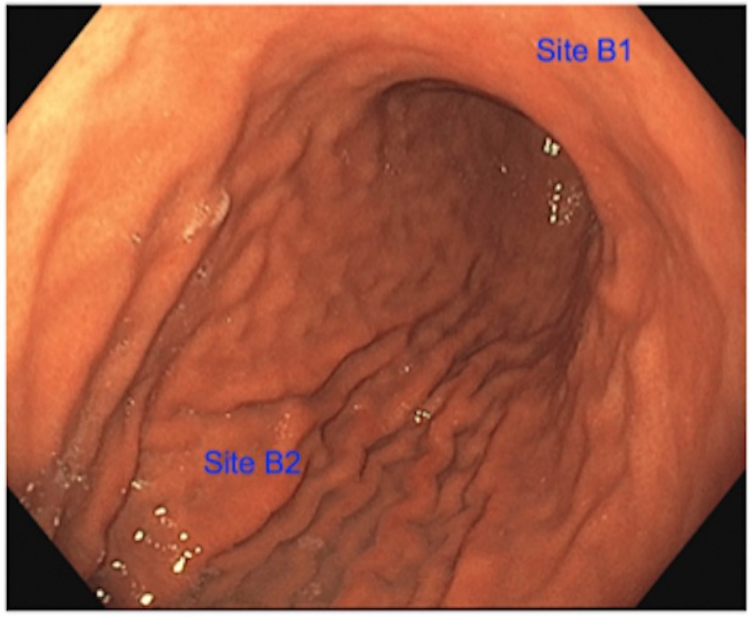
- Two main goals of the endoscopic surveillance exam:
  - ***1) Identify neoplasia***
  - ***2) Risk stratification***

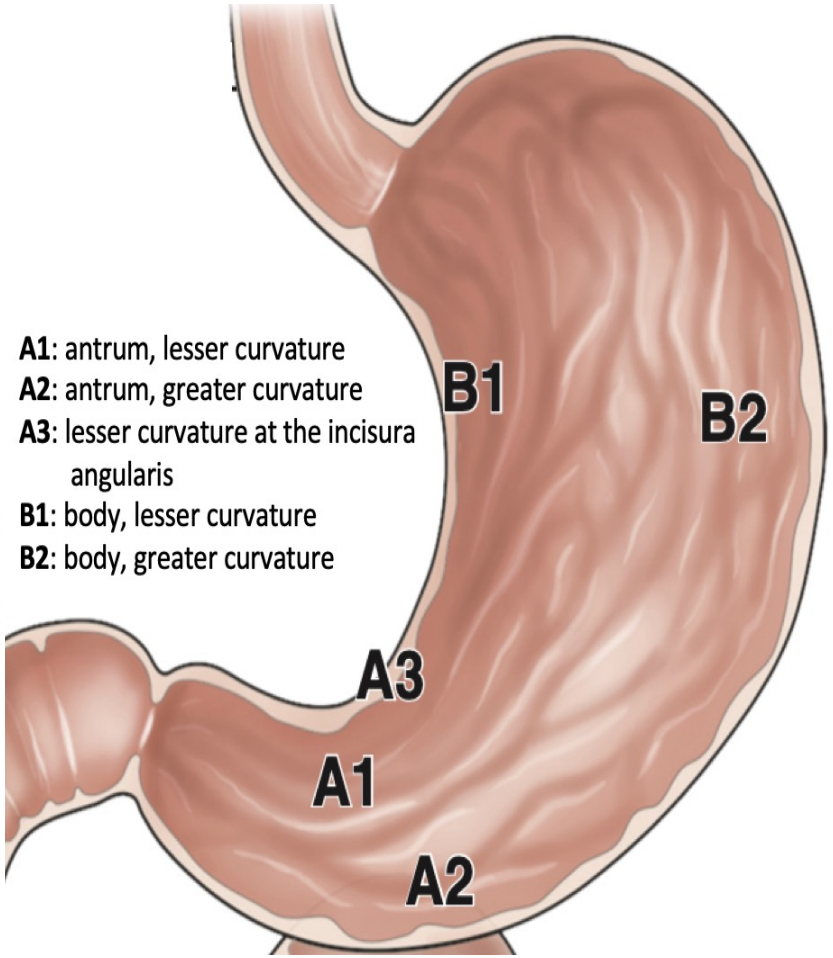
- Some early gastric cancers are diagnosed based on *very subtle* mucosal surface changes and/or color changes

Careful inspection → Detection and Characterization

Endoscopic Surveillance of GIM







Checklist for GIM

- ❑ At minimum, **high-definition white light endoscope (HD-WLE)** is recommended +/- additional image enhancement (e.g. **NBI**)
- ❑ **Mucosal cleaning, insufflation** for adequate visualization
- ❑ **Adequate time** for gastric mucosal inspection (and photo-documentation)
- ❑ *At minimum*, two separate containers with biopsies from the body and antrum/incisura to allow determination of **GIM extent**
- ❑ **Histologic subtyping** for risk stratification (incomplete, complete)

Clinical Gastroenterology and Hepatology 2015;13:480–487

Longer Examination Time Improves Detection of Gastric Cancer During Diagnostic Upper Gastrointestinal Endoscopy

Jun Liang Teh,* Jin Rong Tan,‡ Linus Jian Fa Lau,‡ Nakul Saxena,§,|| Agus Salim,¶ Amy Tay,* Asim Shabbir,* Sydney Chung,*,‡ Mikael Hartman,*,||,# and Jimmy Bok-Yan So*,‡

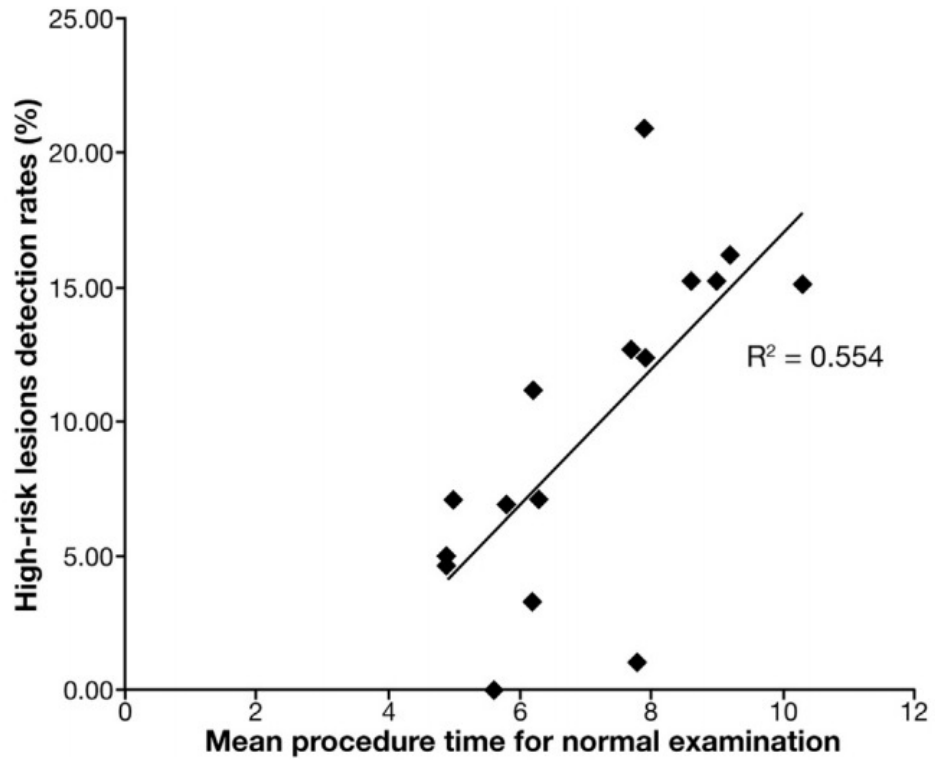


Figure 2. Percentage of EGD examinations detecting high-risk gastric lesions according to mean examination time for 16 endoscopists.

ORIGINAL ARTICLE

Colonoscopic Withdrawal Times and Adenoma Detection during Screening Colonoscopy

Robert L. Barclay, M.D., Joseph J. Vicari, M.D., Andrea S. Doughty, Ph.D., John F. Johanson, M.D., and Roger L. Greenlaw, M.D.

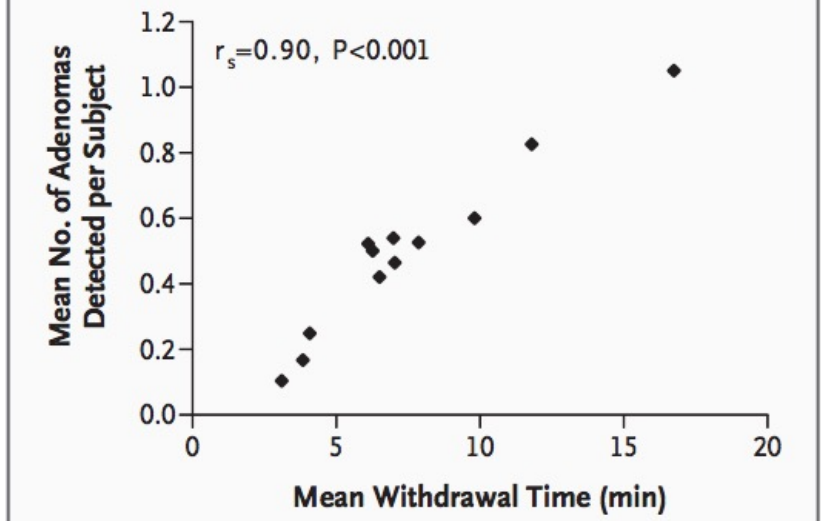
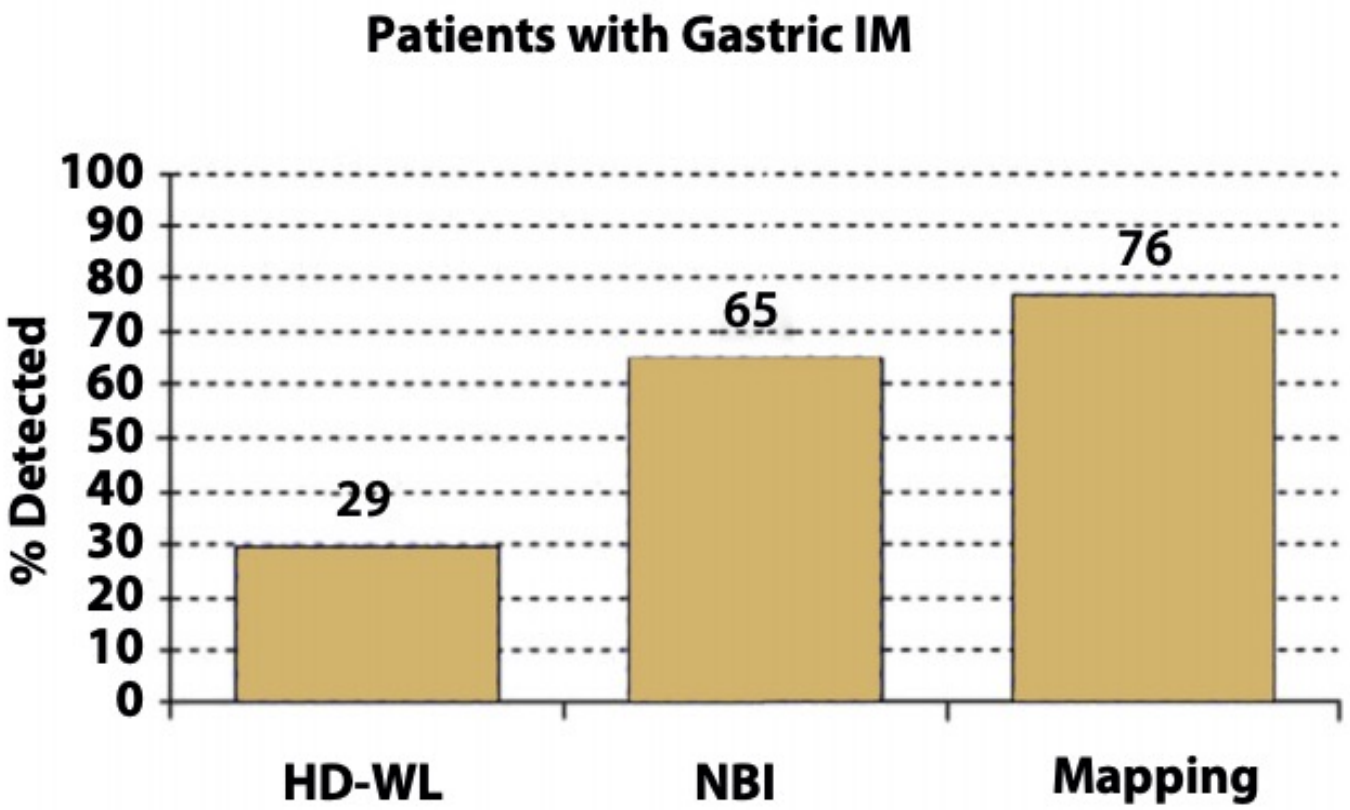


Figure 2. Mean Rates of Detection of Adenomas According to Mean Colonoscopic Withdrawal Times for 12 Endoscopists.

The values are for procedures in which no polyps were removed. The significant correlation between rates of detection of adenomas and withdrawal times was calculated with the use of the Spearman rank-correlation coefficient.

GIM Surveillance: HD-WLE vs. HD-WLE + NBI



HD-WLE is INSUFFICIENT for detection of GIM.

- NBI-targeted + 'mapping' biopsies recommended

112 patients → 96% Hispanic or Asian, 30% had GIM

GIM detected by:

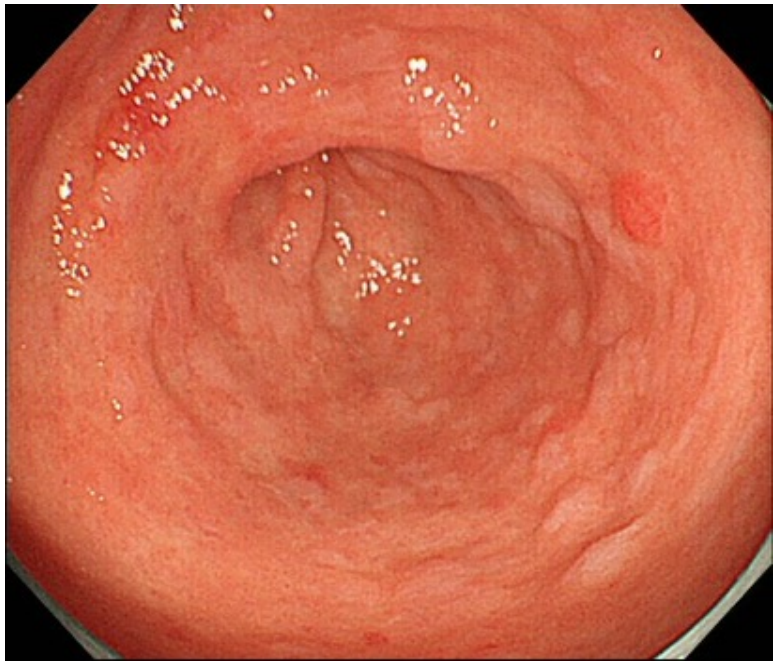
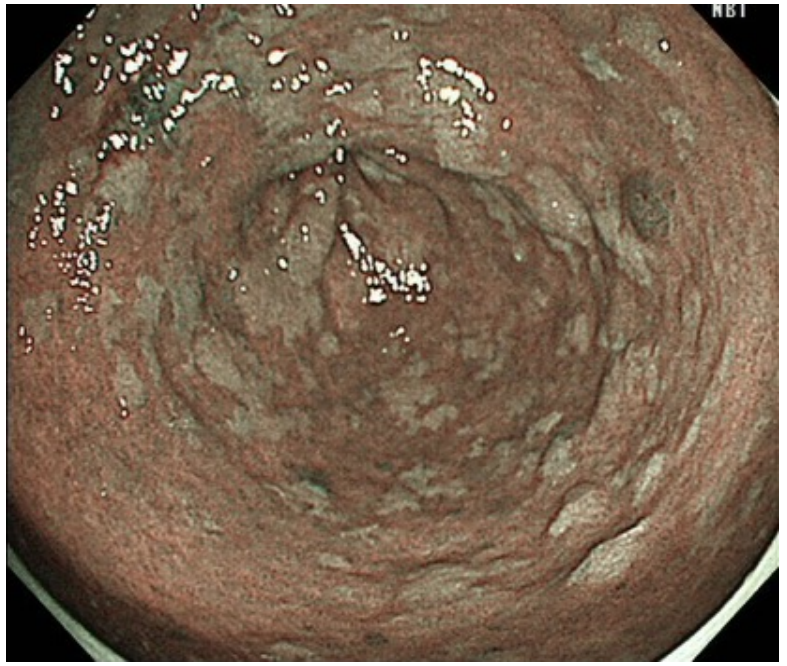
- **NBI** (65%)
- **Mapping Biopsy** (76%)
- **HD-WL** (29%)

GIM detected **solely** by

- NBI in 17.6%,
- Biopsy in 29.4%
- HD-WL in 0%

Mapping + NBI detected "100%" of pts

Buxbaum, GIE 2017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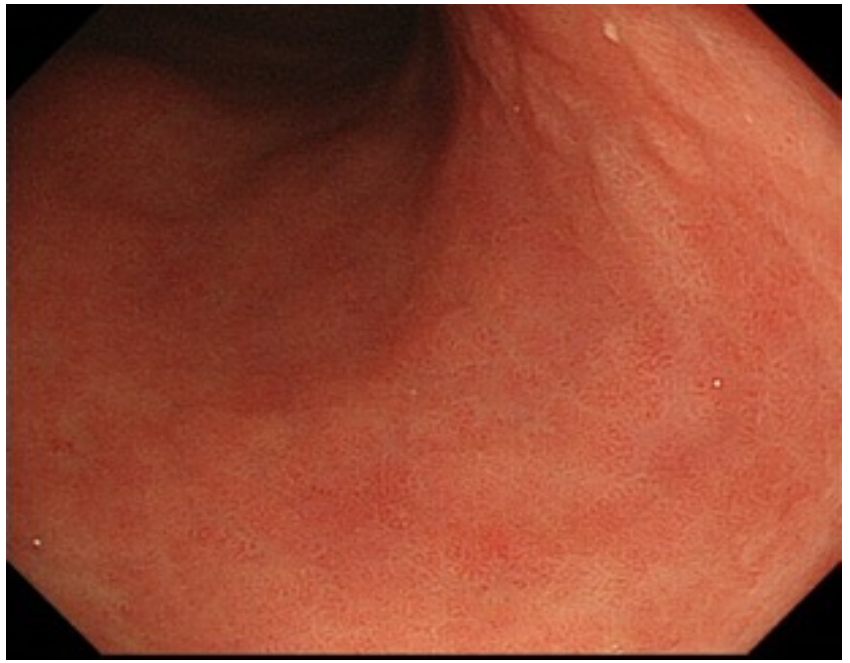
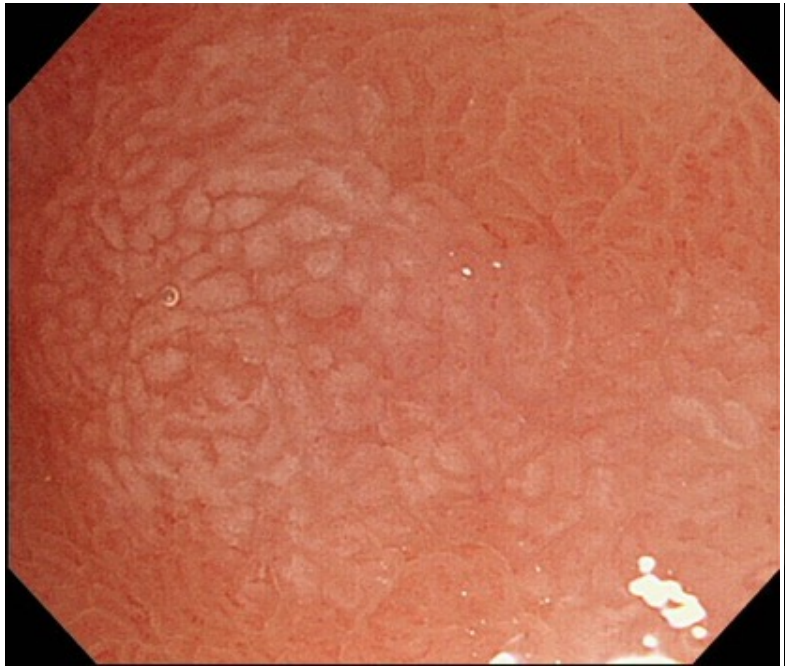
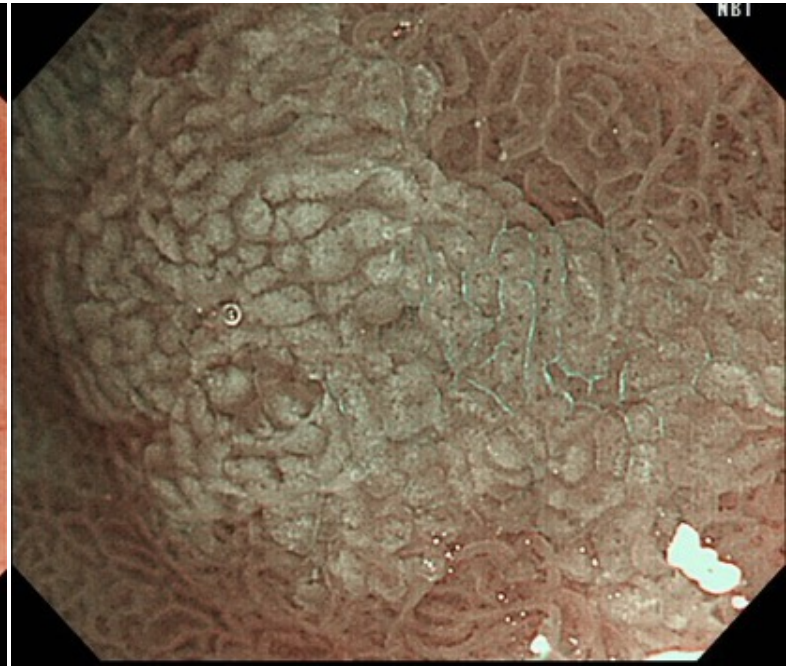
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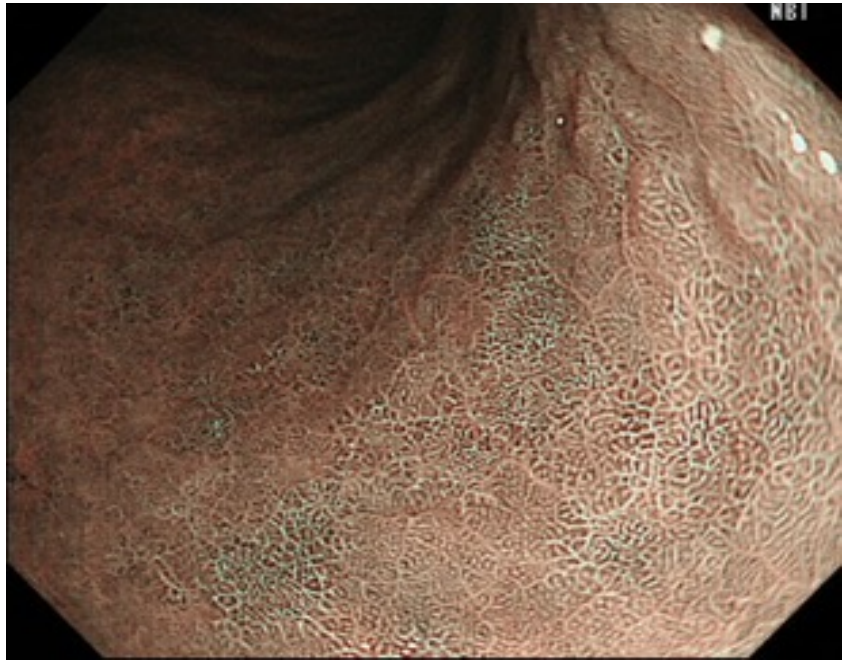
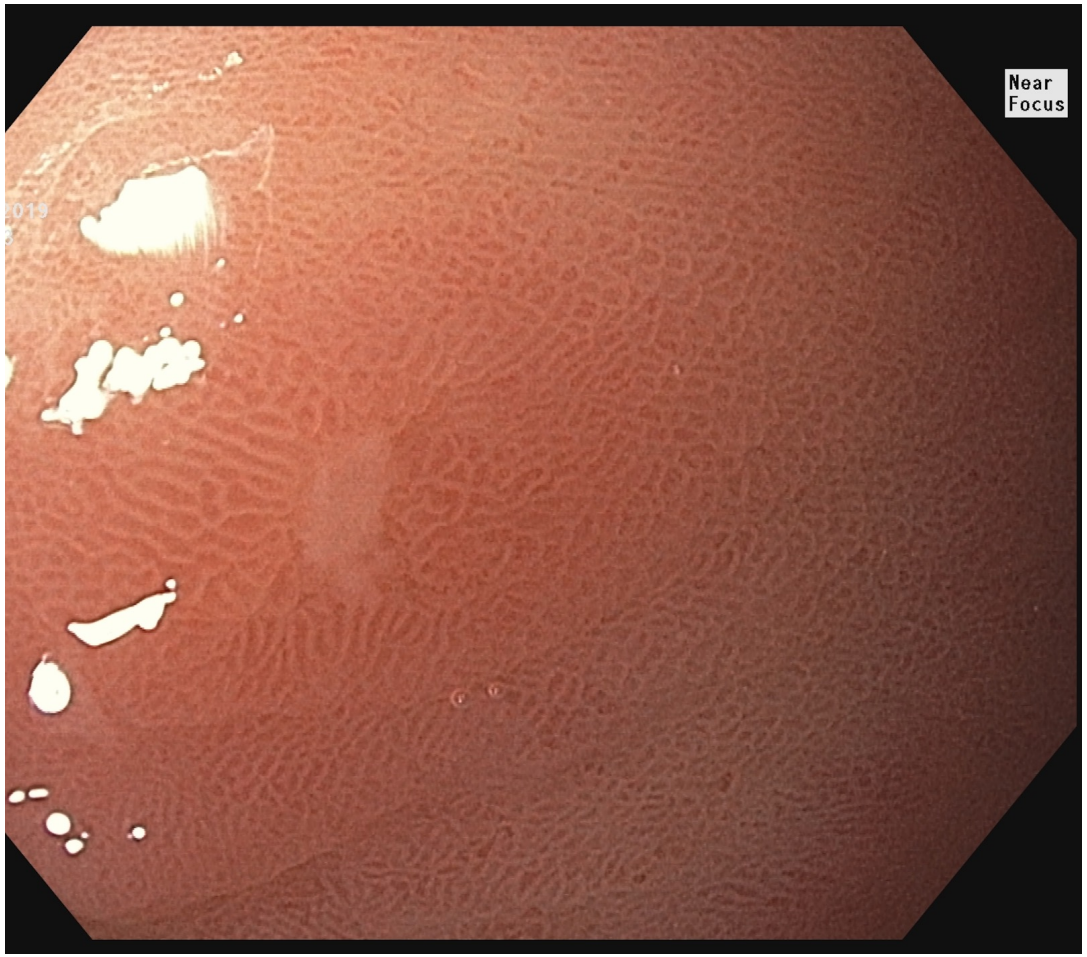
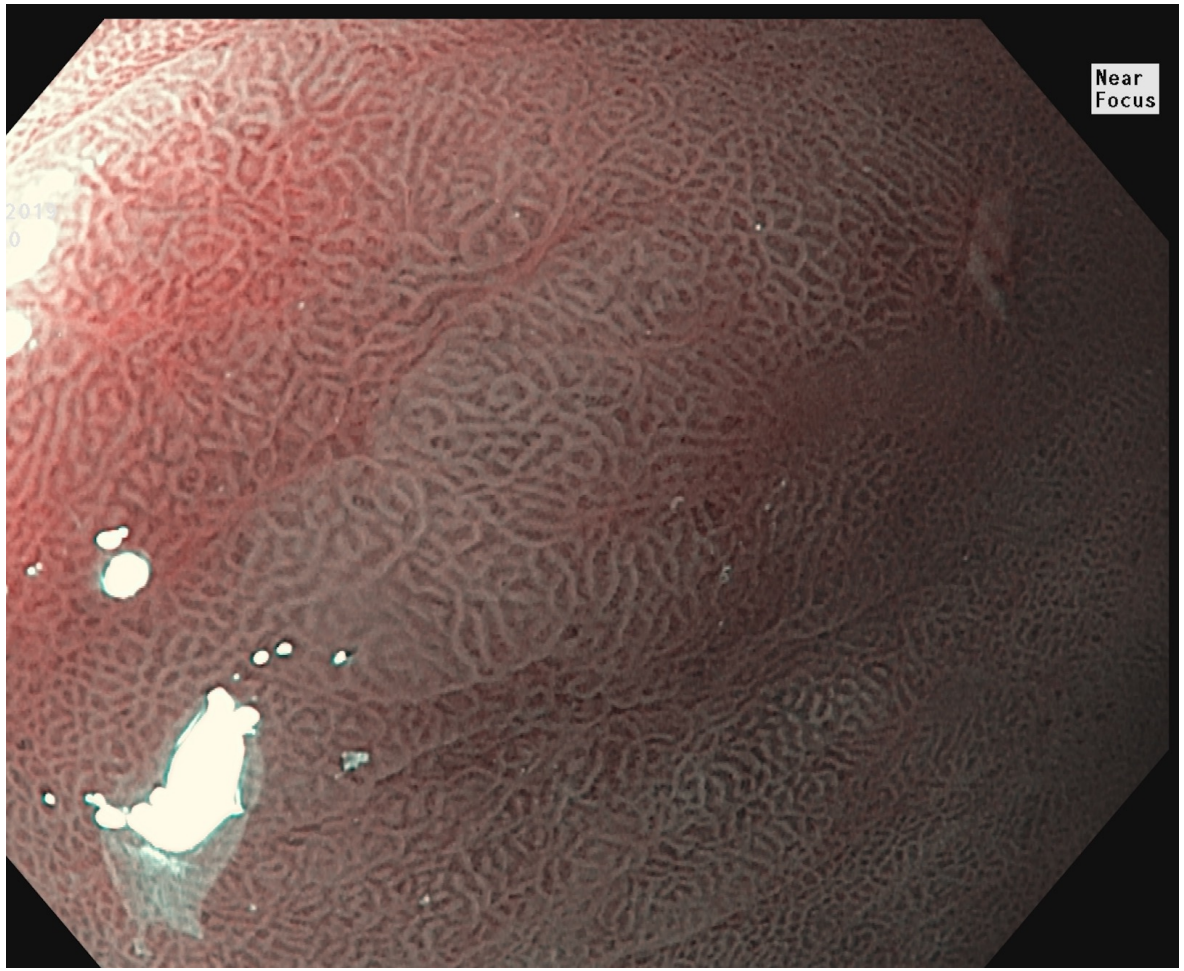

NBI

HD-WLE and (near-focus) NBI





"Tubulovillous mucosa" = associated with GIM

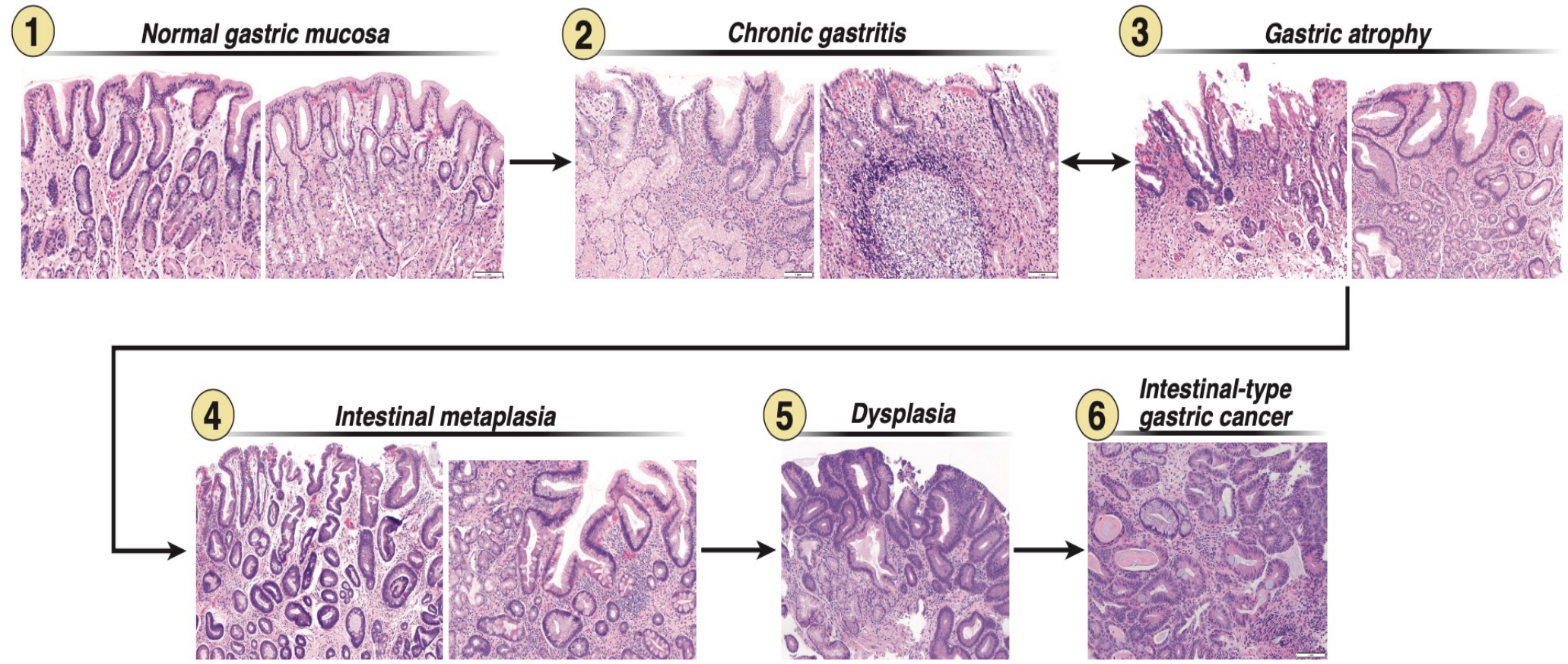
- ✓ accuracy 84% (95% CI, 77% – 91%)
- ✓ positive LR= 4.75 (up to 8.98)

Shah, Gawron, Li AJG 2020
Pimentel-Nunes Endoscopy 2012
Wang PLoS One 2014

What about atrophic gastritis?

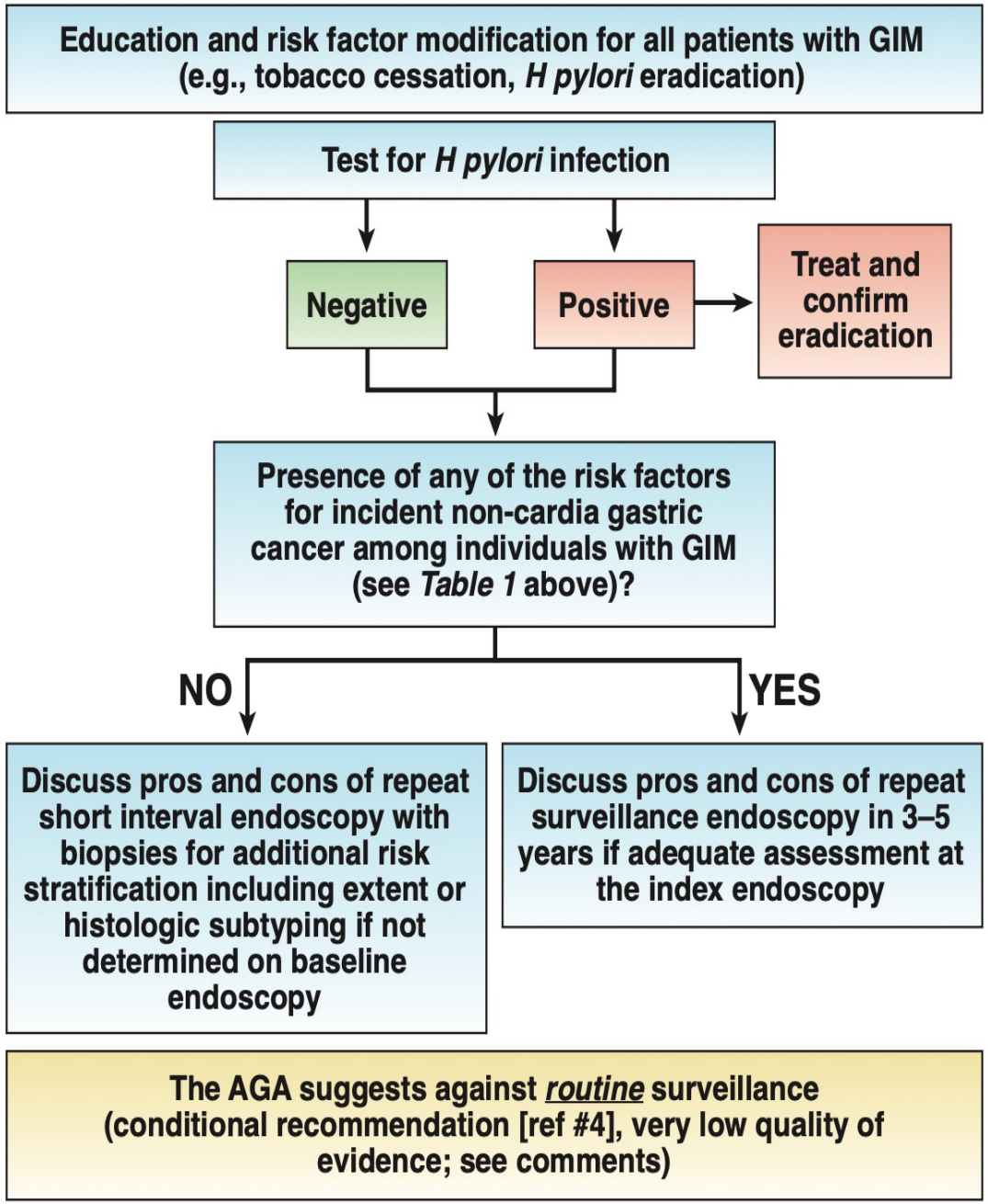
CLINICAL PRACTICE UPDATE | VOLUME 161, ISSUE 4, P1325-1332.E7, OCTOBER 01, 2021

AGA Clinical Practice Update on the Diagnosis and Management of Atrophic Gastritis: Expert Review



Shah et al. *Gastroenterology.* 2021;161(4):1325-1332.

Clinical decision algorithm for GIM management[4]



AGA Clinical Practice Guidelines on Management of Gastric Intestinal Metaplasia

Samir Gupta,[1,2] Dan Li,[3,4] Hashem B. El Serag,[5] Perica Davitkov,[6,7] Osama Altayar,[8] Shahnaz Sultan,[9] Yngve Falck-Ytter,[10,11] and Reem A. Mustafa[12]

Table 1: Factors associated with risk of incident gastric cancer in individuals with GIM

Evidence-based risk factors*		Relative risk of incident GC
H pylori eradication (vs persistent infection)	↓	RR 0.76 (95% CI: 0.36–1.61)
Family history of gastric cancer	↑	RR 4.53 (95% CI: 1.33–15.5)
Incomplete histologic subtype (vs complete)	↑	RR 3.33 (95% CI: 1.96–5.64)
Extensive GIM (vs limited)	↑	RR 2.07 (95% CI: 0.97–4.42)

Take Home Points

- There is marked geographic and racial/ethnic variation in gastric cancer incidence globally
  - US=low incidence country for GC overall, but there are identifiable high-risk groups (e.g. non-white races/ethnicities and early generation immigrants from high incidence countries)

- Noncardia GC (intestinal-type) develops as a stepwise progression of premalignant mucosal changes (AG, IM, dysplasia), with *H. pylori* as the most common primary trigger
  - When detected, *H. pylori* should be eradicated

- GIM is associated with a ~0.16% annual risk of incident GC, but some groups might have higher risk (e.g. extensive GIM, incomplete GIM, family history, persistent *H pylori* infection).
  - The overall prevalence of GIM in the US is ~5%, but there is variability
  - In the US, *routine* surveillance is not recommended, but in higher risk groups every 3 years should be considered

- A high-quality upper endoscopic exam (with appropriate mucosal sampling) is KEY.

- There is a critical need for high-quality evidence to inform recommendations re: GC screening and GIM surveillance in the US
  - Prospective trials comparing clinical outcomes of surveillance vs no surveillance, and optimal intervals; Risk stratification models

Thank you!

Questions?

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Updates in the Diagnosis and Management of Gastric Intestinal Metaplasia

American Foregut Society Annual Meeting

September 25, 2021

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