Hereditary diffuse gastric cancer

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INTRODUCTION

Hereditary diffuse gastric cancer (HDGC) is an inherited form of diffuse-type gastric cancer (DGC), a highly invasive tumor that is characterized by late presentation and a poor prognosis. HDGC is defined by the presence of a pathogenic germline variant in the cadherin 1 (*CDH1)* or alpha-1 catenin (also known as alpha-E-catenin; *CTNNA1)* gene in either an isolated individual with DGC, or in a family with one or more DGC cases in first-degree or second-degree relatives [1]. Lobular breast cancer and nonsyndromic cleft lip/palate are also part of the HDGC syndrome. The term hereditary lobular breast cancer (HLBC) has been proposed as the presence of a pathogenic germline CDH1 variant in either an isolated individual with LBC, or a family with one or more LBC cases in first-degree or second-degree relatives, but no known DGC in either situation.

These pathogenic variants are inherited in an autosomal dominant pattern. The lifetime risk of gastric cancer in individuals from families with pathogenic or likely pathogenic variants in *CDH1* is very high, and diagnosis has been made in individuals in their teens and early 20s. As a result, prophylactic total gastrectomy (PTG) is usually advised, generally between ages 20 and 30. Recommendations are less clear for those with pathogenic or likely pathogenic *CTNNA1* variants, as penetrance is uncertain.

This topic will provide a detailed overview of HDGC, focusing on the identification of high-risk families and genetic counseling and testing. The pathology and molecular pathogenesis of this disorder and technical aspects of PTG for patients with HDGC are presented separately. (See

"Gastric cancer: Pathology and molecular pathogenesis" and "Surgical management of hereditary diffuse gastric cancer".)

MOLECULAR GENETICS

HDGC is inherited as an autosomal dominant trait with high penetrance. The pathogenic germline variants occur in one of two genes, *CDH1* and *CTNNA1*.

CDH1 — Germline truncating pathogenic and likely pathogenic variants of the cadherin 1 (*CDH1*) gene, located on chromosome 16q22.1, were originally described in three Maori families from New Zealand that were predisposed to DGC. Subsequently, germline *CDH1* pathogenic and likely pathogenic variants have been identified in approximately 15 to 50 percent of affected kindreds that meet the historic clinical criteria for HDGC, initially defined by the International Gastric Cancer Linkage Consortium (IGCLC) [2].

The wide range of *CDH1* pathogenic variant estimates has to do with both the background incidence of gastric cancer and the criteria that have been used to define the syndrome:

- For the most part, the frequency of detection of pathogenic and likely pathogenic variants varies inversely with the background incidence of gastric cancer. Thus, detection rates for a *CDH1* pathogenic and likely pathogenic variant in families meeting the historic HDGC criteria [2] were highest (40 to 52.6 percent) in lower incidence countries like Canada, the United States, and the United Kingdom [3], lower in moderate-incidence countries like Germany (25 percent), and lowest in high-incidence countries like Portugal and Italy (22.2 percent) [3] and Japan (15.4 percent) [4]. A series of 183 index cases meeting the 2010 IGCLC clinical criteria for *CDH1* testing [2] from Canada, Portugal, and Italy reported a lower than expected detection rate for a pathogenic or likely pathogenic *CDH1* variants (19 percent) [5]. However, across 144 HDGC probands who lacked a pathogenic or likely pathogenic variant, other potential candidate pathogenic variants were identified in 16 (11 percent), including those in *CTNNA1* (the gene for alpha-catenin), *BRCA2* (the gene associated with hereditary breast and ovarian cancer syndrome), *STK11* (the gene associated with Peutz-Jeghers syndrome), *SDHB*, *PRSS1*, *ATM*, *MSR1*, and *PALB2*. Of clinical importance, in low-incidence countries, the criteria used to define HDGC can be relaxed with little effect on pathogenic variant detection rates [6].

- Detection rates for a *CDH1* pathogenic or likely pathogenic variant before 2010, using guidelines established in 1999, were 25 to 50 percent [6,7]. Using newer updated criteria, detection rates for *CDH1* pathogenic and likely pathogenic variants in countries with a low

incidence of gastric cancer have decreased to 10 to 18 percent [5,8,9]. (See 'Criteria for genetic testing' below.)

Thus far, almost 2800 *CDH1* variants from clinical testing have been deposited into ClinVar, a freely accessible, public archive of variants and associated phenotypes with supporting evidence [10]. Furthermore, over 200 *CDH1* variants have been expertly curated through the *CDH1* variant curation expert panel of ClinGen, a partnered resource that curates the clinical relevance of genes and variants and archives the results of interpretation by recognized expert panels and providers of practice guidelines [11]. Efforts of the ClinGen expert working group have been to create specific *CDH1* variant calling guidelines to standardize variant calling and review variants according to these guidelines in order to improve patient care [12]. Furthermore, new molecular assays such as clinical RNA studies have been shown to help elucidate variant pathogenicity in *CDH1* [13].

Previously, over 155 different germline *CDH1* pathogenic and likely pathogenic variants had been identified through testing of families meeting HDGC criteria; however, variants in *CDH1* continue to be identified in individuals through broad panel testing of probands without clear HDGC phenotypes, thus impacting variant classifications [5,8,12]. As such, some variants, like missense variants, that may previously have had pathogenic assertions in the literature based on functional evidence are being reexamined according to updated specifications for variant calling in *CDH1* [12]. (See 'No family history of diffuse gastric cancer' below.)

The majority of HDGC-associated pathogenic variants are single nucleotide substitutions leading to truncating pathogenic variants or splice site variants; less commonly, there are insertions or deletions of several base-pairs leading to frameshifts with protein truncation. Approximately 5 percent of familial cases are due to structural variants including large rearrangements and large deletions involving multiple exons of the gene [3,14]. All germline pathogenic and likely pathogenic variants are evenly distributed along the gene and lead to functional haploinsufficiency of the cadherin 1 (also known as E-cadherin) protein.

CDH1 is a tumor suppressor gene, and therefore a somatic second hit is required for initiation of tumor formation. The triggers and molecular mechanisms by which the second allele of the *CDH1* gene is inactivated appear to be diverse, and include promoter hypermethylation, mutation, and loss of heterozygosity. The end result is loss of expression of the cell adhesion molecule cadherin 1. This topic is discussed in more detail elsewhere [15]. (See "Gastric cancer: Pathology and molecular pathogenesis", section on 'Hereditary diffuse gastric cancer'.)

CTNNA1 — Pathogenic variants in a second gene, the alpha-1 catenin gene (*CTNNA1)* have also been found in a minority of HDGC families [16,17]. Catenins such as alpha catenin work as

connectors for E-cadherin-mediated cell-cell adhesion.

Guidelines from the IGCLC define HDGC syndrome by the presence of a pathogenic germline variant in either *CDH1 or CTNNA1* in either an isolated individual with DGC, or in a family with one or more DGC cases in first- or second-degree relatives [1]. (See 'Identification of high-risk families' below.)

Little is known about the penetrance of pathogenic *CTNNA1* variants. However, intramucosal foci of DGC have been found in prophylactic gastrectomy specimens from affected individuals [16-18], suggesting that these individuals are at risk for DGC and warrant at least endoscopic surveillance or definitive prophylactic gastrectomy. Analysis of *CTNNA1* variants from commercial multigene panel testing suggest that the penetrance for gastric cancer may be lower than expected, although specific variants may have a significant risk for early onset DGC [18]. (See 'Carriers of CTNNA1 pathogenic or likely pathogenic variants' below.)

RISK OF CANCER IN CARRIERS OF A PATHOGENIC OR LIKELY PATHOGENIC CDH1 VARIANT

Gastric cancer — The most contemporary estimates of the cumulative risk of gastric cancer in carriers of a pathogenic or likely pathogenic variant in *CDH1* by age 80 years are 37 to 42 percent for males and 25 to 33 percent for females. These estimates are derived from *CDH1* pathogenic and likely pathogenic variant-positive kindreds identified through commercial testing for hereditary cancer risk using multigene panel testing, unselected for HDGC clinical criteria [19,20]. Estimates, however, vary widely depending on ascertainment bias, specific pathogenic variant, and number of prior affected family members; risks are probably higher for families meeting the original clinical criteria. As an example in the highly penetrant HDGC families with pathogenic variants in *CDH1* that were ascertained by earlier, stricter, HDGC testing criteria, the lifetime cumulative risk for advanced diffuse-type gastric cancer was found to be 70 percent (95% CI 59-80 percent) for males and 56 percent (95% CI 44-69 percent) for females by the age of 80 years [5,8].

The wide range of penetrance estimates in different clinical scenarios underscores the need for consideration of personal and family history in determining management plans.

The average age of onset of gastric cancer is 38 years, although it ranges from 14 to 82 years. Prophylactic gastrectomy is often advised as early as age 20. (See 'Prophylactic gastrectomy' below.)

The gastric cancers that develop in these individuals are often multifocal and located beneath an intact mucosal surface, making endoscopic identification difficult. (See 'Endoscopic assessment' below.)

Histologically, individual tumor cells are seen to invade the surrounding tissues, and there is no gland formation. In most cases, intracellular mucin is abundant, and it pushes aside the nucleus of the individual cells, resulting in the so-called signet ring carcinoma. (See "Gastric cancer: Pathology and molecular pathogenesis", section on 'Hereditary diffuse gastric cancer' and "Gastric cancer: Pathology and molecular pathogenesis", section on 'Intestinal versus diffuse types'.)

Confirmed intestinal-type gastric cancers are not a part of HDGC, and *CDH1* pathogenic variant analysis specifically for detecting HDGC is not indicated in these families [1].

Breast cancer — Family members of known carriers of a pathogenic or likely pathogenic variant in *CDH1* are also at high risk of developing lobular breast cancer [2,5,21-27]. In the study cited above of 75 *CDH1* pathogenic or likely pathogenic variant-positive HDGC kindreds comprising 3858 probands (89 with breast cancer), the lifelong risk of breast cancer for females was 42 percent (95% CI 23-68 percent) [5]. Others report a cumulative risk of breast cancer to age 80 of 43 and 55 percent, respectively [19,20]. The risk begins to increase before age 30 to 39 [5,20].

Although lobular breast cancers can occur in individuals with HDGC, the term hereditary lobular breast cancer (HLBC) has been defined by the presence of a pathogenic germline *CDH1* variant in either an isolated individual with LBC, or a family with one or more LBC cases in first-degree or second-degree relatives, but no known DGC in either situation [1]. While *CDH1* pathogenic variants can cosegregate with invasive LBC in the absence of diffuse gastric cancer [28], rates of occult gastric carcinoma in such individuals who elect risk-reducing total gastrectomy are high (94 percent in one series [29]), and prophylactic gastrectomy is a consideration despite the lack of a family history. However, in such cases, uncertainty remains about the features that lead to progression of occult cancer cells to clinically impactful disease. Referral to centers with experience in this setting is critical for cases such as these where guidelines recommending prophylactic total gastrectomy are not easily applied. (See 'No family history of diffuse gastric cancer' below.)

The optimal breast cancer screening strategy in females with either HDGC or HLBC is unclear; however, guidelines suggest that these females be managed similarly to other high-risk breast cancer conditions with annual breast magnetic resonance imaging (which can be combined with mammography) starting at age 30, and the option of risk-reducing mastectomy can be

discussed in consideration of personal and family history [1]. (See 'Surveillance for breast cancer' below.)

Other cancers — Although cases of colorectal and appendiceal signet ring cell carcinomas have been reported in carriers of a *CDH1* pathogenic or likely pathogenic variant [23,30-32], there is no evidence for a significantly increased risk of colorectal or other cancer types in such individuals [5,33,34].

IDENTIFICATION OF HIGH-RISK FAMILIES

The presence of a pathogenic or likely pathogenic variant in *CDH1* (much less commonly *CTNNA1*) in a family is usually recognized when a case of DGC occurs in a family member under the age of 50 or when there are several cases in one family.

Genetic counseling and testing — The risk of gastric cancer in asymptomatic carriers of a germline *CDH1* pathogenic or likely pathogenic variant is sufficiently high to warrant genetic counseling for carrier testing in all members of HDGC families and consideration of prophylactic total gastrectomy for carriers [35,36]. The optimal timing of surgery is debated. (See 'Prophylactic gastrectomy' below.)

Criteria for genetic testing — In 2020, consensus guidelines from the International Gastric Cancer Linkage Consortium (IGCLC) for *CDH1* pathogenic variant testing include the following groups [1]:

Family criteria:

- Two or more gastric cancer cases in a family regardless of age, at least one confirmed DGC
- One or more cases of DGC at any age, and one or more cases of lobular breast cancer (LBC) at age <70 years, in different family members
- Two or more cases of LBC in family members <50 years of age

Individual criteria:

- DGC in an individual under the age of 50
- DGC at any age in individuals of Maori ethnicity
- DGC at any age in an individual with a personal or family history (first-degree relative) of cleft lip/palate
- Personal history of DGC and LBC, both diagnosed under the age of 70
- Bilateral LBC diagnosed at age <70

- Gastric in situ signet ring cells or pagetoid spread of signet ring cells on a gastric biopsy in individuals <50 years of age

There are reports of an association between cleft lip/palate and *CDH1* pathogenic or likely pathogenic variants in families with HDGC [37,38].

Performance of genetic testing — A blood sample from an affected family member is the best substrate for index testing [39]. Testing can also be achieved on DNA extracted from saliva. If an affected family member is not able to be tested, another option is testing a sample from an unaffected relative who might be an obligate carrier. Although HDGC is inherited as an autosomal dominant trait and most patients who inherit the pathogenic or likely pathogenic variant will have the disease, 30 to 60 percent of carriers will not develop clinically significant disease; therefore an unaffected obligate carrier can be identified. As an example, suppose that the index case had two unaffected parents. If there is evidence of affected members on one side of the family (for example, a maternal aunt was affected), then it is most likely that the pathogenic or likely pathogenic variant was inherited from an unaffected carrier mother, and she would be the most likely candidate for testing.

Another option is to test DNA from archived paraffin blocks from an affected family member. This is often impractical and should only be considered as a last resort.

Clinical genetic testing is usually accomplished by sequencing of all coding regions of the gene, including intron-exon boundaries [6,19,20]. As noted above, several different types of pathogenic or likely pathogenic variants can be found in HDGC families by sequencing, including nonsynonymous (nonsense), indels (in-frame /frameshift), and splice site variants. It is not known whether there are any genotypic/phenotype correlations and, in particular, if any of the specific pathogenic or likely pathogenic variants in *CDH1* are associated with a different risk of gastric cancer. Once a family pathogenic variant has been identified, it is simple to set up a pathogenic variant-specific assay to assess the carrier status of family members. (See 'Molecular genetics' above.)

Some intragenic deletions have been discovered in families where no pathogenic variant was evident by sequencing [3]. Thus, screening for large genomic deletions with multiplex ligation-dependent probe amplification, next-generation sequencing assays, or alternative methods is also required for definitive diagnosis of a *CDH1* pathogenic variant.

Age to undertake screening — The optimal age to screen individuals from affected families is unclear. Rare cases of DGC have been reported in affected families before the age of 18, but the overall risk of cancer before age 20 is very low (less than 1 percent) [6,23]. Most groups agree that consideration of genetic testing can begin at the age of informed consent (16 or 18 years of

age depending on the geographic place of residence) [8]. However, decisions as to the age at which to institute testing should also take into account the earliest age of cancer onset in the individual family.

MANAGEMENT OF CDH1 VARIANT CARRIERS

Carriers of a pathogenic or likely pathogenic CDH1 variant — A suggested management strategy for carriers of a pathogenic or likely pathogenic variant in *CDH1* that is based upon recommendations of the International Gastric Cancer Linkage Consortium (IGCLC) [1] is presented in the algorithm (algorithm 1). The following discussion will focus on individuals with or without a DGC in the family.

Diffuse gastric cancer in the family

Prophylactic gastrectomy — Prophylactic total gastrectomy (PTG) is the recommended approach for any individual with an appropriate pedigree who has been shown to have a germline *CDH1* pathogenic or likely pathogenic variant. (See "Surgical management of hereditary diffuse gastric cancer", section on 'Indications for prophylactic total gastrectomy'.)

The timing of prophylactic surgery is debated (see "Surgical management of hereditary diffuse gastric cancer", section on 'Timing of prophylactic total gastrectomy'):

- Prophylactic gastrectomy is often advised as early as age 20 [1]. While the mean age of onset of DGC is approximately 38, there are certain kindreds where the mean age of onset is much younger. Some suggest consideration of total gastrectomy in carriers at an age of five years younger than the youngest family member who developed gastric cancer [40].

- The timing of surgery may also vary according to the preferences and physical as well as psychological fitness of the individual. Some patients who receive a recommendation for prophylactic gastrectomy may understandably decide to postpone or refuse the procedure due to young age, fertility concerns, or fear of surgery with accompanying complications. However, it is entirely possible for females to have a successful pregnancy after prophylactic gastrectomy.

  In settings such as these, close endoscopic surveillance may be the only available option [41]. However, given the unreliability of the available tests for screening and follow-up of carriers, patients should be fully educated about the shortcomings of this approach and encouraged to undergo prophylactic surgery or enroll in clinical research protocols. (See 'Endoscopic assessment' below.)

Prophylactic gastrectomy for patients with HDGC is discussed in detail elsewhere. Management issues for patients with an identified *CDH1* pathogenic or likely pathogenic variant but without HDGC syndrome are discussed below. (See "Surgical management of hereditary diffuse gastric cancer" and 'No family history of diffuse gastric cancer' below.)

Individuals who refuse or defer surgery

Endoscopic assessment — There are no reliable screening tests that allow early diagnosis of DGCs in carriers [42]. The gastric cancers that arise in patients with HDGC are signet ring cancers that are located beneath an intact surface epithelium and only become visible on direct mucosal evaluation later in the disease process [43,44]. As a result, prophylactic gastrectomy, rather than endoscopic surveillance, is usually recommended for *CDH1* pathogenic or likely pathogenic variant carriers after age 20. However, as noted above, the timing of the operation may vary according to the preferences, age, and physical as well as psychological fitness of the individual. (See 'Prophylactic gastrectomy' above.)

Among the clinical scenarios where endoscopic surveillance may be considered are the following:

- Pathogenic or likely pathogenic variant carriers who are identified prior to age 20 may be recommended to undergo annual surveillance endoscopy with surgery deferred until after age 20.
- Patients over age 20 who receive a recommendation for prophylactic gastrectomy but who decide to postpone (or refuse) the procedure due to young age, fertility concerns, or fear of surgery with accompanying complications.
- Individuals with variants of undetermined significance and in those in whom a pathogenic or likely pathogenic variant cannot be identified in the index case. (See 'No family history of diffuse gastric cancer' below.)

However, all patients undergoing surveillance rather than prophylactic gastrectomy should be counseled as to the focal nature of these endoscopically invisible lesions and the possibility that they will not be detected by the surveillance procedure. The personal and family history are also important considerations in determining management plans in this setting, especially a decision to defer prophylactic gastrectomy.

Total gastrectomy with perigastric (ie, D1) lymph node dissection is indicated in patients with invasive signet ring cell carcinoma on gastric biopsy. However, IGCLC guidance states that patients with a positive biopsy finding of superficial gastric cancer who still wish to forego

gastrectomy because of age or comorbidity could have endoscopy repeated more frequently (ie, at six-month intervals) [1]. Superficial cancer is defined as a signet ring cell carcinoma that does **not** have any of the following high-risk features on biopsy: deeper than T1a invasion on endoscopy, erosion, a disturbed vascular and pit pattern, or histopathologic signs of invasion into or beyond the muscularis mucosa.

Almost all *CDH1* carriers have superficial signet ring cell adenocarcinoma deposits [45], and there is no way to localize and excise them. Superficial deposits that lack high-risk features can also remain indolent for years, with a low rate of progression to more advanced (>T1a) tumors, based on prospective observational data of patients who underwent endoscopic screening and surveillance for HDGC [41]. However, if the biopsy corresponds to a visual abnormality such as an erosion or ulceration, then the patient is likely to have a more advanced cancer than T1a and should be strongly counselled for oncologic surgery and not surveillance. (See "Surgical management of invasive gastric cancer" and "Total gastrectomy and gastrointestinal reconstruction".)

- **HDGC endoscopic protocol** – Surveillance endoscopy should ideally be performed in a center with a special interest in and experience with HDGC. The optimal frequency of endoscopy is not known. Based upon clinical experience, it is recommended that individuals be offered annual endoscopy [1].

  Endoscopy should be performed using a white light high-definition endoscope, in a dedicated session of at least 30 minutes to allow for careful inspection of the mucosa on repeated inflation and deflation and for collection of biopsies. The mucosa should be thoroughly washed before examination with a combination of mucolytics (N-acetylcysteine) and antifoaming agents (simethicone) mixed with sterile water. Careful inspection of the mucosa with photo documentation of any abnormal areas and an assessment of distensibility on inflation are important. A nondistensible stomach should raise suspicion for a submucosal infiltrative process such as linitis plastica. (See "Gastric cancer: Pathology and molecular pathogenesis", section on 'Intestinal versus diffuse types'.)

  Any endoscopically visible lesions (including pale areas, which may harbor microscopic foci of abnormal cells) should be biopsied. In addition, due to the tiny foci of signet ring cells, which can only be recognized by microscopic analysis, multiple random biopsies are required to maximize the likelihood of identifying them [46-48]. A minimum of 30 biopsies is recommended, with 5 biopsies taken from each of the following anatomic zones: prepyloric area, antrum, transitional zone, body, fundus, and cardia [8]. The biopsies may be taken using standard forceps, ideally with a "spike," as this will sample the lamina

propria in which the signet ring cells may be present [1]. (See "Overview of upper gastrointestinal endoscopy (esophagogastroduodenoscopy)", section on 'Tissue sampling methods'.)

However, even with the most sophisticated techniques, early detection with direct endoscopic visualization is extremely difficult. The cancerous infiltrates are small and widely distributed, making them difficult to identify even with random biopsies [40,49]. Prospective cohort studies with long-term follow-up demonstrate that a systematic approach to random biopsies is more likely to identify signet ring cell carcinoma than biopsies targeted to endoscopic findings alone [41,48]. Nevertheless, other studies suggest that random biopsies can still miss early-stage disease compared with prophylactic total gastrectomy [50-53]. As an example, in one report of 23 patients with pathogenic or likely pathogenic variants in *CDH1* who underwent prophylactic total gastrectomy, 22 (96 percent) had multifocal, microscopic foci of signet ring adenocarcinoma identified with rigorous pathologic reporting [50]. However, preoperative endoscopic evaluation (consisting of at least 15 random mucosal biopsies) only identified signet ring adenocarcinoma in two of these patients (9 percent).

- **Chromoendoscopy** – Chromoendoscopy is not recommended as part of the surveillance strategy for patients with *CDH1* pathogenic or likely pathogenic variant carriers from high-risk families. While it may be used as an investigational tool, it should not be considered part of any expert recommendations.

  Chromoendoscopy involves the use of stains or dyes during endoscopy to improve the visualization and characterization of the gastrointestinal mucosa, has been proposed as a highly sensitive method of endoscopic surveillance for *CDH1* pathogenic or likely pathogenic variant carriers from high-risk families [40,54].

  One group reported success in a series of patients evaluated preoperatively by chromoendoscopy [54]. Using a combination of methylene blue/congo red staining in 33 carriers over a period of five years, from one to six pale regions felt to represent early disease in 24 of 93 procedures (26 percent) were identified. One biopsy was taken from each pale region and signet ring adenocarcinoma was diagnosed in 23 of 56 lesions (41 percent) or 10 of 33 patients. It was shown that disease was successfully identified in foci >4 mm in size. This has not been replicated in other centers. As an example, in a prospective series of 18 consecutive patients with *CDH1* pathogenic or likely pathogenic variants undergoing total gastrectomy at a median age of 45, 17 were found to have a signet ring cell adenocarcinoma; only 2 of 12 asymptomatic patients had it diagnosed preoperatively despite chromoendoscopy with multiple gastric biopsies [55].

Unfortunately, the experience from this institution has not been replicated in other centers. Furthermore, congo red is no longer available for this use due to concerns over toxicity. Chromoendoscopy is discussed in detail elsewhere. (See "Chromoendoscopy".)

Role of PET scan — Positron emission tomography (PET) scanning cannot yet be recommended as an alternative to early prophylactic gastrectomy in carriers of a pathogenic or likely pathogenic variant.

It is proposed that glucose metabolism is enhanced in DGC and that this can be detected using 18-fluoro-deoxyglucose (FDG)-PET scanning.

A single case report details the diagnosis of HDGC in an asymptomatic 38-year-old *CDH1* pathogenic variant carrier using FDG-PET [56]. Upper gastrointestinal endoscopies had been negative, but 1 of 40 random biopsies showed well differentiated signet cell adenocarcinoma. A PET scan demonstrated two areas of FDG accumulation, one in the proximal stomach, and one in the region of the pylorus. A total gastrectomy specimen demonstrated focal intramucosal adenocarcinoma of the signet cell type in the cardiac and antrum area, at locations that matched the PET scan abnormalities.

H. pylori screening — We suggest that individuals who carry a pathologic *CDH1* pathogenic variant who refuse or delay prophylactic gastrectomy be screened for infection with *Helicobacter pylori* (*H. pylori*) and treated if positive.

Infection with *H. pylori* is an important and potentially modifiable risk factor for gastric cancer. Although there is no direct evidence for the benefit of treating *H. pylori* infection in *CDH1* pathogenic variant carriers who choose to defer or delay surgery, successful eradication of *H. pylori* can significantly reduce the risk of developing gastric cancer [57]. Notably, trial participants in this study were not evaluated for genetic susceptibility to gastric cancer, and it is unknown how many individuals in this study, if any, were from families with DGC in one or more relatives. (See "Risk factors for gastric cancer", section on 'Importance of Helicobacter pylori infection'.)

Surveillance for breast cancer — Because of the increased risk of lobular breast cancer (LBC) in females who carry pathogenic or likely pathogenic *CDH1* variants referral to a high-risk breast cancer clinic is appropriate with intensification of surveillance and individualized decision making on the benefits of risk-reducing mastectomy or chemoprevention. (See "Overview of hereditary breast and ovarian cancer syndromes", section on 'CDH1 (Hereditary diffuse gastric cancer syndrome)'.)

The optimal breast cancer surveillance strategy in such females is unclear; however, guidelines suggest annual breast magnetic resonance imaging (which can be combined with mammography) starting at age 30 in females who are carriers, and continuing to age 50 and perhaps longer (algorithm 1) [1]. This approach is similar to that used for females with other inherited high-risk conditions such as hereditary breast and ovarian cancer syndrome. (See "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes", section on 'Breast cancer risk management'.)

Role of risk-reducing mastectomy — For females with a pathogenic or likely pathogenic variant in *CDH1* and HDGC or hereditary lobular breast cancer (HLBC; pathogenic or likely pathogenic variant in *CDH1* with no DGC in the family), discussion of risk-reducing mastectomy as an option is reasonable, although literature on this issue is scant, and decisions are usually made on a case-by-case basis in consideration of both personal and family history, as are decisions on chemoprevention using selective estrogen receptor modulators or aromatase inhibitors [1]. (See "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention".)

For families with HDGC who have competing risks from both breast and gastric cancer susceptibility, the timing and prioritization of prophylactic surgeries should be based on the patient's personal and family history. If the family history is gastric cancer-predominant, the patient is likely to derive a greater survival benefit from initial gastric surgery rather than prophylactic mastectomy. (See "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention" and "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Mastectomy'.)

No family history of diffuse gastric cancer — Clinical genetic testing for cancer risk assessment using multigene panels on germline DNA has become widespread over the past decade. With the inclusion of *CDH1* on many germline multigene cancer panels, primarily because of its role as a high-penetrant breast cancer risk allele [58-60], individuals may be identified as having a *CDH1* pathogenic or likely pathogenic variant but without a personal or family history of DGC or LBC [61,62]. In other situations, an individual may be identified as having a *CDH1* pathogenic or likely pathogenic variant after presenting with a phenotypically consistent tumor such as LBC but without any family history of gastric cancer [29,62,63]. Both germline and somatic *CDH1* pathogenic variants can also be identified through the molecular examination of tumors by tumor sequencing. Whether the pathogenic variant is inherited or not can only be distinguished by examination of germline DNA.

The utility of prophylactic gastrectomy in patients without a personal or family history of DGC who are incidentally found to have an inherited *CDH1* pathogenic or likely pathogenic variant

after clinical genetic testing for cancer risk assessment is evolving.

Recommendations for management of *CDH1* pathogenic or likely pathogenic variant carriers are based upon data generated from high-penetrant HDGC families and, therefore, may not reflect the risk for gastric cancer in individuals with an incidentally detected *CDH1* pathogenic variant. Due to the lack of prospective data available regarding the penetrance of *CDH1* pathogenic variants identified in scenarios outside of personal and family histories that are phenotypically consistent with HDGC, caution is required with regard to assessment and counseling of these individuals [64]. Referral to centers with experience in this setting is critical for cases such as these where guidelines recommending PTG are not easily applied. At the very least, any individual identified with a *CDH1* pathogenic variant should follow the endoscopy screening protocol while deferring PTG (algorithm 1) [1]. (See 'Endoscopic assessment' above.)

The exact context under which the *CDH1* pathogenic or likely pathogenic variant has been identified is important to consider with regard to suggested management. Examples of the scenarios that may be encountered in clinical practice include:

- **Detection of a *CDH1* pathogenic or likely pathogenic variant in a proband with a phenotypically consistent tumor but without a positive family history or those with HLBC** – In this scenario, the proband's tumor may be the initial presentation of the HDGC syndrome. De novo pathogenic variants have been reported [65,66], therefore a lack of a family history should not be interpreted as indicating a low-penetrance pathogenic variant. Furthermore, LBC may be the initial presentation in the family preceding a DGC case [9,22]. Although families have been reported with LBC and no DGC [9], it is not possible to be sure of the penetrance for clinically significant DGC in that kindred. As noted above, in one series of 44 such individuals with hereditary LBC but no family history of DGC, preclinical early occult carcinoma cells were present within the PTG specimens of most individuals (14 of 16 patients) with only one additional patient having had clinical signs of gastric cancer on preoperative endoscopy. Preclinical tumor cells were identified on surveillance endoscopy in 11 of the patients [29].

  The management of these situations is not straightforward. It is likely that penetrance of DGC is lower in these groups, although few data are available [19,20]. It is clear that signet ring carcinomas are reported in carriers with no family history of DGC [29,67] or from families whose background is suspicious for HDGC but that do not strictly meet HDGC diagnostic criteria [62,63], and as a result, annual endoscopic surveillance should be offered to these groups at a minimum, but prophylactic gastrectomy should also be considered [1]. Yearly breast cancer surveillance is also recommended in pathogenic *CDH1*

carriers without a family history of DGC or breast cancer (algorithm 1). Patient referral to a center of expertise, and detailed patient counselling with a team who is familiar with evolving evidence on *CDH1* is paramount. Patient factors including stage of any other cancers diagnosed and overall health status must be taken into consideration, as well as patient values, health care fears, and willingness to undergo a surgery that has noted morbidity and mortality.

- **Detection of a *CDH1* pathogenic or likely pathogenic variant in a proband with a tumor not previously associated with the syndrome** – In this scenario, the *CDH1* pathogenic variant may truly be an incidental finding that may not have been related to the tumor development, or alternatively it may represent an expanded phenotype not previously reported. These patients should be referred to specialist centers for further clinical evaluation and potentially tumor workup and segregation analysis in the research setting. At the very least, any individual identified with a *CDH1* pathogenic variant should follow the endoscopy screening protocol for surveillance for DGC while deferring total prophylactic gastrectomy. Guidelines from the IGCLC also recommend annual breast surveillance in these situations, and that bilateral risk-reducing mastectomy be considered for those with a positive biopsy (algorithm 1) [1]. (See 'Endoscopic assessment' above.)

- **Detection of a *CDH1* pathogenic or likely pathogenic variant in an unaffected individual with no significant personal or family history of cancer** – Population screening using commercially available multigene panel testing has revealed individuals with a pathogenic or likely pathogenic variant in *CDH1* who lack a personal or family history of DGC or LBC. No prospective data are available regarding the penetrance of inherited *CDH1* pathogenic variants in this setting, and there is a lot of uncertainty about how to manage this situation, as evidenced by the variability in recommendations [68-70]. However, the risk for a de novo pathogenic variant must be considered, and in our view, these patients should be referred to specialist centers for consultation about screening and surgical prevention. At the very least, any individual identified with a *CDH1* pathogenic variant should follow the endoscopy screening protocol while deferring total prophylactic gastrectomy.

In all of these situations, specialist referral is recommended and should involve a discussion about the following issues [1]:

- Clinicians must be very cautious about interpreting coding variants identified in non-HDGC families especially if the alterations do not lead to a premature stop codon. (See 'Molecular genetics' above.)

- The magnitude of the cancer risk for patients with pathogenic or likely pathogenic *CDH1* variants who lack a family history of multiple gastric cancers remains uncertain [64,71,72]. However, at least some data suggest that penetrance might be lower in this setting [19,20]. In an analysis of 75 families found to have pathogenic variants in *CDH1* through clinical ascertainment or multigene panel testing (ie, **not** based on strict HDGC testing criteria), the estimated cumulative incidence of gastric cancer to age 80 was 42 percent in males and 33 percent in females [19]. The cumulative incidence of female breast cancer was 55 percent. (See 'Risk of cancer in carriers of a pathogenic or likely pathogenic CDH1 variant' above.)

- Recommendations for PTG of *CDH1* pathogenic variant carriers are based upon penetrance data generated from HDGC families, which by definition were selected for multiple cases or early onset of DGC or LBC and may not reflect the penetrance of *CDH1* pathogenic variants identified by population screening in individuals with no personal or family history of cancer.

- There is limited understanding of the factors that promote progression of small foci of signet ring cancer to DGC in carriers of a *CDH1* pathogenic or likely pathogenic variant. The majority of *CDH1* carriers harbor foci of signet ring cancers in their stomachs, often decades earlier than the average age of DGC development [73]. Particularly for individuals with unexpected *CDH1* variants, it is unclear whether and when these small foci of signet ring cancers will ever progress to fulminant DGC. While guidelines still recommend gastrectomy after age 20 but before age 30 for those with pathogenic *CDH1* variants who are from families with HDGC [64], this may not be the optimal timing for all carriers who lack a family history of HDGC.

Given these uncertainties, it is preferable that *CDH1* testing be undertaken responsibly by ordering providers with appropriate pretest genetic counseling. Once they are identified, clinicians experienced in the management of HDGC in specialist centers should guide the management of these individuals.

To address the lack of prospective data available, multicenter collaborative initiatives such as the Prospective Registry of MultiPlex Testing (PROMPT), have been developed to collect prospective data regarding the phenotypes associated with germline pathogenic variant findings identified from multiplex gene panels. Analysis of *CDH1* and *CTNNA1* specific data will be critical, and this is yet another reason to support referral to a specialist center for management and research ascertainment of these patients.

Variants of uncertain significance or HDGC-like families — As noted above, clinical genetic testing for cancer risk assessment using multigene panels on germline DNA has become widespread over the past decade, and with the inclusion of *CDH1* on many germline multigene cancer panels, individuals may be identified as having a *CDH1* variant of uncertain significance (VUS; ie, a genetic sequence that has an unclear association with any disease).

There are also HDGC-like families fulfilling the first or second HDGC criteria who do not have a pathogenic or likely pathogenic variant in *CDH1* (or *CTNNA1*) [1]. (See 'Criteria for genetic testing' above and 'Carriers of CTNNA1 pathogenic or likely pathogenic variants' below.)

There is a paucity of data resulting in a lack of consensus regarding the clinical utility of surveillance for gastric or breast cancer in these individuals, and further research is required to delineate optimal screening and prevention strategies. However, the following represents our approach, which follows the guidance of the IGCLC (algorithm 1) [1]:

- **HDGC-like families** – Early evidence supports endoscopic screening of first-degree relatives of families who fit *CDH1* testing criteria but where a *CDH1* pathogenic variant has not been identified [74,75]. These patients should be followed closely and offered HDGC surveillance at expert centers, considering their genetic heterogeneity and the potential for not yet discovered cryptic *CDH1* pathogenic variants. The IGCLC guidelines support the use of annual upper endoscopy for at least two years in HDGC-like families, starting at age 40 or 10 years prior to the earliest gastric cancer diagnosis in the family [1]. Prophylactic gastrectomy is not advised as long as surveillance endoscopies are negative. Breast cancer risk assessment should be individualized.

- **VUS** – For patients with a *CDH1* VUS, although the updated IGCLC guidelines suggest considering annual endoscopic gastric surveillance for at least two years, it should ideally be done as a part of a research study [1]. Prophylactic gastrectomy is not advised as long as surveillance endoscopies are negative. Breast cancer risk assessment should be individualized.

CARRIERS OF CTNNA1 PATHOGENIC OR LIKELY PATHOGENIC VARIANTS

As noted above, a minority of individuals with HDGC have pathogenic or likely pathogenic variants in the *CTNNA1* gene. (See 'CTNNA1' above.)

The optimal way to manage these individuals is not established. Although young asymptomatic carriers have been found to harbor intramucosal foci of DGC in prophylactic gastrectomy specimens, penetrance for DGC as well as age of onset are uncertain. As such, we suggest that

at the very least asymptomatic carriers of pathogenic or likely pathogenic CTNNA1 variants should undergo yearly surveillance endoscopy in an expert center, with prophylactic gastrectomy being considered in the context of the penetrance of DGC in the family. This recommendation is consistent with updated guidance from the International Gastric Cancer Linkage Consortium [1]. Any finding of signet ring cells or DGC in endoscopic biopsy should prompt a total gastrectomy.

Little information is available on the risk of lobular breast cancer in such individuals. Breast cancer risk assessment should be individualized.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Gastric cancer".)

SUMMARY AND RECOMMENDATIONS

- **Definition and molecular genetics** – Hereditary diffuse gastric cancer (HDGC) is defined by the presence of a pathogenic germline variant in the cadherin 1 (*CDH1)* or alpha-1 catenin (*CTNNA1)* genes in either an isolated individual with DGC, or in a family with one or more DGC cases in first-degree or second-degree relatives; these patients are also at risk for lobular breast cancer (LBC). (See 'Molecular genetics' above.)

  Lobular breast cancer and nonsyndromic cleft lip/palate are also part of the HDGC syndrome. The term hereditary lobular breast cancer (HLBC) has been proposed as the presence of a pathogenic germline *CDH1* variant in either an isolated individual with LBC or a family with one or more LBC cases in first-degree or second-degree relatives, but no known DGC in either situation.

- **Cancer risk**

  - The lifetime cumulative risk for DGC in individuals from families with a germline *CDH1* pathogenic or likely pathogenic variant is 37 to 42 percent for males and 25 to 33 percent for females. Affected patients generally develop DGC in their teens or early 20s. (See 'Risk of cancer in carriers of a pathogenic or likely pathogenic CDH1 variant' above.)

- Females from HDGC and HLBC families are also at high risk of developing LBC (estimated lifetime risk approximately 50 percent). (See 'Breast cancer' above.)

- Cancer risk for those with inherited *CTNNA1* variants is not well established. (See 'CTNNA1' above.)

- **Genetic testing** – Updated consensus-based criteria are available from the International Gastric Cancer Linkage Consortium (IGCLC) to identify which patients with DGC, LBC, or a family history of DGC and/or LBC should be referred for genetic testing. (See 'Criteria for genetic testing' above.)

  The optimal age to screen individuals from affected families is unclear, and the decision should be informed by the earliest age of cancer onset in the individual family. (See 'Age to undertake screening' above.)

- **Management of carriers of a pathogenic variant** – Specific management guidelines for carriers of pathogenic or likely pathogenic variants in *CDH1* or *CTNNA1* are available from the IGCLC and outlined in the algorithm (algorithm 1).

  - ***CDH1* carriers** – For patients who are carriers of a germline *CDH1* pathogenic or likely pathogenic variant, we recommend prophylactic total gastrectomy rather than periodic surveillance endoscopy (**Grade 1A**). The appropriate timing of surgery may be as soon as age 20 or at an age five years younger than the earliest case of HDGC in the family. (See 'Prophylactic gastrectomy' above.)

    Annual surveillance endoscopy with random biopsies may be considered for patients who are diagnosed as carriers before age 20, and for individuals over the age of 20 who receive a recommendation for prophylactic gastrectomy but who decide to defer, postpone, or refuse the procedure. For patients who are found to have invasive signet ring cancer on gastric biopsy, total gastrectomy with lymph node dissection is indicated.

    Patients with a positive biopsy finding of superficial cancer (ie, signet ring cell carcinoma that does **not** have any high-risk features [deeper than T1a invasion on endoscopy; erosion; a disturbed vascular and pit pattern; or histopathologic signs of invasion into or beyond the muscularis mucosa]) who still wish to forego gastrectomy because of age or comorbidity could have endoscopy repeated more frequently (ie, at six-month intervals). However, if the biopsy corresponds to a visual abnormality such as an erosion, then the patient is likely to have a more advanced cancer than T1a and

should be strongly counselled for oncologic surgery. (See 'Individuals who refuse or defer surgery' above.)

Individuals who carry a pathogenic *CDH1* pathogenic variant who refuse or delay prophylactic gastrectomy should be evaluated for infection with *Helicobacter pylori* (*H. pylori*) and treated if positive. (See 'H. pylori screening' above.)

Females who carry pathogenic or likely pathogenic *CDH1* variants should be referred to a high-risk breast cancer clinic for intensive surveillance and individualized decision making on the benefits of risk reducing mastectomy or chemoprevention. (See 'Surveillance for breast cancer' above.)

- ***CTNNA1* carriers** – The role of prophylactic gastrectomy for carriers of a pathogenic or likely pathogenic *CTNNA1* variant is less well established given the uncertainty of penetrance. We individualize decision making about prophylactic gastrectomy in the context of the penetrance of DGC in the family. This recommendation is consistent with guidance from the IGCLC (algorithm 1). At the very least, asymptomatic carriers of pathogenic or likely pathogenic *CTNNA1* variants should undergo yearly surveillance endoscopy in an expert center. Any finding of signet ring cells or DGC in endoscopic biopsy should prompt a total gastrectomy. Breast cancer risk assessment should also be individualized. (See 'Carriers of CTNNA1 pathogenic or likely pathogenic variants' above.)

- **Pathogenic *CDH1* variants with no family history of DGC or LBC** – Clinical genetic testing for cancer risk assessment using multigene panels on germline DNA may reveal a *CDH1* pathogenic or likely pathogenic variant in an individual without a personal or family history of DGC or LBC. For most patients, we suggest endoscopy screening at a minimum, although prophylactic gastrectomy can be considered in otherwise well individuals, after appropriate counseling about the uncertainty of risk (algorithm 1). Annual breast cancer surveillance is advised. (See 'No family history of diffuse gastric cancer' above.)

- ***CDH1* VUS and HDGC-like families** – Some individuals may be identified as having a *CDH1* variant of uncertain significance (VUS; ie, a genetic sequence that has an unclear association with any disease). There are also HDGC-like families fulfilling the first or second HDGC criteria who do not have a detectable pathogenic or likely pathogenic variant in *CDH1* (or *CTNNA1*). The optimal approach to these patents is unclear. We suggest annual endoscopic gastric surveillance for at least two years rather than prophylactic gastrectomy, a position that is consistent with IGCLC guidelines (**Grade 2C**). Breast cancer risk

assessment should be individualized. (See 'Variants of uncertain significance or HDGC-like families' above.)

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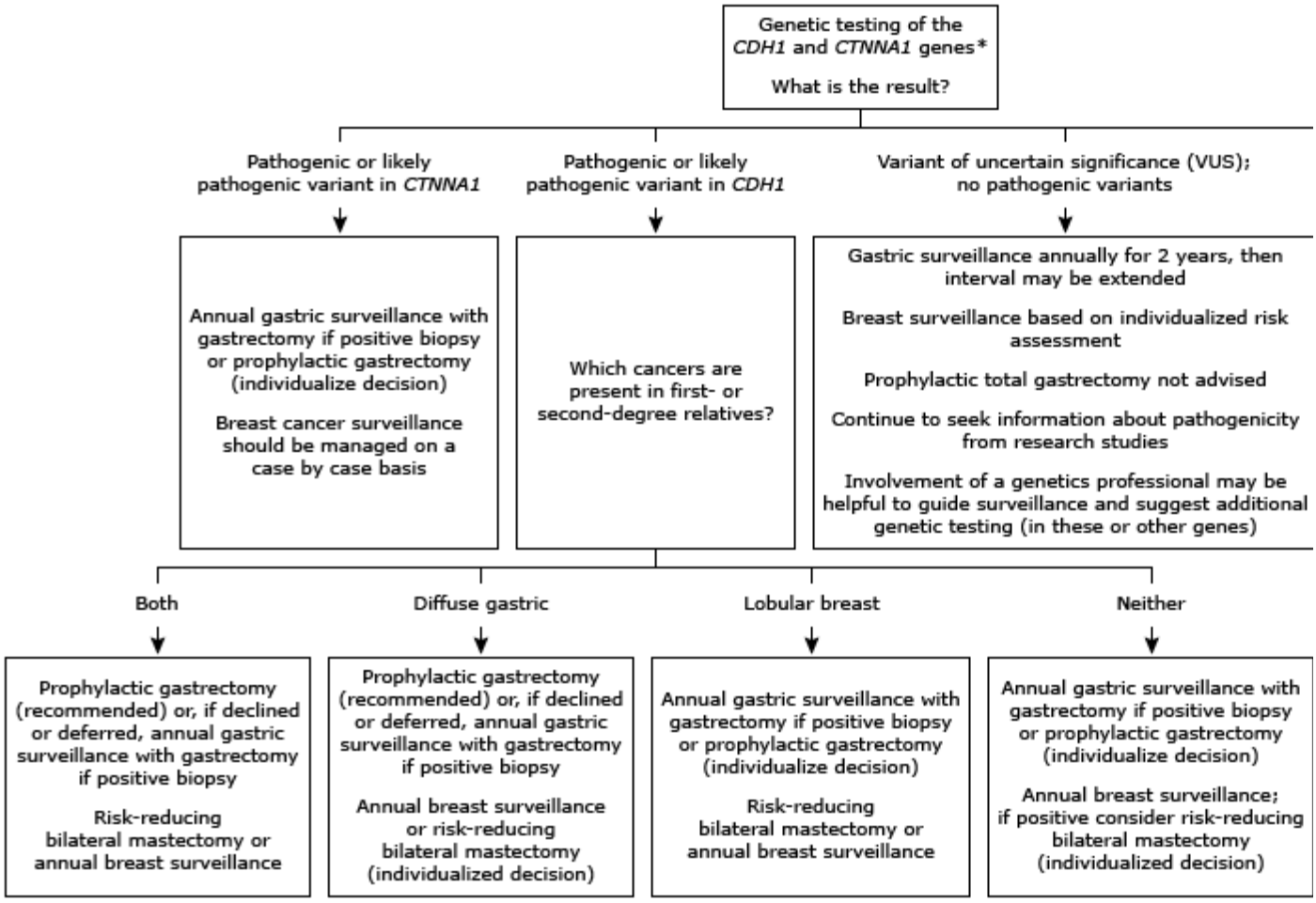
Topic 2511 Version 35.0

GRAPHICS

Management based on genetic test results for *CDH1* and *CTNNA1* (hereditary di genes)



Hereditary diffuse gastric cancer (HDGC) syndrome is a heritable syndrome that can cause gastric cancer (th subtype), and other findings (cleft lip, cleft palate). Appropriate genetic testing and diagnosis is critical for m reducing surgery. Involvement of a genetics professional, oncologist, and/or surgeon with appropriate expe

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CDH1: cadherin-1 gene; *CTNNA1*: alpha-1 catenin gene.

* Indications for genetic testing for *CDH1* and *CTNNA1* may include:

- Personal history:
  - Diffuse gastric cancer, gastric in situ signet ring cells, or pagetoid spread of signet ring cells in the
  - Diffuse gastric cancer at any age if Māori ancestry or if there is a personal or family history of cleft
  - Bilateral lobular breast cancer or diffuse gastric cancer plus lobular breast cancer at <70 years.
- Family history (related first- or second-degree relatives):
  - Gastric cancer in 2 or more individuals, one diffuse.
  - One or more diffuse gastric cancer at any age plus one or more lobular breast cancer in a differen
  - Lobular breast cancer in 2 or more individuals <50 years.
  - Known pathogenic variant in *CDH1* or *CTNNA1*.

Patients without a specific indication for genetic testing may be found to have a *CDH1* or *CTNNA1* variant thr

Adapted from: Blair VR, McLeod M, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical practice guidelines. Lancet Onc

Graphic 131798 Version 2.0

Contributor Disclosures

Pamela Hebbard, MD, FRCS Consultant/Advisory Boards: Merck [Breast cancer]. All of the relevant financial relationships listed have been mitigated. **Kasmintan A Schrader, MBBS, FRCPC, PhD** No relevant financial relationship(s) with ineligible companies to disclose. **Richard M Goldberg, MD** Equity Ownership/Stock Options: Advanced Chemotec Inc [Pancreatic cancer]; Compass Therapeutics [Biliary tract and colorectal cancer]. Consultant/Advisory Boards: AbbVie [GI cancers]; Advanced Chemotherapy Technologies [GI cancer]; AstraZeneca [GI cancer]; Bayer [GI cancer]; Compass Therapeutics [GI cancer]; Eisai [GI cancer]; G1 Therapeutics [GI cancer]; GSK [Colorectal cancer]; Innovative Cellular Therapeutics [Colorectal cancer]; Inspirna [Colorectal cancer]; Merck [GI cancer]; Modulation Therapeutics [Lymphoma]; Novartis [GI cancer]; Sorrento Therapeutics [GI cancer]; Taiho [GI cancer]. Other Financial Interest: Taiho [Expert testimony GI cancer]. All of the relevant financial relationships listed have been mitigated. **Sonali M Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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