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Hereditary Diffuse Gastric Cancer Syndrome and the Role of *CDH1*
A Review

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IMPORTANCE Inherited variants in the tumor suppressor gene *CDH1* are associated with an increased risk of gastric and breast cancers. This review aims to address the most current topics in management of the hereditary diffuse gastric cancer syndrome attributed to *CDH1*.

OBSERVATIONS Consensus management guidelines have broadened genetic testing criteria for *CDH1*. Prophylactic total gastrectomy is recommended for any pathogenic or likely pathogenic *CDH1* variant carrier starting at the age of 20 years. Annual surveillance endoscopy is recommended to those who defer prophylactic total gastrectomy. Women with a *CDH1* variant should initiate magnetic resonance imaging breast surveillance starting at age 30 years. Further research is needed to understand the pathogenesis of early-stage gastric cancers (T1a), which are pathognomonic of hereditary diffuse gastric cancer syndrome, that lead to advanced gastric cancer to develop both treatment and prevention strategies for this patient population.

CONCLUSIONS AND RELEVANCE The heritable *CDH1* gene mutation is of importance to today's surgeons because it is associated with a substantial increased risk of developing both gastric and breast cancers. Management of this cancer syndrome currently uses prophylactic surgery and enhanced cancer surveillance strategies.

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More than 2 decades have passed since the report of familial clustering of diffuse gastric cancer in New Zealand Maōri families and its linkage with germline *CDH1* (OMIM *192090) variants.[1] Individuals who carry pathogenic or likely pathogenic *CDH1* variants are at increased risk of developing gastric and breast cancers. Both clinical experience and general understanding of hereditary diffuse gastric cancer (HDGC) syndrome have increased, albeit with modest advances in our basic understanding of this monogenic disorder. With the expansion of direct-to-consumer genetic testing and rise in multigene panel testing, it is expected that there will be a concomitant increase in the diagnosis of germline pathogenic variants in genes such as *CDH1*.[2] Recognition of these changes underscores the need for clinical awareness of this heritable cancer syndrome and its medical management. To date, our understanding of the HDGC syndrome has resulted from the management of variant carriers with risk-reducing gastrectomy and surveillance endoscopy. Our aim was to review current management guidelines, their rationale and supporting data, and explore the molecular underpinnings of this hereditary cancer syndrome for which surgery maintains a central role.

The search terms *hereditary diffuse gastric cancer* and *germline CDH1* were used to query PubMed for nonreview articles published between January 1, 2000, and January 1, 2020. Only English-language articles were assessed for inclusion in this review.

Criteria for Testing and Diagnosis of HDGC

HDGC syndrome is most commonly characterized by an autosomal dominant pattern of inheritance of inactivating mutations in the *CDH1* tumor suppressor gene.[1,3-5] Families with pathogenic *CDH1* variants are at increased risk of developing diffuse-type gastric adenocarcinoma, lobular breast cancer in women, and cleft lip and palate. The International Gastric Cancer Linkage Consortium has produced consensus management guidelines that include indications for germline genetic testing in individuals who meet specific criteria.[6] Recent modifications have expanded testing criteria to include a diagnosis of a diffuse-type gastric cancer (DGC) at any age in an individual with a personal history of invasive lobular breast cancer (LBC) or DGC in the setting of cleft lip or palate (**Box**). Therefore, cleft lip/palate in the setting of DGC and/or hereditary lobular breast cancer should also raise the suspicion of germline *CDH1* variant carriers. At our institution, we have observed that 16 of 118 families (14%) have documented cleft lip or palate.[7]

Individuals who meet the criteria should be provided genetic counseling and germline testing that should be performed in a certified diagnostic laboratory. Any positive test results from direct-to-consumer kits should be validated in a certified laboratory, because those results have been found to generate conflict-

ing interpretations.[8] Furthermore, based on other reports, genetic testing for *CTNNA1* and *PALB2* variants also should be included.[5,9,10] Other than *CTNNA1* and *PALB2*, to our knowledge, no additional genes have been causally linked to diffuse, but not intestinal-type, gastric cancer.

Lifetime Cancer Risk

Original estimates of cumulative lifetime gastric cancer risk were as high as 70%; however, these were likely overestimates owing to ascertainment bias.[5] Recent studies have revised gastric cancer penetrance estimates downward and now range from 37% to 42% for men and 25% to 33% for women.[11,12] Comparatively, women with pathogenic *CDH1* variants also carry an estimated lifetime lobular breast cancer risk of 42% to 55%. The overall prognosis for advanced gastric cancer due to a germline *CDH1* mutation is expected to be similar to sporadic gastric cancer. Although the risk of gastric cancer will vary among families, to our knowledge, genotype-phenotype correlations to aid cancer risk assessment do not yet exist. Therefore, any family history of diffuse gastric cancer should be considered when counseling patients about their individual cancer risk. There are no convincing data to link the risk of other gastrointestinal cancers to *CDH1* variants, and so adherence to population cancer screening guidelines for other cancers is recommended.

Clinical Management

Initial diagnosis of a germline *CDH1* variant often precipitates referral to a surgeon. However, carriers of pathogenic *CDH1* variants ideally should receive care from a multidisciplinary team of dedicated experts that includes a genetic counselor, dietitian, gastroenterologist, pathologist, and surgical oncologist. This team should be able to provide the most up-to-date expert advice with regard to cancer surveillance, prophylactic gastrectomy, and long-term care for both the patient and affected family members. Because of the elevated risk of gastric cancer and the inherent limitations of endoscopic surveillance, which are discussed in the Gastric Cancer Surveillance section, asymptomatic *CDH1* variant carriers are advised to undergo prophylactic total gastrectomy (PTG). This should occur only after detailed preoperative assessment and counseling of surveillance as an alternative to surgery. Individuals who choose to forego PTG should have annual upper endoscopy for surveillance of early gastric cancer.[13] The primary goal of surveillance endoscopy is to assess for gastric mucosal changes that may signal progression of early cancer foci and exclude more infiltrative (>T1a) lesions. In addition, results of surveillance endoscopy can provide patients the opportunity to make more informed decisions about gastrectomy.[14] Women with pathogenic *CDH1* variants are also advised to begin breast cancer surveillance with annual magnetic resonance imaging at age 30 years.[6] Even though lifetime breast cancer risk in this population ranges from 42% to 55%, expert consensus supports both breast-conserving therapy in the presence of invasive cancer as well as the option for bilateral risk-reducing mastectomy.

Box. Hereditary Diffuse Gastric Cancer Syndrome Genetic Testing Criteria

***CDH1* and *CTNNA1* testing is recommended in the following situations**

Individual criteria

DGC in individuals aged <50 y[a]

DGC at any age in individuals with a personal or family history of cleft lip/cleft palate

History of DGC and LBC in individuals aged <70 y

Bilateral LBC/LCIS in individuals aged <70 y

Gastric biopsy with in situ signet ring cells and/or pagetoid spread of signet ring cells in individuals aged <50 y

Family criteria[b]

≥2 Cases of gastric cancer in family (any age), with at least 1 confirmed DGC

≥2 Cases of LBC in family members aged <50 y

≥1 Case of DGC any age and ≥1 case of LBC in different family members aged <70 y

Abbreviations: DGC, diffuse gastric cancer; LBC, lobular breast cancer.

[a] All diagnoses of DGC and LBC must be histologically confirmed.

[b] Family members must be first- or second-degree blood relatives of each other.

Prophylactic Total Gastrectomy

Preoperative consultation is multifaceted and should include discussion of operative risk along with long-term sequelae of total gastrectomy. This discussion addresses the operative approach, the individual surgeon's expected outcomes, and plans for longitudinal care. Careful assessment and acknowledgment of competing medical risks is necessary, with special attention to untreated drug, tobacco, and alcohol addiction, and eating disorders. Evaluation of preoperative nutrition and education regarding postgastrectomy dietary changes is of utmost importance, and all patients proceeding to PTG should have a baseline endoscopy before surgery to verify that there is no presence of advanced cancer.

Total gastrectomy is recommended in carriers as young as 20 years and is generally not advocated in patients older than 70 years. Even in the setting of an endoscopic gastric biopsy demonstrating a focus of signet ring cells (SRCs), to our knowledge, there are no data suggesting a hurried decision for surgery is warranted. The pathognomonic SRC foci of HDGC are present in nearly all asymptomatic *CDH1* variant carriers and have been found in adolescent individuals.[15] Total gastrectomy is an infrequent operation and should be performed at high-volume gastric cancer centers, preferably with added expertise in the longitudinal care of patients and families with HDGC.[16]

Gastric cancer risk reduction can be achieved only with complete removal of the stomach. Operative approach (open or laparoscopic) should be chosen by the surgeon based on their own outcomes, as neither approach has demonstrated superiority to the other.[17] Esophageal and duodenal margins should be assessed intraoperatively via frozen section to ensure complete removal of

gastric mucosa.[18] Perigastric (D1) lymphadenectomy is sufficient, because lymph node metastasis is an uncommon finding in asymptomatic patients who typically harbor T1a or in situ SRCs. Reconstruction with esophagojejunostomy and a 40- to 50-cm Roux limb is most common. A thorough histopathologic evaluation of gastrectomy explants is essential to ensure the most advanced lesions are identified because there are frequently multiple clusters. The new consensus guidelines have proposed a 3-level protocol that uses both World Health Organization and Laurén classifications; this total-embedding protocol ensures examination of the gastric mucosa in entirety and is expected to increase the number of cancer lesions identified.[6,19]

Although early and late morbidity of PTG have been reported, long-term outcomes specific to patients with HDGC are not well established.[20,21] Perioperative morbidity is low with infrequent severe adverse events, such as anastomotic leak (4%) and intra-abdominal abscess (4%-7%). Long-term complications of gastrectomy include internal hernia and anastomotic stricture, which are also infrequent (1%-5%), likely because this population is generally younger and healthier than patients with sporadic gastric cancer undergoing the same operation.[18,20-23]

Patient-reported outcomes regarding quality of life and satisfaction with the decision to undergo prophylactic surgery have been evaluated. A frequent and expected symptom is the inability to tolerate large meals and overall intolerance of certain foods, which often can return to baseline by 12 months after surgery.[21] In addition, although many patients notice an increase in anxiety or depression, the incidence is similar to that of the general public throughout the course of recovery.[23] Thus far, studies have found that patients' satisfaction with their decision to undergo PTG is high (around 90%).[23,24]

Postgastrectomy care should include easy access to a registered dietitian, with regular evaluation of macronutrient and micronutrient blood levels, as common chronic sequelae also include esophageal dysmotility, dumping syndrome, osteopenia/osteoporosis, nephrolithiasis, and cholelithiasis. Weight loss nadirs at approximately 6 months postgastrectomy and ranges between 12% and 18%; weight loss 1 year after surgery approximates 20% of baseline body weight.[18,21,25,26] The most common chronic symptoms include bile reflux (as many as 50% of the patients), dry mouth, inability to tolerate water, and dumping syndrome, which have been reported to occur more frequently at 1 year post surgery compared with 3 months.[18] Total gastrectomy results in the loss of intrinsic factor secretion and consequently impaired vitamin B_{12} absorption. Intramuscular supplementation of the vitamin is not necessary because oral formulations are adequate to maintain normal B_{12} levels. In addition, altered calcium absorption and resulting osteoporosis are possible, but we have observed in our institution that adherence to dietary supplements may negate these risks.

Micronutrient deficiencies are of particular concern for women of childbearing age. A case series of 6 pregnant women after PTG reported healthy neonates when nutritional counseling and dietary supplementation were implemented.[27] Access to a clinical pharmacist for drug level monitoring may be required because oral medication absorption can be altered after gastrectomy, such as with commonly prescribed antidepressants, antibiotics, and oral contraceptives.

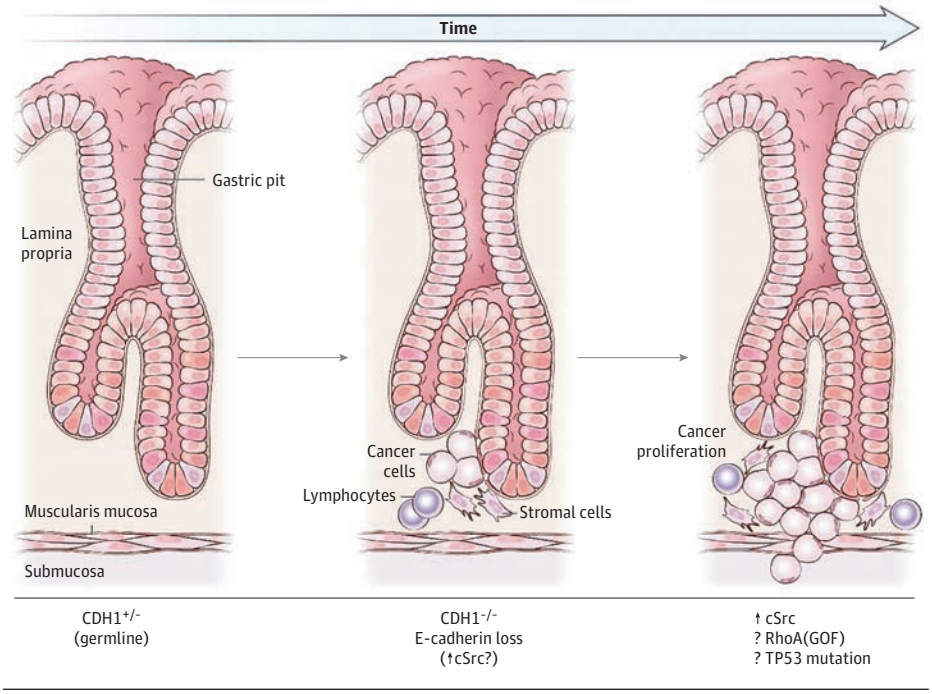
Gastric Cancer Surveillance

Patients who do not choose PTG should receive annual cancer surveillance via upper gastrointestinal endoscopy. The consensus approach to gastric biopsy, the Cambridge method, incorporates extensive white-light examination followed by a minimum of 30 nontargeted (random) gastric biopsies from 5 separate areas of the stomach.[28] This method of surveillance is reported to detect occult SRC foci in 20% to 63% of patients.[13,20,25] *CDH1* gastrectomy explants have been reported to demonstrate SRCs in 80% to 100% of specimens; therefore, the Cambridge method of surveillance carries a high false-negative rate.[15,29,30] Given its poor reproducibility and concern for high false-negative rates, techniques of early gastric cancer surveillance other than the Cambridge method have been explored. Endoscopic ultrasonography combined with the Cambridge method failed to demonstrate an improvement in the sensitivity of detection.[31,32] Chromoendoscopy, which aids in identifying mucosal pale areas, was reported to improve SRC detection rates; however, this technique is limited to detecting only larger cancer lesions.[32] Similarly, autofluorescence and narrow-band imaging as adjuncts to white light endoscopy and random biopsy do not appear to improve occult cancer detection.[33] Confocal endomicroscopy uses a fiberoptic probe during endoscopy to visualize the microstructure of the gastric mucosa, and results of an early-phase clinical trial have demonstrated low SRC detection rates as a solitary surveillance method.[34] Specific attention to targeting pale areas has been suggested to improve SRC foci detection; however, other investigators have reported that these areas are nonspecific for SRC pathologic factors.[33,35-37] Another approach to surveillance focuses on locations within the stomach, but use of this approach is reportedly variable across geographic regions despite no differences in genotypes.[14,38-40] Given that most of these early gastric cancer lesions measure less than 1 mm in diameter and are not visible with standard endoscopy, one approach is to obtain more gastric biopsies.[41] Curtin et al[42] refined and trialed a systematic biopsy technique that obtains 88 nontargeted biopsies and reported a substantially lower false-negative cancer detection rate compared with the consensus method (38% vs 80%).[43]

Lobular Breast Cancer

In addition to an increased risk of gastric cancer, women with pathogenic *CDH1* variants also carry an elevated lifetime risk of invasive lobular breast cancer (LBC). Hereditary LBC is defined by a *CDH1* variant carrier with LBC and/or a positive family history of LBC with no family history of DGC. Similar to linitis plastica of the stomach, E-cadherin–deficient invasive lobular carcinoma does not form a well-defined mass, but rather invades surrounding tissue in single-file sheets/cords. When LBC metastasizes to the peritoneum, the histopathologic characteristics are analogous to the morphologic characteristics of diffuse-type gastric cancer, likely owing to the shared genetic precursor. This observation of shared histopathologic characteristics is also supported by the observation that 87% of families with *CDH1* hereditary LBC demonstrate SRCs on gastrectomy explant.[44] The observed peritoneal tropism of LBC is not well understood. Because LBC does not form a discrete mass and does not

Figure 1. A Model for Stepwise Progression of *CDH1*-Associated Gastric Carcinogenesis



cSrc indicates cellular Src kinase; GOF, gain of function.

reliably produce microcalcifications, mammography has been established to be a poor instrument for detection with sensitivities calculated as low as 34%.[45] Therefore, annual surveillance magnetic resonance imaging in women between age 30 and 50 years is recommended.[6] The addition of ultrasonography for screening of dense breast tissue remains controversial. Most recent consensus guidelines, such as those of Blair et al,[6] state that bilateral risk-reducing mastectomy can be considered, but that breast-conserving therapy for LBC can be adequate. To our knowledge, there is currently no compelling evidence on the incidence of lobular carcinoma in situ or invasive lobular carcinoma from prophylactic mastectomy after a negative surveillance magnetic resonance imaging.[46] The general risks of surgical treatment, both partial or complete mastectomy, are low; therefore, the decision between breast-conserving therapy and bilateral mastectomy should be based on ipsilateral cancer recurrence and lifetime cancer risk. The *CDH1* variant carriers' lifetime risk of developing invasive breast cancer is similar to that of *BRCA* mutation carriers.

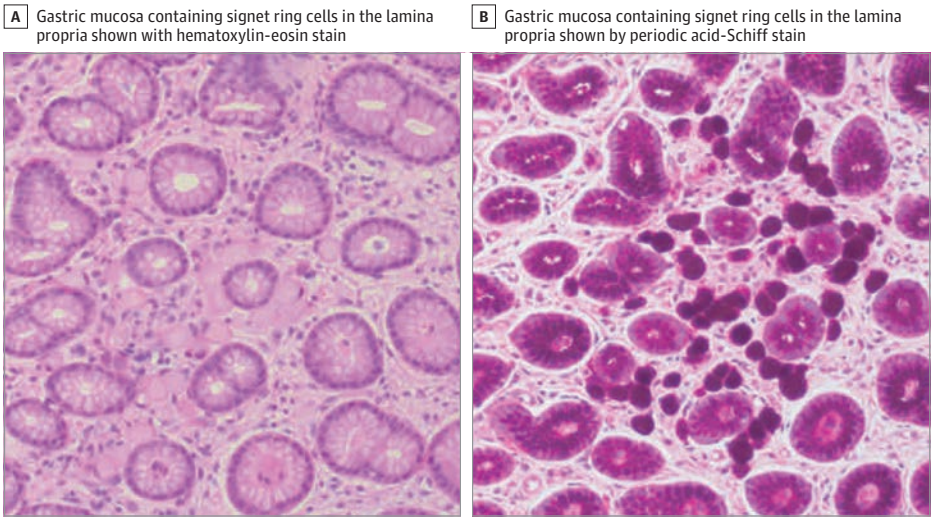
The Role of *CDH1* in HDGC

The *CDH1* gene is located on chromosome 16q22.1 and encodes E-cadherin, a transmembrane glycoprotein located at the adherens junctions in epithelial tissues and has cell-cell adhesion and signal transduction functions.[47] E-cadherin has 3 structural domains: extracellular, transmembrane, and cytoplasmic. The cytoplasmic domain connects to the actin cytoskeleton through various catenins (eg, α, β, and p120) and also regulates basic cellular processes, such as cell signaling, migration, apoptosis, and invasion.[48-50] There are an estimated 155 pathogenic variants in *CDH1*, which range from complete gene deletions to single-nucleotide alterations and occur throughout the entire gene.[28] It follows that loss of normal E-cadherin expression could disrupt gastric epithelial tissue homeostasis ultimately leading to SRC carcinoma (**Figure 1**). It is hypothesized that stochastic and somatic epigenetic and genetic events result in E-cadherin inactivation and the development of multiple (sometimes >100) foci of intramucosal SRC carcinomas (**Figure 2**). It is, however, generally accepted that these early-stage (T1a) SRC cancer foci will remain indolent until the acquisition of a second hit, which may be due to epigenetic (promoter hypermethylation) or genetic (somatic mutation or deletion) phenomena, and results in loss of heterozygosity.[51-53] The specific molecular alterations that foster subsequent progression of these SRC foci to more advanced gastric cancer remain to be proven. In murine models it is known that combined loss of E-cadherin and p53 expression in the gastric epithelium induces diffuse gastric cancer invasion and metastasis.[54] However, it may not be the case that *CDH1* loss of heterozygosity is always necessary for development of invasive, diffuse-type gastric cancer. Park et al[55] found that conditional knockout of classic tumor suppressors *TP53* and *SMAD4* with maintenance of *CDH1* heterozygosity in murine gastric epithelium resulted in metastatic gastric tumors. Many families who meet criteria for genetic testing in the setting of HDGC will not have a *CDH1* variant identified. In a few of those families, the *CTNNA1* gene, which encodes α-catenin (another adherens junction protein), has been causally linked to HDGC.[9] Loss of α-catenin may mimic *CDH1* inactivation in these patients through similar downstream effectors and acquisition of anchorage-independent growth.[56]

Active Research

Multiple areas of basic and translational research are underway to answer outstanding questions related to the early molecular and cellular changes leading to invasive gastric cancer in *CDH1*-variant car-

Figure 2. Intramucosal Gastric Signet Ring Cell Carcinomas



A, Hematoxylin-eosin (original magnification ×40). B, Periodic acid–Schiff (original magnification ×40).

riers. Although the germline *CDH1* mutation is thought to be necessary for cancer initiation, it is likely not sufficient for development of invasive gastric cancer. Therefore, it is necessary to identify the genetic or epigenetic perturbations that cause isolated SRC foci to progress and metastasize. Furthermore, identification of biomarkers of early carcinogenesis may lead to more timely and accurate cancer diagnosis and development of cancer chemoprevention and therapeutic strategies. Clinical research must also include patient-specific risk stratification with more accurate disease penetrance calculations to better guide cancer surveillance and risk-reducing surgery guidelines.

Conclusions

Hereditary diffuse gastric cancer syndrome is a rare genetic disorder that increases lifetime risk of both gastric and breast cancers. Current practice guidelines recommend prophylactic total gastrectomy for *CDH1*-variant carriers because surveillance methods are unreliable and early-stage SRC cancers are commonly identified in gastrectomy explants. Better understanding of the molecular basis of this disease is essential for improving treatment and offering cancer prevention strategies.

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