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Diffuse Gastric and Lobular Breast Cancer Syndrome

Synonyms: DGLBCS, Hereditary Diffuse Gastric Cancer (HDGC)

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Summary

Clinical characteristics

Diffuse gastric and lobular breast cancer syndrome (DGLBCS) is associated with an increased risk, in males and females, of diffuse gastric cancer (DGC), a poorly differentiated adenocarcinoma (also referred to as signet ring cell carcinoma or isolated cell-type carcinoma) that infiltrates into the stomach wall, causing thickening of the wall (*linitis plastica*) without forming a distinct mass. In females with *CDH1*-related DGLBCS, but not in males, there is also an increased risk for lobular breast cancer (LBC), characterized by small, non-cohesive cells dispersed in the stroma or arranged in single-file infiltrating patterns. Cleft lip with or without cleft palate has also been reported in some individuals with *CDH1*-related DGLBCS.

Diagnosis/testing

The diagnosis of DGLBCS can be established in an individual with suggestive findings and a germline heterozygous pathogenic variant in *CDH1* or a germline heterozygous truncating pathogenic variant in *CTNNA1* identified by molecular genetic testing. Affected individuals from families that meet consensus genetic testing criteria for DGLBCS who do not have an identified pathogenic variant in *CDH1* or *CTNNA1* have suspected DGLBCS of unknown genetic cause (also referred to as hereditary diffuse gastric cancer [HDGC]-like).

Management

Targeted therapy: Prophylactic gastrectomy for diffuse gastric cancer is an option from early adulthood in individuals with normal endoscopy / gastric biopsies and a DGLBCS-related *CDH1* pathogenic variant

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regardless of family history or a DGLBCS-related *CTNNA1* pathogenic variant and a family history of DGC and/or LBC.

Supportive care: Management of DGLBCS requires a multidisciplinary team. Standard treatment to eradicate *H pylori* infection; total gastrectomy for early or advanced DGC; perioperative and/or adjuvant therapy for advanced DGC; surgery, hormonal therapy, and perioperative and/or adjuvant chemotherapy for LBC; consider risk-reducing contralateral mastectomy; standard treatments for cleft correction by craniofacial specialists.

Surveillance: For individuals with *CDH1*- or *CTNNA1*-related DGLBCS, referral to a high-risk gastric screening program with a thorough ≥30-minute upper endoscopy with multiple targeted and random biopsies every six to 12 months beginning in early adulthood or five to ten years prior to the earliest gastric cancer diagnosis in the family.

For females with *CDH1*-related DGLBCS or *CTNNA1*-related DGLBCS and personal or family history of breast cancer, referral to a high-risk breast cancer screening program with monthly self-breast exams beginning at age 20 years; annual clinical breast examinations, education on clinical features of breast cancer, and bilateral breast MRI with contrast from age 30 years; annual mammography between MRI screens from age 30-40 years; if MRI is unavailable, breast ultrasound should be combined with mammogram.

In individuals with *CDH1*-related cleft lip/palate, annual audiology and speech evaluation throughout childhood.

In individuals with suspected DGLBCS of unknown cause (also referred to as HDGC-like), referral to a high-risk gastric screening program with a thorough ≥30-minute upper endoscopy with multiple targeted and random biopsies annually beginning at age 40 years or ten years prior to the earliest gastric cancer diagnosis in the family; endoscopy interval can be increased after two consecutive normal biopsies at the discretion of the endoscopist. Referral to a high-risk breast cancer screening program; in those with a personal or family history of breast cancer of any type, monthly self-exams beginning at age 20 years, annual clinical breast exam and education of clinical features of breast cancer beginning at age 30 years; additional breast screening as recommended by high-risk breast cancer specialists.

Evaluation of relatives at risk: Offer at-risk relatives of a proband with *CDH1*- or *CTNNA1*-related DGLBCS predictive testing for the familial pathogenic variant. This will allow identification of individuals who would benefit from intensive surveillance for early cancer detection and/or prophylactic surgeries targeting organs associated with DGLBCS. Offer first-degree relatives of a proband with suspected DGLBCS of unknown genetic cause (HDGC-like) surveillance tailored to the individual's personal and family history.

Pregnancy management: Nutritional consequences of total gastrectomy should be discussed before and during pregnancy. Pregnancy should be delayed at least six to 12 months after total gastrectomy, to allow for weight stabilization and nutritional recovery.

Genetic counselling

DGLBCS is inherited in an autosomal dominant manner. The majority of individuals diagnosed with *CDH1*-related DGLBCS inherited the *CDH1* pathogenic variant from a parent (because of reduced penetrance, the parent from whom the pathogenic variant was inherited may not have developed cancer). Some individuals diagnosed with *CTNNA1*-related DGLBCS have an affected first- or second-degree relative with gastric or breast cancer. Some individuals with DGLBCS have the disorder as the result of a *de novo* pathogenic variant. Each child of an individual with DGLBCS has a 50% chance of inheriting the DGLBCS-related pathogenic variant. If the DGLBCS-related pathogenic variant has been identified in an affected family member, predictive testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

Consensus genetic testing criteria for diffuse gastric and lobular breast cancer syndrome (DGLBCS), also known as hereditary diffuse gastric cancer (HDGC), have been published [Blair et al 2020].

Suggestive Findings

DGLBCS **should be suspected** in a proband with ANY of the following clinical features or family history [Blair et al 2020]:

Clinical features

- Diffuse gastric cancer (DGC) diagnosed at age <50 years
- DGC in an individual of Māori ethnicity diagnosed at any age
- DGC diagnosed at any age in an individual with a personal history or first-degree relative with cleft lip or cleft palate
- DGC and lobular breast cancer (LBC), both diagnosed in an individual at age <70 years
- Bilateral LBC, diagnosed at age <70 years
- Pathologically confirmed gastric signet ring cell carcinoma in situ or pagetoid spread of signet ring cells identified at age <50 years

Family history

- ≥2 first- or second-degree relatives with gastric cancer diagnosed at any age, and at least one of these family members diagnosed with DGC
- ≥1 first- or second-degree relative with DGC at any age and ≥1 first- or second-degree relative with LBC diagnosed at age <70 years
- ≥2 first- or second-degree relatives with LBC diagnosed at age <50 years

Note: Although it is advisable for all cancer diagnoses to be confirmed with histopathology findings, in criteria with two or more cancer diagnoses, at least one should be accompanied by confirmed histologic evidence.

Establishing the Diagnosis

A diagnosis of DGLBCS **can be established** in a proband with any of the clinical features and/or family history in Suggestive Findings and a germline heterozygous pathogenic (or likely pathogenic) variant in *CDH1* or a germline heterozygous truncating variant in *CTNNA1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variant" in this *GeneReview* is understood to include likely pathogenic variants. (2) *CDH1* variants should be classified according to the ClinGen *CDH1* Variant Curation Expert Panel (VCEP) Specifications to the ACMG/AMP Variant Interpretation Guidelines [Luo et al 2023] (see Version 3.1 here). Most DGLBCS-related *CDH1* variants are truncating variants, splice site variants, or missense variants that impact splicing [Lee et al 2018, Garcia Pelaez et al 2023, Luo et al 2023]. However, affected individuals from some families who meet genetic testing for DGLBCS have *CDH1* missense variants that do not affect splicing. Therefore, any *CDH1* missense variant of concern should be reported to the ClinGen *CDH1* VCEP for further investigation. (3) Because ClinGen VCEP interpretation guidelines are not currently available for *CTNNA1*, the general ACMG/AMP variant interpretation guidelines for germline variants may be used [Richards et al 2015].

A proband with one of the clinical features described in Suggestive Findings who does not have an identified pathogenic variant in *CDH1* or *CTNNA1* but meets the following family history criteria has suspected DGLBCS

of unknown genetic cause (also referred to as HDGC-like) and should be offered modified surveillance (see Table 7b) [Blair et al 2020]. Criteria are:

- ≥2 family members (first- or second-degree relatives of each other) with gastric cancer regardless of age of diagnosis, with at least one of these individuals with confirmed DGC; **OR**
- ≥1 family member with DGC at any age and ≥1 different family member with LBC diagnosed at age <70 years (first- or second-degree relatives of each other).

Note: For these criteria, the proband is included in the family member(s).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (serial single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Serial single-gene testing. Sequence analysis and deletion/duplication analysis of *CDH1* are performed first. If no pathogenic variant is detected, analysis of *CTNNA1* should be performed. Note: (1) In individuals without a pathogenic variant identified, germline RNA analysis of *CDH1* and *CTNNA1* may identify pathogenic variants that cause splicing defects. (2) Individuals of Māori ancestry have four equally common *CDH1* pathogenic variants that can be detected by *CDH1* sequence analysis (see Table 8) [Hakkaart et al 2019]. (3) Founder variants have also been reported in the Newfoundland and Portuguese populations (see Table 8).

A multigene panel that includes *CDH1*, *CTNNA1*, and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition, while limiting identification of variants of uncertain significance, and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

Table 1. Molecular Genetic Testing Used in Diffuse Gastric and Lobular Breast Cancer Syndrome

Gene [1, 2]	Proportion of DGLBCS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Identified by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
CDH1	10%-40% [6]	82%-95% [6]	5%-18% [6]
CTNNA1	<2% [7]	100% [7]	None reported

Table 1. continued from previous page.

Gene [1, 2]	Proportion of DGLBCS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Identified by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
Unknown [8]	>60% [7]	NA	

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected these genes.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/ duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. Kaurah et al [2007], Oliveira et al [2009], Hansford et al [2015], Oliveira et al [2015], Lobo et al [2021], Garcia-Pelaez et al [2023], Ryan et al [2024]
7. Majewski et al [2013], Lobo et al [2021]
8. Individuals who meet consensus genetic testing criteria but do not have a pathogenic variant identified in either *CDH1* or *CTNNA1* are classified as suspected DGLBCS of unknown genetic cause (also called hereditary diffuse gastric cancer [HDGC]-like) [Blair et al 2020].

Clinical Characteristics

Clinical Description

Diffuse gastric and lobular breast cancer syndrome (DGLBCS) is characterized by an increased risk of diffuse gastric cancer (DGC) and lobular breast cancer (LBC). Cleft lip with or without cleft palate has been reported in some individuals with *CDH1*-related DGLBCS.

Table 2. Diffuse Gastric and Lobular Breast Cancer Syndrome: Frequency of Select Features

Feature	Frequency of Feature by Gene		Comment
	CDH1	*CTNNA1*	
Diffuse gastric cancer	10%-70% of males [1, 2] 7%-56% of females [1, 2]	49%-57% [3]	Cumulative risk by age 80 yrs
Lobular breast cancer	37%-42% of females [1, 4]	NR	Cumulative risk by age 80 yrs
Cleft lip ± cleft palate	<3% [5]	NR	

NR = not reported to date
1. Hansford et al [2015], Roberts et al [2019], Ryan et al [2024]
2. Initial estimates of gastric cancer risk were established based on a few families, including some high-risk groups, and were possibly influenced by small sample sizes and sampling bias. In addition, inclusion of all gastric cancers (e.g., occult stage 1A) identified at the time of prophylactic gastrectomy resulted in higher risk estimates by approximately twofold (7%-10% to 13%-19%) [Ryan et 2024].
3. Coudert et al [2022]
4. Breast cancer risks from Roberts et al [2019] and Ryan et al [2024] were calculated based on invasive lobular, ductal, and unspecified breast cancers.
5. Cleft lip/palate has been described in at least one individual in 19% of families with *CDH1*-related DGLBCS [Green et al 2022].

Diffuse gastric cancer (DGC). The average age of onset of DGC in the largest cohorts of individuals with *CDH1*-related DGLBCS ranges from age 42 to 49 years [Xicola et al 2019, Garcia-Pelaez et al 2023, Ryan et al 2024], and DGC onset may occur as young as age 14 years [Gullo et al 2018, Xicola et al 2019, São José et al 2023].

Signet ring cancer cells are often identified at the initial endoscopy in individuals with a germline *CDH1* pathogenic variant [Mi et al 2018, Jacobs et al 2019], and in one study only 42% (5/12) had a first-degree relative with DGC [Jacobs et al 2019]. The age of onset and clinical behavior is variable between and within families [Hansford et al 2015, Gullo et al 2018, Blair et al 2020, Garcia-Pelaez et al 2023, São José et al 2023]. Average age of onset of DGC in *CTNNA1*-related DGLBCS is 40 years [Lobo et al 2021, Coudert et al 2022].

Symptoms of DGC are nonspecific in the early stages and consequently tend to be dismissed both by affected individuals and physicians. Intramucosal occult signet ring cell carcinomas have been identified in prophylactic gastrectomy specimens from women with a history of LBC despite not having a personal or family history of gastric cancer [Gamble et al 2022]. By the time specific symptoms appear, affected individuals present with advanced disease [Iyer et al 2020]. Symptoms of late-stage DGC may include abdominal pain, nausea, vomiting, dysphagia, postprandial fullness, loss of appetite, and weight loss. A palpable mass may be present late in the course of DGC. Advanced DGC often involves metastatic spread into the gastrointestinal tract, peritoneum, omentum, mesocolon, and female reproductive tract; metastatic spread to other organs is rare [Decourtye-Espiard & Guilford 2023].

Lobular breast cancer (LBC). LBC is the second most common cancer type in individuals with DGLBCS and can present as invasive LBC or lobular carcinoma in situ. The average age of onset for breast cancer in females with a germline *CDH1* pathogenic variant ranges from 45 to 54 years [Pharoah et al 2001, Xicola et al 2019, Garcia-Pelaez et al 2023, Ryan et al 2024]. In large studies the presence of a germline pathogenic variant in *CDH1* was observed in 0.1%-0.5% of individuals with LBC [Petridis et al 2019, Yadav et al 2021, Adib et al 2022]. Additionally, a cohort analysis of invasive LBC and lobular carcinoma in situ revealed that 8% of individuals with bilateral cancer had a germline *CDH1* pathogenic variant [Petridis et al 2014]. These findings collectively indicate that LBC in women with DGLBCS tends to be bilateral [Petridis et al 2014] and often metastasizes to the gastrointestinal and female reproductive tract and peritoneal surface [Pilonis et al 2021].

Cleft lip with or without cleft palate has been a recurrent finding in individuals with *CDH1*-related DGLBCS. Cleft lip with or without cleft palate has been described in at least one individual in 19% of families with *CDH1*-related DGLBCS [Green et al 2022]. Information regarding the type of cleft and severity are limited. Presence of cleft lip/palate varies among affected individuals from the same family.

Other cancers

- ***CDH1.*** Germline *CDH1* pathogenic variants have been identified in individuals with other primary cancers including other types of gastric cancer, other types of breast cancer, colorectal cancer (CRC), and other cancer types. In a United States study of 212,944 individuals, 141 individuals (0.06%) had a germline *CDH1* pathogenic variant [Adib et al 2022]. Breast cancer (54.6% of individuals) and gastric cancer (39.7% of individuals) were the most common cancer types among individuals with a germline *CDH1* pathogenic variant. CRC was reported in 9.9% of individuals (3.8% had signet ring cell CRC), and other types of cancer were reported in 3.5% of individuals. In a second US study, in 12% of families with a germline *CDH1* pathogenic variant, there was no history of gastric or breast cancer [Xicola et al 2019]; CRC was the most frequent cancer type after gastric and breast cancer in these families. A study of 176 European families with a germline *CDH1* pathogenic variant reported gastric (62%: 38% DGC) and breast (25%: 11% LBC) as the most frequent cancer types; CRC accounted for less than 2%, and other cancer types were even rarer [Garcia-Pelaez et al 2022].
- ***CTNNA1.*** A systematic review including 105 individuals from 41 families with a germline *CTNNA1* truncating pathogenic variant found that only 24% of families met the criteria for DGLBCS, and affected individuals presented most often with DGC at around age 40 years. Affected individuals from the remaining 76% of families with a germline *CTNNA1* truncating pathogenic variant presented with other cancer types, mostly unspecified breast cancer, or remained cancer-free [Lobo et al 2021].

Prognosis

- **DGC.** A single study assessed the survival of individuals with *CDH1*-related DGC and reported that individuals with *CDH1*-related DGC had shorter survival than individuals who met genetic testing criteria but did not have a germline *CDH1* pathogenic variant [van der Post et al 2015b]. When sporadic DGC is detected early (i.e., before it has invaded the stomach wall), the five-year survival rate can be greater than 75%-90%, depending on the geographic region [Pereira et al 2022]. Overall and disease-free survival of individuals with *CDH1*- and *CTNNA1*-related advanced DGC is believed to be the same as individuals with advanced sporadic DGC. The five-year survival rate is less than 30% when DGC is identified at a late stage [Stiekema et al 2013, Pereira et al 2022].
- **LBC.** The reported five-year overall survival rate for infiltrating LBC is approximately 93%; however, the impact of a germline *CDH1* pathogenic variant on the survival rate of individuals with LBC remains uncertain [Han et al 2022]. While some studies have suggested that a somatic *CDH1* variant does not significantly affect the prognosis of individuals with invasive LBC, the presence of both *CDH1* and *ERBB2* variants in LBC tumor tissue has been associated with a poorer prognosis [Ping et al 2016].

Pathophysiology

- **DGC.** The loss of E-cadherin causes individual tumor cells to grow and invade neighboring structures. Malignant cells infiltrate and spread under histologically normal-looking mucosa, causing widespread thickening and rigidity of the gastric wall, a phenomenon known as *linitis plastica* [McColl 2006]. No tumor mass is formed.

  DGC is characterized by the presence of multiple gastric intramucosal signet ring cell carcinomas (SRCC) with abnormal or absent E-cadherin immunohistochemistry. This distinctive signet ring appearance is caused by an accumulation of intracellular mucin that pushes the nucleus to one side. A clearly defined preneoplastic lesion is not seen in DGC. A progression model for DGC developed from studying prophylactic total gastrectomy (PTG) specimens from individuals with a germline *CDH1* pathogenic variant describes isolated neoplastic signet ring cells at the base of the glands and pagetoid spread of signet ring cells below the preserved epithelium of glands/foveolae into the stroma [Carneiro et al 2004, Monster et al 2022]. In individuals with *CDH1* pathogenic variants and in individuals with *CTNNA1* truncating pathogenic variants, these lesions consist of both T1a stage SRCC that have invaded the lamina propria, as well as in situ SRCC that are confined within the basement membrane (pTis). Both the T1a stage and in situ foci show significant overexpression of cytokeratin 7. Although individuals with *CTNNA1*-related DGC also exhibit multifocal intramucosal SRCC, in situ foci have not been observed to date [Benusiglio et al 2019, Decourtye-Espiard & Guilford 2023].

- **LBC.** *CDH1*-related and sporadic LBC share similar histopathologic and immunohistochemical characteristics, including the presence of small tumor cells that are loosely dispersed in the stroma or arranged in single-file infiltrating patterns and absence of E-cadherin staining [Christgen et al 2016, Decourtye-Espiard & Guilford 2023]. LBC can be differentiated from other neoplasms by observing cytoplasmic staining of p120-catenin, while beta-catenin is negative [Blair et al 2020]. *CDH1*-related and sporadic LBC are also both associated with noninvasive conditions such as atypical lobular hyperplasia and lobular carcinoma in situ [Decourtye-Espiard & Guilford 2023].

Phenotype Correlations by Gene

CDH1. Germline pathogenic variants in *CDH1* are associated with an increased risk of DGC, LBC [Garcia-Pelaez et al 2023], and cleft lip with or without cleft palate.

CTNNA1. DGC frequently occurs in families bearing germline truncating variants in *CTNNA1*, while LBC is extremely rare [Lobo et al 2021]. Truncating variants in *CTNNA1* have not been associated with cleft lip/palate.

Genotype-Phenotype Correlations

CDH1. Pathogenic variants located in the *CDH1* linker regions between the extracellular domains have been associated with cleft lip/palate. A specific protein region responsible for calcium ion chelation displayed high intolerance to missense substitutions (between amino acids 253 and 260) [Selvanathan et al 2020].

Penetrance

The penetrance of DGLBCS is reduced.

CDH1. A study that included 75 families with germline *CDH1* pathogenic variants found that by age 80 years, the cumulative incidence of gastric cancer including DGC was 70% (95% CI: 59%-80%) for males and 56% (95% CI: 44%-69%) for females, and the risk of breast cancer including LBC for females was 42% (95% CI: 23%-68%) [Hansford et al 2015].

In a second study not exclusively selected based on strict DGLBC criteria, the cumulative incidence of gastric cancer including DGC by age 80 years was 42% (95% CI: 30%-56%) for males and 33% (95% CI: 21%-43%) for females with a *CDH1* pathogenic variant. Additionally, the estimated cumulative incidence of female breast cancer in this cohort was 55% (95% CI: 39%-68%) [Roberts et al 2019].

A recent analysis of 70 individuals from 11 families from northern Portugal with a *CDH1* founder pathogenic variant (c.1901C>T) showed that fewer than 20% of individuals with the variant developed DGC or LBC, even in a region where gastric cancer is highly prevalent [Barbosa-Matos et al 2021].

In a recent study involving a North American cohort of 7,323 individuals from 213 families with *CDH1* pathogenic variants, the prevalence of gastric cancer was 13.9%, while breast cancer prevalence was 26.3%. Additionally, the lifetime risk for advanced gastric cancer varied significantly depending on family history. The risk ranged from 7%-10% regardless of family history to an estimated 38% in families with three first-degree relatives diagnosed with gastric cancer.

CTNNA1. Initial estimates from 46 individuals from 13 families with a germline *CTNNA1* truncating variant showed a cumulative risk of DGC of 49% and 57% by age 80 years, depending on the statistical method used [Coudert et al 2022]. This may represent a risk overestimation given the low number of families included and their small size.

Prevalence

Approximately 7% of individuals with DGC have been found to have a germline *CDH1* pathogenic variant [Adib et al 2022].

Invasive LBC represents 5%-15% of all invasive breast cancers. In two large studies, a germline *CDH1* pathogenic variant was identified in 0.1%-0.5% of women with LBC [Petridis et al 2019, Yadav et al 2021, Adib et al 2022].

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in *CDH1* and *CTNNA1* are summarized in Table 3.

Table 3. Allelic Disorders

Gene	Disorder
CDH1	Blepharocheilodontic syndrome 1 (OMIM 119580)
CTNNA1	Patterned macular dystrophy 2 (OMIM 608970)

Sporadic tumors of epithelial origin frequently have E-cadherin protein loss at advanced stages. In particular, gastric, breast, non-melanoma skin, ovarian, and pancreatic cancers often contain somatic *CDH1* pathogenic single-nucleotide variants, loss of heterozygosity, and/or promoter hypermethylation in tumor cells that are not present in the germline [Carvalho et al 2012, Corso et al 2013, Busch et al 2017]. In these circumstances predisposition to these tumors is not heritable.

Somatic *CTNNA1* variants have been described in sporadic colorectal, diffuse gastric, breast, lung, and prostate cancers and myeloid leukemia [Sygut et al 2012, Naghi Vishteh et al 2021, Corso et al 2023].

Differential Diagnosis

An estimated 5%-10% of all gastric cancers are thought to present familial clustering [Zanghieri et al 1990, La Vecchia et al 1992]; only a small fraction of gastric cancers are believed to be hereditary and explained by a genetic cause.

Identification of individuals at risk for diffuse gastric and lobular breast cancer syndrome (DGLBCS) is complicated by several factors:

- DGLBCS is one of several hereditary cancer syndromes characterized by gastric and breast cancer and associated premalignant lesions.
- Risk of a hereditary cancer syndrome with an overlapping tumor spectrum may not be apparent in an individual with an unknown/unreported family history presenting with isolated gastric or breast cancer detected at early age [Garcia-Pelaez et al 2022].

Detailed histologic classification of gastric (diffuse vs non-diffuse) and breast (lobular vs non-lobular) cancers is necessary to identify individuals and families at risk for DGLBCS and to facilitate appropriate genetic testing.

Cancer predisposition syndromes that include gastric and/or breast cancer as part of their disease spectrum (despite not being the primary associated cancers) are listed in Table 4.

Table 4. Cancer Predisposition Syndromes in the Differential Diagnosis of Diffuse Gastric and Lobular Breast Cancer Syndrome

Gene(s)	Disorder	MOI	Overlapping Cancer Predisposition	Features of Disorder Distinguishing from DGLBCS
APC	*APC*-assoc polyposis conditions	AD	Gastric cancer	• Gastric cancer often differs histologically from DGC. • CRC is the most commonly assoc cancer. • Adenomatous gastrointestinal polyps • Additional physical features (dental anomalies, CHRPE, osteomas)
BMPR1A *SMAD4*	Juvenile polyposis syndrome	AD	Gastric cancer	Gastrointestinal polyposis
BRCA1 *BRCA2*	*BRCA1*- & *BRCA2*-assoc hereditary breast & ovarian cancer	AD	• Breast cancer • Gastric cancer [1]	Risk of other cancers (ovarian, prostate, pancreatic, & melanoma)

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Overlapping Cancer Predisposition	Features of Disorder Distinguishing from DGLBCS
MAX *SDHA* *SDHAF2* *SDHB* *SDHC* *SDHD* *TMEM127*	Hereditary paraganglioma-pheochromocytoma syndromes	AD	Gastric cancer	• GIST • Risk of other cancers (paragangliomas, pheochromocytomas, renal clear cell) • Pulmonary chondromas
MLH1 *MSH2* *MSH6* *PMS2* *EPCAM*	Lynch syndrome	AD	• Gastric cancer (≤20% is DGC in those w/Lynch syndrome) [2] • Breast cancer [3]	• Gastric cancer often differs histologically from DGC. • CRC is the most commonly assoc cancer. • Risk of other cancers (endometrium, ovary, stomach, small bowel, urinary tract, biliary tract, brain)
MUTYH	*MUTYH* polyposis	AR	Gastric cancer	• Colonic adenomatous polyps • CRC is the most commonly assoc cancer.
PALB2	*PALB2*-related hereditary breast & ovarian cancer (OMIM 620442)	AD	• Gastric cancer • Breast cancer	Risk of other cancers (ovarian & pancreas)
PTEN	Cowden syndrome (See *PTEN* Hamartoma Tumor Syndrome).	AD	Breast cancer	• Risk of other cancers (thyroid, kidney, endometrium) • Physical features (macrocephaly, trichilemmomas, & papillomatous papules)
STK11	Peutz-Jeghers syndrome	AD	• Gastric cancer • Breast cancer	• Risk of epithelial malignancies (CRC, gastric, pancreatic, breast, & ovarian cancers) • Gastrointestinal polyposis • Mucocutaneous pigmentation
TP53	Li-Fraumeni syndrome	AD	• Breast cancer • Gastric cancer	• Risk of many cancer types, most commonly adrenocortical, breast, CNS, osteosarcomas, & soft-tissue sarcomas

AD = autosomal dominant; AR = autosomal recessive; CHRPE = congenital hypertrophy of the retinal pigment epithelium; CNS = central nervous system; CRC = colorectal cancer; DGC = diffuse gastric cancer; DGLBCS = diffuse gastric and lobular breast cancer syndrome; GIST = gastrointestinal stromal tumor; MOI = mode of inheritance

1. Buckley et al [2022]

2. A higher incidence of gastric cancer is reported in individuals with Lynch syndrome younger than age 40 years in Asian kindreds.

3. See gene-specific cancer risks in Table 3 of the Lynch syndrome *GeneReview.*

Management

Clinical practice guidelines for diffuse gastric and lobular breast cancer syndrome (DGLBCS) have been published [Blair et al 2020].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with DGLBCS, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Diffuse Gastric and Lobular Breast Cancer Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Diffuse gastric cancer (DGC)	• Referral to a DGC center of expertise for screening • Endoscopy w/multiple gastric biopsies to assess for macroscopic tumor & microscopic pre-malignant or malignant lesions • Eval for *H pylori* infection given its major role as risk factor in gastric carcinogenesis [1]	• For those w/*CDH1* pathogenic variant or *CTNNA1* truncating pathogenic variant, beginning in early adulthood or 5-10 yrs prior to earliest gastric cancer diagnosis in family w/minimum age of 18 yrs • For those w/suspected DGLBCS of unknown cause, beginning at age 40 yrs or 5-10 yrs prior to earliest gastric cancer case in family, w/minimum age of 18 yrs
Lobular breast cancer (LBC)	**In females:** • Referral to high-risk breast cancer clinic • Clinical breast exam in those age ≥20 yrs • Breast MRI in those age 30-40 yrs • Breast MRI combined w/mammography in those age ≥40 yrs	• Mammography alone is inadequate to identify LBC; if MRI is unavailable, consider incl breast ultrasound. • Note: (1) Recommended for those w/*CDH1* pathogenic variant or *CTNNA1* truncating pathogenic variant & personal or family history of breast cancer. (2) In those w/suspected DGLBCS of unknown cause, breast surveillance is based on individual assessment.
Cleft lip/palate	Eval by multispecialty cleft team	In those w/*CDH1*-related cleft lip/palate
Genetic counseling	By genetics professionals [2]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of DGLBCS to facilitate medical & personal decision making

DGC = diffuse gastric cancer; DGLBCS = diffuse gastric and lobular breast cancer syndrome; LBC = lobular breast cancer; MOI = mode of inheritance

1. Choi et al [2020], Usui et al [2023]

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Prophylactic gastrectomy for diffuse gastric cancer (DGC) is an option from early adulthood in individuals with **normal** endoscopy / gastric biopsies and a germline heterozygous:

- DGLBCS-related *CDH1* pathogenic variant regardless of family history; **OR**
- DGLBCS-related *CTNNA1* pathogenic variant and a family history of DGC and/or LBC.

Note: In individuals with an unclear risk of DGC (e.g., DGLBCS of unknown genetic cause [HDGC-like], *CTNNA1*-related DGLBCS and no family history of DGC), prophylactic gastrectomy is less commonly recommended and intensive endoscopic surveillance should be considered. Individuals should be informed about the limitations of endoscopy and the requirements of endoscopic surveillance for individuals with DGLBCS.

Total prophylactic gastrectomy involves a multidisciplinary team including gastric surgery, gastroenterology, pathology, nutrition, oncology, and palliative care for preoperative and postoperative care. The multidisciplinary team members can counsel individuals on the risks and benefits of total gastrectomy. In determining whether to undergo total gastrectomy, the individual and treating physicians should consider the following:

- Individuals that opt for prophylactic total gastrectomy are initially tested and treated (if identified) for *H pylori* infection to eradicate it prior to total gastrectomy.
- Current guidelines suggest that individuals with *CDH1*- and *CTNNA1*-related DGLBCS should undergo a baseline upper endoscopy before prophylactic total gastrectomy. Signet ring cell carcinoma is detected in 40%-61% of individuals with a germline *CDH1* pathogenic variant and is often identified at initial endoscopy [Mi et al 2018, Jacobs et al 2019].
- In a young, healthy adult, the risk of mortality with prophylactic total gastrectomy in an experienced surgeon's hands is less than 1% [Lynch et al 2005].
- The morbidity from prophylactic total gastrectomy is 100% [Worster et al 2014, Muir et al 2016]. All individuals have immediate and long-term complications including rapid intestinal transit, dumping syndrome, diarrhea, eating habit alterations, and weight loss [van der Kaaij et al 2018, Gallanis & Davis 2023]. The risk for malabsorption increases, including an increased incidence of malnutrition, nephrolithiasis, cholelithiasis, and osteopenia/osteoporosis [Gamble et al 2023].
- Individuals who have undergone prophylactic total gastrectomy in expert centers express minimal to no regret, emphasizing that the perceived benefits outweigh the associated risks [Muir et al 2016, Hallowell et al 2017, Kaurah et al 2019].
- Prophylactic total gastrectomy in young children is not recommended until full physical maturity is reached and should be avoided in adolescents due to its high risk of complications.
- Prophylactic total gastrectomy is not typically recommended for individuals older than age 70 years.
- Following total gastrectomy, surveillance with laboratory examinations and clinical, nutritional, and psychological monitoring is recommended. Laboratory assessments should include a complete blood count, electrolyte levels, blood urea nitrogen, creatinine, and evaluations of liver function. Annual endoscopy to survey the anastomosis may be considered. Vitamin and mineral supplementation are required due to the increased risk of nutrient deficiency (e.g., vitamin B_{12}, iron, calcium, and vitamin D) [Stillman et al 2022].
- An intrauterine device or alternative form of contraception that does not require gastrointestinal absorption is recommended in women with *CDH1*- or *CTNNA1*-related DGLBCS who are considering prophylactic total gastrectomy.

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications by a multidisciplinary team comprising those with expertise in gastric and breast surgery, gastroenterology, nutrition, plastic surgery, oncology, and palliative care is recommended. Table 6 presents a summary of therapeutic approaches currently recommended in individuals with DGLBCS.

Table 6. Diffuse Gastric and Lobular Breast Cancer Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Diffuse gastric cancer (DGC)	Standard treatment to eradicate *H pylori* infection	
	In those w/early DGC: Total gastrectomy involves D-2 dissection, Roux-en-Y esophagojejunostomy, & obtaining proximal margins to ensure removal of gastric mucosa. [1]	

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
	In those w/advanced DGC: Total gastrectomy w/perioperative &/or adjuvant therapy (e.g., radiation, chemotherapy) as recommended by multidisciplinary team w/experience in DGC	
	In children/adolescents w/DGC: If early gastric lesions (pT1a) are identified on surveillance, chemotherapy & radiation therapy are not recommended. In such instances, intensive surveillance should be performed, & interval between endoscopy w/multiple biopsies may decrease from 12 to 6 mos, until total gastrectomy is feasible at full physical maturity. [2]	Chemotherapy & radiotherapy are only recommended in children & adolescents if advanced disease is diagnosed or found during surveillance.
	An intrauterine device or alternative form of contraception that does not require gastrointestinal absorption is recommended in women who have undergone total gastrectomy.	
Lobular breast cancer (LBC)	• Treatment includes surgery, hormonal therapy, & perioperative &/or adjuvant chemotherapy depending on LBC stage, overall individual health, tumor aggressiveness, & predictive biomarkers for targeted therapies. • Mastectomy is the preferred treatment. The timing for breast reconstruction should be discussed.	The extent of LBC lesions will impact treatment recommendations. LBC staging requires clinical imaging, exam before treatment, tumor pathology, & lymph node analysis. The most common classification systems are the American Joint Commission on Cancer & the International Union for Cancer Control. [3]
	• Risk-reducing contralateral mastectomy may be considered. • Chemoprevention can be considered (e.g., selective estrogen receptor modulators or aromatase inhibitors), but due to the significant side effects, long-term applicability is limited. [4]	In those w/germline *CDH1* pathogenic variant & family or personal history of breast cancer
Cleft lip/palate [5]	Standard treatments for cleft correction by craniofacial specialists	Requires multidisciplinary team, incl craniofacial surgeons, otolaryngologists, geneticists, anesthesiologists, speech-language pathologists, nutritionists, orthodontists, prosthodontists, & psychologists [6]

DGC = diffuse gastric cancer; LBC = lobular breast cancer
1. Norton et al [2007]
2. Blair et al [2020]
3. Mamtani & King [2018]
4. Cuzick et al [2014], King et al [2015]
5. In those with *CDH1*-related cleft lip/palate
6. de Ladeira & Alonso [2012], Mink van der Molen et al [2021]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Tables 7a (individuals with *CDH1*- or *CTNNA1*-related DGLBCS) and 7b (individuals with DGLBCS of unknown genetic cause) are recommended.

Table 7a. *CDH1*- or *CTNNA1*-Related Diffuse Gastric and Lobular Breast Cancer Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Diffuse gastric cancer (DGC)	Referral to high-risk gastric cancer screening program	
	Upper endoscopy to incl: • Thorough ≥30-minute exam • Targeted biopsies of all suspicious lesions • Followed by random biopsies from specific anatomic regions using IGCLC Cambridge [1] or Bethesda method [2, 3] Note: Endoscopy permits direct inspection & biopsy of suspicious areas; however, DGC tends to spread in submucosa, where lesions are difficult to identify.	• Every 6-12 mos beginning at age 40 yrs (or 5-10 yrs prior to earliest gastric cancer diagnosis in family), w/minimum age of 18 yrs • Note: (1) For individuals w/unclear risk of DGC, the interval between endoscopies can be increased after 2 consecutive normal endoscopies at discretion of a DGC specialist based on endoscopy findings & family history. (2) Choosing endoscopy surveillance vs prophylactic gastrectomy is challenging; it is difficult to determine if intramucosal lesions identified on endoscopy will remain indolent &/or become aggressive. The efficacy of endoscopic surveillance performed at expert centers to detect early DGC has been reported. [4, 5]
Lobular breast cancer (LBC) [6]	Referral to high-risk breast cancer screening program	
	Self-breast exams	Monthly beginning at age 20 yrs
	• Clinical breast exams • Education on clinical features of breast cancer (e.g., thickening, indrawn nipple, or change in breast skin) • Bilateral breast MRI w/contrast [7, 8]	Annually beginning at age 30 yrs
	• Mammogram • Note: Include breast ultrasound w/ mammogram if breast MRI is not available.	Annually between breast MRI screenings beginning at age 30-40 yrs

Table 7a. continued from previous page.

System/Concern	Evaluation	Frequency
In those w/history of cleft lip/ palate	• Audiology eval • Speech eval [9]	Annually throughout childhood or as recommended by craniofacial specialists

DGC = diffuse gastric cancer; IGCLC = International Gastric Cancer Linkage Consortium; LBC = lobular breast cancer
1. IGCLC Cambridge method recommends a thorough high-definition white light examination of at least 30 minutes in a center of expertise. The session should begin with targeted biopsies from all suspicious lesions, followed by five random biopsies from six specific anatomic regions (prepyloric, antrum, transitional zone, body, fundus, and cardia) [van der Post et al 2015a].
2. Bethesda protocol recommends endoscopic examination with a comprehensive assessment of 22 specific anatomic locations, each of which is meticulously photographed. Four non-targeted biopsies are obtained from each of these 22 sites; any abnormal findings are subjected to biopsy.
3. When comparing the detection rates per endoscopy, the false-negative rates for detection using the Cambridge method and the Bethesda protocol were 80% (12/15) and 37.7% (17/45), respectively [Curtin et al 2021].
4. Three independent prospective longitudinal studies of endoscopic surveillance with multiple biopsies in individuals with DGLBCS showed that endoscopic surveillance, performed in reference centers, may be a reasonable alternative to prophylactic total gastrectomy [Friedman et al 2021, Asif et al 2023, Lee et al 2023]. Further studies with greater statistical power are needed before this approach is implemented in clinical practice.
5. Currently, there are ongoing trials to investigate the utility of probe-based confocal laser endomicroscopy (pCLE) for DGC diagnosis, particularly in identifying early signet ring cell carcinoma lesions [Pilonis et al 2023].
6. In females w/*CDH1*-related DGLBCS or *CTNNA1*-related DGLBCS and personal or family history of breast cancer of any type
7. Mammography has a low sensitivity for detecting lobular breast cancer (LBC) due to its subtle and slow-growing nature. Breast imaging radiologists must be aware of the atypical and subtle mammographic patterns of invasive LBC, which include spiculated masses, architectural distortion, and poorly defined asymmetric densities. Breast MRI can detect tumor margins, size, and multifocality more accurately than ultrasound and mammography.
8. A novel diagnostic approach known as contrast-enhanced spectral mammography (CESM) offers accurate detection similar to breast MRI [Corso et al 2023].
9. Mink van der Molen et al [2021]

Table 7b. Suspected Diffuse Gastric and Lobular Breast Cancer Syndrome of Unknown Genetic Cause: [1] Recommended Surveillance

System/Concern	Evaluation	Frequency
Diffuse gastric cancer (DGC)	Referral to high-risk gastric cancer screening program	
	Upper endoscopy to incl: • Thorough ≥30-minute exam • Targeted biopsies of all suspicious lesions • Followed by random biopsies from specific anatomic regions using IGCLC Cambridge [2] or Bethesda method [3, 4] Note: Endoscopy permits direct inspection & biopsy of suspicious areas; however, DGC tends to spread in submucosa, where lesions are difficult to identify.	• Annually for ≥2 yrs, beginning at age 40 yrs or 10 yrs prior to earliest gastric cancer diagnosis in family, w/minimum age of 18 yrs • Note: The likelihood of a positive biopsy is highest w/initial endoscopy & surveillance intervals can be extended at discretion of endoscopist after 2 yrs. This decision should be based on individual findings from previous endoscopies & family history. [5, 6]

Table 7b. continued from previous page.

System/Concern	Evaluation	Frequency
Lobular breast cancer (LBC)	Referral to high-risk breast-screening program	
	Self-breast exams	Monthly in females beginning at age 20 yrs in those w/personal or familial history of breast cancer of any type
	• Clinical breast exams • Education on clinical features of LBC (e.g., thickening, indrawn nipple, or change in breast skin)	Annually in females beginning at age 30 yrs in those w/personal or familial history of breast cancer of any type
	• Bilateral breast MRI w/contrast [7, 8] • Bilateral breast MRI combined w/ mammography & breast ultrasound	• Frequency should be based on personalized breast cancer risk assessment by experienced team. • Consider MRI in addition to conventional mammography & breast ultrasound for improved results w/LBC diagnosis. [9]

DGC = diffuse gastric cancer; IGCLC = International Gastric Cancer Linkage Consortium; LBC = lobular breast cancer

1. Also referred to as HDGC-like

2. IGCLC Cambridge method recommends a thorough high-definition white light examination of at least 30 minutes in a center of expertise. The session should begin with targeted biopsies from all suspicious lesions, followed by five random biopsies from six specific anatomic regions (prepyloric, antrum, transitional zone, body, fundus, and cardia) [van der Post et al 2015a].

3. Bethesda protocol recommends endoscopic examination with a comprehensive assessment of 22 specific anatomic locations, each of which is meticulously photographed. Four non-targeted biopsies are obtained from each of these 22 sites; any abnormal findings are subjected to biopsy.

4. When comparing the detection rates per endoscopy, the false-negative rates for detection using the Cambridge method and the Bethesda protocol were 80% (12/15) and 37.7% (17/45), respectively [Curtin et al 2021].

5. Three independent prospective longitudinal studies of endoscopic surveillance with multiple biopsies in individuals with DGLBCS showed that endoscopic surveillance, performed in reference centers, may be a reasonable alternative to prophylactic total gastrectomy [Friedman et al 2021, Asif et al 2023, Lee et al 2023]. Further studies with greater statistical power are needed before this approach is implemented in clinical practice.

6. Currently, there are ongoing trials to investigate the utility of probe-based confocal laser endomicroscopy (pCLE) for DGC diagnosis, particularly in identifying early signet ring cell carcinoma lesions [Pilonis et al 2023].

7. Mammography has a low sensitivity for detecting lobular breast cancer (LBC) due to its subtle and slow-growing nature. Breast imaging radiologists must be aware of the atypical and subtle mammographic patterns of invasive LBC, which include spiculated masses, architectural distortion, and poorly defined asymmetric densities. Breast MRI can detect tumor margins, size, and multifocality more accurately than ultrasound and mammography.

8. A novel diagnostic approach known as contrast-enhanced spectral mammography (CESM) offers accurate detection similar to breast MRI [Corso et al 2023].

9. Blair et al [2020]

Evaluation of Relatives at Risk

Family members of a proband with a molecular diagnosis of DGLBCS. Once a molecular diagnosis of DGLBCS has been established in the proband, it is appropriate to offer at-risk relatives predictive testing for the familial *CDH1* or *CTNNA1* pathogenic variant. Predictive genetic testing can reduce morbidity and mortality by identifying individuals with DGLBCS who would benefit from intensive surveillance (see Table 7a) for early cancer detection and/or risk-reduction surgeries targeting organs associated with DGLBC. Of note, predictive testing should be offered in the context of formal genetic counseling.

Family members of a proband with suspected DGLBCS of unknown genetic cause (i.e., a proband with clinical features and a family history consistent with DGLBCS in whom molecular genetic testing has not identified a *CDH1* pathogenic variant or a *CTNNA1* truncating variant, also referred as HDGC-like). It is appropriate to offer first-degree relatives surveillance tailored to the individual's personal and family history (see Table 7b).

See Genetic Counseling, **Predictive testing in minors** for discussion of issues related to testing of this population and issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Nutritional consequences of total gastrectomy should be discussed before and during pregnancy. Pregnancy should be delayed at least six to 12 months after total gastrectomy, to allow for weight stabilization and nutritional recovery. Kaurah et al [2010] reported six healthy pregnancies and infants born to four women after total gastrectomy. However, pregnant women who have undergone prophylactic gastrectomy should be followed closely by their physician and a dietician, as pregnancies after bariatric surgery show an increased risk of adverse perinatal outcomes (e.g., preterm births, intrauterine growth deficiency, and intensive care unit admissions).

Therapies Under Investigation

Clinical trials, targeted therapies, and predictive markers of therapy response directed to DGC or LBC are scarce.

Ongoing studies are mainly investigating alternate medication doses and combining therapeutic agents that are approved for sporadic gastric cancer and other solid tumors (e.g., platinum compounds, fluropyrimidines, and topoisomerase I inhibitors). Immunotherapy for anti-HER2, anti-VEGDR2, and anti-PD1 have been approved for treatment of gastric adenocarcinoma; however, treatment data for DGC is weak.

The MONO study (NCT01197885), a Phase II clinical trial, examined the outcome of zolbetuximab (monoclonal antibody against CLDN18.2: IMAB362) monotherapy in a series of individuals with recurrent or refractory, locally advanced or metastatic, CLDN18.2-positive gastric, gastro-esophageal junction, or esophageal adenocarcinoma. Of the 54 individuals enrolled in this trial, 22 had advanced DGC with CLDN18.2 expression in ≥50% of tumor cells. Zolbetuximab was well tolerated and exhibited antitumor activity with a clinical benefit rate of 23% [Türeci et al 2019]; whether individuals benefiting from this targeted therapy had DGC was not reported.

There are active clinical trials for individuals with invasive LBC or enriched in individuals with lobular histology. These studies are testing small molecules including tyrosine kinase ROS1 inhibition, CDK4/6 inhibition, endocrine therapy strategies, immunotherapy with checkpoint inhibition, and inhibition of HER2 in individuals with HER2 alterations [Mukhtar & Chien 2021]. Novel imaging tools are also being studied to decrease rates of positive margins and improve surgical outcomes [Jones et al 2020].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Diffuse gastric and lobular breast cancer syndrome (DGLBCS) is inherited in an autosomal dominant manner.

Risk to Family Members – Proband with a DGLBCS-Related *CDH1* Pathogenic Variant or *CTNNA1* Truncating Variant

Parents of a proband

- The majority of individuals diagnosed with *CDH1*-related DGLBCS inherited the *CDH1* pathogenic variant from a parent. Because of reduced penetrance, the parent from whom the pathogenic variant was inherited may not have developed cancer. Some individuals diagnosed with *CTNNA1*-related DGLBC have an affected first- or second-degree relative with gastric or breast cancer [Lobo et al 2021].
- Some individuals with DGLBCS have the disorder as the result of a *de novo* pathogenic variant. *De novo* *CDH1* pathogenic variants have been reported [Shah et al 2012, Sugimoto et al 2014].
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing of the parents for the DGLBCS-related *CDH1* or *CTNNA1* pathogenic variant identified in the proband is recommended in order to determine if a parent is at increased risk for diffuse gastric cancer and lobular breast cancer (and should be referred for evaluation/surveillance) and to allow reliable risk assessment for sibs of the proband and other family members.
- If the DGLBCS-related pathogenic variant identified in the proband is not identified in either parent, and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with gonadal (or somatic and gonadal) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.
- The family history of an individual with DGLBCS may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has confirmed that neither parent is heterozygous for the DGLBCS-related pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents.

- If a parent of the proband is affected and/or known to have a DGLBCS-related pathogenic variant, the risk to the sibs of inheriting the pathogenic variant and having DGLBCS is 50%.
- Because DGLBCS is associated with reduced penetrance and intrafamilial clinical variability, age of onset and manifestations may differ among sibs with the same DGLBCS-related pathogenic variant.
- If the DGLBCS-related pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be slightly greater than that of the general population because of the possibility of parental gonadal mosaicism [Pan et al 2021].
- The absence of DGLBCS-related manifestations in parents whose genetic status is unknown cannot be used to predict risk to sibs of a proband because of the possibility of reduced penetrance in a heterozygous parent and the possibility of parental gonadal mosaicism.

Offspring of a proband. Each child of an individual with DGLBCS has a 50% chance of inheriting the DGLBCS-related pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or has a DGLBCS-related pathogenic variant, the parent's family members are at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Genetic cancer risk assessment and counseling. For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling (PDQ® – Health Professional Version (part of National Cancer Institute).

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible if a DGLBCS-related pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing is not possible for family members of a proband with suspected DGLBCS of unknown genetic cause (i.e., a proband with clinical features and a family history consistent with DGLBCS in whom molecular genetic testing has not identified a pathogenic variant in *CDH1* or a truncating variant in *CTNNA1* [see Establishing the Diagnosis]). In these families, it is appropriate to offer first-degree relatives of the proband DGLBCS-related cancer surveillance tailored to the individual's personal and family history (see Table 7b). It is also appropriate to continue the search for a potential genetic cause of DGLBCS in the affected proband.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years). Genetic testing in individuals younger than age 18 years is controversial. Because there have been reports of individuals younger than age 18 years diagnosed with DGLBCS-related cancer [Guilford et al 1998, Gullo et al 2018], it has been suggested that genetic testing in individuals younger than age 18 years may be beneficial, particularly if there is very early onset of diffuse gastric cancer in the family [Caldas et al 1999, Fitzgerald et al 2010]. Overall, a request from parents for testing of asymptomatic at-risk individuals younger than age 18 years should be met with sensitivity and understanding, and comprehensive genetic counseling should be provided to both the parents and the child. The International Gastric Cancer Linkage Consortium (IGCLC) has agreed that genetic testing of at-risk individuals at age 16 years can be considered if the age of onset in the family is early [Fitzgerald et al 2010].

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.
- Counseling about nutritional consequences of prophylactic gastrectomy should be discussed before and during pregnancy (see Pregnancy Management).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

If the DGLBCS-related pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and in families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Cancer Institute (NCI)**
  Phone: 800-4-CANCER
  Email: NCIinfo@nih.gov
  Stomach Cancer
- **No Stomach For Cancer**
  Phone: 608-692-5141
  Email: support@nostomachforcancer.org
  nostomachforcancer.org
- **American Cancer Society**
  Phone: 800-227-2345
  cancer.org
- **CancerCare**
  Phone: 800-813-4673
  Email: info@cancercare.org
  cancercare.org
- **International Society for Gastrointestinal Hereditary Tumours (InSiGHT)**
  insight-group.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Diffuse Gastric and Lobular Breast Cancer Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CDH1	16q22.1	Cadherin-1	CDH1 @ LOVD	CDH1	CDH1
CTNNA1	5q31.2	Catenin alpha-1		CTNNA1	CTNNA1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Diffuse Gastric and Lobular Breast Cancer Syndrome (View All in OMIM)

116805	CATENIN, ALPHA-1; CTNNA1

Table B. continued from previous page.

137215	DIFFUSE GASTRIC AND LOBULAR BREAST CANCER SYNDROME; DGLBC
192090	CADHERIN 1; CDH1

Molecular Pathogenesis

E-cadherin (epithelial cadherin; also known as cadherin-1) is a transmembrane glycoprotein that is predominantly expressed at the basolateral membrane of epithelial cells, where it exerts calcium-dependent cell-cell adhesion and invasion-suppression functions [Takeichi 1991, Berx et al 1995, Nagar et al 1996]. E-cadherin is critical for establishing and maintaining polarized and differentiated epithelia during development [Keller 2002]. It also plays important roles in signal transduction, differentiation, gene expression, cell motility, and inflammation.

Somatic inactivation or down-regulation *CDH1* expression is caused primarily by hypermethylation and somatic mutation (e.g., deletion) of *CDH1* [Oliveira et al 2009, Decourtye-Espiard & Guilford 2023]. *CDH1* promoter methylation is more frequent in primary tumors, while somatic deletion of *CDH1* is more frequent in lymph node metastases [Oliveira et al 2009]. This second hit leads to loss of E-cadherin, which is seen in most diffuse gastric cancers and in lobular breast cancers. Cells deficient in E-cadherin lose their ability to adhere to each other and consequently become invasive and metastasize [Birchmeier 1995, Perl et al 1998]. Additionally, the development of diffuse gastric cancer has been linked to the loss of E-cadherin, which serves as a spatial landmark responsible for orienting the mitotic spindle. This orientation ensures that mitotic division takes place within the epithelial plane, resulting in daughter cells that maintain their integrin-mediated contacts with the basement membrane even after cell division. Consequently, this mechanism reduces the chances of dividing cells being displaced into the gastric lumen or the lamina propria [Humar et al 2007].

The activity of E-cadherin in cell adhesion is dependent on its association with the actin cytoskeleton via undercoat proteins called catenins (α-, β-, and γ-) [Jou et al 1995, Kallakury et al 2001]. Alpha-catenin functions as the primary protein link between cadherins, which constitute adherens junctions, and the actin cytoskeleton. It interacts with several proteins in at least four signaling cancer-associated pathways (Wnt/β-catenin, NF-kB, Hippo-YAP, and hedgehog). The exact mechanisms of disease development in the context of DGLBCS is unknown [Corso et al 2023].

Catenin alpha-1 (also known as alpha E-catenin), encoded by *CTNNA1*, is reported to be essential in inhibiting cell proliferation, promoting apoptosis, repressing invasion, and metastasis in malignancies [Huang et al 2023].

Mechanism of disease causation. Loss of function

Table 8. Pathogenic Variants Referenced in This *GeneReview* by Gene

Gene	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
CDH1	NM_004360.5 NP_004351.1	c.190C>T	p.Gln64Ter	Founder variants in Māori population [Hakkaart et al 2019]
		c.1792C>T	p.Arg598Ter	
		c.2287G>T	p.Glu763Ter	
		c.2386dupC	p.Arg796ProfsTer11	
		c.2398delC	p.Arg800AlafsTer16	Founder variant in Newfoundland population [Kaurah et al 2007]
		c.1901C>T [1]	p.Ala634ProfsTer7 [1]	Founder variant in Portuguese population [Barbosa-Matos et al 2021]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. DNA nucleotide change introduces a new splice site and does not result in the predicted protein change p.Ala634Val. Cryptic splicing causes a 37-bp deletion in exon 12 and premature truncation [Barbosa-Matos et al 2021].

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