Advancing the Science in Gastric Pre-Neoplasia: Study Design Considerations.

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Introduction

Gastric cancer is the third leading cause of cancer-related mortality and the leading infection associated cancer worldwide. In the US, there are estimated 27,510 new cases and 11,140 gastric-cancer related deaths in 2019.¹ Gastric adenocarcinoma (GA) is the most common form of gastric cancer. Histologically, by the Lauren classification, GA can be divided to two types: intestinal GA and diffuse GA.² The Cancer Genome Atlas (TCGA) initiative has identified 4 molecular subtypes of gastric cancers: genomically stable (diffuse), chromosomally stable (intestinal), microsatellite instability, and Epstein-Barr virus subtype.³ GA is also classified based on anatomic location into cardia (CGA) or non-cardia GA (NCGA). NCGA include those arising from the antrum, incisura, body, and/or fundus.⁴

Intestinal-type NCGA (hereafter simply referred to as “NCGA”) results from the complex interaction between genetic, environmental, and microbial determinants, which drive the stepwise progression through a series of discrete histopathologic stages, the “Correa cascade”, from non-atrophic gastritis to gastric preneoplasia (chronic atrophic gastritis (AG),...
gastric intestinal metaplasia (GIM) and dysplasia, prior to malignant transformation to invasive adenocarcinoma in a minority of patients (1–3%). Helicobacter pylori (H. pylori) is the dominant factor in this cascade with an attributable risk of 75–88% but additional pathways are recognized.\textsuperscript{5, 6}

Most factors which account for the prevalence of GIM and its progression to neoplasia lack definitive evidence. Despite the established association of GIM with increased risk of incident NCGA, currently it’s not possible to predict who will develop gastric neoplasia. Furthermore, whether the endoscopic surveillance of GIM to detect early NCGA compared to no surveillance may improve patient-related outcomes, has not been established, particularly in low incidence countries like the US. Whether selected surveillance of GIM for identifiable high-risk groups within, such as racial/ethnic minorities and immigrants, is similarly unclear. These critical knowledge gaps formed the rationale behind the American Gastroenterological Association’s (AGA) Clinical Practice Guideline Committee’s constructing evidence-based guidelines to inform the management of patients who are diagnosed with GIM based on gastric biopsies performed in routine clinical practice.

The technical review team systematically summarized and synthesized the literature to inform pre-defined clinical questions proposed by the AGA guideline panel using standard systematic review methodology. With guidance from the guideline committee, we developed a comprehensive list of direct and indirect evidence needed to inform the guideline questions. The direct evidence included randomized and non-randomized comparative studies that assessed the benefits and/or harms of endoscopic surveillance in patients with GIM. The indirect evidence included the prevalence of GIM, the incidence of intestinal-type NCGA in individuals with GIM, and specified risk factors and biomarkers associated with the development of NCGA in patients with GIM: family history of gastric cancer, racial/ethnic background, immigration status, smoking history, pernicious anemia and/or autoimmune atrophic gastritis, GIM topographic extent, GIM histological subtype, and predictive biomarkers (e.g., H. pylori and its virulence factors (e.g. cagA and vacA), and the pepsinogens).

Our systematic literature search did not identify studies that provide direct evidence to inform our clinical questions, although we were able to identify many studies that informed our questions indirectly. It was evident that there was inconsistent and incomplete methodology among the studies and many publications were missing essential demographic, clinical, endoscopic and/or pathology data. These data elements are necessary to allow a thorough assessment of the events reported and to determine the certainty of that evidence. The lack of direct evidence and the lack of certainty in the indirect evidence limited the guideline’s panel ability to make strong recommendations for a common clinical condition. To stimulate the field to improve clinical outcomes, best practices are intended to guide future research and overcome the limitations of the available evidence.

The aim of this guidance document is to highlight the methodological limitations that the technical review and guideline team encountered in the literature review and provide guidance for future design of high quality studies on GIM as a premalignant finding that is associated with development of gastric cancer. We have provided a general checklist that
will facilitate standardization of future studies to advance the science of GIM with rigorous evidence to inform clinical care. For completeness, we include measures that are important yet were outside the scope of the AGA GIM technical reviews and guidelines (e.g., endoscopy imaging).

Methods

This guidance document is informed by the findings from the systematic review done in the process for developing the AGA clinical practice guidelines for gastric cancer endoscopic surveillance among patients diagnosed with GIM on gastric biopsies obtained during routine endoscopy. The working group comprised the guideline panel and technical review (TR) team. The TR team included a Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodologist, and six clinical domain experts (three gastroenterologists, one pathologist, and two gastroenterology-methodology fellows). We systematically summarized and synthesized the literature to inform pre-defined questions proposed by the AGA guideline panel using standard systematic review methodology.

The systematic review was reported in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) proposal.7, 8 We used the GRADE framework to evaluate the certainty of evidence.9

Each stage from title/abstract screening, full-text screening to data abstraction was completed in duplicate by two independent blinded members of the TR team. Disagreement was resolved by consensus between the two investigators, and if needed, a third investigator acted as the arbiter. Piloted standardized Research Electronic Data Capture (REDCap) forms, which were designed by the TR team in consultation with the guideline panel, were used for each of these stages and for data abstraction.10 These forms were designed to capture all pertinent information regarding GIM diagnosis and management.

We included studies that provided information regarding the prevalence of GIM, factors associated with higher prevalence of GIM, the incidence of gastric neoplasia in patients with GIM, factors associated with higher incidence of gastric neoplasia in patients with GIM, and role of \textit{H. pylori} treatment in preventing the development of gastric neoplasia in patients with GIM. We also aimed to identify studies of different surveillance intervals, but none were identified. For studies of GIM prevalence we excluded studies that included less than 250 subjects and for studies of the incidence of gastric neoplasia in patients with GIM we excluded studies that included less than 20 patients.

To evaluate the methodological quality of the studies, we used different validated quality assessment tools including the Cochrane Collaboration’s tool for assessing the risk of bias in randomized controlled trials, the Newcastle-Ottawa Scale, and the Joann Briggs Institute’s critical appraisal checklist for studies reporting prevalence data.11–13 The full methodologic approach is detailed in the “AGA Institute Technical Review on Gastric Intestinal Metaplasia – Part 1 and Part 2”. We used the data that we extracted including the

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methodological quality of the included studies to propose checklists that will facilitate standardization of future studies of GIM.

Results

A total of 3,716 articles were identified in the literature search, from which 3,136 articles were excluded after removal of duplicates, conference abstracts without full text publication and title/abstract screening. The full texts of 580 articles were reviewed for eligibility. Of these, 329 articles were excluded for not meeting full inclusion criteria. Thus, we abstracted data from 121 articles.

Studies of GIM prevalence

We identified 53 studies from 12 different geographical regions and 29 countries that reported the prevalence of GIM. The studies varied in size from 268 subjects up to 895,323 subjects with median of 871 subjects and interquartile range 437 to 2,129 subjects. The two studies that included more than 100,000 subjects and hence had the largest influence on the pooled point estimates were from pathology databases in Sweden and the United States.\textsuperscript{14, 15}

In general, the individual studies were at moderate to high risk of bias. One of the major limitations of most of the studies was referral bias as most of the patients were referred for endoscopy for an indication not for the purpose of screening for GIM. Additionally, the decision to obtain gastric biopsies was left to the clinician. The other major limitation is that many of studies did not report the biopsy protocol and/or obtained biopsies according to the updated Sydney system.\textsuperscript{16, 17}

Studies of GIM risk factors

In addition to the 53 studies that reported the prevalence of GIM, we also identified 6 studies that reported the prevalence of GIM in \textit{H. pylori}-exposed subjects and one study the reported the prevalence of GIM in first-degree relatives of patients with gastric cancer.\textsuperscript{18–24} Those studies were analyzed separately but had similar limitations to the other studies.

Of the 53 studies that reported the prevalence of GIM, 44 studies reported the \textit{H. pylori} exposure status and only 3 studies reported the \textit{cagA} status.\textsuperscript{20, 25, 26} Table 1 summarizes the number of studies that reported the number of patients with a certain risk factor and the number of studies that provided detailed data to allow us to assess the association between the risk factor and the finding of GIM.

Out of the 53 studies that reported the prevalence of GIM, 12 studies reported the histological subtype\textsuperscript{20, 25, 32, 36–44}, 7 studies reported the extent of GIM\textsuperscript{20, 22, 36, 40, 45–49}, and only 3 reported the OLGIM stage\textsuperscript{48, 50, 51}. Additionally, 3 studies reported the association of dietary habits with finding GIM.\textsuperscript{24, 33, 34} We could not identify any study that reported the prevalence of finding GIM based on biomarkers like pepsinogen I, pepsinogen II, or pepsinogen I/II ratio.
Studies of the incidence of gastric cancer in patients with GIM

We identified 30 studies that reported data informing the incidence of gastric cancer in patients with non-dysplastic GIM. The studies were from 5 different geographical regions and 16 different countries. 10 studies reported the incidence rate with a median number of subjects of 686 (range 129–11,530 and IQR 32–859) and the median duration of follow-up was 7.5 years (range 3–12 and IQR 5–9.75). The number of studies that reported the cumulative incidence at different time intervals was 27 with a median number of subjects of 249 (range 71–60,488 and IQR 151–874) and the median follow-up duration was 6 years (range 2–16 and IQR 5–9.5). We had to exclude several studies because they reported outcomes for all the pre-neoplastic lesions together (i.e. atrophic gastritis, GIM, and/or dysplasia) but did not report separate results for non-dysplastic GIM patients.

Similar to the prevalence studies, the overall risk of bias in the individual studies was moderate to high. Frequently, the included studies did not report obtaining biopsies from both the antrum and body or followed the updated Sydney system. Also, many of the studies used pathology or endoscopy databases or patients referred for endoscopy leading to possible referral bias. As many of the studies relied on databases, the duration of follow-up and the factors that led to discontinuation of follow-up was often unclear.

Studies of risk factors associated with developing gastric cancer

Although many studies reported the number of included GIM patients with certain risk factors, only few studies reported separate gastric cancer incidence data based the presence or absence of our risk factors of interest. Of the 30 studies that reported gastric cancer incidence data in patients with non-dysplastic GIM, the number of studies that reported the incidence based on specific risk factors were limited: extent (2)\(^\text{55,59}\), histologic subtype (7)\(^\text{31,53,58,60-62}\), family history (3)\(^\text{23,31,55}\), and smoking status (1)\(^\text{55}\). The three studies from North America, reported the incidence of gastric cancer based on race and ethnicity.\(^\text{54,55,63}\) None of the studies reported data that allowed us to assess the association of developing gastric cancer in patients with non-dysplastic GIM and alcohol consumption, dietary habits, the presence of certain biomarkers (H. pylori or its virulence factors, pepsinogens), autoimmune gastritis, or OLGIM stage.

It is also important to mention that many of the studies that reported separate results, reported them as cumulative incidences instead of incidence rates which precluded our ability to estimate the incidence rate ratios to account for the time factor in the comparative analyses.

Studies of surveillance strategies and gastric mapping biopsies

Unfortunately, despite the large amount of data the we identified, we were unable to identify any study that directly compared the benefits or harms of different surveillance strategies or gastric mapping biopsies in patients found to have non-dysplastic GIM incidentally. Similarly, we could not identify any study that directly assessed the benefits or harms of mapping strategies or surveillance in high risk subgroups.
**Studies of the endoscopy protocol and the optical diagnosis of gastric preneoplastic lesions**

The PICO questions that we used to answer the critical clinical questions proposed by the guideline panel were not intended to examine studies of the endoscopy protocol and the optical diagnosis of gastric preneoplastic and neoplastic lesions. However, the field of endoscopy imaging is evolving with diverse image-enhanced endoscopy modalities beyond white light endoscopy, including magnification endoscopy, chromoendoscopy (e.g., indigo carmine), and virtual chromoendoscopy (e.g., narrow-band imaging, confocal laser endoscopy).

**Discussion**

We conducted a systematic review to summarize and synthesize the evidence informing predefined PICO questions important for clinical practice. Despite the long-term and wide interest of researchers and clinicians in identifying non-dysplastic GIM and its association with gastric cancer, we were surprised by the lack of direct evidence to inform any of the clinical questions that were proposed by the guidelines committee for a such common clinical finding. Unfortunately, even the large body of indirect evidence that we identified had multiple limitations that precluded reaching moderate or high certainty in the evidence. Based on the limitations that we identified, we are providing suggestions and guidance for future studies and research on non-dysplastic GIM.

**Studies of surveillance strategies**

Surveillance programs in patients with non-dysplastic GIM should aim to prevent the development of neoplastic lesions or identify neoplastic lesions early enough to intervene medically or surgically with an overall goal of reducing gastric cancer and overall mortality and improve, or maintain, quality of life without causing harms. Hence, the ideal trial design would require randomizing patients with non-dysplastic GIM to two different surveillance programs or a surveillance program versus not doing anything. Alternatively, a large prospective cohort study that offers consecutive non-dysplastic GIM patients equal opportunity to participate in a surveillance program then compare patients who agree to do surveillance versus patients who refuse may also provide moderate to high quality evidence if it shows a large effect size. Such studies can be limited to groups with possible higher risk for developing gastric cancer such as patients with extensive disease, incomplete GIM, first degree family history of gastric cancer, or certain races and ethnicities.

**Studies of gastric mapping biopsies strategies**

One of the questions that are frequently raised is the need for repeat endoscopic evaluation in short period of time after identifying GIM incidentally. The intention of repeating endoscopy is to define the extent and subtype of the disease. The indirect evidence that we identified showed that extensive GIM, i.e. GIM involving the corpus or antrum/corpus, may be associated with a higher risk of developing incident gastric cancer. Those patients may benefit from surveillance programs or more intensive surveillance program compared to lower risk patients.
The benefits of such an approach could be assessed by a study that compares the risk of developing gastric cancer in patients with extensive disease versus patients with disease limited to the antrum. This could be done in the settings of a randomized controlled trial evaluating different surveillance programs. Alternatively, a large prospective cohort study of consecutive patients with non-dysplastic GIM could evaluate the differences between the two groups by obtaining biopsies based on the updated Sydney system in every patient.

**Studies to define the incidence of neoplasia in patients with non-dysplastic GIM**

We identified certain measures that should be considered in studies that intend to define the incidence of developing gastric cancer in patients with non-dysplastic GIM. Patients should be recruited consecutively in a protocolized manner and should be all identified using the updated Sydney system, in addition to targeted biopsies of mucosal abnormalities. This will also allow for assessment of the GIM extent and/or OLGA/OLGIM stage. The histological assessment should also include assessment of histological subtype and the presence of H. pylori infection. Additionally, information regarding certain baseline characteristics should be collected including age, race and ethnicity, immigration history, first degree family history of gastric cancer, smoking status (current, past, or never), and alcohol consumption (current, past, or never). The exposure to tobacco and alcohol should be quantified, e.g., pack-years and heavy-alcohol-use-years (>15 drinks per week), respectively. Additional information that is informative includes: dietary habits, the presence of autoimmune gastritis, *H. pylori* virulence factors status, and serologic biomarkers such as pepsinogens. We have proposed a checklist in Table 2.

As our results highlighted, most of the studies that reported the incidence of gastric cancer reported cumulative incidences (number of events/number of patients) at certain time points and only few reported incidence rates (number of events/number of patient-years). By accounting for the duration of follow-up for each patient and possible losses to follow-up, incidence rates inherently adjust for the time variable and provide better estimation of the risk of developing the event if the risk were constant. This is particularly useful when the researcher tries to estimate adjusted incidence rate ratios. Hence, it is helpful to report both cumulative incidences at defined intervals and incidence rates. Ideally, the cohort should be followed for 5–10 years and cumulative incidences should be reported at 1, 3, 5 and 10 years. The number of incident cancers after the first year should also exclude patients who develop cancer in the first year after identifying GIM due to the high likelihood of it being a missed prevalent cancer.

**Studies to define patients with non-dysplastic GIM at high risk for developing incident gastric cancer**

Ideally, a randomized controlled trial that evaluate the benefit of surveillance in patients with suspected high risk will be sufficient to provide evidence with moderate to high certainty. Alternatively, a large cohort study with large effect size can provide similar results. Cohort studies that intend to identify high risk groups, i.e. patients who may benefit from surveillance, should not only use relative risk but also use incidence rate ratios to account for the time variable. They should also conduct and report multivariable analyses that adjust for all the suspected high-risk features including histological subtype, disease extent, first
degree family history of gastric cancer, race and ethnicity, and immigration history. To allow for adjusting for all those variables and any additional variable of interest, this will require a large sample size that may be only achieved on a multi-institutional level. The checklist that we proposed in Table 2 summarizes all the above considerations.

**Studies of the prevalence of GIM and risk of finding GIM on gastric biopsies**

The major limitation of the studies that influenced the pooled prevalence was the fact that they were from pathology databases where patients had indications to have their endoscopy. Additionally, in such studies it is hard to assess if enough biopsies were obtained to avoid sampling error and underdiagnosing GIM. Hence, arguments that such referral bias may lead to over- or under-estimation of the prevalence can be made.

Based on the above, the ideal study design should enroll consecutive or randomly selected patients from pre-defined population and obtain gastric biopsies using the updated Sydney system. Such studies should not include less than 250 patients. We identified certain risk factors that were associated with finding GIM on gastric biopsies. Most of the variables were identified based on univariate analyses and we could not adjust for the other important variable due to the lack of reporting of adjusted relative risks. Hence, future studies that aim to identify patients with higher risk of having GIM on gastric biopsies should report adjusted risk ratios including adjusting for age, race and ethnicities, immigration history, first degree family history, smoking history and alcohol use. We have proposed a detailed checklist that can be used when conducting studies that assess the prevalence of GIM or factor associated with finding GIM on biopsies, Table 2.

**Strengths and limitations**

We used GRADE, an extensively validated methodology, when we evaluated the quality and certainty of evidence in our reports which allows for assessment and transparency in assessing the quality of the evidence. The checklists that we are proposing were based on rigorous evaluation of the clinical and methodological limitation of the available evidence which was summarized and synthesized using standard systematic reviews methodology. We anticipate that adhering with those checklists will allow future studies to provide more certainty in the evidence to allow future guideline panels to make specific recommendations in this common clinical condition.

It is important to acknowledge that the risk factors that we identified were based on the published literature and other risk factors may be missing from the checklists. We also acknowledge that some of the proposals that we suggested may not be possible and were presented for the purpose of explaining the ideal way of answering such challenging clinical questions.

**Conclusion**

We conclude with recommendations to enhance the quality of future studies which examine the etiology of GIM, as well as the risk of developing gastric neoplasia in patients with GIM. We suggest that in light of the methodological limitations among most studies included in the technical reviews and analyses that we conducted, rigorously conducted double blinded
RCT or multi-institutional comparative cohort studies are needed to move the field forward, a necessary challenge. This is of vital importance as continued research gaps and low-quality evidence suggests that further research will likely hinder future patient care and guidelines refinement.

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Table 1.

Study reporting of GIM risk factors in the literature

| Risk factor                                      | Number of studies that reported the number of patients with risk factor | Number of studies that reported separate results according to the risk factor |
|--------------------------------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Race/ethnicity                                  | 5                                                                      | 3<sup>26-28</sup>                                                             |
| First-degree family history of gastric cancer    | 7                                                                      | 4<sup>23, 29-31</sup>                                                         |
| Smoking tobacco                                  | 12                                                                    | 5<sup>29, 32-35</sup>                                                         |
| Alcohol consumption                              | 11                                                                    | 4<sup>29, 32, 34, 35</sup>                                                    |
| Pernicious anemia/ autoimmune gastritis          | 1                                                                     | 1<sup>36</sup>                                                                |

* USA studies only
Checklist for data collection and reporting of studies of incidence gastric cancer in patients with GIM and comparative cohort studies of the risk factors for developing gastric cancer in GIM patients (modifiers for studies of the prevalence of GIM and comparative studies of the risk factors for finding GIM are outlined in the footnote)

| Section/topic                  | Item no. | Checklist item                                                                 |
|-------------------------------|----------|-------------------------------------------------------------------------------|
| Title and Keywords            | 1        | -                                                                             |
| Abstract                      | 2        | -                                                                             |
| Introduction                  | 3        | Regional gastric cancer data for study site(s)                                |
| 3a                             |          | Gastric cancer incidence and mortality (e.g. IARC data)                       |
| 3b                             |          | GIM prevalence (if known)                                                     |
| 3c                             |          | Description of regional practices and policies for GC screening/surveillance  |
| Methods: Recruitment          | 4        | Consecutive or randomly selected patients from a predefined population         |
| Methods: Patient information  | 5        | Demographics: age, gender, race and ethnicity, country and region, country of origin and immigration history. |
| 5a                             |          | Medical history: history of gastric cancer/HGD (included or excluded), GIM (prior endoscopy), gastric surgery (indication, type, date), pernicious anemia/ autoimmune gastritis, hereditary GI/gastric syndrome(s) |
| 5b                             |          | Historical features: first degree family history of stomach cancer, smoking history (quantified), alcohol use history (quantified), dietary habits (salt intake, fruits and vegetables, dairy products) |
| 5c                             |          | Medication history: recorded use and duration (e.g. proton pump inhibitor, aspirin, nonsteroidal anti-inflammatory drugs, antioxidants) |
| 5d                             |          | H pylori status, labs, and treatment history                                     |
| 5e                             |          | Status: ever-infected (any positive H pylori test), current infection (positive active H pylori test), prior infection (positive serology and neg active H pylori test) |
| 5f                             |          | Labs: blood-based (serology), non-invasive (stool antigen, urea breath testing), endoscopy-based (rapid urease test, histology), other (PCR, culture), virulence factors (cagA and vacA) |
| 6a                             |          | Treatment: never-treated, treatment (<1 year vs > 1 year ago), post-treatment testing (yes/no), H pylori eradication success (yes/no) |
| Methods: Endoscopy evaluation | 6        | Endoscopy Imaging modality (yes/no for each): white light endoscopy, image-enhanced endoscopy (magnification, chromoendoscopy (e.g. indigo carmine), virtual chromoendoscopy (e.g. narrow-band imaging), other) |
| 6b                             |          | Endoscopy quality measures (yes/no) (e.g., visualization quality, distension, visual mapping, duration) |
| Methods: Endoscopy biopsy protocol | 7    | For index and follow-up endoscopies                                            |
| 7a                             |          | Sydney system biopsies ** (non-targeted): confirm number of biopsy sites and biopsies/site (1–2 biopsies at the Sydney protocol site), biopsy forceps (jumbo vs standard) |
| 7b                             |          | Targeted biopsies: protocol (yes/no)                                          |
| Methods: Histological evaluation | 8    | Global diagnosis (most advanced lesion: atrophic gastritis, intestinal metaplasia, dysplasia, carcinoma in situ), compartment diagnosis (antrum and corpus; consider incisura), other diagnoses (e.g. ulcer, autoimmune gastritis, polyp, etc.) |
| Section/topic | Item no. | Checklist item |
|--------------|---------|----------------|
| GIM extension: antrum, incisura, corpus, antrum/incisura and corpus | 8b | |
| GIM histological subtype † (complete, incomplete, other), subtyping method (H&E staining (e.g. mucins), other), GIM severity recorded (mild, moderate, severe) | 8c | |
| Gastric scoring system use (yes/no), OLGA/OLGIM stages, other (e.g., Correa score) | 8d | |
| Methods: Comparisons of interest | 9‡ | Race/ethnicity, immigration history, smoking history, alcohol use, dietary intake, first degree family history of gastric cancer, pepsinogens, pernicious anemia and autoimmune gastritis, H. pylori exposure and its virulence factors (cagA and vacA), histological subtype (complete vs. incomplete), topographical extent (extensive vs antrum-limited), OLGIM stage |
| Methods: Follow-up † | 10a | Follow up EGD (e.g. 1, 3, 5 and 10 years) |
| Progression interventions: none/natural history, H. pylori treatment, pharmacological agents, dietary, other | 10b | |
| Semi-annual or annual clinic follow-up between endoscopies | 10c | |
| Follow-up laboratory evaluation (e.g. biomarkers) | 10d | |
| Methods: Outcomes | 11a | Early cancer detection stage 1 and 2; mortality from gastric cancer; overall mortality; complications associated with EGD; natural progression of GIM |
| Quality of life; cost-effectiveness on GIM treatment/surveillance | 11b | |
| Methods: Statistical analysis | 12a ‡, ¶ | Estimate the cumulative incidence at 1, 3, 5 and 10 years; estimate incidence rate |
| Estimate relative risk at 1, 3, 5, and 10 years; estimate incidence rate ratios | 12b ‡, ¶ | |
| Must adjust for age, race/ethnicity, immigration history, first degree family history of gastric cancer, histological subtype, and topographical extent. | 12c ‡, Δ | |

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* The suggested minimum sample size is 250.

** The updated Sydney System: five biopsies encompassing one from the lesser curvature of the antrum within 2–3 cm of the pylorus, one from the great curvature of the antrum within 2–3 cm of the pylorus, one from the lesser curvature of the body 8 cm distal to the cardia, one from the great curvature of the body 8 cm distal to the cardia, and one from the incisura angularis.

† Incomplete GIM may identify patients at higher risk for progression. Further studies are needed. Individual patient-oriented decisions are warranted in the interim, as noted in the guidelines.

‡ For comparative studies only

◊ Not applicable for studies of the prevalence of GIM

§ For prevalence of GIM studies: number of patients with GIM; number of patients with other preneoplastic lesions; number of patients with incomplete GIM; number of patients with extensive GIM; number of patients at different OLGIM stages

‖ For prevalence of GIM studies: Estimate of the prevalence of GIM
For prevalence of GIM studies: Relative risk of finding GIM

For prevalence of GIM studies: Must adjust for age, race/ethnicity, immigration history, smoking history, alcohol use, first degree family history of gastric cancer