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Hereditary Gastric Cancer

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ABSTRACT

Hereditary gastric cancer is an autosomal-dominant inherited condition produced by germline mutation in the E-cadherin/*CDH1* gene. Criteria to define the syndrome have been proposed and include review of the histopathology and pedigree analysis of any family with an aggregation of gastric cancer cases. Of families with two or more cases of diffuse gastric cancer in first- or second-degree relatives aged < 50 years or three or more cases of relatives at any age, up to one half may be attributable to inherited germline mutations in the E-cadherin/*CDH1* gene. The cumulative lifetime risk of developing gastric cancer in *CDH1* mutation carriers is > 70% and women from these families also have an increased risk for developing lobular breast cancer. Prophylactic gastrectomy has been performed in several unaffected *CDH1* mutation carriers, and despite normal endoscopic examinations and negative gastric biopsy specimens, pathologic foci of early gastric cancer were found in the vast majority of surgical specimens. Based on these results, guidelines for genetic testing, counseling, and management of individuals with hereditary diffuse gastric cancer are suggested. Raised awareness among the physician community regarding this syndrome may allow for increased detection and prevention of gastric and breast cancers in these high-risk individuals. (J CANCEROL. 2015;2:21-8)

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INTRODUCTION

Inherited forms of cancer are relatively uncommon, representing 5-10% of many types of adult-onset malignancies, although familial clustering of cancer often constitutes another 20% or more of cases. Recent and rapid advances in molecular genetics have provided an understanding of the cause for many inherited cancer syndromes, offering possibilities for individual genetic testing, family counseling, and preventive approaches. For example, the genetic basis for the majority of individuals with clinically defined familial adenomatous polyposis (*APC* gene), hereditary nonpolyposis colorectal cancer (*HNPCC*, mismatch repair genes), and breast-ovarian cancer syndrome (*BRCA1* and *BRCA2* genes) has been determined. One of the most recently defined inherited cancer syndromes predisposes to gastric cancer (GC) and, in particular, to the pathologically diffuse type of GC[1]. An increased incidence of familial GC has been recognized as a component of several inherited cancer syndromes. For example, up to 10% of mismatch repair-deficient *HNPCC* families include GC, mainly of the intestinal pathologic type, in addition to the more typical colorectal and endometrial cancers[2]. In addition, persons with Li-Fraumeni syndrome *(p53)*, *APC*, and Peutz-Jeghers syndrome *(STK11)*, all exhibit elevated rates of GC compared with the general population. However, several families are specifically predisposed to diffuse GC, together with lobular breast cancer, and share inherited germline mutations in the *CDH1* gene encoding for the E-cadherin protein. The incidence of hereditary diffuse gastric cancer (HDGC) is relatively low compared with the most common inherited cancer syndromes; it accounts for 1-3% of GC, although estimates suggest that up to 10% of patients, particularly young patients, diagnosed with GC will exhibit familial clustering[3].

GASTRIC CANCER EPIDEMIOLOGY

Gastric cancer ranks second in terms of the global gastric cancer burden worldwide[4]. Of interest is that the dramatic decrease of adenocarcinoma of the stomach in the USA and other Western countries including Mexico during the last 70 years has occurred primarily in the intestinal form of the disease, which is associated with achlorhydria, intestinal metaplasia, and *Helicobacter pylori* infection[5]. However, there has been a relative increase in proximal GC, gastroesophageal junction cancers, and distal esophageal adenocarcinomas, particularly associated with Barrett's epithelium[6]. Overall, diet and infection with *H. pylori* are probably the prominent environmental risk factors for GC, but familial aggregation in a variable yet significant proportion of cases suggests the importance of genetic predisposition. Genetics in GC may play a more important role in young patients. In one study performed at a tertiary referral center in Mexico City, up to 16% of GC cases were aged 40 years or younger at presentation, and 15% had a family history of this neoplasm[7]. The majority of cases of GC in Western countries present in advanced stages; thus, the ability to identify individuals at high risk for developing familial GC may allow for intensive screening efforts, or even prophylaxis, to diagnose and treat GC at an early and curable stage.

GENETIC PREDISPOSITION TO GASTRIC CANCER

Approximately 10% of cases of GC, both of the diffuse and intestinal types, show familial clustering[8]. The first clear evidence of a GC susceptibility genetic locus was the identification in 1998 of a germline-inactivating (truncating) mutation in the gene encoding for E-cadherin, called *CDH1*, in a large Maori family from New Zealand with kindred with early-onset diffuse GC[1] (Fig. 1). The family had first been reported to exhibit a familial pattern of GC in 1964[9], and over 30 years, 25 family members from five generations died of the disease. Pathologically, these were all poorly differentiated, diffuse GC. Age at diagnosis of GC ranged upward from 14 years, with the majority occurring in individuals < 40 years of age. The pattern of

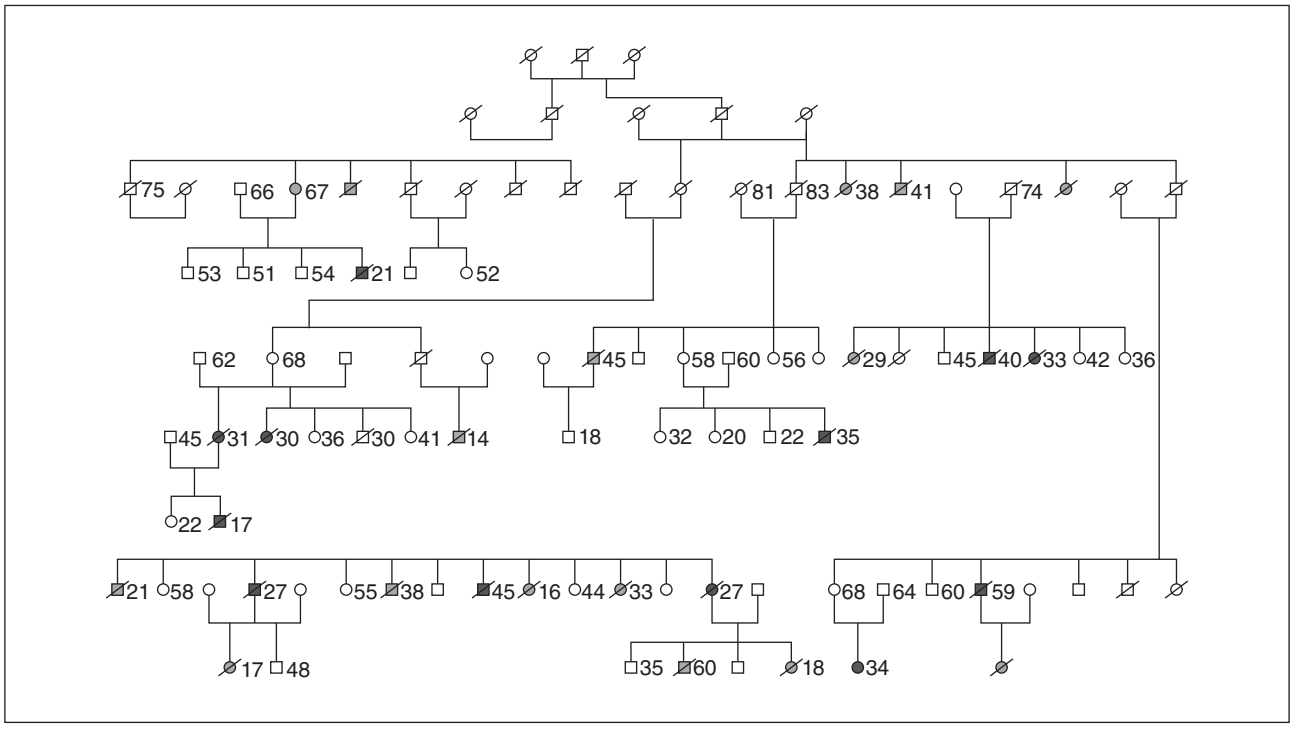

Figure 1. First report of the germline mutation of the *CDH1* gene in hereditary diffuse gastric cancer.
Adapted from Guilford PJ, Hopkins JB, Grady WM, et al. E-cadherin germline mutations define an inherited cancer syndrome dominated by diffuse gastric cancer. Hum Mutat. 1999;14(3):249-55.

inheritance of GC was consistent with an autosomal dominant susceptibility gene with incomplete penetrance. Therefore, Parry Guilford at the Cancer Genetics Laboratory at the University of Otago in New Zealand performed linkage analysis for several candidate genes and found a maximum Lod (likelihood) score at a marker near the E-cadherin gene on chromosome 16q22.1. The proportion of individuals with the haplotype who were affected by GC at the age of 60 years was 70%, providing an approximate penetrance for the disease allele. Indeed, mutational analysis of E-cadherin identified a germline mutation that resulted in premature truncation of the protein. This mutation had been identified previously in sporadic GC and confers worse prognosis[7,10]. It was soon found that HDGC occurred in families from several ethnic backgrounds, as it was shown that E-cadherin/*CDH1*-inactivating germline mutations accounted for a proportion of European ancestry kindred with familial diffuse GC[11,12].

HEREDITARY DIFFUSE GASTRIC CANCER: CLINICAL DEFINITION AND CHARACTERISTICS

Pathologically, all cases of GC cases from families with genetically defined inactivating *CDH1* mutations have shown invasive, poorly differentiated, diffuse GC and display occasional signet-ring cells. There is clearly no association with the pure intestinal type. The estimated cumulative risk of GC by age 80 years in HDGC families is 67% for men and 83% for women[13] (Table 1). Age of onset shows marked variation between and within families. Median age at onset in the 30 Maori *CDH1* mutation carriers who developed GC was 32 years, significantly younger than the median age of 43 years in individuals with GC of other ethnicities. In addition to GC, several other cancers appear to occur at a somewhat elevated incidence in HDGC families. Most notably, lobular breast cancer has been observed to occur

Table 1. Cumulative risk of gastric and breast cancer in E-cadherin/*CDH1* mutation carriers

Age (years)	Male GC (%)	Female GC (%)	Breast Cancer (%)
30	4	4	0
40	9	21	3
50	21	46	10
60	43	64	19
70	52	71	29
80	67	83	39

GC: gastric cancer.
Adapted from Pharoah, et al.[13]

in approximately 20-40% of women from families who carry *CDH1* mutations[13,14]. Of note, E-cadherin mutations have been observed in up to 50% of sporadic lobular breast cancer[15]. In addition, colorectal carcinomas and prostate cancers have been observed in *CDH1* mutation carriers[16], although it remains to be determined whether these common tumors occur at rates above those in the general population.

The International Gastric Cancer Linkage Consortium[16], a group of clinical geneticists, gastroenterologists, surgeons, oncologists, pathologists, and molecular biologists from several different countries, define guidelines for the diagnosis and management of HDGC. The clinical criterion that has been suggested for definition of this syndrome comprises two or more documented cases of diffuse GC in first- or second-degree relatives, with at least one of these diagnosed prior to the age of 50 years, or three or more cases of documented diffuse GC in first- or second-degree relatives, independent of age at onset. Approximately 25-50% of families meeting one of these criteria have identifiable germline mutations in the *CDH1* gene. The remaining families may have unidentified mutations in regulatory elements or mutations in unidentified genes that also contribute to HDGC. Few mutations have been found in families without a case of diffuse GC in an individual aged less than 50 years. This observation, combined with the frequent impracticality of confirming histotype in more than one family member, has led to new testing criteria consisting of a minimum of two first-or second-degree relatives with gastric cancer, provided one is aged < 50 years and one is confirmed as having diffuse type; 48% of families meeting these criteria harbor germline *CDH1* mutations. Fewer than 5% of individuals with diffuse GC under 50 years of age and with no family history of gastric or breast cancer carry germline *CDH1* mutations, although this figure is likely to vary markedly between populations with different rates of sporadic GC. The incidence of *CDH1* mutation carriers is presumably greater for isolated cases in individuals aged < 35 years[17]. A single-nucleotide polymorphism in the promoter region of the *CDH1* gene has been identified to contribute to some cases of HDGC[18,19].

MOLECULAR MECHANISM OF HEREDITARY DIFFUSE GASTRIC CANCER SUSCEPTIBILITY

The E-cadherin gene is a member of the cadherin family of calcium-dependent transmembrane homodimeric cell adhesion molecules expressed in epithelial cells and known to be important in development, cell differentiation, and tissue repair. The E-cadherin cytoplasmic domain is bound to the actin cytoskeleton through an intracellular complex formed of catenin proteins, and this complex is required to maintain intercellular adhesion (Fig. 2). The actin cytoskeleton forms a transcellular network, mediating structural integrity, cellular polarity, and epithelial morphogenesis. Loss of function of E-cadherin through genetic or epigenetic causes may predispose epithelial cells to loss of contact inhibition, unregulated growth, and invasion into adjacent tissues. Transfection and *CDH1* gene expression in malignant epithelial tumor cells abrogates the invasive phenotype[20]; thus, it has been described as a tumor invasion suppressor gene.

A common feature of inherited cancer syndromes is a germline mutation in one allele of a tumor suppressor or DNA repair gene, with somatic loss of the second allele (the second hit) attributable to a

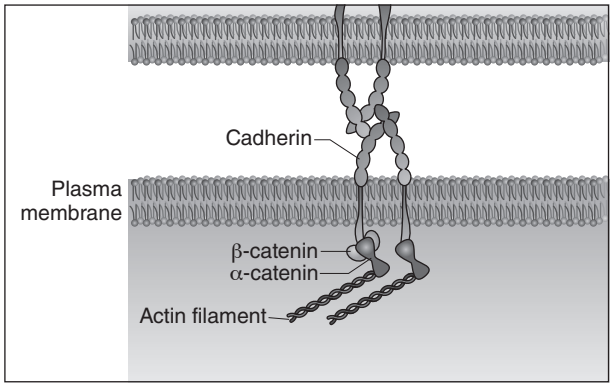

Figure 2. Situation of E-cadherin in the cytoskeleton network. *Adapted from Ishiura S, editor. Intercellular Communication and Tissue Architecture. Tokyo: The University of Tokyo; 2010. Available from: http://csls-text.c.u-tokyo.ac.jp/active/11_01.html*

deletion or a second mutation (termed loss of heterozygocity)[21]. In fact, little or no E-cadherin immunoreactivity is observed in gastric tumors from HDGC families, indicating that the second *CDH1* allele is inactivated somatically[22]. However, unlike the majority of other cancer syndromes, loss of heterozygocity does not appear to occur frequently in HDGC[11,23]. Instead, hypermethylation of the *CDH1* promoter in the remaining wild-type allele appears to result in an epigenetic allelic inactivation or silencing of gene expression[23]. The fact that the second hit on *CDH1* gene expression is frequently not attributable to an irreversible mutation or deletion event also suggests possible therapeutic strategies to recover normal expression of the wild-type gene product in these cancers. Demethylation agents are presently being developed for the treatment of a variety of cancers in phase I trials, and their potential use to reverse E-cadherin gene inactivation is being investigated.

CLINICAL MANAGEMENT OF HEREDITARY DIFFUSE GASTRIC CANCER SYNDROME

Genetic counseling and testing for hereditary diffuse gastric cancer

This should be considered for individuals whose families' pedigrees fit the criteria for HDGC. At this point, it is premature to offer E-cadherin genetic testing for apparently sporadic cases of diffuse GC in patients affected at a young age, because the prevalence of new germline mutations in the population remains unknown. Nor should families with intestinal-type GC be tested, because E-cadherin mutations are implicated only in diffuse-type GC. The complexities and uncertainties surrounding the clinical impact of E-cadherin mutations necessitate that genetic testing be provided in a research center within the counseling framework established for other family cancer syndromes. For HDGC kindred, diagnostic testing would optimally be initiated in a sample from an affected patient to identify pathologic germline E-cadherin mutations. Because the majority of mutations will be unique to a specific family, it is important that genetic testing not be offered to at-risk subjects without proceeding through the diagnostic phase. A negative test result implies that the subject is at the general population risk for this cancer. These individuals would not require additional gastric screening or need to consider prophylactic surgery.

Screening for gastric cancer in hereditary diffuse gastric cancer

Diagnosing GC in its early stages provides the best chance for curative resection but is a difficult task. Symptoms attributable to GC do not appear until the disease is more advanced and are generally nonspecific. When diagnosis of GC is established, the disease is most often locally advanced, with over two-thirds of cases in non-endemic regions presenting with lymph node involvement and, in Mexico, with distant metastatic disease[3]. Endoscopy is generally considered the best method to screen for GC, but diagnosing diffuse GC is more difficult because these lesions tend not to form a grossly visible exophytic mass, but rather spread submucosally as single cells or clustered islands of cells. Improved methods to diagnose these early diffuse lesions are important, especially for those with HDGC. Emerging new technologies included chromoendoscopy (Congo red/methylene blue technique) to aid in endoscopic detection. Even

Table 2. Published data on prophylactic total gastrectomy among E-cadherin mutation carriers

Study	Year	Patients (n)	Cancer in specimen	Multifocality
Hebbard, et al.	2009	23	22/23 (96%)	N/A
Chen, et al.	2011	18	17/18 (94%)	N/A
Lynch, et al.	2008	17	13/17 (76%)	N/A
Carneiro, et al.	2004	9	9/9	5/9 (55.5%)
Barber, et al.	2008	8	8/8	7/8 (87.5%)
Norton, et al.	2007	6	6/6	6/6
Lewis, et al.	2001	6	6/6	5/6 (83.3%)
Charlton, et al.	2004	6	6/6	6/6
Huntsman, et al.	2001	5	5/5	N/A
Chun, et al.	2001	5	5/5	5/5
Medina-Franco, et al.	2007	4	3/4 (75%)	N/A
Newman, et al.	2006	2	0/2	0
Chung, et al.	2007	1	1/1	0/1
Francisc, et al.	2007	1	1/1	1/1
Total		111	102/111 (91.9%)	35/42 (83.3%)

Adapted from Medina-Franco, et al.[24]

with these techniques, in the vast majority of the so-called "prophylactic gastrectomy" series, foci of early GC are found in the surgical specimen despite negative endoscopic preoperative work-up[24,25] (Table 2). For now, the surveillance of individuals predisposed to GC but not desiring prophylactic gastrectomy should include frequent (every 6-12 months) and detailed endoscopic mucosal examination with multiple biopsies of even the subtlest lesions. This approach, however, has proved to be ineffective in the majority of prophylactic surgery series.

Screening and prevention of lobular breast cancer in hereditary diffuse gastric cancer

Although data are somewhat limited, it appears that women in families with HDGC and carrying mutations in the *CDH1* gene have a significant risk of developing lobular breast cancer, with lifetime penetrance estimates from 20 to 40%[13,14]. The correct approach to screening for lobular breast cancer in women with HDGC is not known, but adherence to standard screening recommendations for mammography should be followed. Calcifications are not ordinarily formed by infiltrating lobular carcinomas; thus, more intensive screening with mammography may not be effective. For *BRCA1* and *BRCA2* carriers, screening with magnetic resonance imaging has proved useful[26], but there are no data in patients with HDGC. In patients with *BRCA* syndromes, prophylactic mastectomy has been shown to prevent the development of breast cancer effectively and has resulted in improved long-term survival[27]. Such an approach remains completely investigational for women in HDGC families, and at this point, no data as to its success or even application have been reported. The prognosis of lobular cancers that develop in patients with HDGC is presently unknown, and given the relatively late onset when compared with breast cancer in *BRCA1/2* carriers, prophylactic mastectomies may not be appropriate. Of great interest is whether chemoprevention with tamoxifen or other newly developed agents may benefit women with HDGC. Results from the randomized, placebo-controlled trial NSABP-P1 demonstrated a reduction by 50% in breast cancer in women at elevated risk because of age, familial history, or history of biopsy-proven lobular carcinoma *in situ* (LCIS) who were taking tamoxifen[28]. In particular, the dramatically reduced risk of invasive breast cancer observed in women with a history of LCIS suggests that tamoxifen chemoprevention may be of benefit to women with HDGC, although the incidence of LCIS as a precursor lesion of infiltrating lobular carcinoma in this population is presently unknown.

Prophylactic gastrectomy for the prevention of gastric cancer

Prophylactic total gastrectomy has been recommended for *CDH1* mutation carriers; however, published data remain limited. Plausible explanations for the rare performance of total gastrectomy in this setting include lack of awareness of the HDGC syndrome and, most importantly, clinical implications of removal of the stomach. Indeed, total gastrectomy may be associated with postoperative morbidity (and even mortality) and adverse effects in quality of life. However, if *CDH1* mutation testing could be a sole surrogate predictor of the presence of microscopic disease, then it might change the decision from "prophylactic" to therapeutic total gastrectomy.

In the largest series published to date, Hebbard, et al. reported the results of a retrospective study of prophylactic total gastrectomy[29]. Twenty-three patients from the Canadian province of Newfoundland and Labrador underwent total gastrectomy between February 2006 and November 2008. All of these individuals were confirmed to have a truncating mutation of the *CDH1* gene. Median age at time of surgery was 45 years (range, 26-63 years). Patients came from three different kindred. Preoperative endoscopy and mucosal biopsies revealed the disease in only two of 23 patients (9%). Interestingly, final standardized pathological evaluation of gastrectomy specimens showed evidence of diffuse/signet ring cell carcinoma in 22 of 23 (96%) patients. Another very recent study from Stanford University included 18 consecutive patients with *CDH1* mutations, including 13 without and five with symptoms; each patient underwent total gastrectomy and 17 (94%) were found to have diffuse ring cell adenocarcinoma. Twelve of 13 asymptomatic patients had T1, N0 cancer and only 2/12 (16%) had had it diagnosed preoperatively despite state-of-the-art screening methods. For five symptomatic patients, each (100%) was found to have signet ring cell adenocarcinoma by preoperative endoscopy; three (60%) had lymph node metastases, and two (40%) had distant metastases at the time of the procedure[30]. These studies confirm that in the vast majority of cases, mutation carriers, and sometimes even individuals without a mutation as reported in our experience[24], already have microscopic intramucosal disease, which explains the small (9 and 16%, respectively) proportion of disease revealed by preoperative endoscopic screening. Table 2 summarizes the results of prophylactic total gastrectomy for HDGC. Although larger studies are required to confirm this very high rate of therapeutic gastrectomy among *CDH1* mutation carriers, the data available strongly indicate the presence of intramucosal carcinoma in these individuals. In a recent systematic review, 70 articles were included. Among patients with a positive family history of GC, 1,085 were screened from 454 families, and 38.4% tested positive for germline mutation in *CDH1* gene. Mutation-positive families had a considerable family history of breast and colon cancer. Of the 322 patients screened for *CDH1* mutations by current HDGC criteria, 29.2% tested positive. Among the 76.8% of patients who underwent prophylactic gastrectomy following *CDH1* test results, 87% had positive final histopathology results and 64.6% had signet ring cells identified[31]. Therefore, we can consider the majority of mutation carriers as patients and not as healthy individuals who will ever develop gastric cancer.

Other lessons from the Stanford study is that once the patient has symptoms, the possibility of widespread disease is very high and in asymptomatic patients, even state-of-the-art endoscopy is highly ineffective as a screening method.

The recommended surgical procedure is total gastrectomy, first because multifocal microscopic disease is very common (Table 2), and second, because preclinical evidence suggests that the genetic basis of the HDGC syndrome is so strong that sooner or later cancer will arise in the residual epithelium. Therefore, subtotal gastrectomy is not recommended. This fact also should be considered for patients with a preoperative diagnosis of diffuse gastric cancer and a strong family history.

The optimal age for total gastrectomy is unknown. Although a mean age at onset of 37 years is reported in the literature, the wide age range for GC diagnosis is between 16 and 82 years, which make it difficult to counsel on the screening starting age and the more critical gastrectomy age. Kaurah, et al. recommend total gastrectomy during the early 20s for men and individualization for female mutation carriers due to the dietary consequences of gastrectomy on pregnancy[32]. This is a careful suggestion to save lives and is based on both the therapeutic nature of total gastrectomy in > 90% of mutation carriers and the low sensitivity and failure of current screening, including endoscopy, positron emission tomographic scanning, or chromoendoscopy-directed biopsies. Because long-term results from larger studies continue to be lacking, at present an individualized approach for the timing of total gastrectomy considering multiple variables should be discussed with each *CDH1* mutation carrier.

CONCLUSIONS

The HDGC syndrome is responsible for a minority of GC cases; however, in Mexico, where age at onset is younger, it is possible that genetic participation is greater. Clinical awareness is important to identify *CDH1* mutation carriers. At present, there is no effective screening modality, and the *CDH1* mutation comprises a surrogate predictor of the intramucosal presence of diffuse signet ring cancer cells. During the years to come, total gastrectomy will remain the preventive intervention-of-choice for family members who test positive for heritable mutations at *CDH1*.

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