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# REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

## Gastric Intestinal Metaplasia: Real Culprit or Innocent Bystander as a Precancerous Condition for Gastric Cancer?

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**Gastric intestinal metaplasia (GIM), which denotes conversion of gastric mucosa into an intestinal phenotype, can occur in all regions of the stomach, including cardiac, fundic, and pyloric mucosa. Since the earliest description of GIM, its association with gastric cancer of the differentiated (intestinal) type has been a well-recognized concern. Many epidemiologic studies have confirmed GIM to be significantly associated with subsequent gastric cancer development. *Helicobacter pylori*, the principal etiologic factor for gastric cancer, plays the most important role in predisposing to GIM. Although the role of GIM in the stepwise progression model of gastric carcinogenesis (the so-called "Correa cascade") has come into question recently, we review the scientific evidence that strongly supports this long-standing model and propose a new progression model that builds on the Correa cascade. Eradication of *H pylori* is the most important method for preventing gastric cancer globally, but the effect of eradication on established GIM, is limited, if any. Endoscopic surveillance for GIM may, therefore, be necessary, especially when there is extensive corpus GIM. Recent advances in image-enhanced endoscopy with integrated artificial intelligence have facilitated the identification of GIM and neoplastic lesions, which will impact preventive strategies in the near future.**

*Keywords:* Intestinal Metaplasia; Gastric Cancer; Gastric Adenoma; Gastric Dysplasia; Gastric Atrophy; *Helicobacter pylori*; Autoimmune Gastritis; Endoscopic Diagnosis.

Gastric intestinal metaplasia (GIM) was first described in the late 19th century.[1,2] Some researchers originally misinterpreted GIM as a congenital abnormality (heterotopia) but it was subsequently recognized to be a pathologic change of the gastric mucosa that develops as a consequence of a regenerative process, strongly associated with chronic inflammation and atrophic gastritis.[2,3] Early studies also showed a strong association of GIM with gastric cancer,[3–6] including a close topologic relation between the 2 entities, indicating that most cancers arise within a background of GIM.[7] Later, Ming et al[8] and Stemmermann et al[9] pointed out 2 important findings in this regard: first, that a small subset of gastric cancers was not surrounded by GIM, and, second, that neoplastic glands had direct connections at the neck region of the "pyloric glands," where the metaplastic process also emerged. However, the tumors that they studied were mostly at advanced stages, so the original mucosal architecture might have been destroyed, thus hampering the precise mucosal origin of gastric cancer.

In 1970, Correa et al reported that GIM was more prevalent in cancers of the "intestinal type."[10] Therefore, he considered GIM a precancerous condition and established his famous model delineating the stepwise progression of GIM to gastric cancer, the so-called "Correa cascade,"[11] which was published before the link between *Helicobacter pylori* and gastric cancer was declared by International Agency for Research on Cancer in 1994. Since then, there has been considerable discussion over the validity of this concept for gastric carcinogenesis – as will be discussed later.

## Modern Concept of "Metaplasia": Transcommitment and Transdifferentiation

In current literature, the term "metaplasia" is often misused to encompass transdifferentiation, a process of phenotypic changes in differentiated cells.[12] Satake et al[13] found the presence of scattered goblet-like cells among periodic acid–Schiff–positive normal gastric mucosal cells in 2.7% of 917 biopsy samples and designated this mucosa as gastric "goblet cell metaplasia" in 1982. These goblet-like cells were seen among the pit cells and never occurred in the deeper gland compartment. Goblet cell metaplasia, which can also be observed in the ciliated bronchial mucosa, should be discriminated from true intestinal metaplasia (IM) because it lacks intestinal cell lineage, and may more

***Abbreviations used in this paper:*** **AI, artificial intelligence; AIG, autoimmune gastritis; BLI, blue laser imaging; GI-GIM, gastric-and-intestinal mixed-type-gastric intestinal metaplasia; GIM, gastric intestinal metaplasia; IEE, image-enhanced endoscopy; IM, intestinal metaplasia; LCI, linked color imaging; miRs, microRNAs; NBI, narrow band imaging; NHPGB, non–*Helicobacter pylori* gastric bacteria; OLGA, Operative Link on Gastritis Assessment; OLGIM, Operative Link on Gastric Intestinal Metaplasia assessment; SPEM, spasmolytic polypeptide expressing metaplasia; WLI, white light imaging.**

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properly be named goblet cell hyperplasia, a process provoked by inflammatory cytokine signaling.[14,15] Another example is the "pseudogoblet cells" observed in the esophagus,[16] whose presence can be misinterpreted as evidence of Barrett's esophagus. Because these changes are also not accompanied by other intestinal cell lineages, these examples may be better defined as transdifferentiation rather than metaplasia.

In contrast, metaplasia should be defined as a phenotypic conversion through reprogramming of differentiation at the level of stem/progenitor cells, thereby resulting in clonal changes in the whole gland. "Transcommitment" may be a preferred term for the reprograming event causing clonal changes of the gland, rather than the widely misused "metaplasia" to avoid further misunderstanding.

Under this precise definition of metaplasia as transcommitment, the spasmolytic polypeptide expressing metaplasia (SPEM) observed after acute parietal cell loss by DMP-777 administration[17] may be a misnomer because it was not a clonal event involving the reprograming of the gastric gland into intestinal phenotype. Furthermore, cells that express spasmolytic polypeptide (also known as trefoil factor 2) exist in the isthmus of the normal gastric gland but may have shifted toward the base of the gland as a result of parietal cell loss. Moreover the "SPEM" triggered by administration of DMP-777 can revert to the original gastric gland structures shortly after stopping the drug, suggesting that this type of "SPEM" does not result from reprogramming of differentiation from the stem/progenitor cell population (Figure 1).

In the human atrophic corpus mucosa, altered glands resembling pyloric glands are frequently observed. The term "pseudopyloric gland metaplasia" was first coined in 1922 by Störk.[18] As the name implies, these glands have not been considered as true GIM because they lack intestinal cell phenotypes. Intriguingly, Wada et al[19] reported "pyloric gland metaplasia" and "pseudopyloric gland metaplasia" in the oxyntic mucosa, both of which disappeared within 6 years of *H pylori* eradication. Therefore, these types of "metaplasia" do not represent a fixed phenotype but instead represent adaptive changes that can revert to their original phenotypes. However, spasmolytic polypeptide-expressing cells residing in the bottom of human incomplete GIM[20] should not be labelled as "SPEM" and would be more appropriately understood as a constituent of incomplete GIM.[21]

Despite the misleading connotations attached to the term "metaplasia," we will continue to use the term GIM in this review, with the understanding that it refers to the reprogramming of the gastric stem/progenitor cells to an intestinal phenotype, namely, transcommitment. Of note, IM occurs not only in the stomach, but can also be observed in the esophagus (Barrett's esophagus with goblet cells), gallbladder, pancreas, and uterus, and, hence, GIM in this article specifically denotes IM that arises in the fundic and pyloric glands and excludes the IM found at the gastroesophageal junction because IM found in the gastroesophageal junction zone may derive from different cellular origin (Barrett's esophagus, for example) as reported in the recent consensus report.[22]

## Classification of GIM: Implications for Gastric Cancer Risk

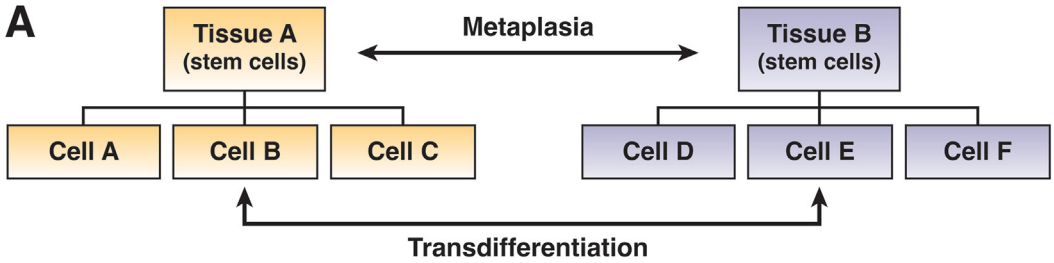
Metaplastic glands in GIM may contain several lineages including intestinal absorptive cells, goblet cells, intestinal endocrine cells, and Paneth cells. When all these intestinal cell lineages are present, GIM has been termed Type I or complete GIM. However, Paneth cells and, even in some cases, absorptive cells may be absent - a morphology termed incomplete GIM (Table 1).[21,23–26] Incomplete GIM may be further subdivided according to the mucin phenotype into sialomucin-expressing subtype (Type II) and sulfomucin-expressing subtype (Type III), which is a colonic-type mucin stainable with high-iron diamine.[27] Type III GIM only accounts for a small proportion of GIM (approximately 10%), yet it is the type most strongly associated with gastric cancer development.[28] In clinical practice, however, such subclassification of incomplete GIM requires special staining, limiting its use for research purpose, and differentiation between incomplete vs complete GIM with routine H&E staining usually suffices.

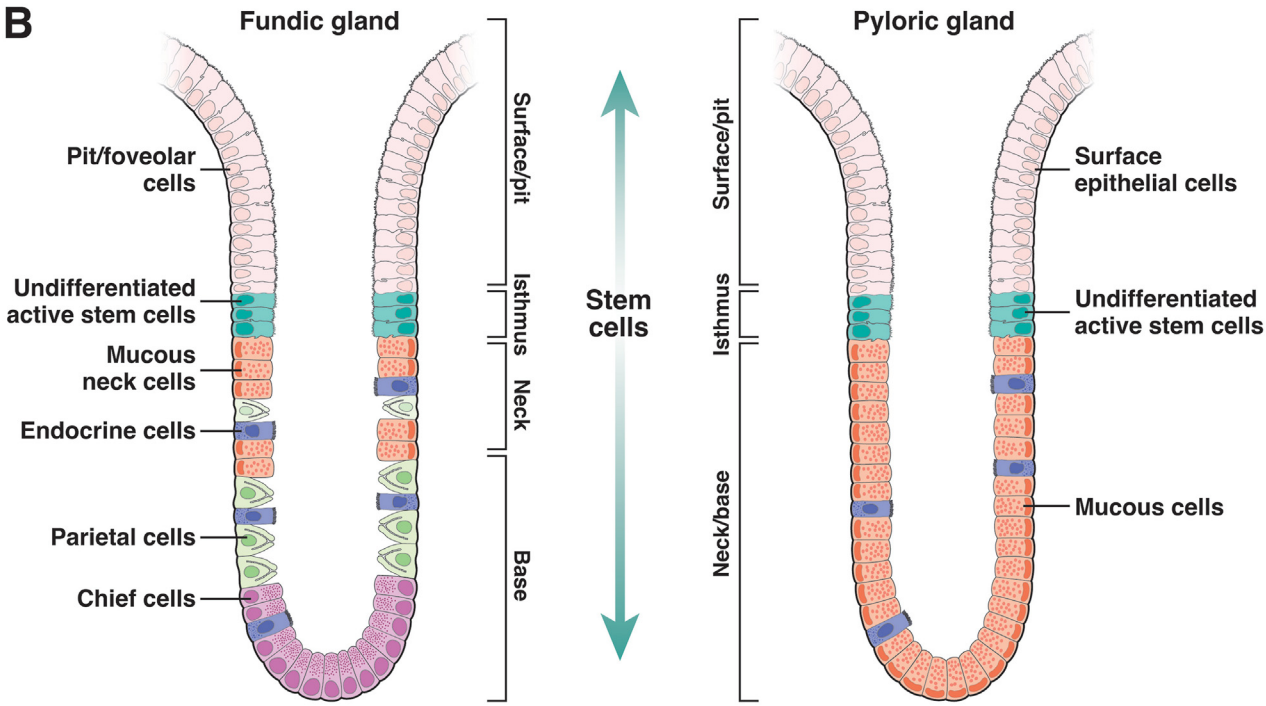
Importantly, human GIM also contains residual cells of gastric lineage, such as gastric endocrine cells,[29–31] which implies that the gastric differentiation program is still operating to some extent. For example, SOX2 (SRY-boxb2), a transcription factor normally expressed in the stomach but not in the intestine, is expressed in GIM.[30,31] Further, mucous cells of GIM often express both gastric (MUC5AC) and intestinal type (MUC2) mucin. Based on the difference in the mucin expression profile, a subclassification of GIM into gastric-and-intestinal mixed-type (GI-GIM) and complete intestinal type (I-GIM; Table 2) was proposed.[19,29,30,32] However, "complete intestinal type (I-GIM)" is terminologically confusing because the distinction between I-GIM and the conventional complete type of GIM was ill-defined. Moreover, special staining for various types of mucins is required for the subtyping, thus its use is limited for research purposes. Interestingly, however, these 2 types of GIM showed a different distribution pattern within the stomach, with GI-GIM predominant in the antrum, whereas I-GIM predominates in the corpus.[21] Regarding trefoil peptide expression, including spasmolytic polypeptide (trefoil factor 2), all 3 forms of trefoil peptide are expressed in the 3 subtypes of GIM.[33] It should be noted that in the incomplete type of GIM, the proliferative zone, although expanded, remains in the middle part of the gland similar to the normal gastric gland, rather than at the bottom of the crypt as seen in the intestinal mucosa.[34]

Collectively, GIM may better be understood as a "hybrid" gland in terms of molecular and cellular phenotype.[31]

## Mechanisms of Reprogramming

A key event instrumental in the formation of GIM is activation of 2 homologous caudal-type homeobox genes, *CDX-1* and *-2*. These transcription factors regulate genes governing intestinal development and cellular differentiation.[35] Ectopic expression of these *CDX* genes in murine gastric glands results in conversion from a gastric



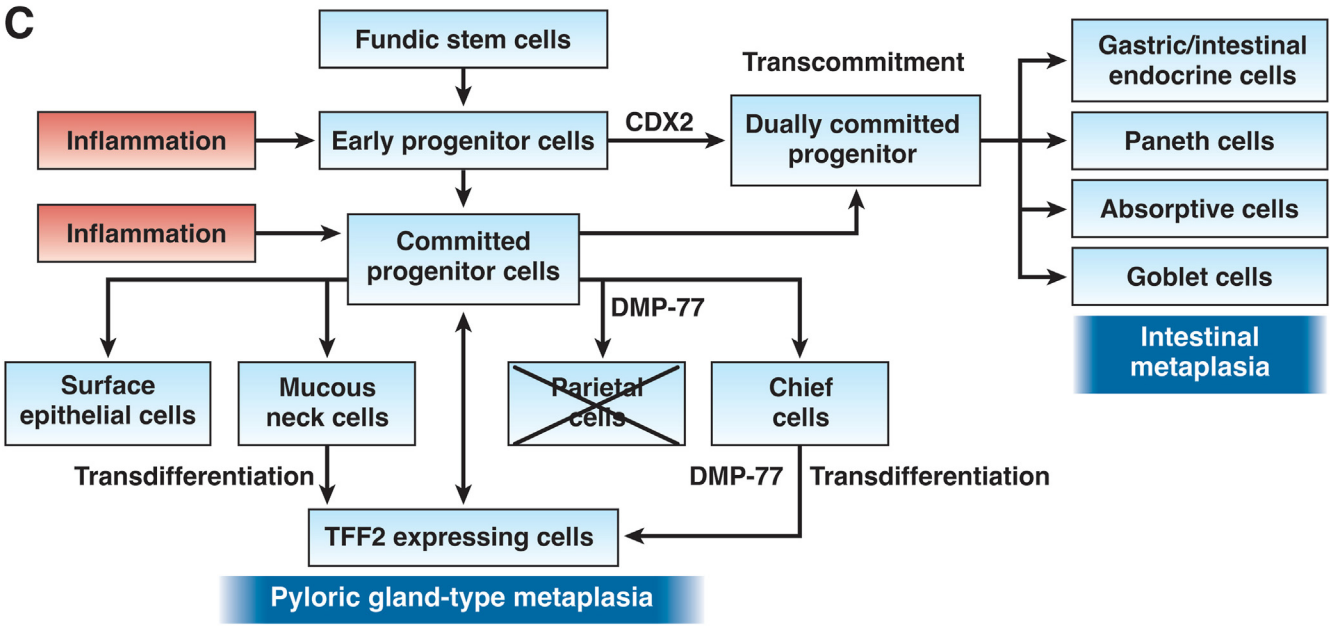



**Table 1.** Subtype of GIM

| Subtype | Mucin subtype | Mucin phenotype | Goblet cells | Absorptive enterocyte | Paneth cells |
|---|---|---|---|---|---|
| Complete | Type I | Gastric (MAC5AC)<br>Sialomucin (MAC2) | ++ | ++ | ± |
| Incomplete | Type II | Sialomucin(MAC2) | ++ | + | - |
| | Type III | Sulfomucin(MAC2) | + | ± | - |

phenotype to IM.[36–39] Several other transcription factors, such as *HNF4a* and *GATA4*, cooperate with *CDX* to regulate intestinal cell lineages or intestinal-specific gene expression, such as sucrase-isomaltase (Supplementary Figure 1).[35,40] Other mechanisms are also involved in the ability of *CDX2* to induce an epithelial phenotype. For example, *CDX2* gene transfection into esophageal cells did not result in enterocyte-type differentiation,[41] which is in sharp contrast to the results with an intestinal epithelial cell line (IEC-6).[42] This may be due to the presence of *p63*, an important master transcription factor for specifying esophageal squamous cell lineage, which may act antagonistically against *Cdx2*.[43]

In human GIM, both *CDX-1* and *CDX-2* are strongly expressed with concomitant expression of intestinal genes.[32,44–47] *CDX-2* expression occurs before that of *CDX-1* and frank GIM development.[45] In support of this temporal sequence of CDX gene expression, Cdx2 expression preceded that of Cdx1 in the *Cdx2* mice model[38,39] and in in vitro experiments in which Cdx2 induced Cdx1.[48]

The molecular mechanisms leading to GIM induction are not fully elucidated. There is evidence for both direct bacterial action.[49–51] and indirect mechanisms through inflammatory cytokine expression acting to increase *CDX2* expression.[52] Other, non–*H pylori* gastric bacteria (NHPGB) may also participate in this process by stimulating inflammation.[53,54] Chronic *H pylori* infection also promotes methylation of CpG sites[55] in chronic gastritis but during the progression to intestinal metaplasia and on to gastric cancer there is progressive demethylation of the *CDX2* gene promoter, resulting in higher CDX2 expression.[56] Specific microRNAs (miRs) may also play a role in this aberrant expression of CDX2.[57]

Interestingly, several other factors considered injurious to the gastric mucosa, such as bile acids,[58,59] can also contribute to induce *CDX* gene expression leading to GIM development, and they may also promote progression to neoplasia. The molecular events leading to GIM, however, have not been studied in the context of autoimmune gastritis (AIG).

## Epidemiology

GIM constitutes a subset of gastric atrophy, for which *H pylori* infection is the most important etiologic factor. The prevalence of *H pylori* infection differs from country to country and depends on sanitary and socio-economic conditions, age, dietary factors, ethnicity, and prior eradication therapy.[60,61] Because the diagnosis of GIM requires endoscopic biopsy sampling, it is difficult to capture the prevalence of GIM in the general population.

Nevertheless, a recent comprehensive literature search provides an estimate of the prevalence of GIM around the

**Figure 1.** Concept of metaplasia and transdifferentiation. (*A*) Concept of metaplasia and transdifferentiation. Transformation from one differentiated cell type to another is defined as transdifferentiation, whereas changes of the differentiation program at the progenitor cell level (reprogramming) resulting in a change from one tissue phenotype to another is defined as metaplasia, as proposed by Slack.[12] Because the reprograming occurs at the progenitor cell level, this results in various differentiated types of cells of a clonal origin. (*B*) A schema of the normal fundic and pyloric glands. In the normal fundic gland, surface pit cells are located in the superior portion (closest to the gastric lumen) and mucous neck cells; enteroendocrine cells, parietal cells, and chief cells are the major cell types in the glandular (deeper) portion. Enteroendocrine cells, such as ECL-cells, ghrelin-containing cells (X/Alike cells), serotonin cells (EC cells), and somatostatin cells (D cells), are also scattered throughout the gland. Normal pyloric glands have surface pit cells and mucous cells in their superior portion and enteroendocrine cells such as G-cells and D-cells in the glandular portion. No parietal cells or chief cells are present in the pyloric gland. In both types of glands, all different types of cells originate from progenitor cells located in the isthmus region of the gland unit and undergo differentiation as they migrate away from this region either toward the surface or the base of the gland. (*C*) A schematic model of transdifferentiation and metaplasia in the fundic gland. Inflammatory stimuli evoke the expression of *CDX2* in the progenitor cells of the gastric fundic mucosa. This triggers a reprograming of differentiation toward an intestinal phenotype. Nevertheless, such intestinal metaplastic glands still retain gastric phenotype containing SP-expressing cells; namely, GIM is formed by dually committed progenitor cells. Thus, GIM containing cells with SP expression should not be labelled SPEM but be considered as a representation of the hybrid nature of GIM. In contrast, chemical insults such as DMP-77 cause loss of parietal cells and disappearance of chief cells. Such acute damage to the fundic glands brings about expansion of mucus neck cell–like cells expressing SP (TFF2). In chronic inflammation, an alteration of the differentiation program at the committed gastric cell lineage, such as mucus neck cells or prechief cells, may result in "pyloric gland type metaplasia." Such changes may represent an example of transdifferentiation. Importantly, however, these SPEM phenotypes in small animal models caused either by acute chemical damage or by chronic infection are reversible. Accordingly, stem/progenitor cells that retain original differentiation programs restore gastric units. G-cells, gastrin-cells; SP, spasmolytic polypeptide; TFF2, trefoil factor 2.

**Table 2.** Subtypes of GIM According to Gastric or Intestinal Mucin Expression

| Subtype | Mucin phenotype | Goblet cells | Absorptive enterocytes | Paneth cells | Endocrine cells |
|---|---|---|---|---|---|
| Gastro- and intestinal mixed (GI) | Gastric (MAC5AC) Intestinal (MAC2) | ++ | + | - | Gastric endocrine cells Intestinal endocrine cells |
| Intestinal (I) | Intestinal (MAC2) | ++ | ++ | ± | Mainly intestinal endocrine cells |

world.[62] According to this report, the prevalence of GIM in the United States was 4.8%. In U.S. veterans, however, a much higher prevalence of GIM was reported, which varied with ethnicity; Hispanic and African Americans had the highest prevalence (29.5% and 25.5%, respectively), but non-Hispanic white veterans also had a prevalence rate (13.7%) that was higher than in the overall population. Higher rates of GIM in these ethnic groups remained after adjustment for *H. pylori* infection, indicating the presence of other undefined GIM risk factors.[63] A large nationwide database study of biopsy samples from the Netherlands, a region of decreasing *H pylori* prevalence, has shown that the incidence of GIM gradually increases with age groups, from about 2% in the youngest age group (age 20–24 years) to >16% in the oldest (80–84 years). Furthermore, the incidence of GIM has decreased markedly from 1991–2005, by about 2%–3% per year, reflecting the cohort effect of the decreasing prevalence of *H pylori* infection in the nation.[64]

A high prevalence of *H pylori* infection is generally correlated with increased GIM presence and gastric cancer risk. In Japan, the prevalence of atrophic gastritis increases with advanced age[65] and reaches a plateau at the level of >80% in those older than 30 years of age with *H pylori* infection. Similarly, the prevalence of GIM in *H pylori*–infected subjects gradually increases with age, starting from <10% in the young (<30 years) to >50% in those older than 60 years of age. In contrast, GIM prevalence in subjects without *H pylori* infection remains low, around 20% even in the oldest age group. The prevalence of GIM is much lower than that of atrophic gastritis, irrespective of *H pylori* infection or age. In East Asia where gastric cancer is common, the prevalence of GIM was 21% (95% confidence interval, 22.6%–25.3%).[62] More recently, GIM prevalence in a population of Chinese Singaporeans (mean age, 59.5 years) in which gastric cancer mortality is in the intermediate range was 44.3%, although most of them did not have advanced stages of GIM (namely, Operative Link on Gastric Intestinal Metaplasia assessment [OLGIM] III–IV).[66]

A high prevalence of GIM (89%) in AIG was reported in a small study of 27 patients.[67] A recent study also showed a high rate of GIM in AIG, especially in the corpus (97%) compared with the antrum (27%).[68] Antral occurrence of IM in AIG may be surprising, but it is possible because the incisura is part of the antrum and some glands containing parietal cells are known to be distributed there. Interestingly in this study, all GIM was of the complete type, with relatively low proliferative activity compared with non-AIG.[68] Another recent study enrolling 211 *H pylori*–negative patients also confirmed a high prevalence of GIM, which increased from 75.8%–84.8% during the mean follow-up period of 7.5 years.[69]

Parietal cell loss, by immune attack and resultant hypo- and achlorhydria, allows overgrowth of NHPGB that can promote inflammation[53,54] leading to GIM. These NHPGB could potentially contribute to gastric cancer both in *H pylori*–associated chronic gastritis and AIG. An intriguing recent report has provided strong supportive evidence that human NHPGB can contribute to the development of premalignant lesion when transplanted into the stomachs of mice.[70]

In this context, concurrent or past *H pylori* infection overlapping with AIG has been well documented.[71] Therefore, it is not surprising that AIG has a high risk for gastric cancer development,[72] although a recent report on an *H pylori*–naïve AIG cohort has challenged this notion.[69] If more rigorous criteria for AIG as used by Rugge et al[69] is applied for the diagnosis, gastric cancer risk in AIG might be smaller than previously thought.

## GIM: Morphologic and Molecular Evidence as a Precursor of Gastric Cancer

GIM itself is a benign condition and may be interpreted as an adaptive phenomenon to an adverse gastric milieu. However, a strong association of GIM with gastric cancer has been a concern for more than a century.[3,5,7] Nevertheless, controversies remain as to whether GIM is a true precancerous condition or a paracancerous condition unrelated to gastric carcinogenesis. In a recent review, Graham and Zou[73] alleged that GIM does not progress to gastric cancer.

However, we will present the evidence that GIM, although not necessarily all GIM, represents a true precursor of a subset of gastric cancer, especially of the well-differentiated (intestinal) type. This will be based on the topologic, temporal, and morphologic relationship of GIM to gastric cancer and to shared genetic changes.

For half a century, Japanese pathologists have investigated the relationship between GIM and gastric cancer, through the study of diminutive cancers (those <5 mm in diameter) to avoid the destruction or distortion of the background mucosa that occurs as the tumors enlarge. Nakamura et al[74] were the first investigators to study such minute cancers, reporting that they were situated adjacent to

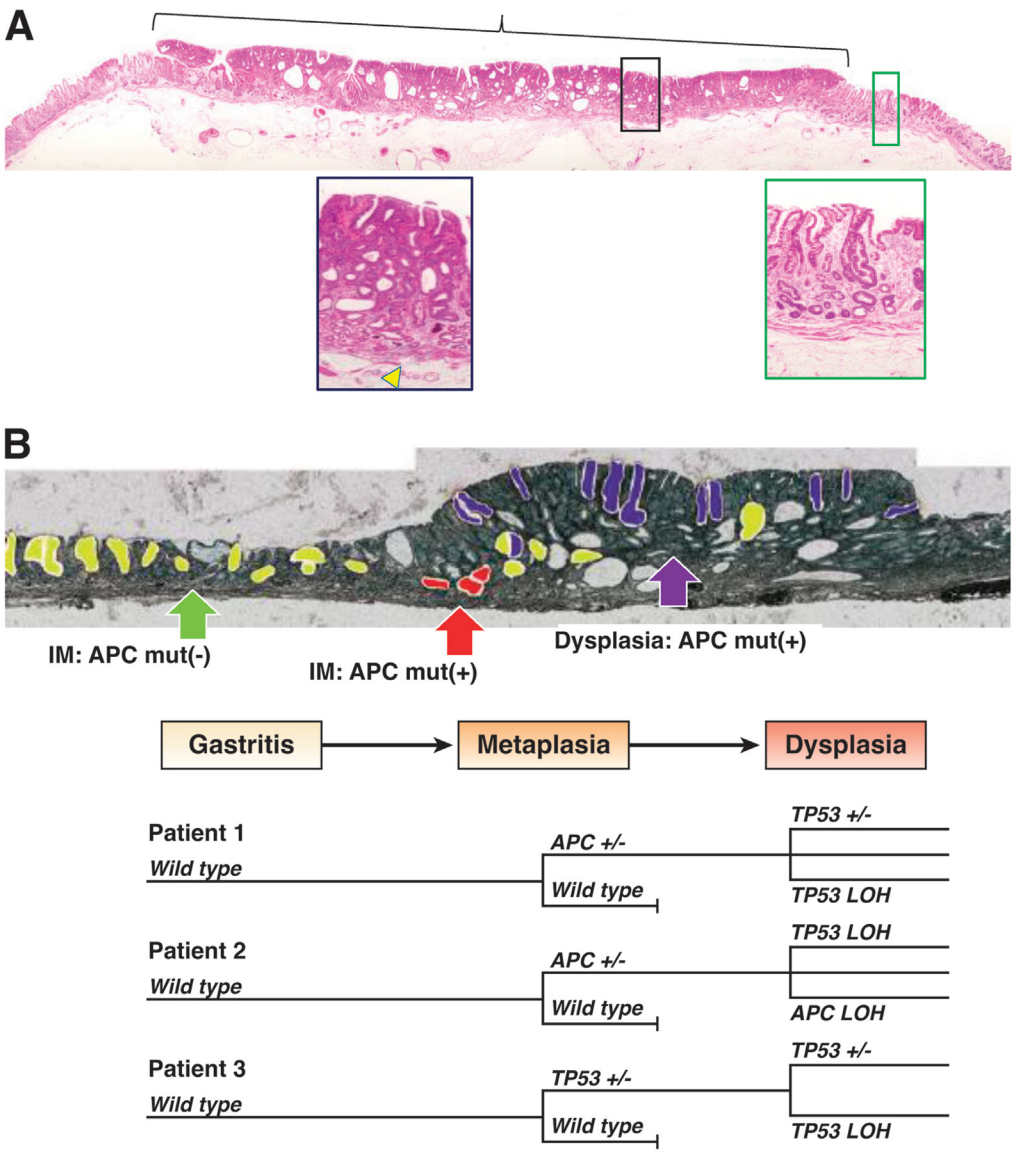



**Figure 2.** A series of morphologic, clonal genetic changes occurring in a single gland within a single tumor tissue. (*A*) A small area of gastric cancer with severe atypia and invasion (*arrowhead in the blown-up image in black frame at bottom left*) within a large adenoma. A biopsy specimen taken from other parts of the tumor would likely be diagnosed as adenoma because this comprises the bulk of the tumor (*black bracketed area*). The tumor is surrounded by incomplete-type IM (*blown-up image framed in green, bottom right*). (*B*) Analyses of microdissected single glands show sequential accumulation of mutations in tumor suppressor genes (*APC, p53*). Glands from IM surrounding the tumor (*yellow*) had no mutations of these genes, but those in the vicinity of tumors (*red*) harbored mutations of *APC* or *p53* identical to those found in the dysplastic area. In glands from dysplastic tissue (*purple*), there were further changes in critical tumor suppressor genes. The tissue architecture displayed advancing morphology from IM to dysplasia. (Adapted from Gutierrez-Gonzalez et al.[100])

GIM. They speculated that these well-differentiated (intestinal) type tumors originated from GIM, and similar findings were confirmed by others.[24] However, studies on minute cancer foci clarified that undifferentiated-type (or so-called diffuse) cancers do not derive from GIM but from the proliferating zone of gastric glands without GIM.[75] From these studies arose the now generally accepted concept that there are 2 distinct pathways leading to different histologic gastric cancer subtypes. Other researchers further claimed that gastric cancer of the differentiated type may not arise solely from GIM but may occur in a non-GIM background.[76–78] Hattori[77] further postulated that gastric cancer originates not from GIM but from the neck region of the gastric glands. Similarly, Kawachi et al[79] investigating extremely small "microscopic" gastric cancer (<3 mm) with immunohistochemical methods to classify the tumors as having gastric, intestinal, mixed, or null phenotypes reported that the smallest lesions (<1.4 mm) had a phenotype resembling the proliferative zones of gastric or incomplete GIM glands. Based on these observations, they concluded that the gastric cancers did not arise from GIM nor express specific intestinal phenotypes, but that the intestinal phenotype was acquired later, as the cancer grew. However, at least a proportion (23%) of these microscopic foci of <1.4 mm in diameter had distinct intestinal mucin phenotypes (intestinal or mixed gastric and intestinal), providing supportive evidence that the intestinal type of gastric cancers originated from GIM. Importantly, they observed that these minute tumors were often located at the proliferating zone of the glands, regardless of the gland type (gastric or GI-mixed). In this regard, their findings were consistent with the hypothesis proposed by Tatematsu et al[80] that most gastric cancers may arise from the neck region of GI-GIM where

proliferating cells are located.[34] Collectively, these studies of minute or microscopic gastric cancers of the intestinal type can be interpreted as evidence that they originate from GIM, mostly from incomplete GIM.

Gastric adenoma (as an aside, gastric dysplasia is the preferred term used in the United States for gastric adenoma; in this article, we use "gastric adenoma" to denote intestinal-type gastric adenoma only, not other types of gastric adenomas such as pyloric gland adenoma or oxyntic gland adenoma) is placed as an intermediate step between GIM and gastric cancer in Correa's cascade.[11,25] Based on the considerable evidence described in this article, there is little doubt of the carcinogenic potential of gastric dysplasia. First, progression of dysplasia to gastric cancer has been well documented, especially in high-grade lesions, although reversal of dysplasia has also been reported in a small proportion of cases.[81–85] Second, previously unrecognized cancer foci have been found consistently within a considerable proportion of adenomas after they have been endoscopically resected. For instance, in 1 study,[86] 46 lesions of gastric adenoma (corresponding to Vienna classification category 3 or 4.1[87]) when diagnosed in biopsy specimens were subsequently upgraded to high-grade adenoma/dysplasia (category, 4.1) and adenocarcinoma (category, 4.2) in 22 (48%) and 7 (15%) cases, respectively, once the resected tumors were examined in their entirety. In a meta-analysis of endoscopically resected low-grade dysplastic lesions, 16.7% and 6.9% of them were upgraded to high-grade dysplasia and cancer, respectively.[88] High-grade cases on biopsy showed a much higher rate of gastric cancer diagnosis after the lesions were endoscopically resected, with a staggering rate of 72.7% in a large Korean study.[89] Thus, there is little doubt that adenoma (dysplasia), even of low grade, is a precursor lesion of gastric cancer or that it can harbor cancer within the tumor – a conclusion that fits well with the Correa model of progressive gastric carcinogenesis.[11,25]

As for gastric neoplasia of the intestinal type, GIM has been observed in the background mucosa of most intestinal-type adenoma cases,[90–92] indicating that they likely arise from similar mechanisms. In fact, incomplete GIM of type III cannot be distinguished from low-grade dysplasia in some cases.[93] Other evidence linking GIM to gastric dysplasia is the coexisting presence of intermediate conditions that lie between GIM and dysplasia. These lesions have been variously labelled indefinite-for-dysplasia,[94] "gastric pit dysplasia,"[95,96] and GIM with basal gland atypia.[97] Addition of these intermediary entities in the precancerous stages would be helpful to better understand the temporal and morphologic changes of GIM that take place during its progression to cancer, and to dissect the molecular events triggering such changes.

In this regard, convincing evidence for the preneoplastic potential of GIM has accumulated from their molecular genetic studies. Elevated levels of CpG island methylation of several genes, including *p16* and *hMLH1*, have been observed in GIM,[98] supporting the idea that GIM is an altered genetic state predisposing to cancer. Consistent with this report, a comprehensive unbiased gene expression analysis classified GIM in the intermediate cluster between chronic gastritis and cancer.[99] Gutierrez-Gonzalez et al[100] reported an identical mutational signature in key tumor suppressor genes in the GIM surrounding the gastric neoplasm (Figure 2). Not only the topologic continuity but also the morphologic transition associated with clonal accumulation of mutations observed in this study offered convincing supportive evidence for the Correa cascade model. Furthermore, isolated glands from GIM surrounding cancer harbored increased methylation of *miR 34-b/c*, a tumor suppressor *miR*, at the level equivalent to those of isolated cancer glands.[101] That same study also noted moderate abnormalities of allelic imbalance that were frequently seen in the isolated glands from cancer, but that were rare in nonmetaplastic glands, again supporting GIM as a precancerous state with significant shared genetic abnormalities to cancer. Yet more evidence for the existence of subsets of high-risk GIM that is predisposed to neoplasia was presented by Huang et al.[102] A signature of shortened telomeres and chromosomal alterations shared by high-risk GIM glands and gastric cancer was identified, which was then applied to a population-based follow-up study in the same cohort. Their results showed that the high-risk molecular signature in GIM predicted progression to cancer.[66] Moreover, Nanki et al[103] demonstrated impressively that organoids derived from GIM and a subset of "indefinite for cancer" organoids derived from gastric cancer cases shared a similar gene expression profile that was distinct from that of normal gastric organoids. Finally, Zhang et al[104] used single-cell transcriptome network analysis across a spectrum of preneoplastic gastric lesions to characterize an intestine-like stem cell phenotype that developed during the progression to GIM, and on to early gastric cancer. In sum, at least a subset of GIM can be defined as a precursor of gastric cancer.

## Gastric Cancer Risk in GIM

Widespread GIM, involving multiple sites of both corpus and antrum, is a risk factor for gastric cancer. A large population-based follow-up study reported that the annual progression rate from GIM to cancer was less than 0.25% per year.[105] Endoscopic mapping biopsy studies have shown that widespread GIM represents a high-risk state. The OLGIM tool,[106] a modification of the Operative Link on Gastritis Assessment (OLGA) system,[107] was proposed for quantitative assessment of stages of GIM based on a systematic biopsy protocol using the updated Sydney System,[108] namely taking biopsy specimens from 5 sites: (1) greater and lesser curvature of the distal antrum, (2) greater and lesser curvature of the proximal corpus (oxyntic mucosa), and (3) lesser curvature at the incisura angularis. It should be borne in mind that GIM is a manifestation of atrophy by the updated Sydney System definition, therefore, each set of the OLGIM stages should be allocated in the same or a higher category of OLGA.[109] A meta-analysis assessing the risk of gastric cancer with both OLGA and OLGIM systems ascertained that higher stages of either OLGA or

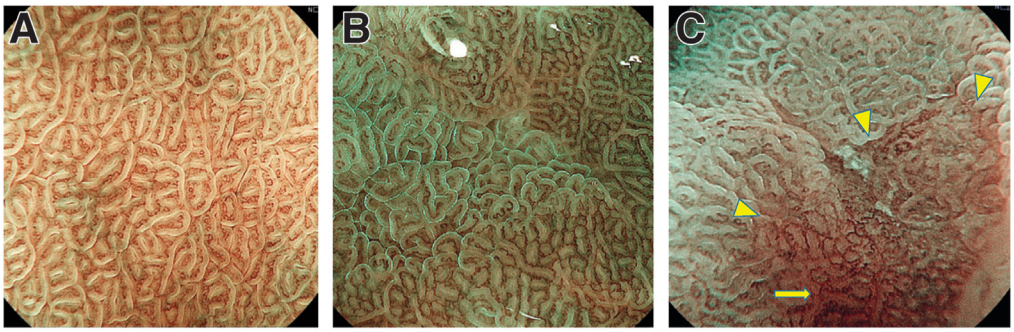



**Figure 3.** BLI of intestinal metaplasia and a small cancer of depressed type. (*A*) Normal white light imaging with magnification of the normal gastric mucosa. (*B*) BLI imaging shows GIM, evidenced by the light blue crest sign. (*C*) GIM with the light blue crest sign surrounds a small, depressed lesion with an abnormal surface mucosal pattern and distorted thick microvessels (*arrow*), leading to the diagnosis of gastric cancer in real time. Note that this lesion is clearly demarcated (*arrowheads*) from the surrounding intestinal metaplasia in most areas, but a section (*left lower part*) seems to be encroached by the tumor.

OLGIM were strongly associated with increased incidences of cancer.[110] Similar findings have been noted in more recent large follow-up studies, based on both Western and Asian cohorts.[66,111,112]

Another feature of GIM that is relevant to gastric cancer risk assessment is the subtype of the GIM, as discussed earlier. Among the 2 subtypes, it has been generally accepted that incomplete GIM is associated with the highest risk of cancer. This is particularly so for type III incomplete GIM in most but not all published studies.[26–28,113]

The 2 most important factors for increased gastric cancer risk with GIM described already in this article (distribution and type of GIM) are in accord with a recent detailed review.[114] However, other risk factors of progression of GIM have also been identified, including persistent *H pylori* infection (in particular, of more virulent strains), age, and smoking.[66,112,114,115]

## Practical Diagnosis of GIM

Although serologic markers for gastric atrophy such as pepsinogens, gastrin, and trefoil factors have been proposed,[66,116,117] none have shown to be sufficiently sensitive nor specific for the diagnosis of GIM. The results were disappointing when gastrin and pepsinogen measurements were applied to a U.S. cohort.[118] Therefore, upper gastrointestinal endoscopy with or without biopsy is the current standard method for diagnosing GIM. Because diagnostic performance with conventional white light imaging (WLI) has been disappointingly poor,[119,120] endoscopists have developed a variety of complementary techniques to facilitate the recognition of GIM such as chromoendoscopic staining with methylene blue or opacification by spraying acetic acid. However, the development of advanced image-enhanced endoscopy (IEE), including narrow band imaging (NBI), flexible spectral imaging color enhancement, blue laser (or light) imaging (BLI), and linked color imaging (LCI), has made such staining methods obsolete because the IEE methods do not require additional spraying steps that could impede direct observation of the gastric mucosa for neoplastic lesions.

The first convincing evidence for identifying GIM using NBI with magnification (identifying the GIM mucosa with the so-called light blue crest sign) was reported by Uedo et al.[121] However, NBI images are dark because of limited light intensity, so NBI is not suitable for scanning the entire surface of the stomach. The second-generation NBI system improved the brightness of the endoscopic images but failed

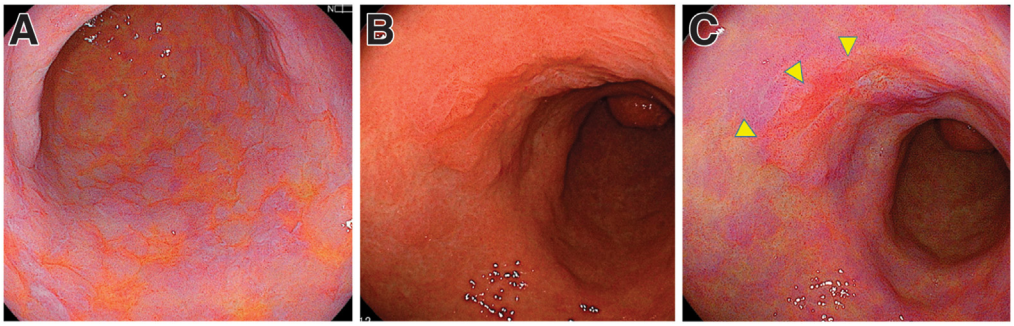



**Figure 4.** LCI images of GIM and of early gastric cancer in comparison with WLI. (*A*) Distant view of lower corpus and antral mucosa with map-like spreading of GIM with purplish color (the "lavender color sign"). Nonmetaplastic gastric mucosa is orange colored. The extent of GIM is easily recognizable with LCI due to the brightness of the field of observation. (*B*) WLI of the antrum with severe IM (*whitish color*). Early gastric cancer with a reddish surface is recognizable. (*C*) The same lesion is more clearly identifiable with LCI (*arrowheads*). Because the color of the neoplastic lesion remains the same, LCI shows distinct color difference between the tumor and the surrounding purplish GIM, facilitating detection of the neoplasm.

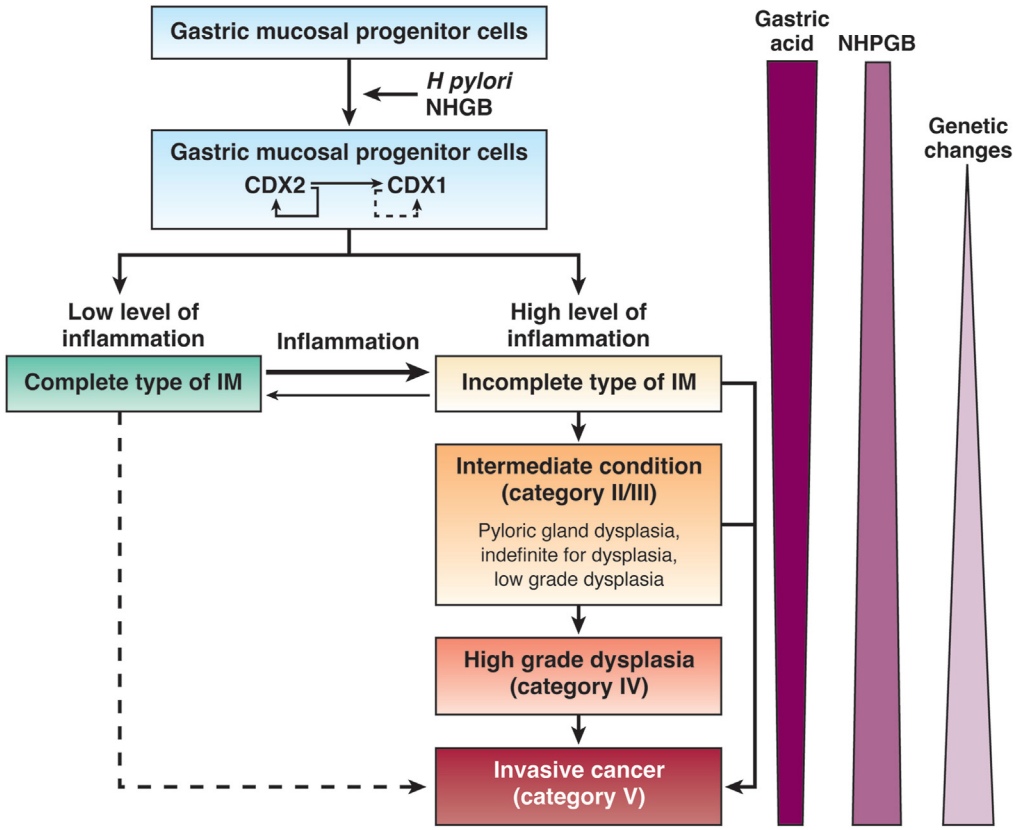



**Figure 5.** A hypothetical model of pathways leading from GIM to the well-differentiated type of gastric cancer. Initiation of GIM is triggered by inflammation, with aberrant expression of CDX2 stimulating the expression of CDX1 to form the complete type of GIM. With less severe inflammation (such as in the early phase of autoimmune gastritis, or the corpus mucosa of *H pylori* gastritis without atrophy), this state usually remains stable and rarely progresses to dysplasia or cancer. However, in the presence of severe inflammation (such as seen with advanced atrophy and hypochlorhydria with the resultant overgrowth of NHPGB) together with additional chemical insults including toxic chemicals, such as nitrosamines from cigarette smoke and bile acids, progression to dysplasia would be promoted. Because CDX2 acts as a tumor suppressor, dominance of CDX2 in complete IM may serve to prevent transformation to dysplasia. Paneth cells present in complete IM may suppress NHPGB and contribute to reduce the inflammation. With continuous inflammation, however, alteration of CDX2 gene expression causing a "caudal shift" of GIM resembling colonic mucosa (type III incomplete GIM) or the lower regions of small intestinal glands.[33] Progressive hypochlorhydria in the gastric mucosa with IM permits overgrowth of NHPGB, further aggravating the inflammatory response, propagating a vicious cycle. Such a milieu predisposes metaplastic mucosa to mutational events in the mucosal cells, leading to neoplasia. However, the progression rate is relatively low and occurs over a long period of time, especially in the early stages.

to show superiority over regular white light endoscopy in detecting early gastric cancers.[122,123]

The BLI system uses 2 laser lights (or diode lights in Europe and the United States) with different wavelengths. BLI allows color-enhancing effects like NBI, but with brighter images. BLI has 2 modes, regular and bright, and the latter mode allows a better view of the distant mucosa because of its higher brightness. GIM can be recognized as a greenish hue with BLI. Neoplastic lesions lack this unique coloration, thus allowing their detection (Figure 3). BLI was reported to be superior to regular white light endoscopy for early gastric cancer detection in a randomized controlled trial.[124]

The most recent development in IEE is LCI, which enhances both red and white color differences via processing ordinary images, facilitating the recognition of mucosal lesions through subtle color alterations. The biggest benefit of this modality is the maintenance of high levels of brightness, allowing efficient inspection of broad area of the gastric mucosa. Distribution of GIM throughout the stomach can be identified with its unique purplish color, the so-called "lavender color sign" (Figure 4*A*).[125] In contrast, neoplastic lesions do not exhibit such color changes, so lesions surrounded by GIM stand out (Figure 4*B* and *C*). A recent multicenter, nationwide, controlled clinical trial of LCI reported about a 50% gain in the detection of early neoplastic lesions in the upper gastrointestinal tract compared with high-definition WLI.[125] In a Chinese trial, detection rate of early gastric cancer was almost 2-fold higher by LCI compared with WLI.[126] LCI was also more useful than WLI for detecting early gastric cancer after eradication of *H pylori*.[127] These clinical data underpin the concept that neoplastic lesions are often surrounded by GIM, indicating transition from GIM to gastric adenomas (dysplasia) based on histologic studies[90–92] and stepwise molecular changes from GIM to gastric cancer reported by Gutierrez-Gonzalez et al.[100]

The large difference in the detection rates of early neoplastic lesions between LCI and WLI even by expert endoscopists in these trials is sobering because it suggests that substantial numbers of cancerous lesions are likely to be missed by conventional endoscopic examinations with WLI alone.

To overcome insufficiency in detecting neoplastic lesions with WLI, there has recently been intensive effort focused on integrating artificial intelligence (AI)–supported endoscopy in enhancing diagnostic performance.[128] Indeed, multiple endoscopy systems based on AI have already been marketed in Japan to assist endoscopists to diagnose lesions throughout the GI tract.

## Management Policy for GIM to Prevent Gastric Cancer

Because only a small proportion of people with GIM will progress to cancer, population screening for GIM is unnecessary.[129] However, in Japan and Korea, where the incidence and mortality of gastric cancer is high, population-based gastric cancer screening programs are well established and are applied irrespective of whether the individual has GIM; this led to early detection of gastric cancer and reduced gastric cancer mortality.[130,131] In Europe, only high-risk groups, with atrophic gastritis or GIM, are recommended to receive periodic endoscopic surveillance. For example, the Management of Epithelial Precancerous Conditions and Lesions in the Stomach II guideline recommends endoscopic surveillance every 3 years for such cases.[132] The outcome data according to this strategy (the original Management of Epithelial Precancerous Conditions and Lesions in the Stomach guideline) have now been reported,[133] and a couple of pitfalls were noted. First, there were cases where the OLGIM grade required upgrading, and, second, a few cancer cases during the follow-up period were reported in the population that was not targeted by the surveillance protocol. For these reasons, the authors of this outcome trial proposed a revised surveillance policy in which serum pepsinogen measurement would be coupled with endoscopic surveillance to reduce miss rates. Recent British and U.S. guidelines also recommend surveillance in high-risk groups, at 3- to 5-year intervals.[134,135] Therefore, a feasible future strategy for most countries to efficiently detect early gastric cancer would be an initial serologic screen to define the high-risk population such as those with gastric atrophy or GIM. Considering that current blood tests (*H pylori* serology plus pepsinogens) have a limited value in the multi-ethnic U.S. cohort,[118] we need newer biomarkers for identifying high-risk groups and/or early stages of neoplasia, examples of which have recently been described.[136,137] Combination of these markers with the rapid development of AI-assisted endoscopy systems might bring about a paradigm shift in our approach to gastric cancer screening. Because both esophageal and gastroduodenal neoplasms can be captured at the same endoscopic examination,[138] the cost-effectiveness of this approach should be more beneficial than estimates obtained from previous cost-analyses that have focused on preventing cancer in a single organ.

For primary prevention of gastric cancer, eradication of *H pylori* is the highest priority. Recent data from the Matsu Islands clearly show that the population-based eradication of *H pylori* can reduce gastric cancer, and gastric cancer–related mortality, as well as GIM.[139] It is noteworthy, however, that the effect of *H pylori* eradication on GIM is limited.[114,129,135] Only a partial recovery of GIM was documented after a long period of follow-up.[140] Although controlled trials have shown that *H pylori* eradication can reduce the incidence of gastric cancer by about 50%,[141] a previous meta-analysis of the effect of eradication in patients with GIM and dysplasia showed no preventive effect on gastric cancer development.[142] Most of these studies conducted outside Japan or Korea raise a concern over the quality of the endoscopic examinations to exclude early cancers. Future studies using AI-assisted endoscopy with IEE (such as LCI) may help identify those patients who are most likely to benefit from *H pylori* eradication therapy.

## Conclusions and Future Directions

Since Correa proposed his stepwise progression model, the concept of GIM as a precancerous condition leading to gastric cancer has been well accepted. Recently Goldenring and Mills[143] proposed that so-called "SPEM" might give rise to gastric cancer. As described in this review, most of the small animal models of "SPEM," even evoked by chronic infection, were reversible, and thus did not recapitulate the human GIM. Our view is that it would be better to consider that spasmolytic polypeptide expressing cells found in human GIM[20,33] represent reprogrammed progenitor cells that generate both gastric and intestinal cell lineages (hybrid state), and, hence, should be discriminated from the "SPEM" resulting from acute parietal cell loss. The detailed morphologic and molecular biological data that we have reviewed provides abundant and convincing evidence that GIM is the precursor of most, if not all, intestinal-type gastric cancer.

GIM is usually the result of chronic *H pylori* infection, although it can also be a consequence of AIG. GIM in AIG in the gastric corpus typically consisted of complete GIM[68] as is the GIM in the corpus found in chronic gastritis without severe atrophy.[21] Gastric cancer risk in complete GIM is much lower than that of the incomplete type.[113] The expression level of *CDX2* may play an important role in reducing the risk of gastric cancer in complete GIM, as suggested by reports showing progressive decreases of *CDX2* expression along the Correa cascade, in contrast to persistent *CDX1*.[144,145] These observations are consistent with CDX2 having tumor suppressor activity.[146,147]

Another important aspect of GIM that we have highlighted is the concept that GIM is of a hybrid nature, having both gastric and intestinal elements. The dominant phenotype may depend on the relative expression levels of certain transcription factors, such as *SOX2* and *CDX2*.[30] We speculate that the ultimate phenotypic fate of a diminutive cancer budding out from the proliferating zone of incomplete GIM may depend on the interaction between the tumor microenvironment and transcriptional factors. The contribution of

mesenchymal cells to this outcome is illustrated by our murine model of GIM, in which the pericryptal fibroblast sheath surrounding the metaplastic gland was newly formed.[148] We hypothesize that very small gastric cancers may lack sufficient signaling from mesenchymal cells to support intestinal differentiation.[149]

In summary, we propose an updated version of the Correa cascade with special reference to key transcription factors (Figure 5). As shown in this figure, we recognize that there are several changes from the simple Correa cascade in the pathways leading to the well-differentiated type of gastric cancer. Despite the apparent heterogeneity and complexity, recent advances in cell and molecular biology are gradually helping uncover the underlying mechanisms leading to gastric carcinogenesis. Based on the temporal, topologic, and genetic relations between GIM and gastric cancer, we can conclude that some GIM, if not all, is a true precursor of gastric cancer.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2023.08.028.

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**Conflicts of interest**
These authors disclose the following: Kentaro Sugano served as an advisor of Fujifilm Co. and received a lecture fee. Steven F. Moss is a consultant for Takeda and Phathom Pharmaceuticals and has served on the advisory board of Redhill Biopharma and American Molecular Labs regarding novel *Helicobacter pylori* therapies and antibiotic resistance testing. The remaining author discloses no conflicts.

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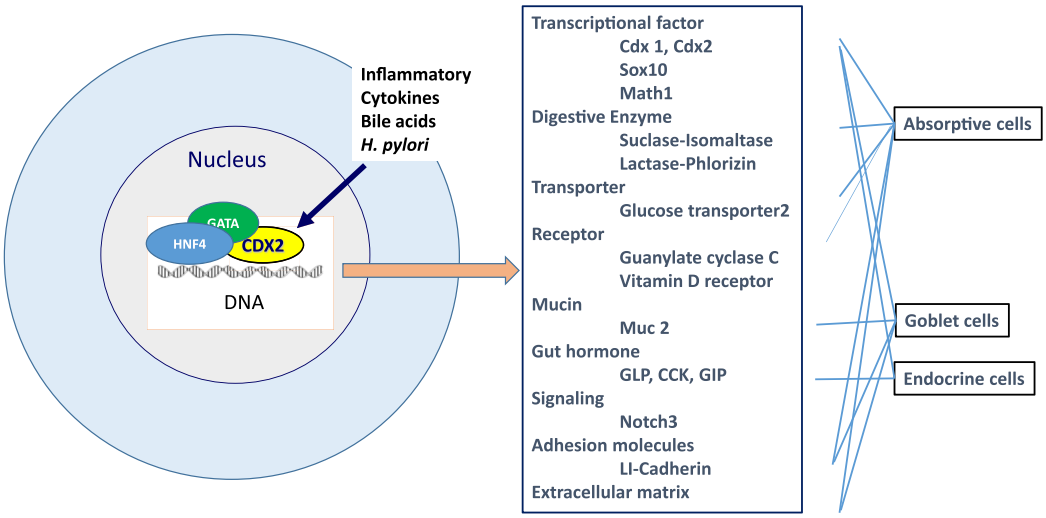


**Supplementary Figure 1.** CDX2 controls multiple genes important in configuring the enterocyte phenotype. Expression of CDX2 is the initial event, triggered in gastric epithelial cells by a variety of factors such as bacteria (most notably *H pylori*), inflammatory cytokines, and bile acids to pave the way to GIM development. In collaboration with many other transcription factors, such as *CDX1, HNF4a*, *GATA4*, and *Tcf4, CDX2* induces genes necessary for shaping intestinal phenotypes. These genes include transcription factors, adherence proteins, transporters, receptors, brush border enzymes, mucin 2, and possibly mesenchymal factors necessary for pericryptal fibroblast sheath formation. CDX2 autoregulates its expression. Thus, GIM, once established, seldom regresses, explaining why GIM represents "the point of no return."