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ACG Clinical Guideline: Diagnosis and Management of Gastric Premalignant Conditions

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Abstract

Gastric premalignant conditions (GPMC) are common and include multifocal atrophic gastritis (AG), gastric intestinal metaplasia (GIM), dysplasia, and certain epithelial polyps. GPMC have an increased risk of progression to gastric adenocarcinoma. Gastric cancer (GC) in the United States (U.S.) represents an important cancer disparity, as incidence rates are 2 to 13-fold greater in non-White individuals. Early-generation immigrants from regions of high GC incidence contribute to the U.S. 5-year survival rates which fall short of global standards. These guidelines represent the first iteration of ACG guidelines on this topic and encompass endoscopic surveillance for high-risk GPMC patients, 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, as well as 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

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CONFLICTS OF INTEREST

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US populations deemed high-risk for GC. Surveillance endoscopy is recommended for individuals at high risk for GPMC progression, as defined by histologic and demographic factors, typically every 3 years, but an individualized interval may be warranted. *H. pylori* testing, treatment and eradication confirmation is recommended in all individuals with GPMC. Extensive high-quality data from U.S. 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 survival in the U.S.

INTRODUCTION

Gastric cancer (GC) is the leading infection-associated cancer and the fourth leading cause of cancer-related mortality globally, with over 1 million new cases diagnosed and over 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 (U.S.) 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 U.S. 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) Several studies and meta-analyses indicate that GC risk and mortality are maintained among immigrants from high to low-incidence countries, (6) with incidence rates ranging from 2-fold to 13-fold higher in specific non-White populations compared to non-Hispanic White individuals. (7, 8) GC ranks among the top 8 leading causes of cancer death in U.S. Hispanic and Asian American populations, compared to ranking 15th in the overall U.S. population. (9) Based on 2020 data from the Pew Research Center, over 40 million people living in the U.S. were born in another country, with approximately one-third 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 U.S. population.

Although GC represents a major cancer disparity in the U.S., this cancer has long been under-recognized 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 U.S. populations that *H. 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, appears 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 U.S. 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 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 and cumulative duration of infection, host genetics and responses, and dietary and environmental factors. While 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 as the primary outcome of interest unless otherwise stated. In this 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 non-endoscopic management of GPMC, and then conclude with two special topic sections on the diagnosis and management of autoimmune gastritis (AIG) and gastric epithelial polyps (GEP) as respective subsets of these patients have an increased risk of GC. As detailed in this document, the diagnosis of GPMC in the U.S. necessitates upper endoscopy, and thus guidance regarding which asymptomatic individuals warrant upper endoscopy for GPMC and GC diagnosis and risk stratification is relevant.

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 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 author 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 two 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, followed by observational studies). In addition to the GRADE recommendations, the authors generated Key Concept statements, which are not amenable to GRADE assessment. We prioritized evidence from U.S. populations, and where U.S. data was limited or lacking, we relied upon high quality data from non-U.S. populations, which is acknowledged in the main text where relevant. Table 2 and Table 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; non-adenocarcinoma gastric cancer; the gastric mucosa-associated lymphoid tissue (MALT) lymphoma (GML), therapeutic management of gastric cancer including endoscopic resection; and post-diagnostic management of gastric cancer 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 U.S. 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. Accordingly, we have compiled a summary identifying key knowledge gaps to guide the future research agenda (Table 5).

Risks factors for gastric cancer in U.S. populations

The U.S. is considered a low-intermediate GC incidence country overall, with an ASIR of 6.5 per 100,000 person-years. However, in certain U.S. populations, the incidence rates of GC are 2–13 times higher versus whites, and surpass those of esophageal cancer or comparable to those of colorectal cancer. (4, 5) GC ranks among the top 8 leading causes of cancer death in U.S. Hispanic and Asian American populations, compared to ranking 15th in the overall U.S. population. (9) Multiple factors are associated with an increased risk of GC, including precancerous gastric mucosal changes (e.g., multifocal AG, 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 autoimmune gastritis (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 U.S. Hispanic and Asian American populations, compared to ranking 15th in the overall U.S. population. (9) Compared with non-Hispanic White individuals, East Asian and Pacific Islander, Black, Hispanic, American Indian and Alaska Native (AIAN) individuals have significantly higher incidence of non-cardia gastric adenocarcinoma (NCGA). (7, 9) A population-based study using California Cancer Registry data reported that age- and sex-standardized incidence of NCGA among individuals 50 years or older (i.e., a screening-age population) were 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 U.S. population.

Immigrant populations contribute in part to the race and ethnicity disparity of GC incidence in the US. 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 markedly higher incidence and mortality of GC among first-generation immigrants from high to low-incidence geographic areas, with the pooled relative risk for all types of GC (measured as standardized incidence ratio) 1.66 (95% 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 for additional discussion).

Family history

Individuals with a family history of GC a 2- to 10-fold higher risk of GC compared to 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 and *H. pylori* infection and strains, shared environmental (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., BRCA). (20, 21) Based on one study, patients with GIM and a first-degree family history of GC have 4.5-fold higher odds (OR, 4.53; 95% CI, 1.33–15.46) of GC compared to patients with GIM and negative family history. (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 versus shared non-genetic 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 gastric cancer

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: 1) Hereditary GC syndromes: hereditary diffuse GC, familial intestinal GC, and gastric adenocarcinoma with proximal polyposis of the stomach; and 2) Hereditary syndromes with an increased GC risk: Lynch Syndrome, hereditary gastrointestinal polyposis syndromes (familial adenomatous polyposis, 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, ATM). (Table 4) Patients with a family history suggestive of hereditary cancer should be referred to Genetic Counseling, and potential endoscopic screening should be individualized based upon the syndrome-specific guidelines and patient preferences. (24–27)

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

Routine screening with upper endoscopy for GC and GPMC in the low-risk general U.S. population is not indicated given the overall low-to-moderate incidence, the lack of cost-effectiveness, and the absence of evidence. While focused screening of high-risk populations in the U.S. may address the GC cancer disparity, there is a lack of evidence in the US to make a recommendation. The evidence is limited to cost-effectiveness studies of U.S. populations and indirect evidence from regions with screening programs, primarily in East Asia.

The indirect 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 U.S. populations with a high incidence of GC, including East Asian individuals, Latino/a groups, Black persons, 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) 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, e.g., male sex, smoker, and with a family history. (29) Examples of nascent screening studies in high risk groups include combined *H. pylori* – FIT testing and opportunistic endoscopy with screening colonoscopy

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

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

The vast 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 over 39 million adults > 40 years-old who underwent screening endoscopy between 2007–2016, 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% relative risk 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 to individuals who were never screened. (43) With implementation of GC screening in Japan and South Korea, approximately 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 prior to 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 U.S., 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 US is 33%, comparable to the pre-screening implementation rates in South Korea and Japan.

These non-U.S. 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 U.S.

Cost-effectiveness studies provide additional indirect evidence for endoscopic screening among at-risk populations in the US. This complements a large body of evidence demonstrating the cost-effectiveness of endoscopic GC screening in East Asian countries and Portugal. (48–52) Saumoy and colleagues assessed the cost-effectiveness of screening for NCGA 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 [QALY]), Hispanic (\$76,070/QALY), and non-Hispanic Black (\$80,278/QALY) individuals, but not for non-Hispanic White individuals (\$122,428/QALY). In contrast, biennial EGD for screening irrespective of histologic findings was not cost-effective. Using the same screening strategies (vs no screening), Shah and colleagues demonstrated the cost-effectiveness of endoscopic GC screening among the most populous East Asian American populations in the U.S. 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 (ICERs) 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 U.S.-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.

Non-invasive biomarkers are a desirable and potentially cost-effective approach for identifying patients who would benefit from upper endoscopy and potential endoscopic resection of neoplasia. Candidate non-invasive tests 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 (MIF-1), trefoil factor family 3, (TFF-3), reprimin, or a combination of these. (55, 56) Blood multiomic technologies are under study and may offer an appealing approach. Overall, and particularly in the U.S., definitive studies are lacking regarding efficacy of non-invasive biomarkers for the purpose of screening or surveillance for GPMC and GC. Based on a review of the evidence, which is summarized in the Supplement 1, non-invasive biomarkers are lacking that would 1) replace upper endoscopy or 2) serve as a method to discriminate subjects at low versus high-risk of GPMC, GPMC progression, or GC and warrant referral for upper endoscopy.

Quality endoscopy considerations

The endoscopic and histopathologic evaluations are the core of GPMC diagnosis. A primary goal of upper endoscopy is the early detection of gastric dysplasia and cancer, ideally at a stage for which endoscopic resection is curative. A second goal is the diagnosis and assessment of the severity and extent of AG and GIM to identify the patients 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 exam 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: 1) individuals with known GPMC or prior GC with indications for surveillance; 2) individuals at increased risk for GPMC or GC (e.g., family history, early-generation immigrant from high-incidence region); 3) 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 early 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 gastric mucosa should be routinely documented in the endoscopic report, analogous to reporting bowel preparation quality in colonoscopy reports.

Endoscopists trained 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 endoscopist training level. (29, 69–72)

Photodocumentation of each of the gastric stations and any abnormal findings is important to structure the endoscopic exam. 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 U.S. population and considering time feasibility, we advocate for, at minimum, photodocumentation of six anatomic stations: three antegrade images of the corpus-greater curvature, corpus-lesser curvature, and antrum-pylorus; and three 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 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 monitor) to be HD compatible. All major endoscopy manufacturers now offer HD gastroscope systems in the US (Olympus 190 series; Pentax 2990i and 2790i; Fujinon 590 series). (75) HDWLE systems offer electronic magnification of 1.5x or 2x.

Chromoendoscopy is achieved with topical dyes or “virtually” with modifications of light wavelength or computer image processing herein, labeled as image-enhanced endoscopy (IEE). Topical dye chromoendoscopy evaluates the mucosa after spraying Lugol’s iodine or indigo carmine. Virtual chromoendoscopy is the most practical for use in the US. The optical image processing utilizes one of three commercially available modalities: Narrow Band Imaging (NBI) from Olympus, Fujinon Intelligent Color Enhancement (FICE) from Fujinon and IScan® from Pentax. Emerging endoscopic technologies and the potential environmental impact of a GPMC surveillance program are reviewed in Supplement 1.

Recognition and categorization of GPMC

Endoscopy can identify GPMC as visible non-polypoid or polypoid mucosal changes, or as ‘non-visible’ mucosal changes that are identified incidentally on biopsies collected for other purposes (e.g. evaluation of dyspepsia). Three mucosal changes should be identified endoscopically: 1) AG, 2) GIM, and 3) dysplasia. Endoscopy alone cannot reliably

differentiate between dysplasia (i.e., indefinite for dysplasia/ IND, low-grade dysplasia/ LGD, high-grade dysplasia/HGD) and early GC 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. Recognition of GPMC mucosal changes on HDWLE is the important initial step in the gastric evaluation, and IEE. Herein, we use the term “HDWLE with IEE” to refer to the common U.S. setting with the use of HDWLE with NBI, with or without optical zoom. (77) We note that NBI 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, confocal endomicroscopy), and contrasts with IEE with linked color imaging (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 (RAC) venules. (Figure 2). Gastric folds are typically 5–10mm thick in the fundus and body and traverse in parallel, with flattening towards 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 RAC appear 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 four hallmark endoscopic findings that characterize gastric atrophy: 1) pallor, 2) loss of gastric folds, 3) prominence of the visible submucosal vessels (submucosal venules) and 4) a border between atrophic and normal mucosa in patients with *H. pylori*-related atrophic gastritis (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 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 in two patterns, *H. pylori*-related atrophic gastritis and autoimmune gastritis (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 atrophic gastritis, 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 specificity

of 90% and is better appreciated using NBI. (85) Other features of GIM on HDWLE and NBI with near-focus are: light blue crest sign (LBC, sensitivity of 48–89% and specificity of 93–96% (85–87)), marginal turbid band (MTB, sensitivity 100% and specificity 66%), (86) and the “white opaque substance (WOS)” sign, which appears as nodular patches of white raised mucosa and histologically represents accumulation of lipid droplets. (88) The LBCs 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 early GC are nonspecific and subtle. Dysplasia manifests either erythema or pallor, slight 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 (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 or endoscopic submucosal dissection when feasible. (93)

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, corpus), severity and extent of AG and GIM, and subtype of GIM. The Sydney system for evaluation of gastritis was developed in the 1990s, and consists of systematic biopsies of five 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 five sites and placed in two separate jars (antrum/incisura and corpus). Biopsies may be “directed” within each of the five 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, 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 upon 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 U.S. (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 GPMC refers to the proportion of GIM or atrophy in individual biopsies in each compartment (antrum, incisura, corpus). Increased severity of GPMC 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. OLGA/OLGIM is not routinely used in the U.S. and therefore U.S. specific data are limited (Figure 4).

All samples concerning for dysplasia, including IND, LGD, HGD, should be reviewed by a pathologist with expertise in gastrointestinal pathology. Many cases are diagnosed as 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 non-steroidal anti-inflammatory drug use, are addressed and removed as 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 gastric cancer differently (e.g., carcinoma in situ may be classified as cancer, but in the U.S. this would be classified as HGD).

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 U.S. 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, 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 1.5–3.5-fold. (17, 114–119) We emphasize that the risk factors for the development GPMC and GC and the progression from GPMC to GC overlap, yet the dominant risk factors likely vary for the three 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

Non-dysplastic 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 gastric cancer, compared to normal gastric mucosa. (120) This study excluded the first two 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 one 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 0.16% (95% CI, 0.15%–0.17%). (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, diet), (123, 124) which 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 2.0–20-fold higher risk of progression to GC. (22, 123) These risk factors include corpus-extended GPMC, incomplete-type GIM, moderate-severe AG or GIM (i.e., OLGA/OLGIM III-IV, see **INSERT** and Supplement 2), and family history of GC in a first-degree relative. In 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

while 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 U.S. 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.

Histologic Determinants of Non-dysplastic 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 U.S., since GIM is often diagnosed incidentally on upper endoscopy performed for other indications and without adequate sampling. (129) In one U.S. population-based study, 66% of patients with GIM had the anatomic location categorized as “not otherwise specified”. (129) In the U.S., the GIM histological subtypes are rarely reported on pathology reports.

Anatomic extent. In retrospective cohort studies conducted in US populations, corpus-extended GIM appears to have a higher risk of progression to GC compared to GIM limited to the antrum and incisura. (22, 108, 129) The findings are generally similar in high-risk populations outside the U.S. 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 non-significant higher risk of GC compared to 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 to 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 U.S. 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 one biopsy specimen containing AG/GIM, is associated with lower risk than multifocal AG/GIM, which is defined as at least two biopsies containing AG/GIM.

Histologic severity. Moderate to severe AG/GIM is associated with substantially higher risk of GC compared to mild AG/GIM and is a strong predictor of progression. However, reporting of histologic severity of AG/GIM in routine U.S. clinical practice is not always performed. As previously noted, OLGA/OLGIM is a histopathologic staging system that considers both the anatomic location and histologic severity of AG/GIM that is regularly used in other Western countries (e.g., Europe, Latin America) but not the U.S. Based on robust data, including a meta-analysis of two 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 relative risk of GC compared to mild-intermediate AG/GIM (stage 0/I/II). (113, 131, 132) The use of OLGA/OLGIM staging is limited in the U.S., and therefore, data are minimal in U.S. 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.

GIM subtype. Several studies and meta-analyses consistently report a several-fold higher risk of progression in patients with incomplete-type GIM compared to complete-type GIM histology. (133–135) One meta-analysis published in 2021 of 12 cohort studies comprising nearly 6500 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- 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) Also based on meta-analysis, the presence of only complete-type GIM does not appear to confer a higher risk of GC compared to 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 since no studies were identified from U.S. populations.

Active *H. pylori* infection. Active infection is another risk factor associated with GPMC progression, whereas successful *H. pylori* eradication is associated with stable histology or 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.

Additional Determinants of Non-dysplastic GPMC Progression

A family history of GC, particularly in a first-degree relative, is a strong risk factor for incident GC among patients with non-dysplastic GPMC, although there are mixed data. (17) Based on a meta-analysis of four studies, including one from the U.S., 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, as only the U.S. study showed an association. (17) Family history showed a null association in the Singapore “GCEP” study with multi-ethnic 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 U.S. population-based study reported a null association between smoking history and GIM progression. (22) In 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 to non-smokers, while 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-U.S. populations regarding the predictive value of serum biomarkers (e.g., pepsinogens), with respect to 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. Additionally, 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 to 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 shown to have invasive cancer within 12 months. (125, 150) In one retrospective study in Australia, of 160 dysplasia patients, 26.9%, 57.5%, and 15.6% were classified as HGD, LGD, and IND, respectively, the majority of which were classified as non-polypoid (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 exam, and 4.8% developed an interval cancer (defined as >12 months following index). The literature has also demonstrated similar rates of HGD “regression”, ranging from 0–33% 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 when associated with a visible lesion, as detailed below, as a diagnostic and therapeutic intervention. One retrospective study of 119 patients with biopsy-confirmed IND found that on resection, 26 (21.8%) had early gastric cancer; lesion, and diameter ≥ 10 mm and surface erythema were both independently associated with gastric cancer. (154) In the Australian cohort cited above, among patients with LGD undergoing surveillance only (mean follow-up 2.3 $\pm$ 2.1 (SD) years), 7.9% had cancer identified at the index exam, 5.3% developed interval cancer, 28.9% had unchanged pathology, while 57.9% demonstrated no dysplasia on follow-up exams. These LGD estimates are similar in other cohorts. (1, 139, 141, 149) As in the case of non-dysplastic GPMC progression, U.S. data and novel biomarkers are needed.

GPMC “Regression”

Longitudinal data from large prospective non-U.S. cohorts (e.g., Singapore, northern Europe, Colombia, Chile) support the observation that GPMC may improve or “regress”, particularly in AG after *H. pylori* eradication in patients with less severe baseline histology. (22) (101, 123, 126) (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, Correa Score) provide an ordinal system to detect change, yet the global diagnosis (e.g., AG, GIM) may not change. Lastly, there is important inter-observer variability among pathologists, particularly with mild AG and IND/LGD.

Endoscopic surveillance and intervals for non-dysplastic GPMC

The sojourn time of non-dysplastic GPMC to GC is relatively long, which allows the opportunity for endoscopic surveillance for early gastric neoplasia detection and resection. Resection of early gastric neoplasia prior to 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 exam is to identify neoplasia, while the secondary purpose is to appropriately risk-stratify patients with GPMC. The individual surveillance endoscopy recommendation should be based upon patient-physician decision-making, patient comorbidities, and overall prognosis. (Figure 5).

Surveillance vs. no surveillance based on risk. There are no prospective randomized controlled trials evaluating patient outcomes associated with endoscopic surveillance vs no surveillance, nor surveillance intervals, especially the impact on gastric cancer-related mortality within or outside the U.S. There is, however, a sizeable body of non-U.S. 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 GPMC categorized as high-risk 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 non-dysplastic GPMC may be considered low-risk. In a cross-sectional study of 415 U.S. 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 exam, as 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 exam (~1–2 years) with Sydney protocol biopsies. (155) However, there are currently no U.S. 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 U.S. population in mind are illustrative and provide guidance regarding an individualized approach 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, underscoring the critical 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/mortality and is cost-effective (\$40,706/QALY) from a U.S. 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) For comparison, colorectal cancer screening in the average-risk population compared to no screening results in 286–335 life-years gained per 1000 (LYG/1000). Based on the microsimulation analysis by Thiruvengadam, endoscopic surveillance of incidentally diagnosed GIM results in 87–190 LYG/1000 in all-comers, 351–851 LYG/1000 in individuals with a first-degree family history of GC, 157–335 LYG/1000 in individuals with anatomically extensive or incomplete-type GIM, and only 43–97 LYG/1000 in individuals with antrum-limited, complete-type GIM. (157)

Based on available data, including indirect data from modeling studies cited above, we would recommend that patients with GPMC and any of the following high-risk features be considered for endoscopic surveillance at the 3-year interval: GIM histology (corpus-extension, 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 every 3 years based upon the global literature, with consideration of a 2-year interval if they have any of the above risk factors.

The plan for endoscopic surveillance for a patient would be individualized, and is based upon 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 may also warrant surveillance. (130) In case above, if the complete GIM limited to the antrum were graded as mild-moderate, but the patient is a male with ongoing heavy tobacco use, surveillance could be discussed.

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 U.S., 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 since: 1) concomitant *H. pylori* infection may impact the diagnostic certainty of dysplasia; 2) *H. pylori* eradication is associated with reduced risk of progression, particularly for IND and LGD; and 3) 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 volumes or experience in managing GPMC, or if there is concern about the quality of the initial exam, referral to a high volume center with ESD expertise is preferred. This exam serves several purposes that are relevant for clinical decision-making, specifically allowing: 1) repeat visualization to characterize the area in question; 2) biopsies of the surrounding flat mucosa along with Sydney protocol biopsies, for informing surveillance intervals; and 3) repeat evaluation for other neoplasia missed on the index sampling, 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 mucosa. For visible lesions found on endoscopy, endoscopic resection serves both diagnostic and therapeutic purposes. One out of four 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 complete 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 following dysplasia resection is indicated after resection given the high risk of metachronous lesions. (161, 162) The duration of surveillance following resection is not clear. Borrowing from the literature of metachronous gastric cancer occurrence following endoscopic resection of early gastric cancer, surveillance should continue for at least 10 years post-resection, 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 10mm, with HGD, or depressed lesions are more likely to harbor carcinoma and should be resected with ESD. (160, 167) Compared to 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 post-procedure 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 <20mm 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.

Non-visible dysplasia.

In patients with dysplasia without visible lesions, so-called ‘non-visible 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 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 non-visible HGD, with pathology confirmed by an expert GI pathologist, the second-look exam 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 following measures to reduce inflammation (*H. pylori* eradication, NSAID cessation). With *H. pylori* infection, the second-look endoscopy is ideally performed at least one 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 non-visible IND/LGD where there is concomitant erosive esophagitis; PPI initiation or optimization 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 non-visible dysplasia, patients who are medically appropriate should enter regular endoscopic surveillance. Patients with non-visible HGD should undergo endoscopic surveillance in 3–6 months, while for those with non-visible IND or LGD, every 6–12 months is reasonable. Additional risk factors such as a prior history of GC, multifocal GPMC, family history of gastric cancer 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 GPMC surveillance intervals is reasonable. Apart from the natural histologic course of GPMC, 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.

While there is a role of endoscopic ultrasound (EUS) in staging early gastric cancer (EGC), data do not support the use of EUS in the evaluation of GPMC. In addition, Japanese pathologists recognize the concept of intraepithelial carcinoma, but this concept is not accepted by most Western pathologists. (109) EGC is defined as adenocarcinoma limited to the mucosa, including the muscularis mucosae (T1a) and submucosa (T1b). The management of EGC is outside of the scope of these guidelines.

***Helicobacter pylori* eradication:** *H. pylori* is the dominant global risk factor for gastric cancer and has been classified by the World Health Organization's International Agency for Research on Cancer (IARC) as a group 1 or definite carcinogen. (173) The attributable risk is 75–89% for noncardia GC, 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, since it is not sufficient alone to prevent progression. (174, 175)

The majority of the literature supporting the eradication of *H. pylori* for patients with GPMC comprises a range of studies, from population eradication to eradication in patients with resected early GC. In multiple clinical trials, observational studies, and meta-analyses, successful eradication of *H. pylori* was associated with a substantial reduction in GC

incidence and mortality. (176–178) (ACG *H. pylori* GL) In the meta-analysis of 22 studies (8 RCTs, 16 cohort) by Ford, et. al., *H. pylori* eradication was associated with 46% and 39% risk reductions of GC incidence and mortality, respectively, in studies with follow-up ranging from 4–22 years. (176) In the meta-analysis by Kahn et. al., of 9 RCTs (6967 patients) of *H. pylori* eradication in patients with EGC after endoscopic resection, there was a 53% reduction in GC incidence, in studies ranging from 3–6 years of follow-up. Also in this study, patients with GPMC treated for *H. pylori* infection demonstrated an improvement in histology, but with a non-significant trend (OR 0.47; 95% CI 0.42–1.07) towards GC incidence reduction. (179) (See Supplement 1). As an aside, the gastric mucosa-associated lymphoid tissue (MALT) lymphoma (GML) 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 U.S. populations. However, two independent observational studies from 2020 and 2023 from U.S. 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 ASA. 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.

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 impact GC risk. Maintaining a healthy weight is also important, although the association between obesity and noncardia GC 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 gastric cancer 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 gastric cancer outcome data according to anatomic subsite. There are no data in U.S. populations concerning diet and

behavioral factors and the risk of GPMC progression. The uncertain benefit of positive diet and behavioral changes with respect to 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, 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 gastric cancer and GPMC

Proton pump inhibitors (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 (eg, GERD, 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 GPMC patients. Potassium-competitive acid blockers (PCAB), the newer class of potent gastric acid-suppressors that also inhibit the proton pump, have been less studied with respect to their association with gastric neoplastic risk. (184) (See Supplement 1 for further discussion).

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 (non-metaplastic atrophy) or non-native 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 upon 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. (Supplement Figure 1). 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).

AIG is a preneoplastic condition and endoscopic surveillance is indicated to allow for early detection and management of neoplasia. AIG is associated with well-differentiated neuroendocrine tumors (NET) of ECL cells (also termed type I gastric carcinoid tumor). However, the independent association between AIG and gastric adenocarcinoma in the absence of concomitant *H. pylori* infection has been called into question. (186–188) 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 leads to persistent stimulation of gastrin production from the antrum. Gastrin is trophic for both parietal and ECL cells.

Based on recent data, in the absence of *H. pylori* infection, the risk of gastric adenocarcinoma in patients with AIG appears to be similar to that of the baseline general population. (189) 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, 190–196) 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 non-metaplastic AG.

There are no randomized controlled trials of surveillance versus 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 gastric cancer 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 over age 50. (197, 198) (Supplement Algorithm 1). 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, etc). Patients with AIG are also at increased risk for non-neoplastic complications including other autoimmune disorders, particularly autoimmune thyroid disease and type I diabetes mellitus, nutritional deficiencies (due to achlorhydria/hypochlorhydria), and dermatologic manifestations. (199)

Diagnosis of Gastric Epithelial Polyps

GEP are found in approximately 3–10% of EGDs performed in the U.S. and most are incidental fundic gland polyps (FGPs, 40–77%), followed by hyperplastic polyps (14–40%) and gastric adenomas (3–25%). (200) However, there is regional variation, which may reflect chronic PPI use (FGP association) and *H. pylori* prevalence (association with hyperplastic and adenomatous polyps). (106, 201, 202) Most GEP arise in the setting of inflammatory conditions (e.g. *H. pylori* gastritis, AIG), and a limited number occur 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 FGP 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. (203, 204) 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, GAPPS, and MUTYH-associated polyposis). These patients should be referred for genetic evaluation and colonoscopy, their management is reviewed in detail in prior literature. (205) Approximately one-third of FGPs in patients with FAP have surface dysplasia, but most do not progress except in patients with GAPPS. (206)

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. (207–209) 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. (210, 211) Neoplastic transformation is seen mostly in hyperplastic polyps >10mm. 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 (WHO). (212) Because gastritis-associated dysplastic polyps have been termed “adenomas” (213–215) rather than “endoscopically defined dysplastic lesions”, recent guidelines may create misunderstanding. (216, 217) 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 ≥20mm. 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. (211, 218, 219) Gastric adenomas arising in the setting of normal gastric mucosa rarely occur and this is usually in the setting of FAP. (206, 213, 220)

Gastric NET 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. (221)

Endoscopic management of Gastric Epithelial Polyps

The endoscopic approach to GEP is based on histologic subtype, polyp size, and morphologic features. However, during the index 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 ≥20mm, 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. (222) Data extrapolated from colon polypectomies suggests that diminutive polyps ($\leq 3\text{mm}$) may be removed completely with forceps, but snare polypectomy is suggested for polyps $>3\text{mm}$. (223, 224) 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. (203, 204) Excision of FGPs is only suggested if the polyp is $>10\text{mm}$ 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 $>10\text{mm}$. (225, 226) Therefore several guidelines recommend resection of all hyperplastic polyps $>10\text{mm}$ or $>5\text{mm}$. (29, 227) 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 $>5\text{mm}$, although it seems prudent to resect hyperplastic polyps $>10\text{mm}$. Adenomas are more likely to harbor microscopic carcinoma foci (5 to 10% in small case series, and up to 50% in polyps $>20\text{mm}$). (219) Most consortia recommend resection of all adenomas regardless of size. (29, 217, 228) Similar to flat lesions with dysplasia, hyperplastic polyps or adenomas $\leq 10\text{mm}$ can be removed with EMR, but ESD should be considered for lesions $>10\text{--}20\text{mm}$. (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, 217) Current evidence demonstrates no clear benefit from performing surveillance endoscopy after complete excision of high-risk sporadic FGP. (229) 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 $>10\text{mm}$ surveillance endoscopy can be considered within 12 months (208, 230) Subsequent surveillance endoscopies for adenomas and hyperplastic polyps are dictated by the background mucosa, per GPMC surveillance recommendations herein.

CONCLUSIONS

The GPMC research agenda is extensive to support the implementation and evolution of the diagnosis and management of gastric premalignant conditions in the U.S. (Table 5). Critical areas include the study of health outcomes related to GPMC surveillance, barriers to prevention in marginalized populations, novel biomarkers, evolution of endoscopic technologies (eg, IEE, AI, therapeutics), novel *H. pylori* treatment and adjuvant measures, chemoprevention (e.g., GIM), and impact on gastric cancer incidence and survival. Coordination with pathology colleagues at the local and national levels is imperative. Research in autoimmune gastritis and gastric epithelial polyps 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.

The Guidelines for the management of gastric premalignant conditions are a paradigm shift in U.S. clinical practice, to provide surveillance recommendations that align with those of the esophagus and colon. Implementation and change in clinical practice will require concrete initiatives and include training and quality initiatives. It is anticipated that this will begin to address the marked U.S. gastric cancer disparity, and the burden on minority and marginalized populations. The overarching goals are to reduce the incidence in the U.S., increase the detection of early stage disease (early gastric cancer), and to significantly increase the 5-year survival rates in the near term.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AG	Atrophic gastritis
AIG	Autoimmune gastritis
ASIR	Age standardized incidence rate (per 100,000 population)
BRCA	breast cancer gene (1 and 2)

CRC	Colorectal cancer
EGD	Esophagogastroduodenoscopy
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
GC	Gastric cancer
FGP	Fundic gland polyp
GIM	Gastric intestinal metaplasia
GML	gastric mucosa-associated lymphoid tissue (MALT) lymphoma
GPMC	Gastric premalignant conditions
HDWLE	High-definition white light endoscopy
HGD	High-grade dysplasia
HpAG	Helicobacter pylori associated atrophic gastritis
IEE	Image enhanced endoscopy
LCI	Linked color imaging
LGD	Low-grade dysplasia
LBC	Light blue crest
MAPS	Management of precancerous conditions and lesions in the stomach
MTB	Marginal turbid band
NBI	Narrow band imaging
NCGA	Noncardia gastric adenocarcinoma
OLGA	Operative link on gastritis assessment
OLGIM	Operative link on gastric intestinal metaplasia assessment
QALY	Quality-adjusted life year
PICO	Population , intervention, comparison, outcome
US	United States
WLE-HD	white light endoscopy with high definition

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SCREENING OF GASTRIC CANCER AND GASTRIC PREMALIGNANT CONDITIONS

Recommendations: Gastric cancer screening

1. We suggest against routine screening with upper endoscopy for GC and GPMC in the general population in the U.S. (*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*)

DIAGNOSIS OF GASTRIC PREMALIGNANT CONDITIONS

Non-invasive evaluation of GPMC

Recommendations: GPMC non-invasive diagnosis

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

Endoscopic evaluation of GPMC

Recommendations: GPMC endoscopic diagnosis

3. 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*)
4. 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*)

Histologic diagnosis of GPMC

Recommendations: GPMC histologic diagnosis

3. 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, two 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*)
4. In individuals with GIM, we suggest that the histological subtype of GIM (incomplete, complete, mixed) be reported for the purpose of GPMC

risk stratification and informing surveillance. (*Low quality of evidence, conditional recommendation*).

5. 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, corpus). (*Very low quality of evidence, conditional recommendation*).

MANAGEMENT OF GASTRIC PREMALIGNANT CONDITIONS

Recommendations: Non-dysplastic GPMC Surveillance

3. 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:
 - High-risk GIM histology:
 - Incomplete GIM histological subtype, versus complete subtype
 - Corpus-extension, defined as corpus involvement also with antrum or incisura involvement
 - Any GIM histology with one of the following risk factors for GC:
 - Family history of gastric cancer 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*)
4. In individuals with moderate to 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*)
5. In individuals with low-risk GIM or atrophy, we suggest against endoscopic surveillance. Low-risk groups include:
 - Complete type GIM, without evidence of incomplete GIM
 - GIM of focal anatomic extent that is confined to the antrum
 - None of the high-risk clinical criteria listed in Recommendation 9 above
 - AG that is mild in severity

(*Very low quality of evidence, conditional recommendation*).

Endoscopic Management of Dysplastic GPMC

Recommendations: Endoscopic Management of Dysplastic GPMC

3. In patients with dysplasia (IND, LGD, HGD) and visible margins, we suggest endoscopic resection in clinically appropriate patients. (Low quality of evidence, conditional recommendation)
4. In patients with dysplasia (IND, LGD, HGD) without visible margins, we suggest a repeat endoscopic evaluation with HDWLE and IEE by an experienced endoscopist. (Low quality of evidence, conditional recommendation).
5. 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).
6. In patients with confirmed complete resection of dysplasia, we suggest endoscopic surveillance. We recommend surveillance exams 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).

Non-endoscopic Management of GPMC

Recommendations: GPMC Non-endoscopic Management

3. We recommend *H. pylori* eradication in patients with GPMC (AG, GIM, dysplasia) and resected early gastric cancer to reduce the risk of progression to gastric cancer and metachronous early gastric cancer, respectively. (*Moderate quality of evidence, strong recommendation*).
4. We do not suggest the use of ASA, NSAIDs, COX-2 inhibitors, or antioxidants for individuals with GPMC for the purpose of gastric cancer chemoprevention. (*Very low quality of evidence, conditional recommendation*).

SPECIAL TOPICS: AUTOIMMUNE GASTRITIS AND GASTRIC POLYPS

Autoimmune gastritis, a gastric premalignant condition

Recommendations: Autoimmune Gastritis

3. Among individuals diagnosed with AIG, we recommend assessment for *H. pylori* infection with a non-serological test, eradication treatment if positive, and post-treatment testing to confirm eradication (Low quality of evidence, strong recommendation).
4. 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

Recommendations: Gastric Epithelial Polyps

3. We recommend endoscopic resection of all gastric adenomas, regardless of size, to exclude and prevent dysplasia and early gastric cancer. For adenomas that are not amenable to endoscopic resection, we recommend referral for surgical resection, if clinically appropriate. (Low quality of evidence, conditional recommendation).
4. We could not make a recommendation on the endoscopic resection of all hyperplastic polyps greater than 10mm in size based upon the current evidence.
5. 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).

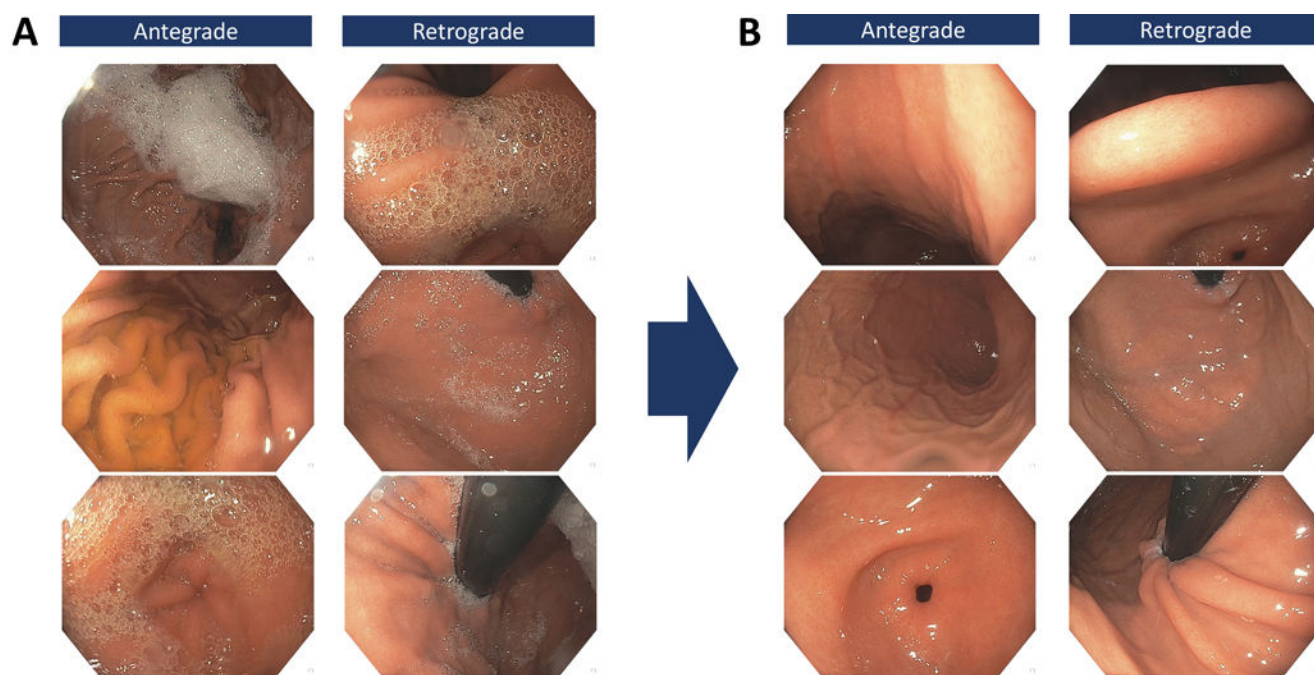


Figure 1. Systematic endoscopic evaluation of the stomach

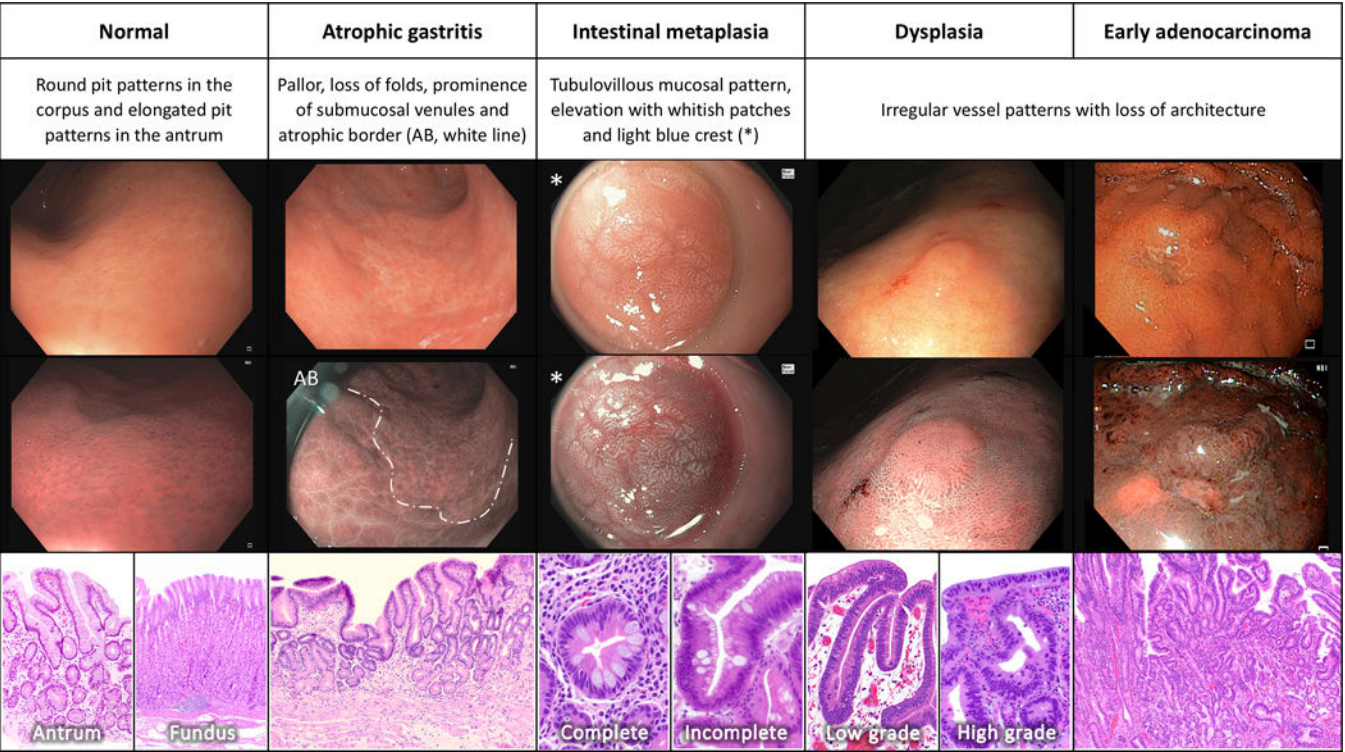


Figure 2. The Correa Cascade: Endoscopy and Histology correlation

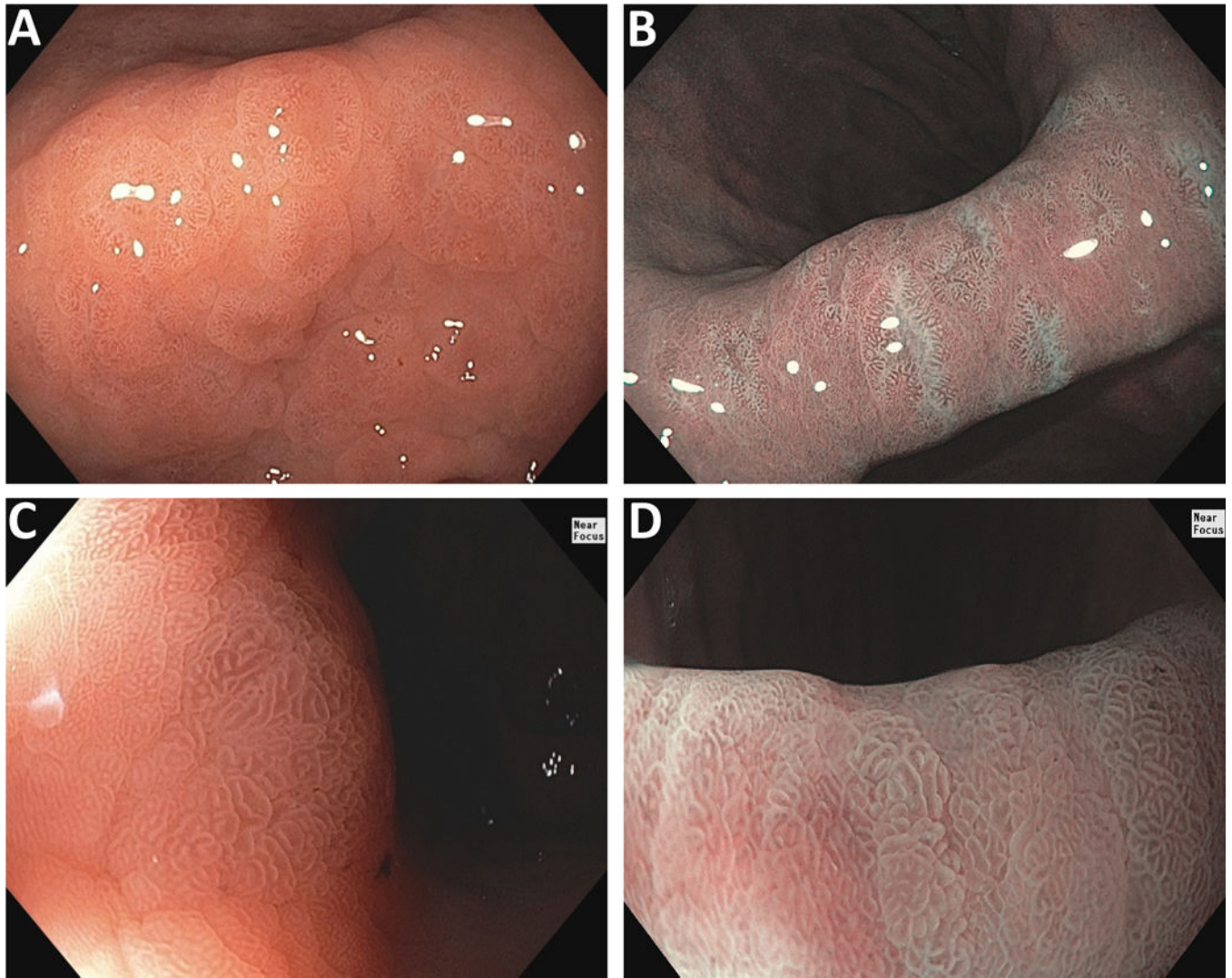


Figure 3. Gastric intestinal metaplasia on HDWLE with or without NBI and near-focus. A) HDWLE; B) NBI; C) HDWLE with near-focus; D) NBI with near-focus. The patchy aspect of GIM is demonstrated in C. In the left area, normal glandular structures are arranged in a regular honeycomb pattern. In the central area, the tubulovillous white glandular structures of intestinal metaplasia are observed. The light blue crests (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 exam with near-focus facilitates targeted biopsies within the framework of the Sydney system biopsy protocol.

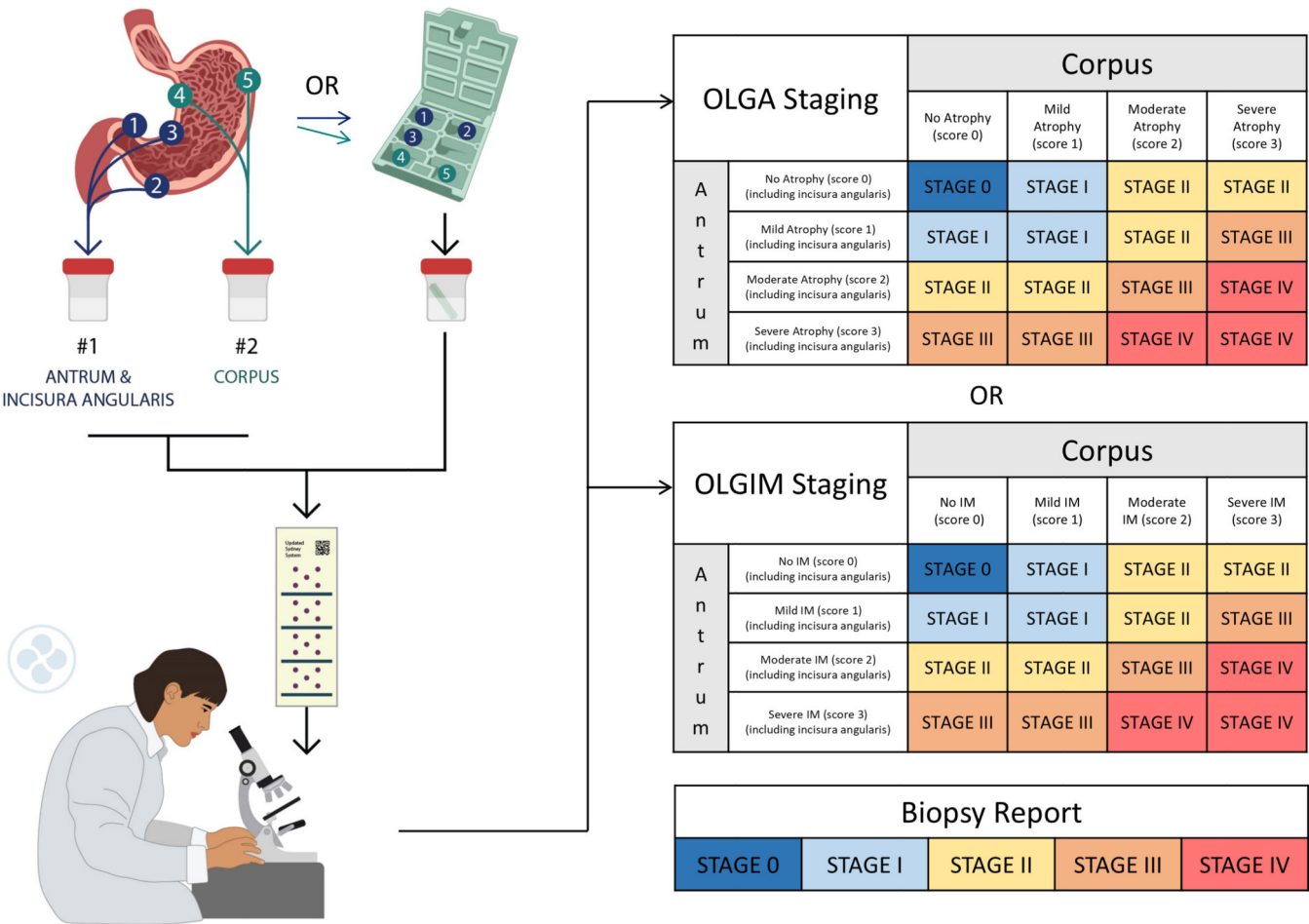


Figure 4. The OLGA/OLGIM Histology Staging System

Non-dysplastic GPMC Management

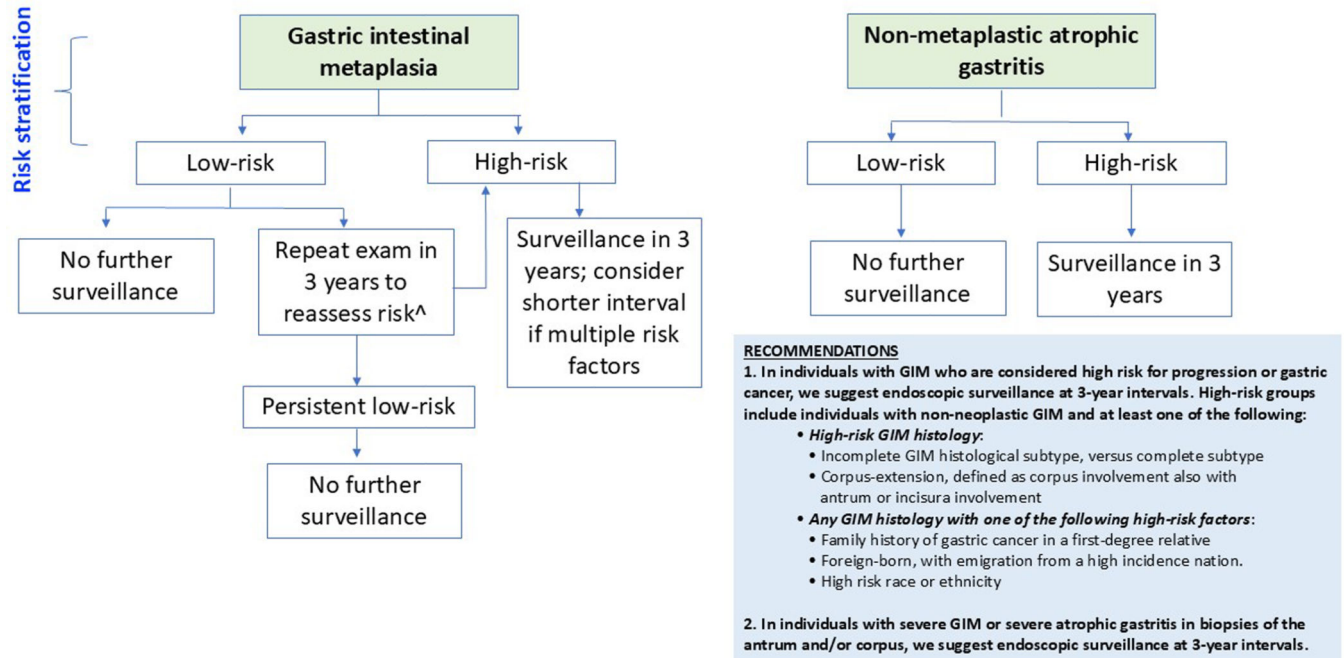


Figure 5. Non-dysplastic GPMC Management Algorithm

- All patients should be tested for *H. pylori* using non-serologic methods, treated if positive, and confirmed to be eradicated, irrespective of GPMC histology, severity, grade, or visible vs invisible. Ideally, *H. pylori* eradication should be confirmed at least several weeks prior to the endoscopic surveillance exam since active *H. pylori* infection can impact endoscopic and histologic appearance of GPMC.
- The surveillance exam comprises HD-WLE with image enhancement for mucosal inspection and systematic protocol biopsies.
- The algorithms presented assume that patients are medically appropriate for endoscopic surveillance
- Some studies in non-U.S. 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 exam (~1–2 years) with Sydney protocol biopsies. There are no U.S. data to inform such practice. If there is concern regarding the quality of the initial examination or based on 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.

Dysplastic GPMC Management

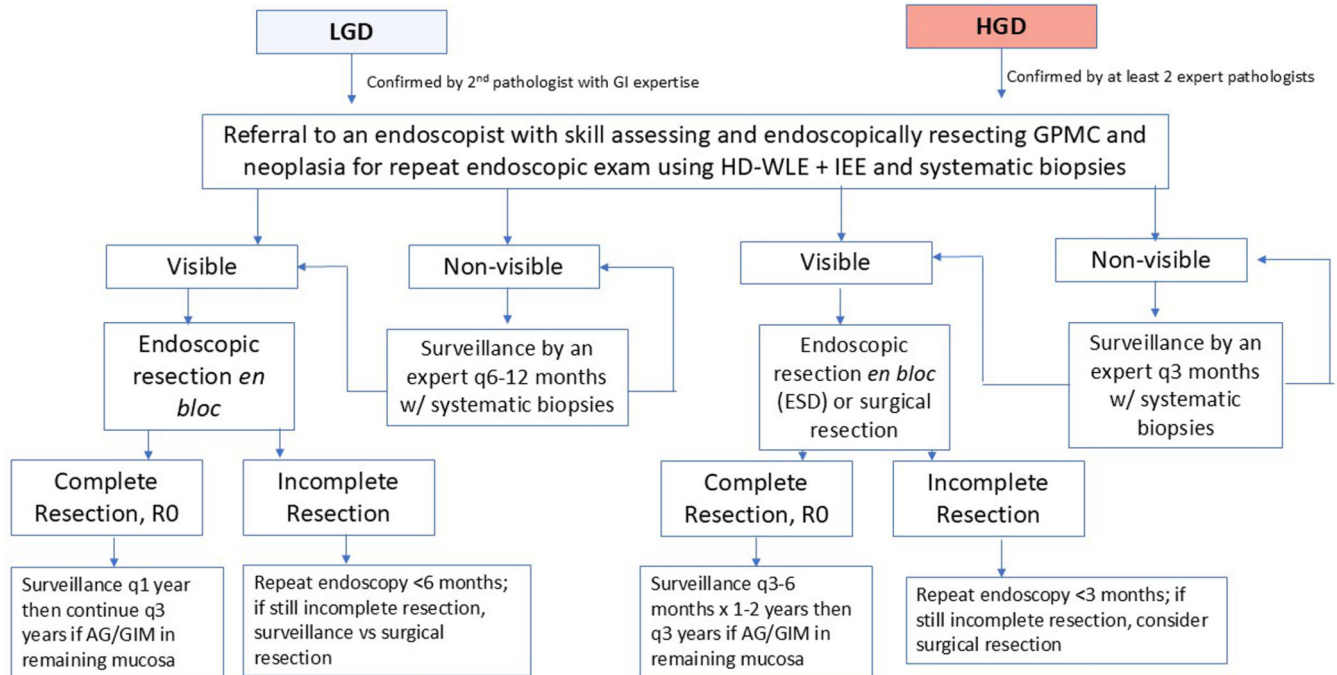


Figure 6. Dysplastic GPMC Management Algorithm

- All patients should be tested for *H. pylori* using non-serologic methods, treated if positive, and confirmed to be eradicated, irrespective of GPMC histology, severity, grade, or visible vs invisible. Ideally, *H. pylori* eradication should be confirmed at least several weeks prior to the endoscopic surveillance exam since active *H. pylori* infection can impact endoscopic and histologic appearance of GPMC.
- The surveillance exam comprises HD-WLE with image enhancement for mucosal inspection and systematic protocol biopsies.
- The algorithms presented assume that patients are medically appropriate for endoscopic treatment and surveillance.
- Patients with indefinite dysplasia (IND) have elevated risk of gastric neoplasia and warrant follow up. The diagnosis of IND should be confirmed by a 2nd pathologist with GI expertise. If this is confirmed, patients should undergo repeat high quality endoscopy with HD-WLE + 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 exam 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 non-visible LGD. In patients without confirmed IND on the repeat exam, surveillance should be according to the results of the systematic biopsies (e.g. every 3 years if GIM and risk factors).

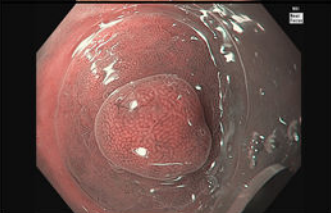
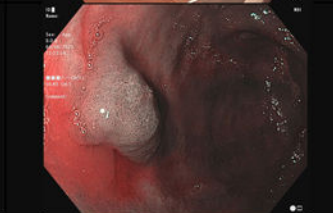
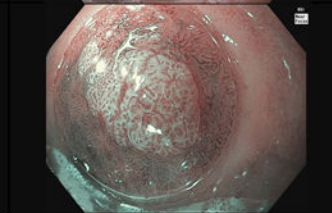
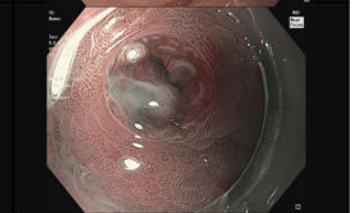
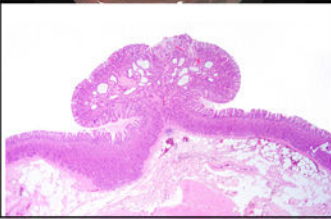
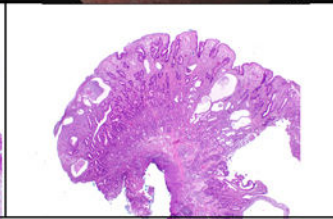
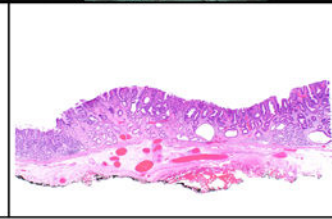
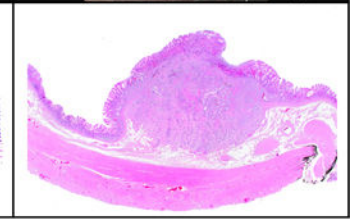
Fundic gland polyp	Hyperplastic polyp	Adenomatous polyp	Neuroendocrine tumor
Typically small, hyperemic , sessile, with a smooth surface contour	Smooth, red buttered, with white exudates	Velvety, pink, lobulated appearance	Variable presentation (red or yellowish), hyperemic, multifocal
			
			
			

Figure 7. Gastric epithelial polyps: Endoscopy and Histology correlation

Table 1: Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Strength of Recommendations, Quality of Evidence, and Implications for the Patients & Clinicians^{14–16}

Strength of Recommendation	Criteria
	Factors influencing the strength of the recommendation include the quality of the evidence, clinical 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 confidence 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.

Table 2. Recommendations for the Management of GPMC**Gastric cancer screening**

1. We suggest against routine screening with upper endoscopy for GC and GPMC in the general population in the U.S. (*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 non-invasive diagnosis

3. We suggest against the use of noninvasive biomarkers for the purpose of GPMC or GC screening or surveillance in the U.S. (*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. 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*)

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, two 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, 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, 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:

- High-risk GIM histology:

- Incomplete GIM histological subtype, versus complete subtype
- Corpus-extension, defined as corpus involvement also with antrum or incisura involvement
- Any GIM histology with one of the following risk factors for GC:

- Family history of gastric cancer 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 moderate to 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:

- Complete type GIM, without evidence of incomplete GIM
- Complete GIM of focal anatomic extent that is confined to the antrum
- None of the 'high-risk' clinical criteria listed in Recommendation 9 above
- 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, 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, 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 exams 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 non-endoscopic management

16. We recommend *H. pylori* eradication in patients with GPMC (AG, GIM, dysplasia) and resected early gastric cancer to reduce the risk of progression to gastric cancer and metachronous early gastric cancer, respectively. (*Moderate quality of evidence, strong recommendation*).

17. We do not suggest the use of ASA, NSAIDs, COX-2 inhibitors, or antioxidants for individuals with GPMC for the purpose of gastric cancer chemoprevention. (*Very low quality of evidence, conditional recommendation*).

Autoimmune Gastritis (AIG)

18. Among individuals diagnosed with AIG, we recommend assessment for *H. pylori* infection with a non-serological test, eradication treatment if positive, and post-treatment 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 (GEP)

20. We recommend endoscopic resection of all gastric adenomas, regardless of size, to exclude and prevent dysplasia and early gastric cancer. 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 10mm in size based upon the current evidence. (*Insufficient evidence; no recommendation*).

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*).

Table 3. Key Concepts for the Management of GPMC**Gastric cancer epidemiology and screening**

- The epidemiologic and biologic risk factors overlap, and yet are distinct, for the three 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 controlled trials from the U.S. 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-year 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 and *H. pylori* eradication are considerations 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.
- First generation immigrant populations contribute to the race and ethnicity disparity of GC incidence in the US. Endoscopic screening and *H. pylori* eradication are considerations 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 and Central/South America. Eastern Europe includes western Russia. The South America high incidence area encompasses the Andean region from Colombia to Chile. Nearly one-third of first generation immigrants in the U.S. emigrate from high incidence nations. Immigrant generation and level of acculturation impact risk.

GPMC endoscopic and histologic diagnosis

- The high-quality endoscopy exam has five main components: 1) use of HDWLE; 2) adequate gastric distension using insufflation (CO₂ or air) in order to flatten the gastric folds and expose the gastric mucosa adequately; 3) mucosal cleansing to clear all debris, mucous and bubbles; 4) standard photodocumentation; 5) adequate gastric inspection time. Gastric exam time and photodocumentation are surrogate quality metrics for the gastric evaluation. The 2–3 minute upper endoscopy for GPMC patients falls short of the standard of care.
- HDWLE and IEE are appropriate for individuals with at increased GC risk, those with suspected GPMC or GC during endoscopy, and those undergoing GPMC surveillance. In the U.S., IEE with NBI, with or without optical zoom, is the most common technology.
- 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 include information specific to stomach location (e.g., antrum, incisura, corpus), AG and GIM severity (biopsy-specific), AG and GIM extent (e.g., antrum, corpus), as well as the subtype of GIM (e.g., complete, incomplete).
- The diagnostic challenges for GPMC and dysplasia include biopsies sampling errors (e.g., AG and GIM patchy multi-focality), and the interobserver variability among pathologists, particularly with indefinite (IND) and low-grade dysplasia (LGD).

GPMC endoscopic surveillance

- Delineation of GPMC surveillance intervals requires further study in the U.S. Patients with multiple risk factors for GC may be considered for shorter than 3-year intervals. For example, an individual with extensive GIM and with a family history of GC, may be considered for a 2-year 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 non-dysplastic 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 while race, ethnicity, and country of origin are important risk factors for prevalent GPMC and GC, these factors are not proven to be *independent* predictors of progression, although U.S. 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-year 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. Referral to expert centers is reasonable.
- HGD without visible mucosal abnormalities: within 3 months.
- LGD or IND without visible mucosal abnormalities: within 12 months.
- In patients with endoscopically resected dysplastic lesions, the optimal post-resection 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.
- HGD without visible mucosal abnormalities: 3 months.
- LGD or IND without visible mucosal abnormalities: 6–12 months.

Autoimmune gastritis (AIG)

- AIG is considered a gastric preneoplastic condition since, by definition, there is corpus atrophy, either with or without GIM. AIG is associated with an increased risk of well-differentiated neuroendocrine tumors (NETs) of enterochromaffin-like (ECL) cells (also termed type I gastric carcinoid tumor) and possibly gastric adenocarcinoma (with prior or current *H. pylori* infection).
- The overlap of *H. pylori* associated GPMC and AIG is common and thus the same risk stratification parameters apply. Individuals with AIG are also established to be at risk for type I carcinoids. In patients with AIG, surveillance with HD-WLE and IEE is a consideration. The interval is determined based on GPMC risk stratification parameters (e.g., family history of GC, etc.), 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 >10mm at the index endoscopy. An individualized approach is warranted, with resection or biopsies, as clinically appropriate, and with consideration of endoscopic surveillance within 12 months.

Table 4. Hereditary and genetic gastric cancer syndromes

Familial gastric cancer syndromes: • Hereditary diffuse gastric cancer (HDGC) • CDH1 germline mutations (E-Cadherin) • Familial intestinal gastric cancer (FIGC) • GC and proximal polyposis of the stomach (GAPPS) 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 (LFS, HBOCS) • Lynch Syndrome, hereditary breast and ovarian cancer syndrome, and Li-Fraumeni syndrome • Hereditary homologous recombination deficiency (DNA repair) • BRCA1, BRCA2, PALB2, ATM

Notes.

• 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 GWAS studies, which are limited in number (e.g., Asia, Europe, Latin America). In addition, there are gene variants which influence the *H. pylori*-environmental interactions, and specifically the inflammatory response (e.g., pro-inflammatory cytokine genotypes).

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

Gastric cancer screening in the U.S.
• Randomized controlled 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 U.S. studies may incorporate ‘convenience endoscopy’ paired with screening colonoscopy for patients at high-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 non-invasive biomarkers (e.g., pepsinogens), alone or in combination, need 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, GIM detection rate). • Development of training interventions for U.S. endoscopists for the diagnosis and management of GPMC. • 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 indefinite for dysplasia and low-grade dysplasia. • 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., EGC diagnosis proportion, GC incidence, GC 5-year 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 non-visible gastric dysplasia (i.e. “second look endoscopy”). • Health-system research on optimization of referrals to high-volume ESD centers/providers in the U.S. Perform microsimulation analyses with U.S. 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.
Non-endoscopic 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, PCAB) on GPMC and GPMC progression.
Autoimmune Gastritis
• Clarify the risk of adenocarcinoma in patients with autoimmune gastritis, with and without <i>H. pylori</i> 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. <i>H. pylori</i> infection, 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 EGC, incorporation of novel imaging technologies, pathology protocols, and endoscopy therapeutics.