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ACG Clinical Guideline: Diagnosis and Management of Gastric Premalignant Conditions

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Gastric premalignant conditions (GPMC) are common and include atrophic gastritis, gastric intestinal metaplasia, dysplasia, and certain gastric epithelial polyps. GPMC have an increased risk of progression to gastric adenocarcinoma. Gastric cancer (GC) in the United States represents an important cancer disparity because incidence rates are 2- to 13-fold greater in non-White individuals, particularly early-generation immigrants from regions of high GC incidence. The US 5-year survival rate for GC is 36%, which falls short of global standards and is driven by the fact that only a small percentage of GC in the US is diagnosed in the early, curable stage. This document represents the first iteration of American College of Gastroenterology guidelines on this topic and encompasses endoscopic surveillance for high-risk patients with GPMC, the performance of high-quality endoscopy and image-enhanced endoscopy for diagnosis and surveillance, GPMC histology criteria and reporting, endoscopic treatment of dysplasia, the role of *Helicobacter pylori* eradication, general risk reduction measures, and the management of autoimmune gastritis and gastric epithelial polyps. There is insufficient evidence to make a recommendation on upper endoscopic screening for GC/GPMC detection in US populations deemed high-risk for GC. Surveillance endoscopy is recommended for individuals at high risk for GPMC progression, as defined by endoscopic, histologic, and demographic factors, typically every 3 years, but an individualized interval may be warranted. *H. pylori* testing, treatment, and eradication confirmation are recommended in all individuals with GPMC. Extensive high-quality data from US populations regarding GPMC management are lacking, but continue to accrue, and the quality of evidence for the recommendations presented herein should be interpreted with this dynamic context in mind. The GPMC research and education agendas are broad and include high-quality prospective studies evaluating opportunistic endoscopic screening for GC/GPMC, refined delineation of what constitutes "high-risk" populations, development of novel biomarkers, alignment of best practices, implementation of training programs for improved GPMC/GC detection, and evaluation of the impact of these interventions on GC incidence and mortality in the US.

KEYWORDS: gastric premalignant conditions (GPMC); gastric intestinal metaplasia (GIM); gastric atrophy; H. pylori; gastric cancer; clinical guideline

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INTRODUCTION

Gastric cancer (GC) is the leading infection-associated cancer and the fourth leading cause of cancer-related mortality globally, with more than 1 million new cases diagnosed and more than 768,000-related deaths in 2020 (1,2). There is marked variation in GC incidence globally, with the highest incidence rates reported in Eastern Asia, Eastern Europe, and Latin America (2). The overall United States is considered a low-incidence country with an age standardized incidence rate (ASIR) of 6.5 per 100,000 person-years with an estimated 26,890 new cases and 10,088-related deaths in 2023 (3). However, specific US populations, such as immigrants from high-GC incidence countries and certain non-White populations, have substantially higher GC incidence rates, with rates exceeding those for esophageal cancer and in some cases approaching those for colorectal cancer (4,5,230). Several studies and meta-analyses indicate that GC risk and mortality are maintained among immigrants from high-incidence to low-incidence countries (6), with incidence rates ranging from 2- to

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13-fold higher in specific non-White populations compared with non-Hispanic White individuals (7,8). GC ranks among the top 8 leading causes of cancer death in US Hispanic and Asian American populations, compared with ranking 15th in the overall US population (9). Based on 2020 data from the Pew Research Center, more than 40 million people living in the United States were born in another country, with over 70% immigrating from high-incidence GC countries (6). By 2065, it is estimated that Asian and Hispanic individuals, the immigrant groups with the highest GC risk, will comprise nearly 70% of the US population.

Although GC represents a major cancer disparity in the United States, this cancer has long been underrecognized as a public health concern. There is a growing body of evidence demonstrating that the burden of GC in high-risk populations is sufficiently high to justify prevention and early detection interventions. There is also evidence from US populations that *Helicobacter pylori* treatment is associated with reduced GC incidence (10,11). A combination of primary prevention strategies with the *H. pylori* "screen and eradicate" approach for reducing GC incidence, and secondary prevention strategies predominantly focused on early detection of GPMC/GC through endoscopic screening and surveillance of precancerous conditions, seems to be the optimal approach to reducing GC mortality as has been clearly demonstrated in Asian countries. However, the potential impact of implementation of precision strategies on GC incidence and mortality in US populations is unknown given the lack of national data.

Gastric adenocarcinoma, in most cases, is preceded by a typically asymptomatic precancerous cascade of discrete histopathological stages and is therefore amenable to surveillance—analogous to the practice of endoscopic and colonoscopic surveillance of esophageal and colorectal precancerous conditions, respectively. These histopathologic stages, referred to as the "Correa cascade," progress from normal mucosa and chronic gastritis to atrophic gastritis (AG), multifocal AG (MAG), gastric intestinal metaplasia (GIM), low-grade or high-grade dysplasia (LGD/HGD), and finally, adenocarcinoma. *H. pylori* is the dominant risk factor for noncardia gastric adenocarcinoma, the most common form of GC, with an attributable risk of 75%–89% (12). AG, GIM, and dysplasia constitute gastric premalignant conditions (GPMC). Early gastric cancer (EGC) is defined as adenocarcinoma that has not invaded past the submucosal layer, irrespective of lymph node involvement, and resection is typically curative (>95% 5-year overall survival) (13). This multifactorial process is driven by *H. pylori* virulence factors, the cumulative duration of *H. pylori* infection, host genetics and responses to *H. pylori* infection, and dietary and environmental factors, such as tobacco exposure. Although the multifactorial stages of the Correa cascade best align with intestinal GC, the principles herein apply to diffuse GC, albeit with an alternate balance of host genetic, microbial, and environmental factors. High-risk populations for GPMC parallel high-risk populations for GC. The risk factors for prevalent GPMC, GPMC progression to GC, and GC overlap and yet have differences, which are areas of active investigation.

The focus of this clinical guideline is the diagnosis and management of GPMC, with noncardia gastric adenocarcinoma being the primary outcome of interest unless otherwise stated. The diagnosis of GPMC in the US necessitates upper endoscopy, and thus, guidance regarding which asymptomatic individuals warrant upper endoscopy for GPMC and GC diagnosis and risk stratification is relevant. In this first iteration of the American College of Gastroenterology (ACG) clinical guideline on GPMC, we first discuss methodology, followed by a review of GC screening, diagnosis of GPMC, endoscopic and nonendoscopic management of GPMC, and then conclude with 2 special topic sections on the diagnosis and management of autoimmune gastritis (AIG) and gastric epithelial polyps (GEP) because respective subsets of these patients have an increased risk of GC. Extensive high-quality data from US populations regarding GPMC management are lacking but continue to accumulate; the quality of evidence for the recommendations presented herein should be interpreted with this dynamic context in mind.

METHODS

This document presents official recommendations from the ACG on the diagnosis, management, and surveillance of GPMC in adults. These guidelines are established to support clinical practice and suggest preferable approaches to a typical patient with a particular medical problem based on the currently available published literature. When exercising clinical judgment, particularly when treatments pose significant risks, healthcare providers should incorporate this guideline in addition to patient-specific medical comorbidities, health status, and preferences to arrive at a patient-centered care approach that maximizes benefit to patients and minimizes harm.

The guideline is structured in the format of statements that were considered to be clinically important by the content authors and were approved by the Governing Board. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process was used to assess the quality of evidence for each statement (Table 1) (14). The quality of evidence is expressed as high (we are confident in the effect estimate to support a particular recommendation), moderate, low, or very low (we have very little confidence in the effect estimate to support a particular recommendation) based on the risk of bias of the studies, evidence of publication bias, heterogeneity among studies, directness of the evidence, and precision of the estimate of effect (15). A strength of recommendation is given as either strong (recommendations) or conditional (suggestions) based on the quality of evidence, risks vs benefits, feasibility, and costs taking into account perceived patient-based and population-based factors (16). Furthermore, a narrative evidence summary for each section provides important definitions and further details for the data supporting the statements.

The ACG Practice Parameters Committee and ACG leadership identified and approved a group of experts in the area of GC and GPMC for the writing group. The writing group formulated PICO questions to guide the subsequent literature search, development of recommendation statements and key concepts, GRADE assessments, and the preparation of the full-guideline document. The PICO questions and subsequent recommendations were reviewed and approved by 2 GRADE methodologists. The authors, in consultation with a certified medical librarian, conducted an electronic search using MEDLINE, EMBASE, and the Cochrane Library through October 2023, with literature update through August 2024. The search was limited to English language and fully published articles. For each PICO question developed, the authors reviewed the existing literature, with a focus on studies of the highest quality of evidence (e.g., when available, systematic reviews and meta-analyses, followed by randomized controlled trials [RCTs], and followed by observational studies). In addition to the GRADE recommendations, the content authors generated key concept statements, which are not amenable to GRADE

Table 1. Grading of Recommendations, Assessment, Development, and Evaluation: strength of recommendations, quality of evidence, and implications for the patients and clinicians (14–16)

Strength of recommendation	Criteria
	Factors influencing the strength of the recommendation include the quality of the evidence, clinical-reported and patient-reported outcomes, risk of harm, and costs
Strong	Strong recommendations are offered when the desirable effects of an intervention clearly outweigh the undesirable effects Implications from a patient and clinician perspective: • Patients: Most people in this situation would want the recommended course of action, and only a small proportion would not • Clinicians: Most patients should receive the recommended course of action
Conditional	Conditional recommendations are offered when trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced Implications from a patient and clinician perspective: • Patients: Some individuals would want the suggested course of action, whereas others may not. Appropriate discussion regarding pros/cons/alternatives is appropriate to come to a patient-specific decision • Clinicians: A shared decision-making model through a discussion regarding the evidence and alternatives is appropriate, taking into consideration patients' values and preferences
Quality of evidence	**Criteria**
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confident in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

assessment. We prioritized evidence from US populations, and where US data were limited or lacking, we relied on high-quality data from non-US populations, which is acknowledged in the main text where relevant. Tables 2 and 3 summarize the recommendations and key concept statements, respectively. Table 4 details hereditary GC risk factors. The following topics are beyond the scope of this guideline: management of hereditary GC syndromes, GIM of the cardia, nonadenocarcinoma GC, gastric mucosa-associated lymphoid tissue lymphoma, therapeutic management of GC including endoscopic resection, and postdiagnostic management of GC other than *H. pylori* eradication.

This is the first iteration of this ACG guideline, and it is expected that the quality of evidence informing the respective recommendations will significantly increase. We anticipate and hope that robust data from the US will continue to accumulate and inform future iterations of this topic guideline, especially data related to opportunistic screening, risk stratification, and outcomes of endoscopic surveillance.

SCREENING OF GC AND GPMC

Recommendations: GC screening

1. We suggest against routine screening with upper endoscopy for GC and GPMC in the general population in the United States (Very low quality of evidence, conditional recommendation).
2. We cannot make a recommendation on opportunistic screening for GC and GPMC with upper endoscopy in individuals considered high-risk for GC based on immigration status, race and ethnicity, and certain environmental factors due to insufficient direct evidence from US populations (Insufficient evidence, no recommendation).

Risks factors for GC in US populations

The United States is considered a low-intermediate GC incidence country overall, with an ASIR of 6.5 per 100,000 person-years. However, in certain US populations, the incidence rates of GC are 2–13 times higher vs White individuals (230). Multiple factors are associated with an increased risk of GC, including precancerous gastric mucosal changes (e.g., MAG, GIM, and dysplasia), non-White race or Hispanic ethnicity, early-generation immigrant from a high-GC incidence region, family history of GC, specific inherited cancer syndromes, persistent *H. pylori* infection, tobacco smoking, and possibly AIG (6,8,17,18). Other than *H. pylori* infection, the attributable risk of these factors for GC alone and in combination, as well as the interaction with other environmental factors such as smoking and diet, is not known.

Race, ethnicity, and immigration history

GC varies substantially by race and ethnicity. GC ranks among the top 8 leading causes of cancer death in US Hispanic and Asian American populations, compared with ranking 15th in the overall US population (9). Compared with non-Hispanic White individuals, East Asian and Pacific Islander, Black, Hispanic, and American Indian and Alaska Native (AIAN) individuals have significantly higher incidence of noncardia gastric adenocarcinoma (NCGA) (7,9). A population-based study using California Cancer Registry data reported that age-standardized and sex-standardized incidence of NCGA among individuals of 50 years or older (i.e., a screening-age population) was 1.8- to 13.3-fold higher in the most populous non-White groups compared with non-Hispanic White individuals (5). In fact, the incidence rates of NCGA in certain groups, such as Japanese Americans (33.6 [27.0–41.4] per 100,000 person-years) and Korean Americans (70.0 [60.5–80.5] per 100,000 person-years) were similar or considerably higher than the incidence rates of colorectal cancer among the general US population (230).

Table 2. Recommendations for the management of GPMC

GC screening
1. We suggest against routine screening with upper endoscopy for GC and GPMC in the general population in the United States (Very low quality of evidence, conditional recommendation)
2. We cannot make a recommendation on opportunistic screening for GC and GPMC with upper endoscopy in individuals considered high-risk for GC based on immigration status, race, and ethnicity, and certain environmental factors due to insufficient direct evidence from US populations (Insufficient evidence, no recommendation)
GPMC noninvasive diagnosis
3. We suggest against the use of noninvasive biomarkers for the purpose of GPMC or GC screening or surveillance in the United States (Very low quality of evidence, conditional recommendation)
GPMC endoscopic diagnosis
4. In patients undergoing upper endoscopy, we recommend a high-quality endoscopic evaluation of the stomach to identify GPMC (or GC). This includes achieving adequate mucosal visualization with cleansing and insufflation, visual station mapping, photodocumentation of anatomic landmarks and any abnormalities, and adequate gastric evaluation time (Low quality of evidence, strong recommendation)
5. In patients undergoing upper endoscopy for evaluation of GPMC, we suggest the use of HDWLE and IEE for gastric examination (Low quality of evidence, conditional recommendation)
GPMC histologic diagnosis
6. In individuals at increased risk for or with suspected GPMC or GC, we suggest systematic gastric sampling according to the updated Sydney biopsy protocol. At minimum, 2 separate containers should be used for the antrum/ incisura, and for the corpus. Targeted biopsies of any other mucosal abnormalities should be placed in additional separate containers (Low quality of evidence, conditional recommendation)
7. In individuals with GIM, we suggest that the histological subtype of GIM (incomplete, complete, and mixed) be reported for the purpose of GPMC risk stratification and informing surveillance (Low quality of evidence, conditional recommendation)
8. In individuals with GIM, we suggest that the anatomic extent and severity of GIM be reported for the purpose of risk stratification and informing GPMC surveillance. Anatomically limited GIM is confined to the antrum and incisura, whereas anatomically extensive GIM also involves the corpus. The severity refers to the proportion of atrophy or GIM in individual biopsies from each compartment (antrum, incisura, and corpus) (Very low quality of evidence, conditional recommendation)
GPMC surveillance
9. In individuals with GIM who are considered high risk for GC, we suggest endoscopic surveillance at 3-year intervals. High-risk groups include individuals with GIM and at least one of the following criteria: (i) High-risk GIM histology: • Incomplete GIM histological subtype vs complete subtype • Corpus-extension, defined as corpus involvement also with antrum or incisura involvement (ii) Any GIM histology with one of the following risk factors for GC: • Family history of GC in a first-degree relative • Foreign-born, with emigration from a high-incidence nation • High-risk race or ethnicity, including East Asian, Latino/a, Black, and AIAN individuals (Very low quality of evidence, conditional recommendation)
10. In individuals with severe GIM or AG in biopsies of the antrum or corpus, we suggest endoscopic surveillance at 3-year intervals (Very low quality of evidence, conditional recommendation)
11. In individuals with low-risk GIM or atrophy, we suggest against endoscopic surveillance. Low-risk groups include (i) Complete type GIM, without evidence of incomplete GIM (ii) Complete GIM of focal anatomic extent that is confined to the antrum (iii) None of the "high-risk" clinical criteria listed in Recommendation 9 above (iv) AG which is mild in severity (Very low quality of evidence, conditional recommendation)
Endoscopic management of dysplastic GPMC
12. In patients with dysplasia (IND, LGD, and HGD) and visible margins, we suggest endoscopic resection in clinically appropriate patients (Low quality of evidence, conditional recommendation)
13. In patients with dysplasia (IND, LGD, and HGD) without visible margins, we suggest a repeat endoscopic evaluation with HDWLE and IEE by an experienced endoscopist (Low quality of evidence, conditional recommendation)
14. In patients appropriate for endoscopic resection of dysplasia, particularly endoscopic submucosal dissection, we recommend referral to a high-volume center with appropriate expertise in the diagnosis and therapeutic resection of gastric neoplasia (Low quality of evidence, strong recommendation)

Table 2. (*continued*)

15. In patients with confirmed complete resection of dysplasia, we suggest endoscopic surveillance. We recommend surveillance examinations be performed by an experienced endoscopist and using HDWLE and IEE, with biopsies according to the systematic biopsy protocol in addition to targeted biopsies (Low quality of evidence, strong recommendation)
GPMC nonendoscopic management
16. We recommend testing for *Helicobacter pylori* (and eradication treatment if positive) in patients with GPMC and resected early GC to reduce the risk of progression to GC and metachronous early GC, respectively (Moderate quality of evidence, strong recommendation)
17. We do not suggest the use of aspirin, nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, or antioxidants for individuals with GPMC for the purpose of GC chemoprevention (Very low quality of evidence, conditional recommendation)
Autoimmune gastritis
18. Among individuals diagnosed with AIG, we recommend assessment for *H. pylori* infection with a nonserological test, eradication treatment if positive, and posttreatment testing to confirm eradication (Low quality of evidence, strong recommendation)
19. There is insufficient evidence to make a formal recommendation on endoscopic surveillance in individuals with AIG. Given the increased risk of type 1 neuroendocrine tumors and the possible increased risk of GC, individualized surveillance may be considered (Low quality of evidence, conditional recommendation)
Gastric epithelial polyps
20. We recommend endoscopic resection of all gastric adenomas, regardless of size, to exclude and prevent dysplasia and early GC. For adenomas that are not amenable to endoscopic resection, we recommend referral for surgical resection, if clinically appropriate (Low quality of evidence, conditional recommendation)
21. We could not make a recommendation on the endoscopic resection of all hyperplastic polyps greater than 10 mm in size based on the current evidence (Insufficient evidence, no recommendation)
22. In individuals with GEP, with the exception of fundic gland polyps, we recommend systematic gastric biopsies (e.g., updated Sydney protocol) be obtained from the surrounding flat mucosa given the high prevalence of GPMC, *H. pylori* infection, and AIG in these patients (Very low quality of evidence, conditional recommendation)

AIAN, American Indian and Alaska Native; AIG, autoimmune gastritis; GC, gastric cancer; GEP, gastric epithelial polyps; GIM, gastric intestinal metaplasia; GPMC, gastric premalignant condition; HDWLE, high-definition white light endoscopy; HGD, high-grade dysplasia; IEE, image-enhanced endoscopy; IND, low-grade dysplasia; LGD, low-grade dysplasia.

Immigrant populations contribute in part to the race and ethnicity disparity of GC incidence in the United States. GC incidence varies widely across different nations and geographic regions, with the highest incidence regions being East Asia, Eastern Europe, and Central and Andean South America (2). A systematic review and meta-analysis reported significantly higher incidence and mortality of GC among first-generation immigrants from high-incidence to low-incidence geographic areas, with the pooled relative risk (RR) for all types of GC (measured as standardized incidence ratio) 1.66 (95% confidence interval [CI] 1.52–1.80) for men and 1.83 (95% CI 1.69–1.98) for women, and for NCGA specifically, 1.80 (1.65–1.95) for men and 1.62 (1.47–1.76) for women (6) (see Supplement 1, Supplementary Digital Content 1, http://links.lww.com/AJG/D556 for additional discussion).

Family history

Individuals with a family history of GC have 2- to 10-fold higher risk of GC compared with individuals without a family history, based on observational studies (19). Multiple factors may contribute to the familial aggregation of GC, such as shared genetic predisposition, shared *H. pylori* infection and strains, shared environmental factors (lifestyle, diet, and cultural factors), and combinations thereof (19). Overall, approximately 10% of patients with GC have a positive family history, while only about 1%–3% are related to inherited cancer syndromes; although, the proportion may be greater with the recent identification of the importance of pathogenic germline variants such as the hereditary homologous recombination deficiency (e.g., breast cancer gene [BRCA]) (20,21). Based on one study, patients with GIM and a first-degree family history of GC had 4.5-fold higher odds (odds ratio [OR] 4.53, 95% CI 1.33–15.46) of GC compared to patients with GIM but without a family history of GC (22). In a recent prospective single-center pilot screening study from California, among individuals with a family history of GC in a first-degree relative ($n = 61$; mean age 59 years old), 27 (44%) had GIM and 4 (7%) had dysplasia on screening endoscopy (23). Although it is challenging to parse out shared genetic vs shared nongenetic contributors, the increased risk of GPMC and GC among individuals with a first-degree family history of GC provides rationale for considering this population for endoscopic screening on an individual basis.

Inherited cancer syndromes with increased risk of GC

Individuals who carry pathogenic variants of GC susceptibility genes are at a substantially higher lifetime risk of GC. There are 2 groups of hereditary cancer syndromes with increased GC risk: (i) Hereditary GC syndromes: hereditary diffuse GC, familial intestinal GC, and gastric adenocarcinoma with proximal polyposis of the stomach and (ii) Hereditary syndromes with an increased GC risk: Lynch syndrome, hereditary gastrointestinal (GI) polyposis syndromes (familial adenomatous polyposis [FAP], Peutz-Jeghers syndrome, juvenile polyposis, and *MUTYH*-associated polyposis), hereditary breast and ovarian cancer syndrome, and Li-Fraumeni syndrome, and hereditary homologous recombination deficiency (*BRCA1*, *BRCA2*, *PALB2*, and *ATM*) particularly in the setting of *H. pylori* infection (Table 4). Patients

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Table 3. Key concepts for the management of GPMC

GC epidemiology and screening
• The epidemiologic and biologic risk factors overlap, and yet are distinct, for the 3 outcomes of GPMC prevalence, GC incidence, and GPMC to GC progression. Mechanistic studies and novel biomarkers are needed to improve our understanding and surveillance paradigms for GPMC to GC progression
• There are no randomized clinical trials from the United States nor other populations evaluating the efficacy of GC screening. The large observational studies from East Asia and meta-analyses of these studies demonstrate that endoscopy for GC screening is associated with a substantial reduction in GC mortality, and a 5-yr survival of nearly 70%. This is primarily driven by the increased detection of early-stage GC (eligible for endoscopic resection), rather than a decrease in incident GC.
• Endoscopic screening should be considered in persons with a family history of GC (first-degree relative) on an individualized basis. Endoscopy would start at age 45–60 or 10 years before the diagnosis of GC in the youngest affected family member. These individuals should be screened for *H. pylori* and eradicated if positive.
• First generation immigrant populations contribute to the race and ethnicity disparity of GC incidence in the US. Endoscopic screening should be considered on an individualized basis, with shared decision-making, in the highest-risk individuals. GC incidence varies widely across nations and geographic regions, with the highest incidence regions being East Asia, Eastern Europe (including western Russia), and Central/South America. The South America high-incidence area encompasses the Andean region from Colombia to Chile. Immigrant generation and level of acculturation affect risk. These individuals should be screened for *H. pylori* and eradicated if positive.
GPMC endoscopic and histologic diagnosis
• A high-quality endoscopy examination of the gastric compartment has 5 main components: (i) use of HDWLE; (ii) adequate gastric distension using insufflation (CO_2 preferably, or air) to flatten the gastric folds and expose the gastric mucosa adequately; (iii) mucosal cleansing to clear all debris, mucous and bubbles; (iv) standard photodocumentation; and (v) adequate gastric inspection time. Gastric examination time and photodocumentation are surrogate quality metrics for the gastric evaluation. The 2–3 min upper endoscopy, especially for patients with GPMC, falls short of the standard of care.
• HDWLE and IEE (e.g., narrow band imaging, blue laser imaging, etc) are appropriate for individuals with at increased GC risk, those with suspected GPMC or GC during endoscopy, and those undergoing GPMC surveillance. Near focus and optical zoom are helpful but not mandatory for GPMC detection.
• The coordination between the gastroenterologist and pathologist for pathology reporting is critical for delineation of the patient GPMC surveillance plan. This coordination is needed at the local level ("local advocates"), as well as the national society level. Pathology report details should include information specific to stomach location (e.g., antrum, incisura, and corpus), AG and GIM severity (biopsy-specific), AG and GIM extent (e.g., antrum and corpus), the subtype of GIM (e.g., complete, incomplete, mixed), severity of dysplasia (IND, LGD, HGD), and presence/absence of *H. pylori* organisms, at a minimum.
• The diagnostic challenges for GPMC and dysplasia include sampling error during biopsies (e.g., AG and GIM patchy multifocality), the interobserver variability among pathologists, particularly for IND and LGD, and the variable training among gastroenterologists for the detection of GPMC and early GC.
GPMC endoscopic surveillance
• Delineation of GPMC surveillance intervals requires further study in the US. Patients with multiple risk factors for GC may be considered for shorter than 3-yr intervals. For example, an individual with extensive GIM and with a family history of GC may be considered for a 1-2-yr surveillance interval. Patient-physician decision-making for GPMC surveillance is appropriate in these cases
• We suggest against performing routine repeat endoscopy within 12 months in individuals with nondysplastic GPMC for the purpose of risk stratification unless there are concerns regarding the quality of the endoscopy or adherence to the Sydney biopsy protocol
• We acknowledge that some studies suggest that White race, ethnicity, and country of origin are important risk factors for prevalent GPMC and GC; yet, these factors are not proven to be independent predictors of progression, although US and global studies are limited in this domain. However, endoscopic surveillance of individuals with GPMC who identify as a high-risk race or ethnicity, or who emigrated from a high-incidence region, should be recommended for 3-yr endoscopic surveillance given the substantial increased risk of GC in these groups
• In patients with IND or LGD without visible lesions, the rates of progression are modest yet measurable. The surveillance intervals are proposed but have not been evaluated in prospective studies. We suggest a repeat endoscopic exam in 12 months if advanced neoplasia was confidently ruled out. Referral to an endoscopist with expertise in diagnosing and ideally resecting gastric neoplasia is reasonable.
• Patients with HGD without visible mucosal abnormalities have a high probability of either already having a prevalent GC or progressing to GC within a short time frame. A repeat endoscopic exam within 3 months with an endoscopist with expertise in diagnosing and ideally endoscopically resecting gastric neoplasia is suggested.
• In patients with endoscopically resected dysplastic lesions, the optimal postresection surveillance interval has not been investigated in prospective studies. Shorter intervals may be warranted in patients with additional risk factors for synchronous or metachronous GC
Autoimmune gastritis
• AIG is considered a gastric preneoplastic condition because, by definition, there is corpus atrophy, either with or without GIM. AIG is associated with an increased risk of well-differentiated neuroendocrine tumors of enterochromaffin-like cells (also termed type I gastric carcinoid tumor) and possibly gastric adenocarcinoma.
• The overlap of *H. pylori*-associated GPMC and AIG is common, and thus, the same risk stratification parameters apply, as does testing for active *H. pylori* infection and eradication treatment if positive. Individuals with AIG are also established to be at risk for type I carcinoids. In patients with AIG, surveillance with HD-WLE and IEE should be considered. The interval is determined based on GPMC risk stratification parameters (e.g., family history of GC), which should be individualized
Gastric epithelial polyps
• The malignant potential of GEP is based on histology, polyp size, and the presence of specific polyposis syndromes. All patients with hyperplastic or adenomatous GEP should have standard Sydney protocol biopsies and testing for active *H. pylori* infection, given the increased prevalence of GPMC in this setting
• There is insufficient evidence to recommend endoscopic resection of hyperplastic polyps >10 mm at the index endoscopy. An individualized approach is warranted, with consideration of resection or biopsies, and 12 month surveillance, as clinically appropriate.

AG, atrophic gastritis; AIG, autoimmune gastritis; GC, gastric cancer; GEP, gastric epithelial polyps; GIM, gastric intestinal metaplasia; GPMC, gastric premalignant condition; HDWLE, high-definition white light endoscopy; HGD, high-grade dysplasia; IEE, image-enhanced endoscopy; IND, low-grade dysplasia; LGD, low-grade dysplasia.

Table 4. Hereditary and genetic gastric cancer syndromes

Familial gastric cancer syndromes
• Hereditary diffuse gastric cancer
• *CDH1* germline mutations (E-Cadherin)
• Familial intestinal gastric cancer
• Gastric cancer and proximal polyposis of the stomach
Hereditary syndromes with increased gastric cancer risk
• Gastrointestinal polyposis syndromes with increased gastric cancer risk
• Familial adenomatous polyposis, Peutz-Jeghers syndrome, juvenile polyposis, *MUTYH*-associated polyposis
• Cancer syndromes with increased gastric cancer risk
• Lynch syndrome, hereditary breast and ovarian cancer syndrome, and Li-Fraumeni syndrome
• Hereditary homologous recombination deficiency (e.g. *BRCA1, BRCA2*)

Common germline gene variant syndromes are important regarding the biology; however, to date, they are not clinically actionable. Common gene variants with gastric cancer risk are often identified in genome-wide association studies, which are limited in number (e.g., Asia, Europe, and Latin America). In addition, there are gene variants which influence the *H. pylori*-environmental interactions, and specifically the inflammatory response (e.g., proinflammatory cytokine genotypes).

with a family history suggestive of hereditary cancer should be referred to Genetic Counseling, and potential endoscopic screening should be individualized based on the syndrome-specific guidelines and patient preferences (24–27).

Screening for GPMC and GC in high-risk US populations: US evidence, a work in progress

Routine screening with upper endoscopy for GC and GPMC in the low-risk general US population is not indicated given the overall low-to-moderate incidence, the lack of cost-effectiveness, and the absence of evidence. Although focused screening of high-risk populations in the United States may address the GC cancer disparity, there is a lack of evidence in the United States to make a recommendation. In addition to the epidemiologic data identifying high-risk US populations, the current evidence base in the US for screening is mostly limited to cost-effectiveness studies and indirect evidence from regions with screening programs, primarily in East Asia.

The epidemiological evidence suggests that high-risk groups who may benefit from screening include those with a family history of GC, specific hereditary syndromes, foreign-born immigrants from high-incidence regions, and US populations with a high incidence of GC, including East Asian individuals, Latino/a groups, Black individuals, and AIAN individuals. Cancer screening and surveillance specific to high-risk race and ethnic populations is proposed to be both ethical and efficacious, particularly with respect to GC (28), at least until accurate biological biomarkers are available. The age of 45–60 would be reasonable given that the prevalence of GPMC is significant by age 45 in high-risk populations, and also since this aligns with the colorectal screening recommendations. Persons with multiple risk factors may also be appropriate to consider, for example, male sex, smoker, and with *H. pylori* infection (29). Examples of nascent screening studies in high risk groups include combined *H. pylori*-fecal immunochemical testing and opportunistic endoscopy with screening colonoscopy.

There is consistent evidence in the form of large observational epidemiological studies identifying populations in the United States who are at increased risk for GPMC and GC, and among whom the rates of GC mirror rates in populations were GC screening studies have been conducted (5,30,31). However, there are no large US-based observational studies or RCTs directly evaluating the impact of screening for GC vs no screening in these populations. There are also no relevant studies of GC screening vs no screening from other global regions with heterogeneous populations as in the United States, although notably, some Western countries do advocate for opportunistic endoscopic screening (29,32–34,231). The most robust, albeit indirect, evidence comes from studies conducted in East Asia, where GC screening has been consistently associated with substnatially reduced GC-related mortality and increased 5-year survival (see below).

Only 1 clinical trial from the United States has evaluated the impact of GC screening in a high-risk population, and this was a small prospective pilot screening program conducted between 2017 and 2020 within the Kaiser integrated health system (23). Of 61 individuals with a first-degree family history of GC, 44% had GIM and 7% had LGD, consistent with the classification as an at-risk group.

The majority of evidence demonstrating the impact of endoscopic GC screening on early GC detection is from Asia. Multiple observational studies from East Asia have unequivocally demonstrated mortality benefits associated with endoscopic GC screening (35–40). In the study analyzing data from the Korean National Cancer Screening Program, which included more than 39 million adults of older than 40 years who underwent screening endoscopy between 2007 and 2016, the sensitivity of endoscopy for GC ranged from 66% to 69% (vs 17%–24% for radiographic screening) and with specificity consistently exceeding 99% (41). The mortality data from this South Korea program revealed that organized GC screening among individuals aged ≥40 years was associated with 47% (OR 0.53, 95% CI 0.51–0.56) lower GC mortality compared with no screening (35).

In the meta-analysis by Zhang et al (42), which included 342,013 individuals from Asian countries, endoscopic screening was associated with an overall 40% RR reduction in GC mortality (RR 0.60, 95% CI 0.49–0.73); however, endoscopic screening was not associated with lower GC incidence, indicating that early detection of gastric neoplasia is the primary driver of the observed mortality and survival benefits. As further support, data from the Korean National Cancer Screening Program demonstrated that screening endoscopy was associated with 2-fold higher odds (OR

2.10, 95% CI 1.90–2.33) of diagnosing localized GC compared with individuals who were never screened (43). With implementation of GC screening in Japan and South Korea, now at least 50% of GC are early-stage and only 12%–16% are metastatic at the time of diagnosis, which is in stark contrast to <30% being diagnosed as early-stage before implementation of screening in these countries (4). This has translated to current 5-year overall survival rates for GC in South Korea and Japan >60%–70%, whereas the 5-year overall survival was about 30% before implementation of these programs (44–46). In the United States, nearly 40% of GC are metastatic at the time of diagnosis, and only 15% diagnosed in the curative early-stage GC (47). The current 5-year GC survival rate in the United States is 36%, comparable with the prescreening implementation rates in South Korea and Japan.

These non-US data provide evidence that systematic screening among individuals from high-risk populations is associated with markedly improved GC mortality and survival, related to higher proportion of cancer diagnosed in an early, curative stage. However, the data regarding endoscopic screening for GPMC and GC in US populations are essentially nonexistent, which precludes a specific recommendation for GC screening in US high-risk populations.

Cost-effectiveness of risk-based screening for GPMC and GC in the United States

Cost-effectiveness studies provide additional indirect evidence for endoscopic screening among at-risk populations in the United States. This complements a large body of evidence demonstrating the cost-effectiveness of endoscopic GC screening in East Asian countries and Portugal (48–52). Saumoy *et al.* assessed the cost-effectiveness of screening for GC using upper endoscopy bundled with screening colonoscopy, in the US screening-age population, stratified by race and ethnicity (53). The study found that endoscopy starting at age 45–50 years with continued surveillance when GIM or more advanced pathology is diagnosed was cost-effective for East Asian ($71,451/quality adjusted life years [QALYs]), Hispanic ($76,070/QALY), and non-Hispanic Black ($80,278/QALY) individuals, but not for non-Hispanic White individuals ($122,428/QALY). By contrast, biennial esophagogastroduodenoscopy for screening irrespective of histologic findings was not cost-effective. Using the same screening strategies (vs no screening), Shah et al demonstrated the cost-effectiveness of endoscopic GC screening among the most populous East Asian American populations in the United States disaggregated by country of birth (54). One-time endoscopy at the time of screening colonoscopy, with continued surveillance if GIM or more advanced pathology was diagnosed, demonstrated the lowest incremental cost-effectiveness ratios among Chinese, Japanese, and Korean Americans (all <$75,000/QALY). The above studies examined bundled endoscopy with screening colonoscopy; thus, the findings cannot necessarily be extrapolated to those who undergo noninvasive colorectal cancer screening or those who opt out of colorectal cancer screening.

In summary, direct, high-quality US-based data in the form of randomized trials or large observational studies evaluating the impact of screening on patient-important outcomes in US populations are nonexistent. We acknowledge the extensive evidence from specific Asian countries demonstrating the benefits of endoscopic screening in increasing the detection of early-stage GC and reducing GC-related mortality in populations with high GC burden. The panel cannot at this time make a recommendation on screening for GPMC and GC with upper endoscopy in high-risk US populations given the lack of robust US evidence, the invasiveness and risks of upper endoscopy, and projected costs (including ill-defined insurance coverage). Endoscopic screening should be considered in individuals with certain hereditary genetic syndromes or a first-degree family history of GC on an individualized basis (e.g., starting at the age 10 years before the youngest first-degree family member with GC). The deficiency of US-based studies in this area delineates a critical knowledge gap with important public health implications given the current and growing proportion of US adults at increased risk for GC, which define this cancer disparity.

DIAGNOSIS OF GPMC

Noninvasive evaluation of GPMC

Recommendations: GPMC noninvasive diagnosis

3. We suggest against the use of noninvasive biomarkers for the purpose of GPMC or GC screening or surveillance in the United States (Very low quality of evidence, conditional recommendation).

Noninvasive biomarkers are a desirable and potentially cost-effective approach for identifying individuals who would benefit from upper endoscopy to detect GPMC/GC and resect, if appropriate. Candidate noninvasive tests that have been evaluated include *H. pylori* IgG, *H. pylori* CagA or VacA (strain-specific virulence factors), pepsinogen I, pepsinogen II, gastrin, gastrin-17, C-reactive protein, migration inhibitory factor 1, trefoil factor family 3, reprimo, or a combination of these (55,56). Blood multiomic technologies are under study and may offer an appealing approach. Overall, and particularly in the United States, definitive studies are lacking regarding efficacy of noninvasive biomarkers for the purpose of screening or surveillance for GPMC and GC. Based on a review of the evidence, which is summarized in Supplement 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/D556), currently there are no noninvasive biomarkers that would (i) replace upper endoscopy or (ii) serve as a method to discriminate subjects at low vs high risk of GPMC, GPMC progression, or GC and warrant referral for upper endoscopy.

Endoscopic evaluation of GPMC

Recommendations: GPMC endoscopic diagnosis

4. In patients undergoing upper endoscopy, we recommend a high-quality endoscopic evaluation of the stomach to identify GPMC. This includes achieving adequate mucosal visualization with cleansing and insufflation, visual station mapping, photodocumentation of anatomic landmarks and any abnormalities, and adequate gastric evaluation time (Low quality of evidence, strong recommendation).
5. In patients undergoing upper endoscopy for evaluation of GPMC, we suggest the use of high-definition white light endoscopy and image-enhanced endoscopy for gastric examination (Low quality of evidence, conditional recommendation).

Quality endoscopy considerations

The endoscopic and histopathologic evaluations are the core of GPMC diagnosis and risk stratification. The primary goal of upper endoscopy is the early detection of gastric dysplasia and cancer, ideally at a stage for which endoscopic resection is curative. The secondary goal is the diagnosis and assessment of the severity and extent of AG and GIM to identify the individuals who would benefit from ongoing surveillance for early dysplasia/cancer detection purposes. This section is focused on the endoscopic and histological assessment and diagnosis of GPMC, while the same core principles of the high-quality endoscopic examination apply to endoscopy in general (57,58).

Individuals who warrant endoscopy with high-definition white light endoscopy (HDWLE) and image-enhanced endoscopy (IEE), as well as systematic biopsy sampling, are (i) individuals with known GPMC or prior GC with indications for surveillance, (ii) individuals at increased risk for GPMC or GC (e.g., family history and early-generation immigrant from high-incidence region), and (iii) individuals with an endoscopic appearance concerning for GPMC.

A high-quality evaluation of the entire gastric mucosa is the foundation for identifying GPMC and GC, noting that 4.7%–11.3% of neoplastic lesions are missed on upper endoscopy completed within 3 years of GC diagnosis (59–61). Neoplastic lesions are often subtle and endoscopic miss rates even approach 25%, particularly in less-experienced endoscopists. Complete mucosal evaluation is best achieved by using insufflation to adequately distend the gastric folds, mucosal cleansing, and spending sufficient time evaluating all gastric areas ("stations") (Figure 1). Although adequate mucosal cleansing can often be achieved with water irrigation alone, the use of mucolytic and defoaming agents (i.e., simethicone and N-acetylcysteine) significantly improves mucosal visibility scores and reduces total procedure time (62–64). Standardized cleansing scores are available (65,66). The quality of visualization of the gastric mucosa should be routinely documented in the endoscopic report, analogous to reporting bowel preparation quality in colonoscopy reports.

Training endoscopists to perform a detailed gastric evaluation and recognize and classify lesions significantly increases the detection of GPMC and reduces the time to referral for endoscopic resection (67,68). Surrogate measures for a quality endoscopic evaluation include endoscopic visualization time and photodocumentation, which are analogous to documentation of withdrawal time and photodocumentation of landmarks during colonoscopy. Retrospective data from high-incidence regions demonstrate that GPMC detection rates increase after detailed gastric evaluation (e.g., 6–7 minutes) conducted after mucosal cleansing is completed, independent of the endoscopist training level (29,69–72).

Photodocumentation of each of the gastric stations and any abnormal findings is important to structure the endoscopic examination. Additional reasons include correlation with histological findings and monitoring the findings over time for surveillance or referral for endoscopic treatment. Photodocumentation protocols in East Asia and Latin America generally recommend photodocumentation of at least 20 stations (73). Observational studies suggest that such protocols alone significantly increase the detection of GPMC in high-risk patients, although the data are mixed (67,74). When extrapolating this evidence to the overall low-incidence US population and considering time feasibility, we advocate for, at minimum, photodocumentation of 6 anatomic stations: 3 antegrade images of the corpus-greater curvature, corpus-lesser curvature, and antrum-pylorus, and 3 retrograde images of the incisura, corpus-greater curvature, and fundus-cardia (57,58,73). Mucosal abnormalities warrant dedicated images.

High-definition endoscopy and image-enhanced endoscopy

High-definition (HD) is defined as an image with more than 650 to 720 lines of resolution and requires all components of the system (endoscope chip, processor, transition cables, and

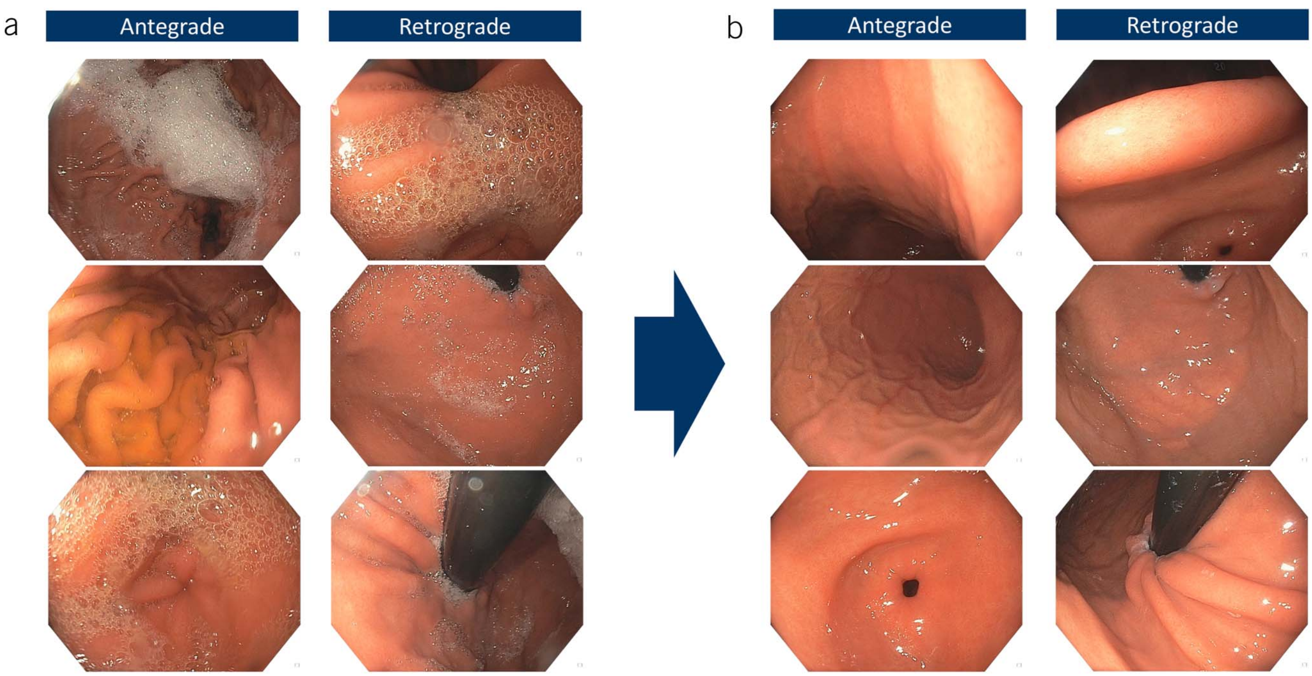

Figure 1. Systematic stomach endoscopic evaluation with cleansing, insufflation, and photodocumentation. Inadequate (**a**) and high quality (**b**) visualization.

monitor) to be HD compatible. All major endoscopy manufacturers now offer HD gastroscope systems in the United States (Olympus 190 series; Pentax 2990i and 2790i; Fujinon 590 series) (75). HDWLE systems offer electronic magnification of ×1.5 or ×2.

Chromoendoscopy is achieved with topical dyes or "virtually" with modifications of light wavelength or computer image processing herein, labeled as IEE. Topical dye chromoendoscopy evaluates the mucosa after spraying Lugol iodine or indigo carmine. Virtual chromoendoscopy is the most practical for use in the United States. The optical image processing uses 1 of 3 commercially available modalities: narrow band imaging (NBI) from Olympus, Fujinon Intelligent Color Enhancement from Fujinon (including blue laser imaging (BLI) and linked color imaging (LCI), and iScan from Pentax. Emerging endoscopic technologies and the potential environmental impact of a GPMC surveillance program are reviewed in Supplement 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/D556).

Recognition and categorization of GPMC

Endoscopy can identify GPMC as visible nonpolypoid or polypoid mucosal changes, or as "nonvisible" mucosal changes that are identified incidentally on biopsies collected for other purposes (e.g., evaluation of dyspepsia). Three mucosal changes should be identified endoscopically: (i) AG, (ii) GIM, and (iii) dysplasia. Endoscopy alone cannot reliably differentiate between dysplasia (i.e., indefinite for dysplasia [IND], LGD, HGD) and early carcinoma, and histologic confirmation is needed (76). Gastric polyps and polypoid lesions are discussed separately.

We suggest using HDWLE and virtual IEE to evaluate the gastric mucosa to optimize the identification and characterization of GPMC. Herein, we use the term "HDWLE with IEE" to refer to the common US setting with the use of HDWLE with NBI or BLI, with or without optical zoom (77). We note that NBI/BLI in the stomach has inadequate illumination for a wide-field view, as compared with the narrow-lumen esophagus (78). NBI is therefore less efficacious for detecting, as opposed to characterizing gastric lesions. This is true for many optical biopsy technologies (e.g., Raman and confocal endomicroscopy), and contrasts with IEE with LCI, that uses short wavelengths to produce bright images even for distant views (78).

The first step in recognizing GPMC is becoming familiar with the appearance of normal gastric folds, pit patterns, and the regular arrangement of collecting venules (Figure 2). Gastric folds are typically 5–10 mm thick in the fundus and body and traverse in parallel, with flattening toward the antrum (79). Healthy gastric mucosa has round pit patterns in the corpus and elongated pit patterns in the gastric antrum on HDWLE, which are more apparent with IEE. Healthy gastric mucosa with regular arrangement of collecting venules appears as red spidery vessels in the corpus (80).

Gastric atrophy is the loss of glandular mass with variable lamina propria fibrosis, with or without replacement by metaplastic tissue (GIM). There are 4 hallmark endoscopic findings that characterize gastric atrophy: (i) pallor, (ii) loss of gastric folds, (iii) prominence of the visible submucosal vessels (submucosal venules), and (iv) a border between atrophic and normal mucosa in patients with *H. pylori*-related AG (HpAG) (81). Among these changes, the loss of gastric folds is the most sensitive change followed by increased visibility of the submucosal venules (sensitivity 67%/specificity 85% and sensitivity 48%/specificity 87%, respectively) (82). Separating antral and corpus biopsies into distinct specimen jars and correctly orienting the specimens

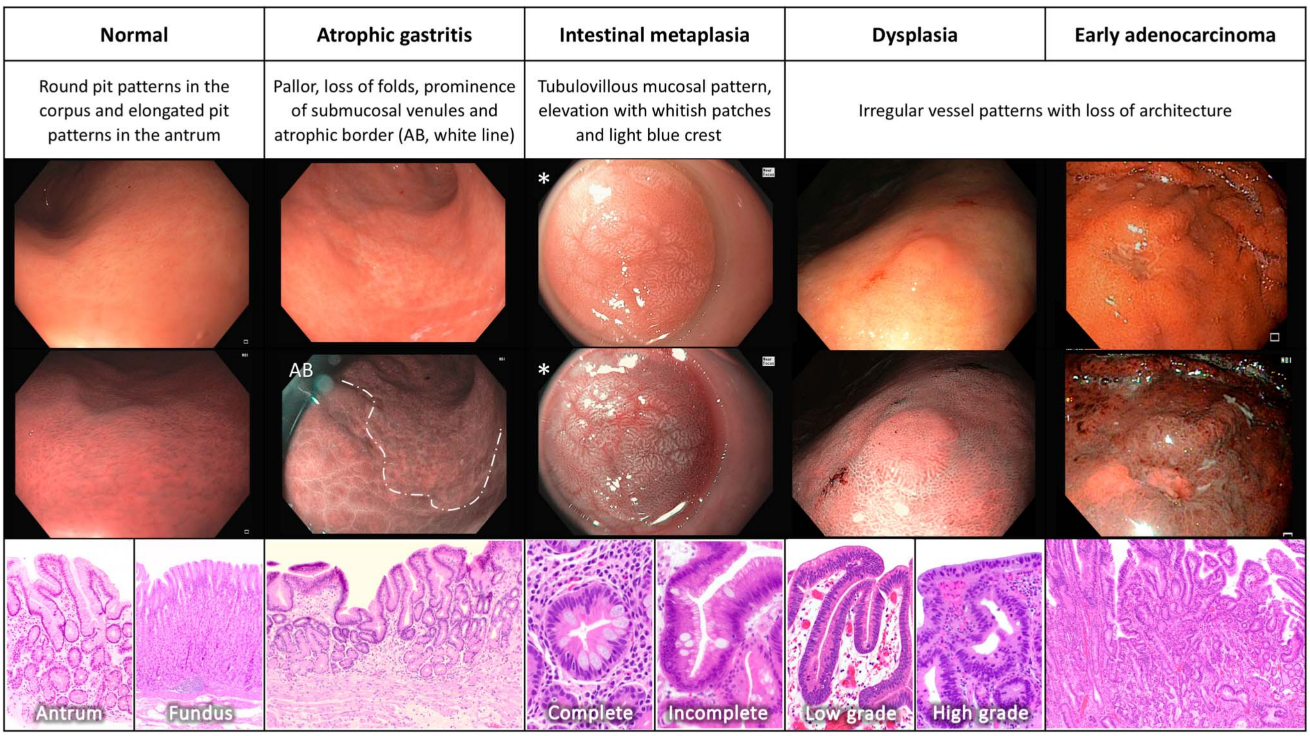

Figure 2. The Correa cascade: endoscopy (HDWLE, NBI) and histology correlation. HDWLE, high definition white light endoscopy; NBI, narrow band imaging.

during paraffin-embedding may assist pathologists with reporting AG, which is often underdiagnosed and subject to interobserver variability. Most examples of gastric atrophy can be divided into 2 patterns, HpAG and AIG. HpAG develops in the gastric antrum and incisura and may extend proximally. In some individuals, especially if there is persistent infection, there is the replacement of the normal glandular tissue by multifocal metaplastic tissue. The border of the atrophic mucosa can be identified endoscopically and is used by the Kimura Takemoto system to estimate atrophy severity and the risk of progression through the Correa cascade (83). AIG, also termed autoimmune metaplastic AG, is detected in the gastric corpus and fundus with characteristic sparing of the antrum unless there is concomitant HpAG (84). Diagnosing gastric atrophy based on endoscopy alone may be inaccurate and should be confirmed and its extent evaluated using a standardized biopsy protocol (see below).

On HDWLE, GIM appears as irregular, patchy, white mucosa with a tubulovillous pattern (Figure 3). The tubulovillous pattern is associated with a sensitivity of 89% and a specificity of 90% and is better appreciated using NBI (85). Other features of GIM on HDWLE and NBI (or BLI) are the light blue crest sign (sensitivity of 48%–89% and specificity of 93%–96%) (85–87), marginal turbid band (sensitivity 100% and specificity 66%) (86), and the "white opaque substance" sign, which appears as nodular patches of white raised mucosa and histologically represents accumulation of lipid droplets (88). The light blue crests are fine, light blue-white lines on the crests of the epithelial surface. One limitation is the moderate interobserver reliability of these endoscopic findings; improved agreement comes with experience (85,89,90).

The mucosal changes of dysplasia and EGC are nonspecific and subtle. Dysplasia manifests either erythema or pallor, slight

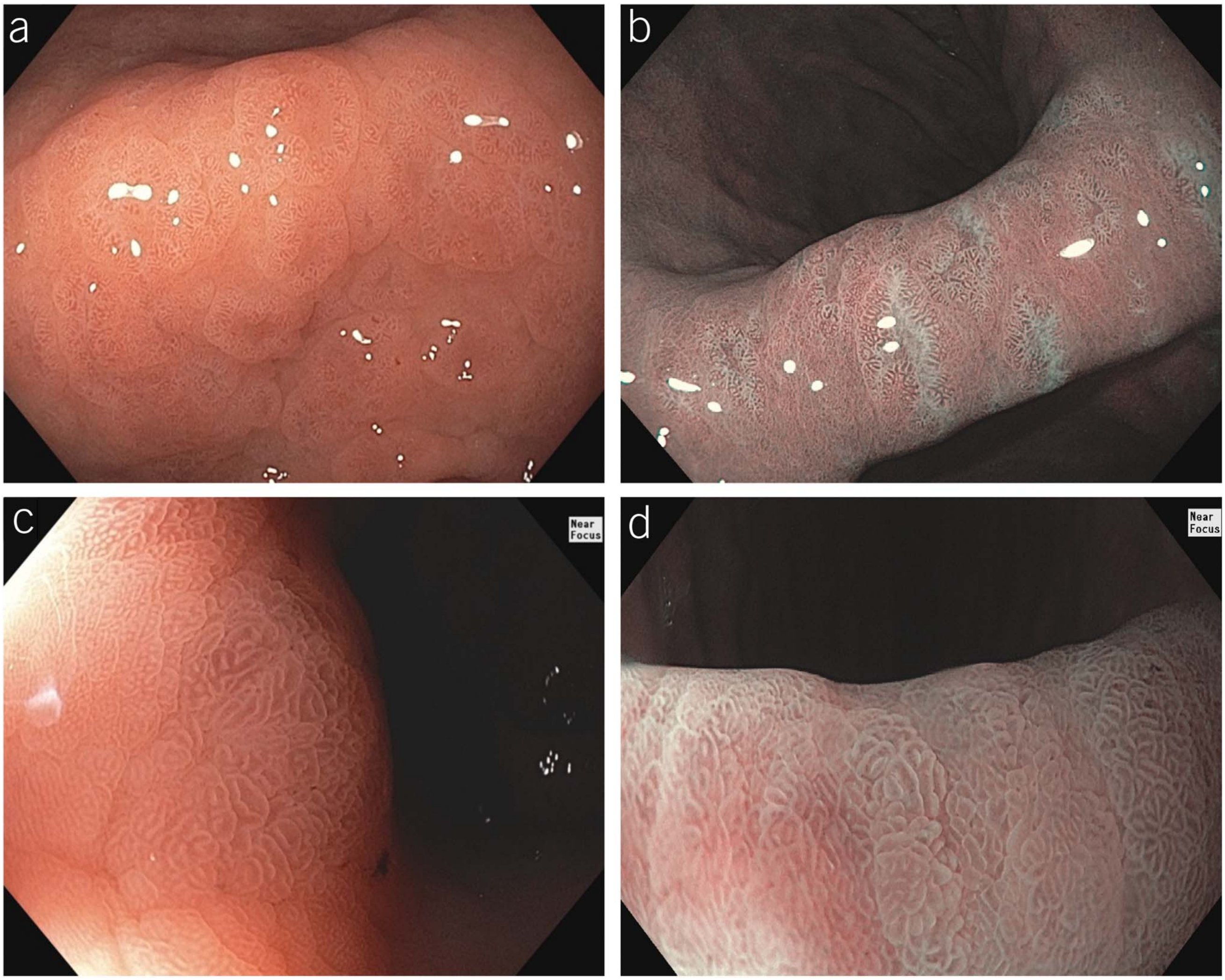

Figure 3. Gastric intestinal metaplasia on HDWLE with or without NBI and near-focus: (**a**) HDWLE, (**b**) NBI, (**c**) HDWLE with near-focus, and (**d**) NBI with near-focus. The patchy aspect of GIM is demonstrated in (**c**). In the left area, normal glandular structures are arranged in a regular honeycomb pattern. In the central area, the tubulovillous white glandular structures of intestinal metaplasia are observed. The LBCs are thin white or blue lines located at the borders of the tubulovillous glands (**c** and **d**). LBCs often appear in whitish color on NBI and are specific for GIM. The NBI examination with near-focus facilitates targeted biopsies within the framework of the Sydney system biopsy protocol. GIM, gastric intestinal metaplasia; HDWLE, high-definition white light endoscopy; LBC, light blue crest; NBI, narrow band imaging.

elevation or depression, thickening, abnormal convergence or flattening of gastric folds, or irregular mucosal vessels with loss of mucosal architecture (91,92). Ulcerated lesions often reflect invasive adenocarcinoma, with higher likelihood of submucosal invasion (at least stage T1b) and lymph node metastases that generally preclude patients from endoscopic treatment. In patients with HpAG, mucosal changes may persist even after successful *H. pylori* eradication therapy. In such patients, reddish depressed lesions may represent precursors to carcinomas that should undergo detailed evaluation, biopsies or endoscopic mucosal resection (EMR), or endoscopic submucosal dissection (ESD) when feasible (93).

Histologic diagnosis of GPMC

Recommendations: GPMC histologic diagnosis

6. In individuals at increased risk for or with suspected GPMC or GC, we suggest systematic gastric sampling according to the updated Sydney biopsy protocol. At minimum, 2 separate containers should be used for the antrum and incisura, and for the corpus. Targeted biopsies of any other mucosal abnormalities should be placed in additional separate containers (Low quality of evidence, conditional recommendation).
7. In individuals with GIM, we suggest that the histological subtype of GIM (incomplete, complete, and mixed) be reported for the purpose of GPMC risk stratification and informing surveillance (Low quality of evidence, conditional recommendation).
8. In individuals with GIM, we suggest that the anatomic extent and severity of GIM be reported for the purpose of risk stratification and informing GPMC surveillance. Limited GIM is confined to the antrum and incisura, whereas anatomically extensive GIM also involves the corpus. The severity refers to the proportion of atrophy or GIM in individual biopsies from each compartment (antrum, incisura, and corpus) (Very low quality of evidence, conditional recommendation).

Gastric pathology reporting

The pathology reporting of GPMC requires coordination between the endoscopist and pathologist at the local level in accordance with national standards. Explicit details include information specific to stomach location (e.g., antrum and corpus), severity and extent of GPMC (AG, GIM, dysplasia), subtype of GIM, and presence/absence of *H. pylori* organisms. The Sydney system for evaluation of gastritis was developed in the 1990s and consists of systematic biopsies of 5 sites, the greater and lesser curvatures of the antrum and corpus, and the incisura angularis (94–96) (Figure 2). Typically, 1–2 biopsies are obtained at each of the 5 sites and placed in 2 separate jars (antrum/incisura and corpus). Biopsies may be "directed" within each of the 5 Sydney zones if the endoscopic appearance suggests GPMC. "Targeted" biopsies refer to biopsies obtained for mucosal abnormalities and lesions, which are placed in a separate jar. The incisura, as an epithelial transition zone, is often the first zone to display AG or GIM in the setting of *H. pylori* gastritis and increase the likelihood of detecting GPMC.

GIM subtyping separates GIM into complete and incomplete types. This determination is readily made on hematoxylin and eosin (H&E)-stained sections without the need for additional special stains if the specimens are adequately cut and processed. Felipe described further subtyping based on mucin histochemical stains (e.g., high iron diamine staining): type I (complete) and types II and III (both considered incomplete), but this level of discrimination is typically reserved for research purposes and is not needed clinically (97,98). There are limited data on patient-related outcomes associated with GIM subtyping in the United States (17). However, in high-risk populations, there are strong, consistent data that support GIM subtyping as complete vs incomplete (or mixed if both are present) to delineate the risk for progression to neoplasia (97,99–101).

The severity of AG and GIM refers to the proportion of atrophy or GIM in individual biopsies in each compartment (antrum, incisura, and corpus). Increased severity of AG/GIM is consistently associated with higher risk of neoplastic progression, independent of anatomic extent (22). Mild atrophy can be difficult to appreciate; however, extensive loss is readily apparent. Intestinal metaplasia in up to one-third and two-thirds of glands can be regarded as mild and moderate, respectively, whereas greater than two-thirds is considered severe (94,95). The Operative Link for Gastritis Assessment and Gastric Intestinal Metaplasia (OLGA/OLGIM) is a validated histologic scoring system that considers both the extent and severity of AG/GIM and is strongly associated with risk of progression based on robust non-US data. OLGA/OLGIM is not routinely used in the United States, and therefore, US-specific data are limited (Figure 4, Box 1).

All samples concerning for dysplasia, including IND, LGD, and HGD, should be reviewed by a pathologist with expertise in GI pathology. Many cases of IND and LGD are "downgraded" to negative for dysplasia after expert review (102). The IND category is often applied in the presence of obscuring inflammation, but attention to histomorphologic details on review by an expert pathologist can most often clarify the presence vs absence of dysplasia (102). It is important to ensure that causes of inflammation, such as *H. pylori* infection and/or nonsteroidal anti-inflammatory drug use, are addressed and removed because superimposed inflammation can make the diagnosis of dysplasia challenging (see below). In general, the histologic features of LGD are similar to those of colorectal tubular adenomas, with enlarged hyperchromatic nuclei that are aligned perpendicular to the cell basement membranes of the affected glands. HGD shows loss of this nuclear polarity with an erratic arrangement of enlarged hyperchromatic nuclei. Some examples of gastric dysplasia show gastric rather than intestinal type differentiation, instead showing pyloric gland or foveolar cell differentiation (103). Describing differences in classification systems across different countries is beyond the scope of this document. However, it is worth recognizing that some areas of the world may classify HGD and early GC differently (e.g., carcinoma *in situ* may be classified as cancer, but in the United States, this would be classified as HGD).

STOMACH

MANAGEMENT OF GPMC

Recommendations: nondysplastic GPMC surveillance

9. In individuals with GIM who are considered high risk for GC, we suggest endoscopic surveillance at 3-year intervals. High-risk groups include individuals with GIM and at least one of the following criteria:
   (i) High-risk GIM histology:
   - Incomplete GIM histological subtype, vs complete subtype
   - Corpus-extension, defined as corpus involvement also with antrum or incisura involvement

   (ii) Any GIM histology with one of the following risk factors for GC:
   - Family history of GC in a first-degree relative
   - Foreign-born, with emigration from a high-incidence nation
   - High risk race or ethnicity, including East Asian, Latino/a, Black, and AIAN individuals

   (Very low quality of evidence, conditional recommendation).
10. In individuals with severe GIM or AG in biopsies of the antrum or corpus, we suggest endoscopic surveillance at 3-year intervals (Very low quality of evidence, conditional recommendation).
11. In individuals with low-risk GIM or atrophy, we suggest against endoscopic surveillance. Low-risk groups include
   (i) Complete type GIM, without evidence of incomplete GIM
   (ii) GIM of focal anatomic extent that is confined to the antrum
   (iii) None of the high-risk clinical criteria listed in Recommendation 9 above
   (iv) AG that is mild in severity

   (Very low quality of evidence, conditional recommendation).

The epidemiology of GPMC

High-risk populations for GPMC parallel high-risk populations for GC. AG is the most common GPMC with an estimated prevalence of 15% in the United States overall, although these estimates should be considered in the context that AG is often underdiagnosed and subject to interobserver variability (104). Based on data from Western populations, GIM is observed in approximately 5%–15% of patients undergoing upper endoscopy with gastric biopsies (17,105,106). The prevalence of both AG and GIM is significantly higher in certain populations such as non-White groups and first-generation immigrants from high-incidence nations where the GPMC prevalence may approach 40% in 40–60-year-olds (107).

Based on limited data from Western populations, the prevalence of dysplasia ranges from 0.5% to 3.75%, but some cohorts report higher prevalence depending on the population (e.g., populations with GIM, high racial and ethnic diversity, and family history in a first-degree relative) (108–112). Variability in the reported prevalence of dysplasia across studies may also stem from variability based on histologic interpretation. For example, IND or even LGD may arguably represent an inflammatory or regenerative process as opposed to true neoplastic transformation. Indeed, even in studies with expert GI pathologists, low interobserver agreement for LGD has been demonstrated (kappa 0.2), although the agreement is higher for HGD (113). Further compromising our understanding of the true burden of the spectrum of GPMC from an epidemiological standpoint is that these conditions are generally asymptomatic and require a high-quality endoscopy with appropriate biopsies to diagnose.

Chronic *H. pylori* infection is the leading risk factor for GPMC, although less common etiologies, such as AIG, are recognized. GPMC are more common in non-White individuals and immigrants from high GC incidence regions. Additional risk factors include male sex, having a first-degree relative with GC, smoking and dietary factors. Each of these factors may confer an independent risk of prevalent GPMC ranging from approximately 1.5- to 3.5-fold (17,114–119). We emphasize that the risk factors for the development of GPMC and GC and the progression from GPMC to GC overlap, yet the dominant risk factors likely vary for the 3 domains, and will vary in different populations. For the transition from GPMC to GC, the principal drivers and their respective biomarkers are critical need areas for research.

Nondysplastic GPMC and the risk of progression

Individuals with confirmed GPMC have a higher risk of intestinal-type gastric adenocarcinoma. One population-based study from Sweden, a low GC incidence nation, reported that AG and GIM were associated with minimally adjusted hazard ratios (95% CI), of 5.0 (3.8–6.7) and 6.5 (4.8–8.9), respectively, for noncardia GC, compared with normal gastric mucosa (120). This study excluded the first 2 years of follow-up and did not provide details regarding *H. pylori* status, surveillance history, anatomic extent, or other relevant histological features (e.g., GIM subtype). Based on other studies, including 1 comprehensive meta-analysis, the overall baseline risk of progression of AG and GIM is low and parallels the rate of progression of other preneoplastic changes (e.g., Barrett's esophagus and low-risk colorectal adenomas) (22,121,122). Based on meta-analysis, the 10-year cumulative risk of progression to GC among patients with histologically confirmed GIM is 1.6% (95% CI 1.5%–1.7%) (22). The baseline risk of GC among individuals with GPMC varies significantly depending on histological features, anatomic extent, microbial (e.g., persistent *H. pylori* infection), family history and hereditary factors, and other factors with less defined risk estimates (e.g., tobacco and diet) (123,124); this is why appropriate risk stratification is the main branch point informing the management of patients with GPMC.

Individuals with GIM and additional risk factors for progression have anywhere from 2.0- to 20-fold higher risk of progression to GC (22,123). These risk factors include corpus-extended AG/GIM, incomplete-type GIM, moderate-severe AG or GIM (i.e., OLGA/OLGIM III-IV, see INSERT and Supplement 2, Supplementary Digital Content 2, http://links.lww.com/AJG/D557), and family history of GC in a first-degree relative. By contrast, some individuals with mild GPMC (e.g., mild unifocal AG or GIM) may show regression, particularly after confirmed *H. pylori* eradication and improvement in the severity of background gastritis (22,120,122,123,125,126). Some studies suggest that although race, ethnicity, and country of origin are significant risk factors for GPMC and GC, these factors are not proven to be independent predictors of progression, also noting that US studies are limited (22,127). That said, endoscopic surveillance of individuals with GPMC who identify as a high-risk race or ethnicity, or who emigrated from a high-incidence region, should be considered for endoscopic surveillance given the substantial increased risk of GC in these groups.

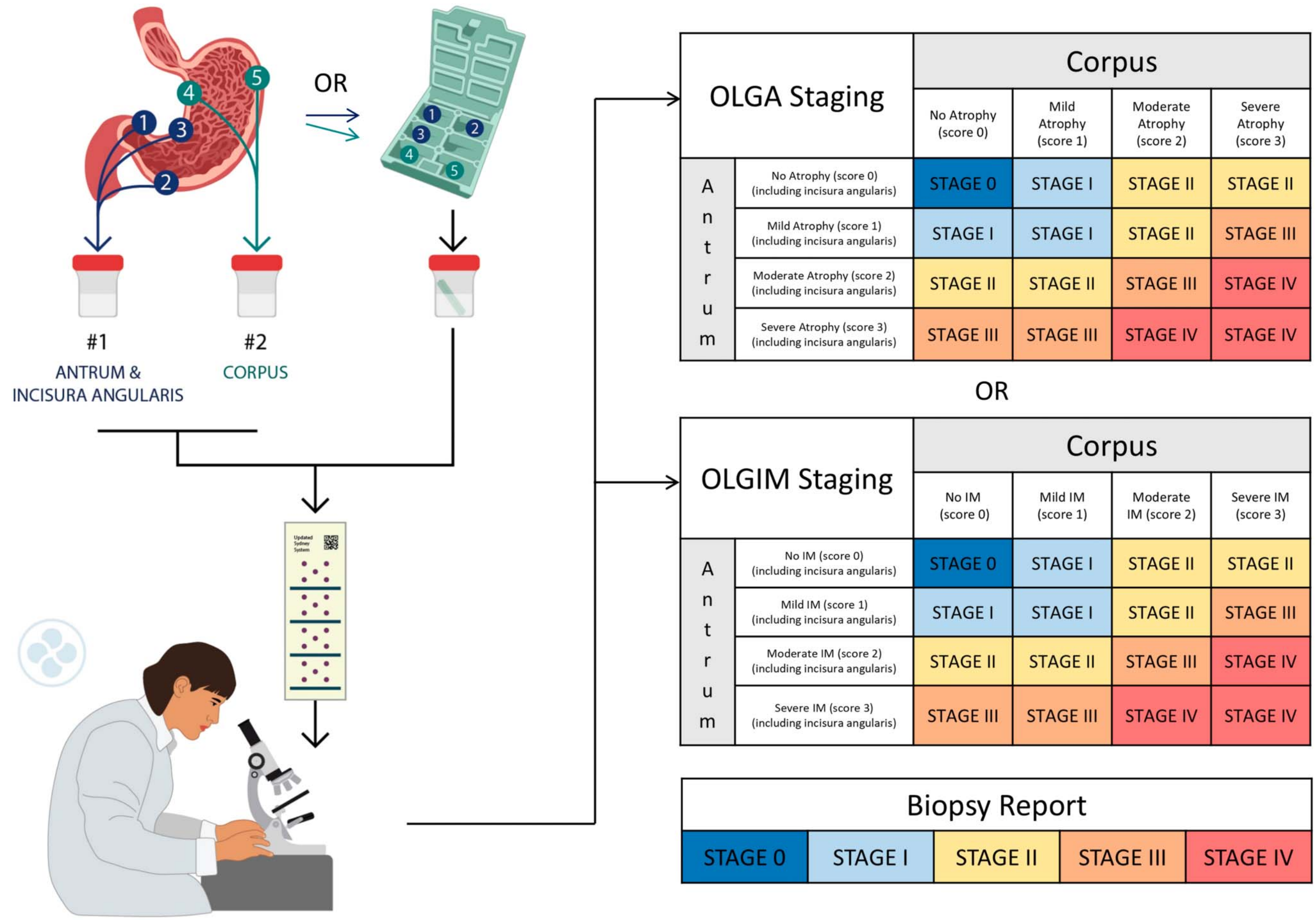

Figure 4. The OLGA/OLGIM histology staging system (see Box 1). OLGA, Operative Link on Gastritis Assessment; OLGIM, Operative Link on Gastric Intestinal Metaplasia Assessment.

Histologic determinants of nondysplastic GPMC progression

Appropriate sampling of the gastric mucosa using the Sydney protocol allows determination of anatomic extent, GIM subtype, histopathological stage/severity, and the presence of *H. pylori* infection or AIG (95,113,128). Obtaining robust estimates of the risk of GC associated with each of these factors is challenging, particularly in the United States, because GIM is often diagnosed incidentally on upper endoscopy performed for other indications and without adequate sampling (129). In 1 US population-based study, 66% of patients with GIM had the anatomic location categorized as "not otherwise specified" (129). In the United States, the GIM histological subtypes are rarely reported on pathology reports.

Anatomic extent. In retrospective cohort studies conducted in US populations, corpus-extended GIM has a higher risk of progression to GC compared with GIM limited to the antrum and incisura (22,108,129). The findings are generally similar in high-risk populations outside the United States. For example, a retrospective analysis of a large cohort of high-risk Colombian patients undergoing surveillance endoscopy with 20 years of follow-up reported that individuals with corpus-extended GIM had a statistically nonsignificant higher risk of GC compared with individuals with antrum-limited GIM (OR 2.1, 95% CI 0.7–6.6) (101). A meta-analysis by Shao et al reported that compared with patients without GIM as the reference group, patients with GIM limited to the antrum had a 4-fold (OR 4.06, 95% CI 2.79–5.91; $I^2 = 27.4\%$) higher risk of GC, while those with corpus extension had a 7.4-fold (OR 7.39, 95% CI 4.94–11.06; $I^2 = 37.8\%$) higher risk of GC; no US studies were included in this meta-analysis (130). GPMC focality is also relevant but similarly depends on obtaining a sufficient number of gastric biopsies. Unifocal AG or GIM, defined as 1 biopsy specimen containing AG/GIM, is associated with lower risk than multifocal AG/GIM, which is defined as at least 2 biopsies containing AG/GIM. Moderate to severe AG/GIM, as noted below, even if anatomically limited to the antrum, is still considered high-risk and such individuals should be considered for surveillance.

Histologic severity. Moderate to severe AG/GIM is associated with substantially higher risk of GC compared with mild AG/GIM and is a strong predictor of progression. However, reporting of histologic severity of AG/GIM in routine US clinical practice is not always performed. As previously noted, OLGA/OLGIM is a histopathologic staging system that considers both the anatomic location and the histologic severity of AG/GIM that is regularly used in other Western countries (e.g., Europe and Latin America) but not the United States. Based on robust data, including a meta-analysis of 2 prospective cohort studies from Italy and the Netherlands, moderate-severe AG/GIM (stage III/IV) was associated with a 27.7-fold (95% CI 3.75–204.87) higher RR of GC compared with mild-intermediate AG/GIM (stage 0/I/II) (113,131,132). The use of OLGA/OLGIM staging is limited in the United States, and therefore, data are minimal in US populations. As with GIM subtype, gastroenterologists should work with their local pathologists to optimize protocols for the routine reporting of histologic severity given its value as a risk stratification parameter.

STOMACH

Box 1. **OLGA and OLGIM (see Figure 4)**

Background. The Operative Link for Gastritis Assessment (OLGA) and Operative Link for Gastric Intestinal Metaplasia Assessment (OLGIM) are validated histopathological staging systems that consider both the anatomic location and histological severity of AG and GIM. They were developed primarily for staging *H. pylori*associated atrophy with or without metaplasia. These systems necessitate adequate quality biopsies obtained separately from the antrum/incisura and corpus. (See Supplement 2, Supplementary Digital Content 2,http://links.lww.com/AJG/D557for additional background). The OLGA/OLGIM system is in widespread use in Europe and some centers in Asia and Latin America. A limited number of U.S. centers use OLGA/OLGIM. OLGA/OLGIM stages range from 0 (normal pathology) to IV (moderate/severe AG +/− GIM of the antrum and corpus). There is lower interobserver variability for OLGIM than for OLGA. OLGA/OLGIM staging is a strong predictor of progression to GC in high-risk populations. Higher stages of OLGA/OLGIM (III-IV) in patients with *H. pylori*-associated gastritis are consistently associated with a substantially higher risk of progression to gastric cancer compared to lower stages (0-I). OLGA/OLGIM II is considered an intermediate-risk category and individual risk assessment is helpful. In the Singapore GCEP cohort, the largest cohort of patients with GPMC published to date, the incidence of early gastric neoplasia was 543.8 per 10000 person-years in individuals with OLGIM III/IV (versus 21.5 in OLGIM I). OLGA/OLGIM staging should not be applied to patients with autoimmune gastritis (AIG) in the absence of *H. pylori*infection, since AG and GIM only occur in the corpus in patients with *H. pylori*-negative AIG. **Implementation in Practice**. In centers where OLGA/OLGIM staging is routinely used, we suggest that individuals with OLGA/OLGIM III/IV (without dysplasia) undergo surveillance endoscopy every 3 years based upon the global literature, with consideration of a 2-year interval if they have any additional demographic or clinical risk factors (e.g., family history). For patients who are intermediate-risk (OLGA/OLGIM II), endoscopic surveillance in 3 years may be considered if multiple additional high-risk factors are present. US studies are needed regarding the value versus the burden of routine OLGA/OLGIM staging and the impact on gastric cancer prevention and early detection.

GIM subtype. Several studies and meta-analyses consistently report a several-fold higher risk of progression in patients with incomplete-type GIM compared with complete-type GIM histology (133–135). One meta-analysis published in 2021 of 12 cohort studies comprising nearly 6,500 individuals reported a pooled RR of dysplasia and GC of 3.72 (95% CI 1.42–9.72) and 5.16 (95% CI 3.28–8.12), respectively, in patients with incomplete-type vs complete-type GIM (99). A second 2021 meta-analysis, with subgroup analysis according to geography, reported that incomplete GIM was associated with a significantly higher risk of GC (pooled RR for GC 4.05, 95% CI 1.65–9.93) or dysplasia/GC (pooled RR for dysplasia/GC 4.65, 95% CI 2.30–9.92) in Western European populations (136). In addition, based on meta-analysis, the presence of only complete-type GIM does not seem to confer a higher risk of GC compared with patients without GIM (pooled OR 1.55, 95% CI 0.91–2.65) (130). It should be noted that among patients with confirmed GIM, the incomplete type is common, with an estimated pooled prevalence of 42% (95% CI 34–49), although some studies report a higher prevalence (123). The evidence is consistent across lower incidence regions such as Western Europe but is still indirect because no studies were identified from US populations.

Active* H. pylori *infection. Active *H. pylori* infection is strongly associated with GPMC progression, whereas successful *H. pylori* eradication may be associated with stable histology or even regression in some individuals. *H. pylori* eradication is considered an adjunct intervention to GPMC surveillance (see below). Although uncommon, patients may have refractory *H. pylori* infection after failure of several lines of appropriate *H. pylori* therapy—these patients are particularly high risk and should be offered surveillance endoscopy at a 3-year interval, which is primarily based on expert opinion (a shorter interval should be considered if additional GC risk factors).

Additional determinants of nondysplastic GPMC progression

A family history of GC, particularly in a first-degree relative, is a strong risk factor for incident GC among patients with nondysplastic GPMC, although there are mixed data (17). Based on a meta-analysis of 4 studies, including 1 from the United States, among patients with GIM, having a first-degree relative with GC was associated with 4.5-fold higher odds of GC (OR 4.53, 95% CI 1.33–15.46), but with very low certainty of evidence, because only the US study showed an association (17). Family history showed a null association in the Singapore "GCEP" study with multiethnic Asian populations (94). Hereditary and germline genetic factors are increasingly recognized; however, their role as a determinant of GPMC prognosis remains to be defined (21).

Active tobacco smoking is a modifiable risk factor associated with a higher prevalence of GPMC, and possibly progression, although the data are mixed and population-based data are limited (22). One US population-based study reported a null association between smoking history and GIM progression (22). By contrast, in the GCEP cohort, patients with OLGIM II-IV and a smoking history >20 pack-years had a 3.7-fold (95% CI 1.03–13.2) higher risk of early gastric neoplasia compared with nonsmokers, whereas those with <20 pack-years did not (HR 2.06, 95% CI 0.41–10.3) (123). Smoking cessation should be recommended regardless due to the broad positive health impacts; however, there are insufficient data to inform whether smoking per se warrants consideration of GPMC surveillance independent of the risk factors described above.

Other putative markers of GPMC progression risk include microbial dysbiosis, changes in the non-*H. pylori* gastric microbiome, and tissue-level molecular changes (137,138). Tissue-level factors certainly hold promise for developing a personalized approach to GPMC surveillance; however, there is currently insufficient evidence to inform clinical practice, and most studies have been performed in East Asian populations. Similarly, there are mixed data in non-US populations regarding the predictive value of serum biomarkers (e.g., pepsinogens), about progression of GPMC to GC (123,125). Novel, ideally noninvasive, biomarkers represent a critical unmet need to better delineate individuals at highest risk for GPMC progression.

Dysplastic GPMC and risk of progression

The diagnosis of dysplasia (or "intraepithelial neoplasia") is subject to interobserver variability, especially for IND and LGD, and less so for HGD, even among expert pathologists (125). In one study, among 47 patients initially diagnosed with IND, a re-review by expert GI pathologists resulted in the same diagnosis in

25 (53.2%), and reclassification as negative for dysplasia (23.4%), LGD (21.3%), and even HGD (2.1%), in the remaining individuals (139). This diagnostic uncertainty informs the interpretation of risk estimates for dysplasia progression reported in the current literature. In addition, many studies analyze dysplasia as a composite outcome agnostic of dysplasia grade. One population-based study from Sweden reported a 7.1-fold (95% CI 5.1–9.8) higher standardized incidence ratio (SIR) for dysplasia progression to noncardia GC (reference: normal mucosa), compared with SIRs of 3.0 (95% CI 2.5–3.7) and 3.7 (95% CI 2.9–4.6) for AG and GIM, respectively, but did not provide SIRs according to dysplasia grade (120).

It is undeniable that HGD is associated with a synchronous carcinoma or a high rate of progression to invasive carcinoma. The rate of progression of HGD has been estimated to be 47%–100% over 4–48 months (139–149). One nationwide cohort study from a low-incidence region demonstrated that approximately one-quarter of patients with HGD were diagnosed with invasive cancer within 12 months (125,150). In one retrospective study in Australia, of 160 patients with dysplasia, 26.9%, 57.5%, and 15.6% were classified as HGD, LGD, and IND, respectively, the majority of which were classified as nonpolypoid (70.6%) (139). In this cohort, among patients with HGD undergoing surveillance only (mean follow-up 1.0 ± 1.4 [SD] years), 42.9% had cancer identified on their index examination, and 4.8% developed an interval cancer (defined as >12 months after index). The literature has also demonstrated similar rates of HGD "regression," ranging from 0% to 33% which underscores the challenges of sampling error in research and in patient care (139–148,151–153).

IND and LGD have a lower rate of progression to more advanced neoplasia and may even show regression. Based on more recent longitudinal cohort data from both low-intermediate and high-GC incidence regions, a measurable percentage of IND/LGD do in fact regress or remain stable on long-term follow-up (123,125,126,148). Notwithstanding, IND/LGD demonstrate a significant rate of progression, especially considering that diagnostic upstaging to more severe lesions occurs in a minority, up to 30% based on most cohort studies (120,139,148). Endoscopic resection is recommended for IND or LGD as a diagnostic and therapeutic intervention when associated with a visible lesion, as detailed below. One retrospective study of 119 patients with biopsy-confirmed IND found that on resection, 26 (21.8%) had early GC; lesion, and diameter ≥10 mm and surface erythema were both independently associated with GC (154). In the Australian cohort cited above, among patients with LGD undergoing surveillance only (mean follow-up 2.3 ± 2.1 [SD] years), 7.9% had cancer identified at the index examination, 5.3% developed interval cancer, 28.9% had unchanged pathology, whereas 57.9% demonstrated no dysplasia on follow-up examinations. These LGD estimates are similar in other cohorts (1,139,141,149). As in the case of nondysplastic GPMC progression, US data and novel biomarkers are needed.

GPMC "regression"

Longitudinal data from large prospective non-US cohorts (e.g., Singapore, northern Europe, Colombia, and Chile) support the observation that GPMC may improve or "regress," particularly after *H. pylori* eradication in patients with less severe baseline histology (22,101,120,123,125,126). This observation nuances the notion that GIM represents a "point of no return." Robust observational cohort data also suggest that even LGD may show improvement, particularly in the setting of *H. pylori* eradication. That said, in general, robust data regarding risk factor modification are not consistently ascertained in these observational studies. A principal challenge in studies is the inherent multifocal ("patchy") nature of GPMC, wherein sampling error and misclassification are significant. In addition, gastric histopathology scoring systems (e.g., OLGA/OLGIM and Correa Score) provide an ordinal system to detect change, yet the global diagnosis (e.g., AG and GIM) may not change. Finally, there is important interobserver variability among pathologists, particularly with mild AG and IND/LGD.

Endoscopic surveillance and intervals for nondysplastic GPMC

The sojourn time of nondysplastic GPMC (AG/GIM) to GC is relatively long, which allows the opportunity for endoscopic surveillance for early gastric neoplasia detection and resection. Resection of early gastric neoplasia before submucosal invasion is potentially curative and is in marked contrast to the poor prognosis associated with advanced-stage GC. The primary purpose of the high-quality endoscopic surveillance examination is to identify neoplasia, while the secondary purpose is to appropriately risk-stratify patients with GPMC. The individual surveillance endoscopy recommendation should be based on patient-physician decision-making, patient comorbidities, and overall prognosis (Figure 5).

Surveillance vs no surveillance based on risk. There are no prospective RCTs in the US or globally that have evaluated the impact of endoscopic surveillance vs no surveillance, nor surveillance intervals, on important outcomes, especially the impact on GC-related mortality. There is, however, a sizeable body of non-US observational data from low-intermediate and high-incidence regions supporting that endoscopic surveillance vs no surveillance is associated with an earlier stage of GC among patients with high-risk GPMC defined based on the clinical and histopathological factors detailed above (42). Patients with GPMC who are at low risk for neoplastic progression (e.g., complete-type GIM limited to the antrum with no additional risk factors) are unlikely to benefit from routine interval endoscopic surveillance. Indeed, a substantial proportion of patients with nondysplastic GPMC may be considered low-risk. In a cross-sectional study of 415 US Veterans who underwent Sydney protocol biopsies, 73% had focal GIM, while the remainder were classified as extensive GIM (118). In the GCEP study, less than 15% were categorized as high-risk, which is similar to other cohort studies (113,123). Some caution is merited in classifying individuals as low-risk based on a single endoscopic examination because studies have demonstrated that up to 30% of patients originally classified as low-risk based on an index endoscopy without systematic biopsies are upstaged to high-risk histological classification on repeat short-interval endoscopic examination (~1–2 years) with Sydney protocol biopsies (155). However, there are currently no US data to support performing a repeat endoscopy with Sydney protocol biopsies within 12 months among patients who are initially classified as low-risk. An individualized approach is recommended.

Surveillance intervals. The optimal surveillance interval for individuals with GPMC is not defined and should be determined based on individual risk assessment until more precise data are available. Data from microsimulation and cost-effectiveness analyses conducted with a US population in mind are illustrative and provide guidance regarding an individualized approach

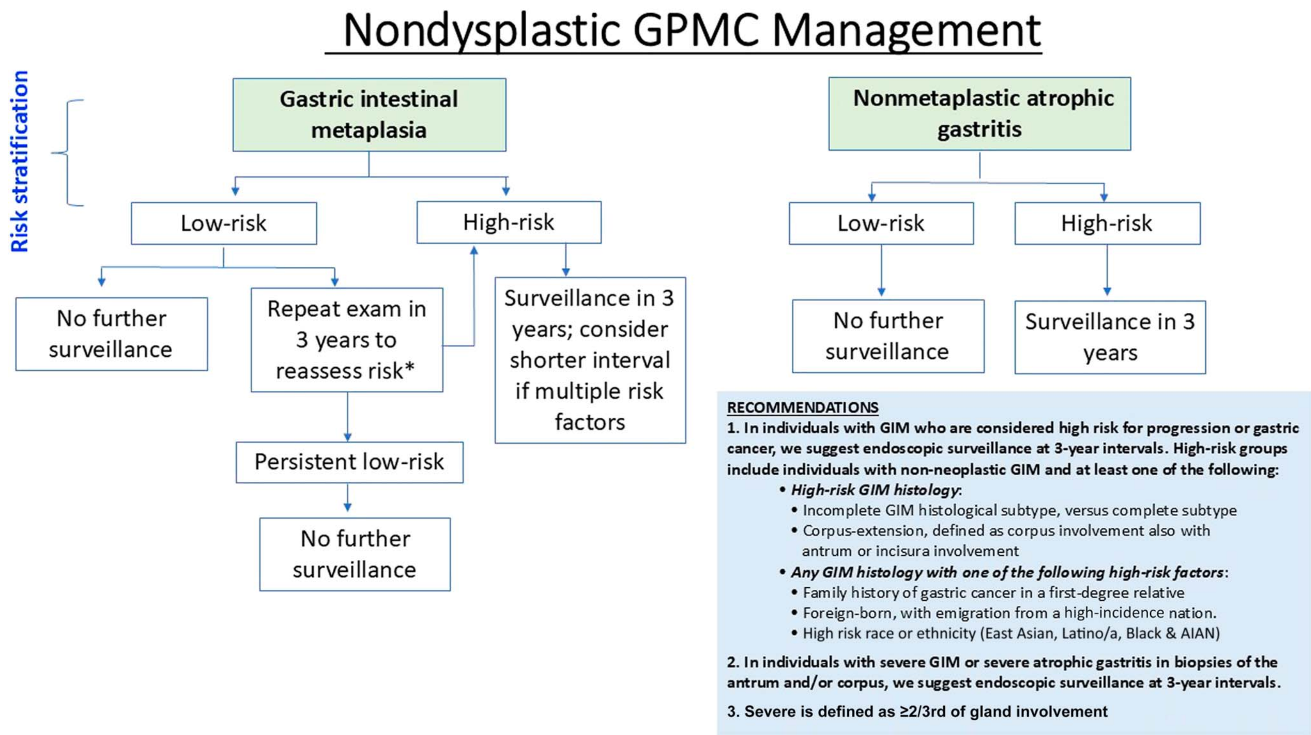

Figure 5. Nondysplastic GPMC management algorithm. All patients should be tested for *H. pylori* using nonserologic methods, treated if positive, and confirmed to be eradicated, irrespective of GPMC histology, severity, grade, or associated visible vs nonvisible lesion. Ideally, *H. pylori* eradication should confirmed at least 1-2 months before the endoscopic surveillance examination because active *H. pylori* infection can affect endoscopic and histologic appearance of GPMC. The surveillance examination comprises HDWLE with IEE for mucosal inspection and systematic protocol biopsies. The algorithms presented assume that patients are medically appropriate for endoscopic surveillance. *Some studies in non-US populations have demonstrated that approximately 30% of patients originally classified as low-risk, based on the initial examination diagnosing GPMC, are upstaged to high-risk histological classification on repeat short-interval endoscopic examination (~1–2 years) with Sydney protocol biopsies. There are no US data to inform such practice. If there is concern regarding the quality of the initial examination, or patient preference and patient-physician shared decision-making, repeat surveillance in 3 years can be considered among individuals with GIM deemed low-risk based on the initial examination. Individuals with GIM and multiple risk factors for GC should be considered for surveillance at shorter than 3-year intervals. GIM, gastric intestinal metaplasia; GPMC, gastric premalignant condition; HDWLE, high-definition white light endoscopy.

to endoscopic surveillance vs no surveillance in patients with GPMC (156,157). One study found that the cost-effectiveness of endoscopic surveillance of GIM was highly sensitive to the rate of progression to GC, again underscoring the importance of risk stratification (53). Another microsimulation analysis demonstrated that surveillance of incidentally detected GIM every 5 years in all patients is associated with reduced GC incidence and mortality and is cost-effective ($40,706/QALY) from a US healthcare perspective; however, in high-risk individuals, namely those with a family history of GC, anatomically extensive or incomplete-type GIM, a 3-year surveillance was the favored strategy and was cost-effective (157). Based on the microsimulation analysis by Thiruvengadam, endoscopic surveillance of incidentally diagnosed GIM results in 87–190 life-years gained (LYG)/1,000 in all-comers, 351–851 LYG/1,000 in individuals with a first-degree family history of GC, 157–335 LYG/1,000 in individuals with anatomically extensive or incomplete-type GIM, and only 43–97 LYG/1,000 in individuals with antrum-limited, complete-type GIM (157). For context, colorectal cancer screening in the average-risk population compared with no screening results in 286-335 LYG/1,000.

Based on available data, including indirect data from modeling studies cited above, we recommend that patients with GPMC and any of the following high-risk features be considered for endoscopic surveillance at every 3-year intervals: GIM histology (corpus-extension and incomplete-type), family history of GC in a first-degree relative, and demography (immigration from a high-incidence nation, race, and ethnicity considerations). Severe GIM or atrophy histology in the antrum/incisura or corpus also warrants surveillance. The principal race and ethnic groups at-risk include East Asians, Latino/a, Black, and AIAN individuals (28). In centers where OLGA/OLGIM staging is used, we suggest that individuals with OLGA/OLGIM III/IV (without dysplasia) undergo surveillance endoscopy at least every 3 years based on the global literature, with a low threshold to consider a shorter interval (e.g., 2-year). This is based on observational data from the GCEP cohort (one of the largest GIM surveillance cohorts to date) demonstrating that individuals with OLGIM III/IV had a 20-fold higher independent risk of neoplasia (adjusted HR 20.8; 95% CI, 5.04-85.6), with over 50% of early gastric neoplasia being diagnosed within 2 years of the index exam (range: 12.7-44.8 months) (123).

In summary, the plan for endoscopic surveillance for a patient with AG/GIM should be individualized based on risk stratification and should also consider shared patient-physician decision-making. The patient with complete GIM limited to the antrum would not warrant surveillance, yet if the GIM were graded as severe in the antrum/incisura biopsies, surveillance is reasonable. Patients with multiple risk factors do warrant surveillance (130).

Endoscopic management of dysplastic GPMC

Recommendations: endoscopic management of dysplastic GPMC

12. In patients with dysplasia (IND, LGD, and HGD) and visible margins, we suggest endoscopic resection in clinically appropriate patients (Low quality of evidence, conditional recommendation).
13. In patients with dysplasia (IND, LGD, and HGD) without visible margins, we suggest a repeat endoscopic evaluation with HDWLE and IEE by an experienced endoscopist (Low quality of evidence, conditional recommendation).
14. In patients appropriate for endoscopic resection of dysplasia, particularly endoscopic submucosal dissection, we recommend referral to a high-volume center with appropriate expertise in the diagnosis and therapeutic resection of gastric neoplasia (Low quality of evidence, strong recommendation).
15. In patients with confirmed complete resection of dysplasia, we suggest endoscopic surveillance. We recommend surveillance examinations be performed by an experienced endoscopist and using HDWLE and IEE, with biopsies according to the systematic biopsy protocol in addition to targeted biopsies (Low quality of evidence, strong recommendation).

Endoscopic management of dysplastic GPMC

In patients diagnosed with dysplastic GPMC, management depends on the grade of dysplasia, presence and characteristics of a visible lesion, status of the surrounding mucosa (e.g., severe GIM), active *H. pylori* infection, and individual patient considerations. We acknowledge that in other regions of the world, particularly East Asia, the diagnosis of dysplasia or invasive carcinoma may be made based on endoscopic appearance using IEE typically in conjunction with magnification endoscopy, with final confirmation and staging based on the *en bloc* resected lesion. In the United States, the reality is that the diagnosis of dysplasia generally hinges on confirmation from biopsy sampling. Poor quality of samples (e.g., preparation artifacts), absent targeted biopsies, or significant mucosal inflammation (e.g., *H. pylori* infection) may compromise the accuracy of dysplasia diagnosis. We recommend that any biopsies concerning for dysplasia be reviewed by an expert GI pathologist. In all patients diagnosed with active *H. pylori* infection, it is recommended that eradication treatment be immediately provided with confirmation of eradication because (i) concomitant *H. pylori* infection may affect the diagnostic certainty of dysplasia; (ii) *H. pylori* eradication is associated with reduced risk of progression, particularly for IND and LGD; and (iii) active *H. pylori* infection may compromise delineation of the resection margin for visible lesions (158). However, awaiting eradication confirmation should not delay endoscopic management, especially for patients with HGD, given the high rates of synchronous cancer and short-interval progression (Figure 6).

If the index examination diagnosing dysplastic GPMC was performed by a provider with limited volume or experience in managing GPMC, or if there is concern about the quality of the initial examination, referral to a high-volume center with expertise is preferred. This examination serves several purposes that are relevant for clinical decision-making, specifically allowing (i) repeat visualization to characterize the area in question; (ii) systematic protocol biopsies of the surrounding flat mucosa to inform surveillance intervals; and (iii) repeat evaluation for other neoplasia missed on the index exam, given that several studies have demonstrated rates of missed synchronous cancers around 10%, even in expert hands (159).

Visible dysplasia. Dysplasia can be visible and delineated by areas of nodularity, erythema, pallor, or depression. Dysplasia can also be found incidentally on macroscopically normal appearing mucosa. For visible lesions found on endoscopy, endoscopic resection serves both diagnostic and therapeutic purposes. One of 4 lesions with biopsies showing LGD is upstaged after complete endoscopic resection (17% upstaged to HGD and 7% to carcinoma) (160).

All patients with dysplastic GPMC associated with a visible lesion amenable to endoscopic resection should be referred for endoscopic resection if medically appropriate. If the visible lesions and involvement are too extensive or if the lesion characteristics are not favorable for a compete resection, then surgical consultation is indicated. This discussion should be reserved for patients with biopsy-confirmed HGD or who have multifocal LGD with multiple additional risk factors for progression. Ongoing surveillance after dysplasia resection is indicated given the high risk of metachronous lesions (161,162). The duration of surveillance after resection is not clear. Borrowing from the literature of metachronous GC occurrence after endoscopic resection of EGC, surveillance should continue for at least 10 years postresection, and perhaps longer, if medically appropriate (163,164).

Endoscopic resection of LGD is safe (perforation and bleeding rates are <1% and <7%, respectively) and is associated with reduced rates of progression to HGD or carcinoma (165,166). Lesions greater than 10 mm, with HGD, or depressed lesions are more likely to harbor carcinoma and should be resected with ESD (160,167). Compared with EMR, ESD has significantly higher rates of "*en bloc*" resection, higher rates of complete resection (negative histologic margins), and lower recurrence rates but requires longer procedure times and results in significantly higher perforation rates (<1%–5%; OR 3.5 and 4.7 in separate meta-analyses) (167–169). No significant differences in postprocedure bleeding have been reported between EMR and ESD. The learning curve for ESD is higher than for other endoscopic procedures. Expert proficiency requires at least 150 cases in a Western training environment, which underlies the recommendation to refer patients to high-volume centers (170). Hybrid ESD allows safe en bloc resection of gastric lesions <20 mm with shorter times than conventional ESD (171). Ideally, patients with high-risk lesions who are candidates for endoscopic resection should also be discussed in a multidisciplinary setting including pathologists, therapeutic endoscopists, and surgeons. Patients should be counseled regarding the rate of recurrence, the risk of metachronous lesions, and thus, the need for ongoing endoscopic surveillance of the remnant mucosa. The surveillance recommendation should be based on the final histopathologic diagnosis and whether complete resection was achieved. Patients should also be counseled that if the final histology demonstrates cancer, additional treatment including surgery may be indicated depending on the cancer stage, grade, and patient-level factors.

Nonvisible dysplasia. In patients with dysplasia without visible lesions, so-called "nonvisible dysplasia," the rates of progression are also significant (125,150). In such cases, a short-interval endoscopy with detailed evaluation using HDWLE and IEE is

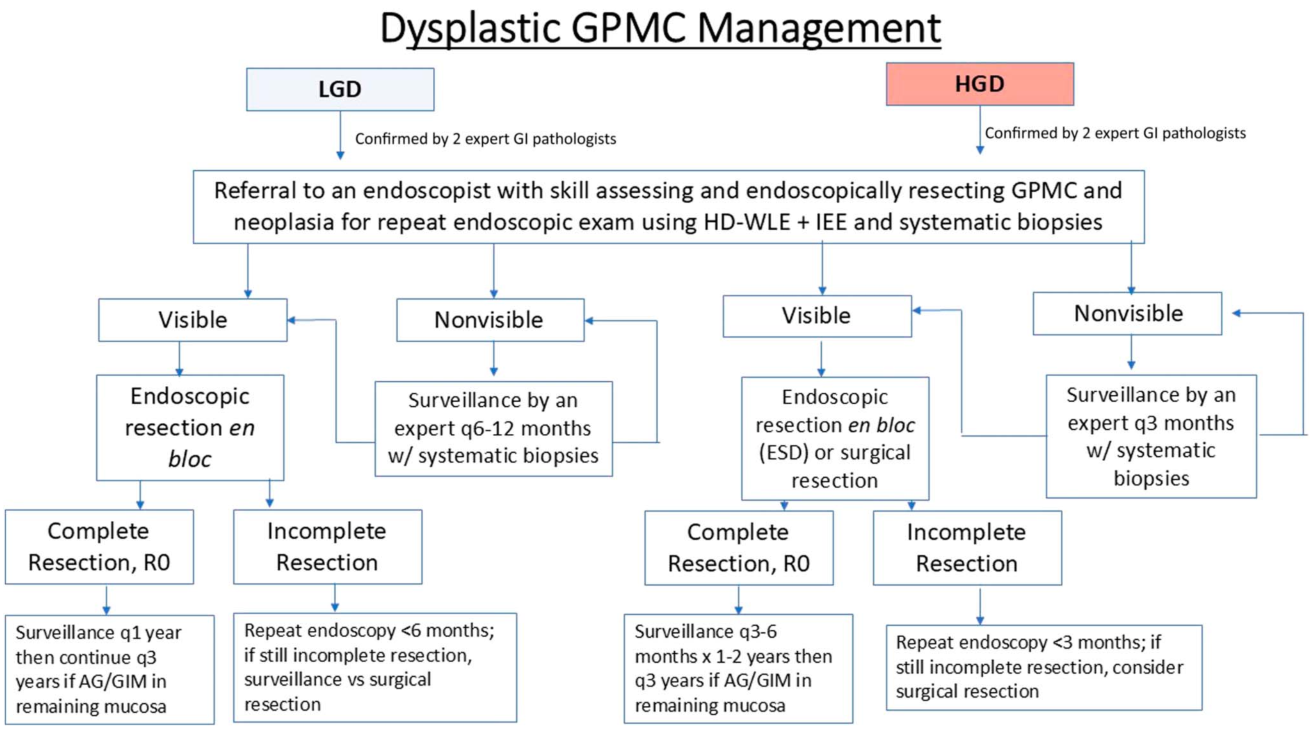

Figure 6. Dysplastic GPMC management algorithm. All patients should be tested for *H. pylori* using nonserologic methods, treated if positive, and confirmed to be eradicated, irrespective of GPMC histology, severity, grade, or visible vs nonvisible lesion. Ideally, *H. pylori* eradication should confirmed at least several weeks before the endoscopic surveillance examination because active *H. pylori* infection can affect endoscopic and histologic appearance of GPMC. The surveillance examination comprises HDWLE with IEE for mucosal inspection and systematic protocol biopsies. The algorithms presented assume that patients are medically appropriate for endoscopic treatment and surveillance. Patients with IND have elevated risk of gastric neoplasia and warrant follow-up. The diagnosis of IND should be confirmed by a second pathologist with gastrointestinal expertise. If this is confirmed, patients should undergo repeat high-quality endoscopy with HDWLE + IEE with biopsies obtained according to the systematic biopsy protocol, in addition to any biopsies targeted toward visibly abnormal areas, in 6–12 months (assuming the baseline examination diagnosing IND was of sufficient quality). The subsequent management algorithm is dictated by the presence vs absence of an associated visible lesion, and management should parallel that for visible vs nonvisible LGD. In patients without confirmed IND on the repeat examination, surveillance should be according to the results of the systematic biopsies. GIM, gastric intestinal metaplasia; GPMC, gastric premalignant condition; HDWLE, high-definition white light endoscopy; HGD, high-grade dysplasia; IEE, image-enhanced endoscopy; IND, indefinite dysplasia; LGD, low-grade dysplasia.

recommended, along with targeted biopsies of any mucosal abnormalities and nontargeted biopsies according to the Sydney biopsy protocol. This so-called second-look endoscopy should be performed by an experienced endoscopist in a high-volume center with EMR/ESD expertise. The second-look endoscopy has been shown to detect focal neoplastic lesions in 90% of patients (172). In patients with initial nonvisible HGD, with pathology confirmed by an expert GI pathologist, the second-look examination is also helpful given the risk of a synchronous cancer. In patients with IND/LGD and confirmation by an expert GI pathologist, the time frame for the second-look should be within 6–12 months and, ideally, after measures to reduce inflammation (*H. pylori* eradication and nonsteroidal anti-inflammatory drug cessation). In patients with active *H. pylori* infection and IND/LGD, the second-look endoscopy should be performed at least 1 month after confirming eradication, which allows time for the background inflammation to improve. This principle has been useful in the evaluation of esophageal intestinal metaplasia (Barrett's esophagus) and nonvisible IND/LGD where there is concomitant erosive esophagitis; initiation or optimization of gastric acid suppressing medications (e.g., PPI) in this analogous scenario improves inflammation and improves the accuracy of the dysplasia diagnosis.

If high-quality upper endoscopic examination using HDWLE with IEE by an experienced endoscopist confirms nonvisible dysplasia, patients who are medically appropriate should enter regular endoscopic surveillance. Patients with nonvisible HGD should undergo endoscopic surveillance in 3–6 months, while for those with nonvisible IND or LGD, every 6–12 months is reasonable. Additional risk factors such as a prior history of GC, multifocal GPMC, family history of GC in a first-degree relative, or persistent *H. pylori* may be considered for shorter interval surveillance. If dysplasia is not demonstrated on consecutive subsequent high-quality examinations over a 2-year period with IEE and targeted/Sydney biopsies, then returning to non-dysplastic GPMC surveillance intervals is reasonable. Endoscopic surveillance is subject to variability related to endoscopist technique, training, experience, and equipment; therefore, we additionally recommend that examinations be performed by an experienced endoscopist in high-volume centers.

Although there is a role of endoscopic ultrasound in staging early GC, data do not support the routine use of endoscopic ultrasound in the evaluation of GPMC. In addition, Japanese pathologists recognize the concept of intraepithelial carcinoma, but this concept is not recognized by most Western pathologists (109). Early GC is defined as adenocarcinoma limited to the mucosa, including the muscularis mucosae (T1a) and submucosa

(T1b). The management of early GC is outside of the scope of these guidelines.

Nonendoscopic management of GPMC

Recommendations: GPMC nonendoscopic management

16. We recommend *H. pylori* eradication in patients with GPMC (AG, GIM, and dysplasia) and resected EGC to reduce the risk of progression to GC and metachronous EGC, respectively (Moderate quality of evidence, strong recommendation).
17. We do not suggest the use of aspirin, nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, or antioxidants for individuals with GPMC for the purpose of GC chemoprevention (Very low quality of evidence, conditional recommendation).

H. pylori eradication

H. pylori is the dominant global risk factor for GC and has been classified by the World Health Organization's International Agency for Research on Cancer as a group 1 or definite carcinogen (173). The attributable risk is 75%–89% for noncardia gastric adenocarcinoma, which initiates and perpetuates the carcinogenesis cascade (12). *H. pylori* eradication is consistently associated with a significant reduction of GC incidence and mortality (174). In patients with high-risk GPMC, *H. pylori* eradication serves as an adjunct measure because it is not sufficient alone to prevent progression, again underscoring the role of endoscopic surveillance in individuals with high-risk GPMC (174,175).

The literature supporting *H. pylori* eradication in patients with GPMC comprises a range of studies, from population eradication to eradication in patients with resected early GC. In multiple RCTs (and meta-analyses of these RCTs), as well as observational studies successful eradication of *H. pylori* was associated with a substantial reduction in GC incidence and mortality (176–178). In the meta-analysis of 22 studies (8 RCTs, 16 cohort) by Ford et al (176), *H. pylori* eradication was associated with 46% and 39% risk reductions of GC incidence and mortality, respectively, in studies with follow-up ranging from 4 to 22 years. The risk reduction is significantly greater in individuals without GPMC at baseline (234). In the meta-analysis by Kahn et al, of 9 RCTs (6,967 patients) of *H. pylori* eradication in patients with EGC after endoscopic resection, there was a 53% reduction in GC incidence, in studies ranging from 3 to 6 years of follow-up. Also in this study, patients with GPMC treated for *H. pylori* infection demonstrated an improvement in histology, but with a nonsignificant trend (OR 0.47, 95% CI 0.42–1.07) toward GC incidence reduction (179) (see Supplement 1, Supplementary Digital Content 1, http://links.lww.com/AJG/D556). As an aside, the gastric mucosa-associated lymphoid tissue lymphoma is typically a low-grade B-cell neoplasia strongly associated with *H. pylori*-driven gastritis. A recent meta-analysis demonstrated a pooled complete remission of 75% with *H. pylori* eradication, with the effect modifier of t(11;18) status (180).

Until recently, the benefit of *H. pylori* eradication on GC incidence and mortality had not been directly demonstrated in US populations. However, 2 independent observational studies from 2020 to 2023 from US cohorts (a nationwide Veterans Health Administration and a Kaiser Northern California Health System cohort) demonstrated that *H. pylori* eradication resulted in a substantial and significant risk reduction, albeit delayed (e.g., 8 years post-eradication) (10,181).

Chemoprevention for GPMC

Apart from *H. pylori* eradication treatment, chemoprevention of GC for patients with GPMC is not currently recommended given the lack of potential agents and supporting data. Anti-inflammatory agents and antioxidants may reduce the risk of progression by inhibiting cytokines, prostaglandins, and angiogenesis (182). In secondary analyses, cardiovascular medications have also been studied, including statins, metformin, and aspirin. Quality prospective trials with GC incidence and mortality as the primary endpoints are lacking. The existing literature is compromised by heterogeneity, medication usage precision (dosage, regularity, and duration), concurrent medications, data completeness, and the population studied. These data are further discussed in Supplement 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/D556).

General prevention measures

In patients with GPMC, general behavioral recommendations are warranted related to tobacco and alcohol use, salt intake, and fresh fruit and vegetable consumption given that all of these factors are modifiable and may affect GC risk. Maintaining a healthy weight is also important, although the association between obesity and noncardia gastric adenocarcinoma is not as robustly established as the association with cardia and esophageal adenocarcinoma.

The quality of evidence related to the association between diet and behavioral factors and GC risk, specifically among individuals with GPMC, is low and the data are challenging to extrapolate due to heterogeneity in study design, population, exposure assessment, confounder adjustment, and recall bias. Few studies provide data specific to individuals with GPMC, and many studies also do not provide GC outcome data according to anatomic subsite. There are no data in US populations concerning diet and behavioral factors and the risk of GPMC progression. The uncertain benefit of positive diet and behavioral changes about GC risk specifically is balanced by other known health benefits. Tobacco use may have the strongest association with GC among the behavioral factors, and patients with GPMC should receive smoking cessation counseling. In Supplement 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/D556), we describe relevant data regarding the association between diet and behavioral factors and GC risk, emphasizing those studies that evaluated patients with GPMC or suspected GPMC.

Chronic acid suppression on the risk of GC and GPMC

PPIs irreversibly inhibit the H+/K+ ATPase (proton pump) leading to potent gastric acid suppression (183). Although PPIs are now among the most widely prescribed medications worldwide (e.g., gastroesophageal reflux disease and dyspepsia), the long-term carcinogenic risk related to chronic PPI use is unclear. Specifically, it is uncertain whether chronic hypochlorhydria due to PPI use and the resultant hypergastrinemia and potential gastric pancolonization of the antrum and corpus by *H. pylori* and other microbes (and their byproducts) increases the risk of gastric malignancy particularly in patients with GPMC. Potassium-competitive acid blockers, the newer class of potent gastric acid-suppressors that also inhibit the proton pump, have been less studied about their association with gastric neoplastic risk (184) (see Supplement 1, Supplementary Digital Content 1, http://links.lww.com/AJG/D556, for further discussion).

SPECIAL TOPICS: AIG AND GASTRIC POLYPS

Autoimmune Gastritis

Recommendations: AIG

18. Among individuals diagnosed with AIG, we recommend assessment for *H. pylori* infection with a nonserological test, eradication treatment if positive, and posttreatment testing to confirm eradication (Low quality of evidence, strong recommendation).
19. There is insufficient evidence to make a formal recommendation on endoscopic surveillance in individuals with AIG. Given the increased risk of type 1 neuroendocrine tumors (NETs) and the possible increased risk of GC, individualized surveillance may be considered (Low quality of evidence, conditional recommendation).

AIG is an immune-mediated condition whereby autoantibodies target and destroy parietal cells, resulting in progressive inflammation and eventual replacement of the native oxyntic mucosa with connective tissue (nonmetaplastic atrophy) or nonnative epithelium (metaplastic atrophy), in a background of chronic inflammation. Antral-sparing is the *sine qua non* of AIG in the absence of prior or concurrent *H. pylori* infection, based on systematic biopsies. The diagnosis is supported by positive autoantibodies to parietal cells and intrinsic factor. Autoantibodies alone have inadequate positive and negative predictive value for the diagnosis. Pernicious anemia is a rare, late-stage complication of AIG characterized by vitamin B12 deficiency, megaloblastic anemia, and usually with autoantibodies to intrinsic factor (see Supplementary Figure 1, Supplementary Digital Content 4, http://links.lww.com/AJG/D559). AIG is a progressive condition without cure or evidence of regression over time (185). There is a female:male predominance of approximately 3:1, and associations with older age and autoimmune disorders (see further discussion in Supplement 1, Supplementary Digital Content 1, http://links.lww.com/AJG/D556).

AIG is a preneoplastic condition, and endoscopic surveillance is indicated to allow for early detection and management of neoplasia. The ongoing inflammation in AIG leads to progressive oxyntic gland loss and the replacement of native glands with pyloric, intestinal, and pancreatic metaplasia and variable fibrous tissue. The parietal cell loss and resulting hypochlorhydria or achlorhydria lead to persistent stimulation of gastrin production from the antrum. Gastrin is trophic for both parietal and enterochromaffin-like cells. AIG is associated with well-differentiated NETs of enterochromaffin-like cells (also termed type I gastric carcinoid tumors). However, the independent association between AIG and gastric adenocarcinoma in the absence of concomitant *H. pylori* infection has been called into question (186–188).

Based on recent data, in the absence of *H. pylori* infection, the risk of gastric adenocarcinoma in patients with AIG seems to be similar to that of the baseline general population (186). In another Italian study of patients with corpus-restricted atrophy, at median follow-up of 5 (1–17) years, the annual incidence rate person-year of HGD/GC was 0.5% (187). However, caution is warranted given the relatively short follow-up time of the recent studies from the vantage point of cancer progression. Prior literature reporting an increased association did not appropriately control for current *H. pylori* infection, thus precluding assessment of an independent association between AIG and gastric adenocarcinoma specifically (179,186,189–195). Indeed, most of these studies were performed in an era before the formal discovery of *H. pylori* or when *H. pylori* prevalence was substantially higher than in the modern era. These findings underscore the importance of testing for *H. pylori* in any patient with metaplastic or nonmetaplastic AG.

There are no RCTs of surveillance vs no surveillance for the purpose of early neoplasia detection in patients with histologically confirmed AIG. However, given the increased risk of gastric NET and possibly gastric adenocarcinoma, endoscopic surveillance is suggested in the context of shared decision-making. In patients with pernicious anemia, there is evidence to suggest that the risk of GC is highest within the first year of diagnosis, and thus, endoscopy should be considered in patients with a new diagnosis of pernicious anemia, with particular consideration of women 50 years or older (196,197) (see Supplementary Algorithm 1, Supplementary Digital Content 3, http://links.lww.com/AJG/D558). Otherwise, there are limited data regarding risk stratification parameters in individuals with AIG; accordingly, we suggest that the endoscopic surveillance interval should be determined based on the same risk stratification factors as described above for GPMC in general (e.g., family history of GC, anatomic extent, and severity of GPMC). Patients with AIG are also at increased risk for nonneoplastic complications including other autoimmune disorders, particularly autoimmune thyroid disease and type I diabetes mellitus, nutritional deficiencies (due to achlorhydria/hypochlorhydria), and dermatologic manifestations (198).

Gastric epithelial polyps

Recommendations: GEP

20. We recommend endoscopic resection of all gastric adenomas, regardless of size, to exclude and prevent dysplasia and EGC. For adenomas that are not amenable to endoscopic resection, we recommend referral for surgical resection, if clinically appropriate (Low quality of evidence, conditional recommendation).
21. We could not make a recommendation on the endoscopic resection of all hyperplastic polyps greater than 10 mm in size based on the current evidence.
22. In individuals with GEP, with the exception of fundic gland polyps, we recommend systematic gastric biopsies be obtained from the surrounding mucosa given the high prevalence of GPMC, *H. pylori* infection, and AIG in these patients (Very low quality of evidence, conditional recommendation).

Diagnosis of GEP

GEPs are found in approximately 3%–10% of esophagogastroduodenoscopies performed in the United States, and most are incidental fundic gland polyps (FGPs, 40%–77%), followed by hyperplastic polyps (14%–40%) and gastric adenomas (3%–25%) (199). However, there is regional variation, which may reflect chronic PPI use (FGP association) and *H. pylori* prevalence (association with hyperplastic and adenomatous polyps) (106,200,201). Most GEPs arise in the setting of inflammatory conditions (e.g., *H. pylori* gastritis and AIG), and a limited

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number occurs in polyposis syndromes. Repeated episodes of mucosal injury and repair ultimately may lead to genetic mutations that induce neoplasia. Most polypoid gastric dysplastic lesions arise in a background of gastritis and metaplasia. Therefore, biopsy of the flat mucosa surrounding the gastric polyp and Sydney protocol biopsies are indicated, unless the polyp is clearly an FGP.

Sporadic FGPs are typically small, hyperemic, sessile and have a smooth surface contour (Figure 7). They occur exclusively in the gastric fundus and corpus. Occasionally sporadic FGPs harbor surface dysplasia; however, the risk of progression for these patients is essentially nil (202,203). FGPs may develop after long-term PPI use and are not associated with an increased risk of gastric adenocarcinoma. Multiple FGPs (>50) in young patients, especially those not taking PPIs, should raise suspicion for FAP and other polyposis syndromes (i.e., attenuated FAP, gastric adenocarcinoma, proximal polyposis of the stomach [GAPPS], and MUTYH-associated polyposis). These patients should be referred for genetic evaluation and colonoscopy, and their management is reviewed in detail in prior literature (204). Approximately one-third of FGPs in patients with FAP have surface dysplasia, but most do not progress except in patients with GAPPS (205).

Gastric hyperplastic polyps (particularly large ones) and adenomas are considered premalignant conditions (GPMC). Gastric hyperplastic polyps have a smooth, red buttered appearance with white exudates. While usually small and dome shaped, they can become lobulated or pedunculated with superficial erosions. Hyperplastic polyps are associated with gastric atrophy with or without intestinal metaplasia (206–208). Thus, it is important to biopsy the surrounding mucosa with a systematic gastric sampling protocol. Hyperplastic polyps may harbor dysplasia in 1.9%–19% of cases and undergo malignant transformation in up to 2% of cases (209,210). Neoplastic transformation is seen mostly in hyperplastic polyps >10 mm. Hyperplasia of the foveolar epithelium is a separate entity, with white flat lesions and a foveolar pit pattern. Limited evidence suggests that foveolar hyperplasia is a benign entity associated with chronic PPI use.

Sporadic gastric adenomas are rare. Polypoid gastritis-associated dysplastic lesions have been traditionally classified as adenomas, including by the World Health Organization (211). Because gastritis-associated dysplastic polyps have been termed "adenomas" (212–214) rather than "endoscopically defined dysplastic lesions," recent guidelines may create misunderstanding (215,216). Adenomas or adenomatous polyps are usually single lesions, pedunculated or sessile, in the antrum or incisura. They have a velvety pink lobulated appearance. They most often occur in the setting of *H. pylori*-associated gastric atrophy with or without metaplasia, arguing for systematic biopsies of the surrounding mucosa. Approximately 40% of adenomatous polyps harbor dysplastic foci, particularly those ≥20 mm. Adenomatous gastric polyps are also strongly associated with synchronous GC, which reflects the "field effect" of the surrounding mucosa harboring other stages along the Correa cascade (210,217,218). Gastric adenomas arising in the setting of normal gastric mucosa rarely occur, and this is usually in the setting of FAP (205,212,219).

Gastric NETs are typically hyperemic and multifocal but can have diverse endoscopic presentations difficult to differentiate from other GPMC. The diagnosis and management of NETs are beyond the scope of this guideline and are reviewed elsewhere (220).

Endoscopic management of GEP

The endoscopic approach to GEP is based on histologic subtype, polyp size, and morphologic features. However, during the index

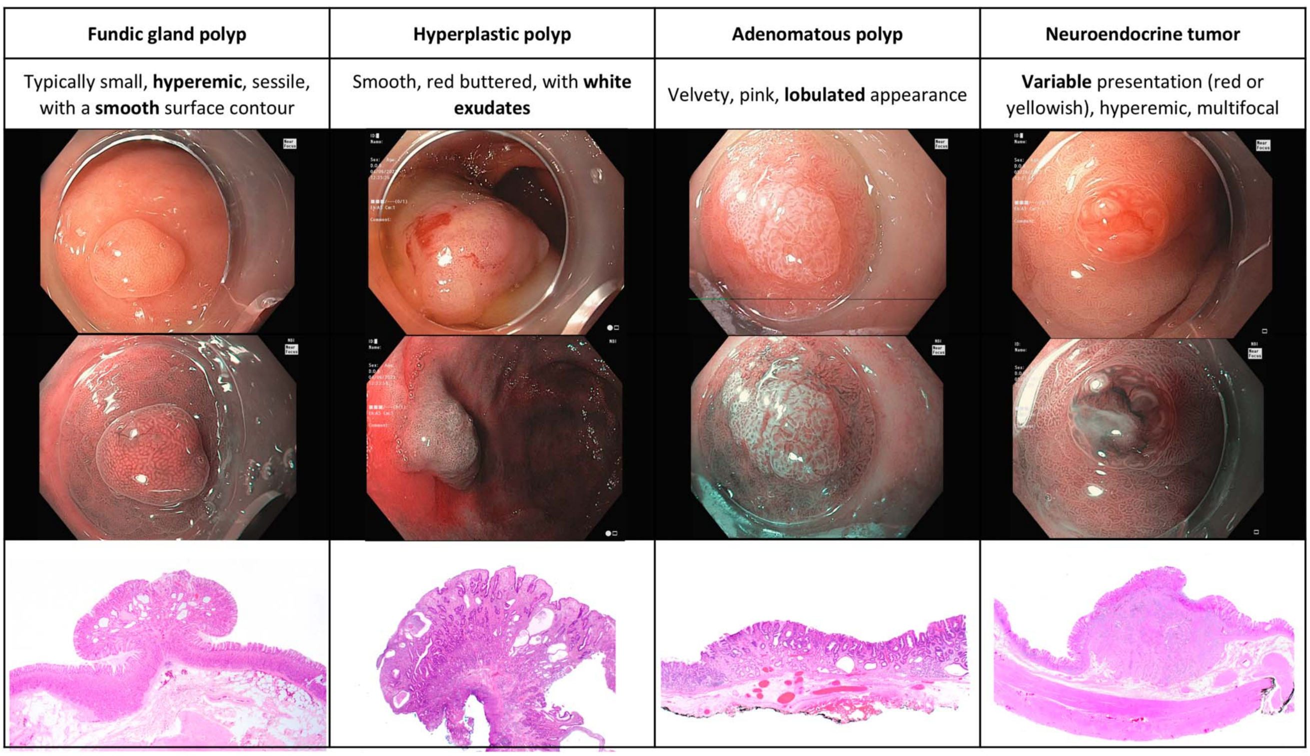

Figure 7. Gastric epithelial polyps: endoscopy (HDWLE, NBI) and histology correlation. HDWLE, high definition white light endoscopy; NBI, narrow band imaging.

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Table 5. Knowledge gaps and future research directions for GPMC and gastric cancer

Gastric cancer screening in the United States
• Randomized clinical trials are needed to evaluate the utility of GC/GPMC screening on GC incidence and mortality, and potential harms of screening
• Risk prediction models for GC/GPMC are needed to identify the optimal screening population. Initial US studies may incorporate "convenience endoscopy" paired with screening colonoscopy for patients at increased risk for GC. The optimal threshold for GC/GPMC screening using endoscopy alone without bundling with colonoscopy needs to be evaluated thereafter
• The effectiveness of existing noninvasive biomarkers (e.g., pepsinogens), alone or in combination, needs to be evaluated for their effectiveness for screening high-risk GC/GPMC populations. Novel noninvasive screening modalities (e.g., blood-based testing) are needed for GC/GPMC screening
• Barriers and adherence to GC/GPMC screening of eligible groups warrant investigation, particularly among marginalized high-risk groups
Diagnosis of GPMC
Endoscopic evaluation
• Implementation and validation of upper endoscopy quality metrics specifically targeting the gastric compartment (e.g., mucosal cleansing scores, gastric photodocumentation, and GIM detection rate)
• Development of training interventions for US endoscopists for the diagnosis and management of GPMC/GC
• The role of novel imaging (e.g., LCI) and synergistic technologies (machine learning, AI) in clinical algorithms warrant evaluation, along with cost-effectiveness studies
Histopathologic evaluation
• Develop standardized gastric pathology reporting systems, with consideration of GPMC
• Advance methods to improve adherence to systematic biopsy protocols among gastroenterologists and related gastric pathology reporting among pathologists
• Evaluate the outcomes for the current histology markers of GIM high-risk subtypes (e.g., incomplete and extensive GIM)
• Implement methods to improve the interobserver variability for reporting dysplasia, with a focus on IND and LGD
• Develop protocols for the use of the OLGA/OLGIM system in the gastroenterology and pathology disciplines, and investigate patient outcomes
GPMC endoscopic surveillance and dysplasia treatment
• Develop registries for the evaluation of the clinical impact of GPMC surveillance programs (e.g., proportion of GC diagnosed as early GC, GC incidence, and GC 5-yr survival)
• Investigate the optimal interval for endoscopic surveillance in patients diagnosed with GPMC according to a risk-stratified approach, which includes when to stop surveillance
• Develop robust risk prediction models that accurately predict AG/GIM progression in US populations and are prospectively validated
• Identify noninvasive (e.g., serum-based) and tissue-based markers of progression that are prospectively validated in US populations
• Prospective studies to evaluate the natural history of indeterminate and low-grade dysplasia
• Prospective studies to evaluate the optimal timeframe and approach to repeat endoscopic evaluation of nonvisible gastric dysplasia (i.e., "second-look endoscopy")
• Health-system research on optimization of referrals to high-volume ESD centers/providers in the United States. Perform microsimulation analyses with US data to evaluate the impact of ESD access and clinical outcomes for patients with dysplasia
• Develop and implement a standardized ESD curriculum in advanced endoscopy training programs
Nonendoscopic management of GPMC
• Enhanced efforts to identify chemoprevention agents for GPMC progression
• Develop robust interventional trials to understand the impact of diet and behavioral changes (e.g., smoking) on GPMC prevalence and GPMC progression
• Develop robust clinical trials to better understand the impact of chronic gastric acid suppression (e.g., PPI and PCAB) on GPMC and GPMC progression
Autoimmune gastritis
• Clarify the risk of adenocarcinoma in patients with autoimmune gastritis, with and without *H. pylori* infection
• Improve detection of autoimmune gastritis with attention to appropriate biopsy protocols
Gastric epithelial polyps
• Design studies to understand the natural history of hyperplastic polyps and adenomas, and the modulatory effects of background mucosal disorders (e.g., *H. pylori* infection and GPMC)
• Larger studies describing the risk of dysplasia and carcinoma in gastric polyps (5–20 mm)
• Prospective studies describing the adequate time interval for surveillance after resection of hyperplastic polyps and adenomatous polyps
Education initiatives
• Training initiatives, following the example of East Asia programs, are imperative to improve outcomes related to the diagnosis of GPMC and (early) GC, incorporation of novel imaging technologies, pathology protocols, and endoscopy therapeutics

AG, atrophic gastritis; AI, artificial intelligence; AIG, autoimmune gastritis; EGC, early gastric cancer; ESD, endoscopic submucosal dissection; GC, gastric cancer; GIM, gastric intestinal metaplasia; GPMC, gastric premalignant condition; LCI, linked color imaging; OLGA, Operative Link on Gastritis Assessment; OLGIM, Operative Link on Gastric Intestinal Metaplasia Assessment; PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

endoscopy, the definitive histologic subtype may not be clear. Therefore, obtaining biopsies from any GEP that is not an obvious FGP is recommended for histopathological assessment. One meta-analysis showed that forceps biopsy of hyperplastic and adenomatous polyps can miss foci of HGD or carcinoma. Specifically, 25% of these polyps were upgraded after complete excision, with gastric HGD in 16.7% and adenocarcinoma in 6.9%. Upstaging is more frequent in lesions ≥20 mm, and lesions with depressed or nodular features (160). If there are no contraindications, small GEP should be completely excised for both diagnosis and therapy, considering that complete excision is more likely to reveal dysplasia neoplasia (221). Data extrapolated from colon polypectomies suggest that diminutive polyps (≤3 mm) may be removed completely with forceps, but snare polypectomy is suggested for polyps >3 mm (222,223). In patients with larger polyps, concerns for bleeding, or incomplete resection, a "biopsy-then-resect" approach is advised allowing time to discuss with the patient the risks and benefits of endoscopic resection or referral.

The resection and surveillance plan should be tailored to the polyp subtype if previous histology results are available. FGPs (in the absence of FAP) seldom harbor dysplasia or adenocarcinoma (202,203). Excision of FGPs is only suggested if the polyp is >10 mm or ulcerated. Hyperplastic polyps may harbor dysplasia or carcinoma. Despite heterogeneity in the literature, with most reports being >30 years old or from high-incidence countries, carcinoma foci were frequently reported in polyps >10 mm (224,225). Therefore, several guidelines recommend resection of all hyperplastic polyps >10 mm or >5 mm (29,226). However, in weighing the uncertain benefit due to quality of the data and indirectness with the potential risk of complications due to resection (e.g., bleeding), we could not make a recommendation regarding the resection of all hyperplastic polyps >5 mm, although it seems prudent to resect hyperplastic polyps >10 mm. Adenomas are more likely to harbor microscopic carcinoma foci (5%–10% in small case series and up to 50% in polyps >20 mm) (218). Most consortia recommend resection of all adenomas regardless of size (29,216,227). Similar to flat lesions with dysplasia, hyperplastic polyps or adenomas ≤10 mm can be removed with EMR, but ESD should be considered for lesions >10–20 mm (160,167).

Most international GI societies recommend surveillance endoscopy after resection of hyperplastic polyps or adenomas, but high-quality data informing optimal surveillance intervals are lacking (29,216). Current evidence demonstrates no clear benefit from performing surveillance endoscopy after complete excision of high-risk sporadic FGP (228). Considering that gastric adenomas are strongly associated with synchronous neoplasia (up to 30%), follow-up endoscopy is recommended within 12 months regardless of background mucosa (e.g., GIM). In patients with resected hyperplastic polyps >10 mm, surveillance endoscopy can be considered in 12 months (207,229). Subsequent surveillance endoscopies for adenomas and hyperplastic polyps are dictated by the background mucosa, per GPMC surveillance recommendations herein.

CONCLUSIONS

The GPMC research agenda to support the implementation, evolution, and optimization of clinical practice related to the diagnosis and management of GPMC in the United States is extensive (Table 5). Critical areas include the study of health outcomes related to GPMC surveillance, screening for GC, barriers to prevention in marginalized populations, novel diagnostic and prognostic biomarkers, advancement of endoscopic technologies (e.g., IEE, AI, and therapeutics) and gastroenterology training, novel *H. pylori* treatment and adjuvant measures, and chemoprevention, specifically as these relate to the impact on GC incidence and mortality. Coordination with pathology colleagues at the local and national levels is imperative. Research in AIG and GEP is needed, each area with substantial knowledge gaps. In parallel, training initiatives, following the example of East Asia programs, are critical, particularly in the areas of endoscopic diagnosis and therapeutics.

These ACG Guidelines for the management of GPMC are a paradigm shift in US clinical practice. Implementation and change in clinical practice will require concrete targets and include training and quality initiatives. It is anticipated that this will begin to address the marked US GC disparity, and the burden on minority and marginalized populations. The overarching goals are to reduce GC incidence in the United States, increase the detection of early stage disease (early GC), and to significantly increase the 5-year survival rates in the near term.

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CONFLICTS OF INTEREST

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