2.04.154	Germline Genetic Testing for Hereditary Diffuse Gastric Cancer (CDH1, CTNNA1)		
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Section:	2.0 Medicine	**Page:**	Page 1 of 16

Policy Statement

I. Germline genetic testing for *CDH1* variants to identify individuals with or at risk for hereditary diffuse gastric cancer (HDGC) may be considered **medically necessary** for individuals meeting **any** of the following criteria (see Policy Guidelines section):
   A. A diagnosis of diffuse gastric cancer (DGC) before age 50 years
   B. A diagnosis of DGC at any age in individuals of Maori ethnicity, or with a personal or family history of cleft or lip palate
   C. A diagnosis of bilateral lobular breast cancer before age 70 years
   D. Personal or family history of both DGC and lobular breast cancer, one diagnosed before age 70 years
   E. Two 1st- or 2nd-degree relatives (see Policy Guidelines section) with a diagnosis of gastric cancer at any age, one DGC
   F. Two 1st- or 2nd-degree relatives (see Policy Guidelines section) with a diagnosis of lobular breast cancer before 50 years of age

II. Germline genetic testing for *CDH1* variants in individuals not meeting the above criteria is considered **investigational**.

III. Germline genetic testing for *CTNNA1* variants to identify individuals with or at risk for HDGC is considered **investigational** (see Policy Guidelines section).

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

1st-degree relatives are parents, siblings, and children.

2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.

Testing Strategy

- In individuals with a known familial *CDH1* variant, targeted testing for the specific variant is recommended.
- In individuals with unknown familial *CDH1* variant:
  - To identify clinically significant variants, National Comprehensive Cancer Network (NCCN) advises testing a close relative (see above) who has cancer related to hereditary diffuse gastric cancer syndrome, because that individual has the highest likelihood of obtaining a positive test result. Testing family members without a related cancer diagnosis could be considered if family members with a related cancer are unwilling or unavailable for testing.
- The International Gastric Linkage Consortium recommends germline genetic testing for *CTNNA1* variants to identify individuals with or at risk for HDGC who meet criteria for *CDH1* testing and have had *CDH1* testing with no *CDH1* variant identified. Consideration could be given to targeted testing at risk family members when a *CTNNA1* variant has been previously identified in a close family member. However, the evidence on follow-up of asymptomatic *CTNNA1* mutation carriers who had small diffuse gastric cancer foci found on prophylactic gastrectomy is based on very limited sample size and it is not known if those

findings would have led to invasive cancer (Benusiglio et al, 2019). Without additional study of long-term follow-up with endoscopic surveillance and large cohort studies there is risk of unneeded prophylactic gastrectomy.

Testing Unaffected Individuals

- In unaffected family members of potential *CDH1* variant families, most test results will be negative and uninformative. Therefore, it is strongly recommended that an *affected* family member be tested first whenever possible to adequately interpret the test. Should a *CDH1* variant be found in an affected family member(s), DNA from an *unaffected* family member can be tested specifically for the same variant of the affected family member without having to sequence the entire gene. Interpreting test results for an unaffected family member without knowing the genetic status of the family may be possible in the case of a positive result for an established disease-associated variant but leads to difficulties in interpreting negative test results (uninformative negative) or variants of uncertain significance because the possibility of a causative *CDH1* variant is not ruled out.

Testing Minors

- The use of genetic testing for *CDH1* variants for identifying hereditary diffuse gastric cancer syndrome has limited or no clinical utility in minors, because there is no change in management for minors as a result of knowledge of the presence or absence of a deleterious variant. In addition, there are potential harms related to stigmatization and discrimination. Exceptions to this might be based on family history and/or high risk ethnicity.

Description

Hereditary Diffuse Gastric Cancer (HDGC, sometimes called signet ring gastric cancer) is an autosomal dominant syndrome characterized by the development of diffuse gastric cancers. CDH1 is a tumor suppressing gene that encodes the cell-to-cell adhesion protein E-cadherin. Germline variants in the CDH1 gene have been associated with an increased risk of developing HDGC and lobular breast cancer. Testing for CTNNA1 variants has also been proposed for individuals with or at risk for HDGC. Knowledge of variant status in individuals at potentially increased risk may impact health care decisions to reduce risk.

Related Policies

- Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
- Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Germline genetic testing for CDH1 variants is available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale

Background

Hereditary Diffuse Gastric Cancer

Hereditary Diffuse Gastric Cancer (HDGC, sometimes called signet ring gastric cancer) is an autosomal dominant syndrome primarily characterized by an increased lifetime risk of diffuse gastric cancer (DGC). The condition is rare. In the general U.S. population, the lifetime risk of developing gastric cancer is 0.8%. Approximately 20% of all gastric cancers are DGCs, and 1% to 3% of these are due to HDGC (approximately 5 to 10 per 100,000 births). The incidence of HDGC is estimated at 5 to 10 per 100,000 births. The diffuse type of gastric cancer is difficult to diagnose on upper endoscopy and as a result, most cases of DGC are diagnosed at late stages. The average age at diagnosis is 37 years. The 5-year relative survival is 5.9% for gastric cancer that has metastasized, compared to 28% for localized gastric cancer.[1,]

CDH1

CDH1 is a tumor suppressing gene located on chromosome 16q22.1 that encodes the cell-to-cell adhesion protein E-cadherin. Germline variants in the *CDH1* gene have been associated with an increased risk of developing HDGC and lobular breast cancer.[2,3,] A diagnosis of HDGC can be confirmed by genetic testing, although 20% to 40% of families with suspected HDGC do not have a *CDH1* variant on genetic testing. Pathogenic *CDH1* variants have been described in Māori families in New Zealand, and individuals of Maori ethnicity have a higher prevalence of diffuse-type gastric cancer than non-Maori New Zealanders. Therefore, guidelines include Maori ethnicity as a risk factor for HDGC. Cleft lip/palate has been described in some HDGC families and is also included in *CDH1* genetic testing guidelines.

CTNNA1

CTNNA1, which encodes the protein Catenin Alpha-1, is a suspected tumor suppressor and susceptibility gene for HDGC.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities

[Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Genetic Testing for *CDH1* Variants in Individuals Without Suspected Hereditary Diffuse Gastric Cancer Who are at Risk for Hereditary Diffuse Gastric Cancer

Clinical Context and Test Purpose

The purpose of *CDH1* variant testing in individuals without suspected hereditary diffuse gastric cancer (HDGC) who are at risk for HDGC is to inform a decision about initiating surveillance and, if appropriate, treatment with prophylactic total gastrectomy (PTG; complete removal of the stomach) and/or prophylactic mastectomy.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals without cancer or without cancer that is related to HDGC, but who are at risk for HDGC. Criteria have been established to identify individuals at risk and include the following:[4,]

- Two gastric cancer cases in a family, one confirmed diffuse gastric cancer (DGC) regardless of age; or
- DGC diagnosed before age 50 years without a family history; or
- Personal or family history of DGC and lobular breast cancer, one diagnosed before age 70 years; or
- Two cases of lobular breast cancer in family members before 50 years of age; or
- DGC at any age in individuals of Māori ethnicity, or with a personal or family history of cleft lip/cleft palate; or
- Bilateral lobular breast cancer before age 70 years.

Interventions

The test being considered is genetic testing for *CDH1* variants.
Knowledge of variant status in individuals at potentially increased risk of a *CDH1* variant may impact healthcare decisions to reduce risk.

Comparators

The comparator of interest is risk assessment without genetic testing (e.g., based on family history alone).

Outcomes

The specific outcomes of interest are development of HDGC or lobular breast cancer, overall survival (OS), disease-specific survival, and harms of treatment including prophylactic gastrectomy and mastectomy.

Study Selection Criteria

Head-to-head studies comparing health outcomes with and without the test provide direct evidence. Randomized controlled trials (RCTs) are preferred but are unlikely to be conducted due to the rarity of the condition.

To establish a chain of evidence for clinical utility of a genetic test, evidence is needed to demonstrate:

1. An established association between the marker and future disorder AND
2. There is a pre-symptomatic phase for the disorder and interventions or surveillance are available AND

3. Interventions in the pre-symptomatic phase are likely to improve outcomes (i.e., prevent or delay onset of disease, or detect disease at an earlier stage during which treatment is more effective, or discontinuation of ineffective or unnecessary interventions).

Review of Evidence

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

There is no direct evidence of the clinical utility of *CDH1* genetic testing to improve the net health outcome.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Association between CDH1 Variants and Risk of Cancer

Penetrance estimates derived from studies of families with pathogenic *CDH1* variants are shown in Table 1. Estimates from families with *CDH1* variants selected based on strict clinical criteria have been higher than those derived from multigene panel testing in individuals not meeting these criteria. Hansford et al (2015) conducted a penetrance analysis on 75 families with identified CDH1 pathogenic variants (N=3858 relatives).[5,] In this cohort, the cumulative incidence of gastric cancer by age 80 years was 70% (95% confidence interval [CI], 59% to 80%) for male participants and 56% (95% CI, 44% to 69%) for female participants. The risk of breast cancer for female participants was 42% (95% CI, 23% to 68%) by age 80 years. As indicated by results of multigene panel testing, these penetrance estimates are likely overestimates for individuals who harbor a variant but do not have a family history.

Roberts et al (2019) conducted a retrospective cohort study of 75 families (N=1679 individuals, 238 with an identified *CDH1* pathogenic variant).[6,] This cohort was not exclusively ascertained based on strict HDGC genetic testing criteria. Penetrance estimates were calculated using data from 41 of the 75 families with complete pedigrees available (54.7%). The cumulative incidence was significantly elevated relative to Surveillance, Epidemiology, and End Results (SEER) program incidence for gastric cancer in men and women, and for breast cancer in women. The cumulative incidence was not significantly elevated for colorectal cancer for men or women. This study indicated that gastric cancer risk in individuals with *CDH1* pathogenic variants identified by multigene panel testing who do not meet established clinical testing criteria is significantly lower than *CDH1* pathogenic variant risk estimates generated by studies with more biased ascertainment strategies.

Table 1. Penetrance Estimates for *CDH1* Variants

Study, Year	Study Design	Penetrance Analysis Population, Ascertainment Criteria	Cumulative Incidence (95% CI)		
			Gastric Cancer	Breast Cancer	Other Secondary Cancers
Hansford et al (2015)[5,]	Retrospective cohort	75 families (N=3858 relatives) 17 families from 34/183 index cases meeting IGCLC 2010 clinical criteria for HDGC and with *CDH1* variants 58 additional families (some previously reported)	Men: 70% (59% to 80%) Women: 56% (44% to 69%)	42% (23% to 68%)	Not assessed
Roberts et al (2019)[6,]	Retrospective cohort	75 families (N=1679 relatives) Penetrance estimates are from 41 families with complete pedigree information *CDH1* variants identified through clinical ascertainment and multigene panel testing from August 2013 to June 2018	Men: 42% (30% to 56%) Women: 33% (21% to 43%)	55% (39% to 68%)	Colorectal: Men: 7% (0% to 17%) Women: 4% (0% to 11%)

CI: confidence interval; HDGC: hereditary diffuse gastric cancer; IGCLC: International Gastric Cancer Linkage Consortium.

Cancer Risk Reduction Strategies in Individuals with *CDH1* Variants

Prophylactic Total Gastrectomy

The effectiveness of PTG to reduce gastric cancer risk in asymptomatic individuals with *CDH1* variants has been described in case reports and case series, with occult cancer frequently observed on pathological examination.[7,8,9,]

Although it carries surgical risks and can impact quality of life, current guidelines recommend offering the procedure to *CDH1* variant carriers between ages 20 and 30 because it is the only method to eliminate the risk of gastric cancer in such individuals.[10,]

Endoscopic Surveillance

For individuals who decline or are unable to undergo PTG, endoscopic surveillance is an option but it is less effective than PTG. Benesch et al (2021) conducted a systematic review of endoscopic surveillance using 2 different strategies: the Cambridge Protocol, which employs a systematic examination of the stomach with 30 biopsies, and random biopsies.[11,] The reviewers identified 34 cases reports and case series, representing a total of 266 individuals. The test sensitivity and negative predictive value of random biopsies were 20.9% and 15.2%, respectively, and for the Cambridge Protocol, 27.1% and 22.1%, respectively. The authors concluded that the Cambridge Protocol has not been shown to improve test performance over random biopsies. Given the poor test performance of endoscopic surveillance, the authors recommended that individuals choosing surveillance over PTG should be fully informed of its poor performance.

Benesch et al (2021) also conducted a retrospective cohort study of 97 consecutive asymptomatic individuals in Newfoundland and Labrador with a *CDH1* variant.[11,] All had been identified using genetic testing criteria at the time of presentation from 2002 to 2017. From 2002 to 2020, 67 individuals had undergone PTG, and 17 of 53 females had undergone prophylactic mastectomy. The sensitivity of endoscopic biopsies was 28.0% with a negative predictive value of 18.2%.

Asif et al (2023) conducted a prospective cohort study as part of a natural history study of hereditary gastric cancers to evaluate the effectiveness of endoscopic surveillance for detection of gastric signet

ring cell carcinoma [12]. Patients age 2 years and older (N=270) who were asymptomatic carriers of pathogenic or likely pathogenic *CDH1* variants were enrolled. At data cutoff, a total of 467 endoscopies had been performed, with a median of 1 procedure (interquartile range [IQR], 1 to 3) per patient. A total of 38,803 total gastric biopsy samples were collected, of which 1163 (3%) were positive for signet ring cell carcinoma. Overall, 101 of 270 (37%) patients had signet ring cell carcinoma cancer foci detected during the initial screening endoscopy; positive cancer foci were detected in 382 anatomic regions in all 270 patients. For patients with 2 or more surveillance endoscopies, signet ring cell carcinoma was detected in 76 of 120 patients (63%). There were 98 of 270 patients (36%) that went on to have PTG. Only two (less than 1%) of the 467 endoscopies had non-targeted biopsy samples that were negative for signet ring cell carcinoma while having a positive targeted biopsy. Authors concluded that repeated endoscopic surveillance is a plausible alternative to PTG when used with thorough clinical and pathological gastric assessment.

Breast Surveillance and Risk-Reducing Mastectomy

Estimates of the risk of breast cancer in individuals with a *CDH1* variant range from 42% to 55% (Table 1), and case series have reported lobular carcinoma *in situ* in individuals from families with *CDH1* variants who have undergone prophylactic bilateral mastectomy.[13] There is a lack of prospective data on imaging for lobular breast cancer, and surveillance guidelines rely heavily on the evidence base from individuals with germline *BRCA1/2* pathogenic variants. For individuals at risk for HDGC, guidelines recommend annual breast surveillance starting at age 30 years and consideration of bilateral risk-reducing mastectomy.[14]

Section Summary: Genetic Testing for *CDH1* Variants in Individuals Without Suspected Hereditary Diffuse Gastric Cancer Who are at Risk for Hereditary Diffuse Gastric Cancer

There is no direct evidence of the clinical utility of *CDH1* testing in asymptomatic individuals. Penetrance estimates for gastric cancer range from 42% to 70% in men and 33% to 56% in women. Penetrance is higher in individuals from families with more gastric cancer cases and is lower in individuals identified by methods such as multigene panel testing. A chain of evidence can be established from studies demonstrating an association between *CDH1* variant status and increased risk of developing HDGC or lobular breast cancer, and the availability of PTG to reduce risk of gastric cancer.

Genetic Testing for *CDH1* Variants in Individuals With Suspected Hereditary Diffuse Gastric Cancer

Clinical Context and Test Purpose

The purposes of germline genetic testing for *CDH1* variants in individuals with suspected HDGC are:
1) to confirm a diagnosis of HDGC
2) to inform decisions about initiating surveillance and, if appropriate, treatment with prophylactic gastrectomy or mastectomy
3) to guide decisions about genetic testing for at-risk family members

Populations

The relevant population of interest is individuals with diffuse gastric or lobular breast cancer who are suspected of having HDGC. In individuals with such cancer, criteria have been established to identify individuals at risk and include the following:

- DGC diagnosed before age 50 years without a family history; or
- Personal or family history of DGC and lobular breast cancer, 1 diagnosed before age 70 years; or
- DGC at any age in individuals of Maori ethnicity, or with a personal or family history of cleft lip/cleft palate; or
- Bilateral lobular breast cancer before age 70 years.

Interventions

The test being considered is germline genetic testing for *CDH1* variants.

Comparators
The comparator of interest is standard care without genetic testing for *CDH1* variants.

Outcomes
The specific outcomes of interest are development of HDGC or lobular breast cancer, OS, disease-specific survival, and harms of treatment including prophylactic gastrectomy and mastectomy.

Study Selection Criteria
Head-to-head studies comparing health outcomes with and without the test provide direct evidence of clinical utility. Randomized controlled trials are preferred but are unlikely to be conducted due to the rarity of the condition.

In the absence of direct evidence, a chain of evidence is needed.
To establish a chain of evidence of the clinical utility of a genetic test to benefit an individual with a condition, evidence is needed from studies demonstrating:

- The clinical validity of testing AND
- A definitive diagnosis cannot be made based on history, physical examination, pedigree analysis, and standard diagnostic studies/tests alone; AND

A definitive diagnosis:

- Leads to changes in clinical management of the condition that improve outcomes; or
- Eliminates the need for further clinical workup or invasive testing; or
- Leads to discontinuation of interventions that are unnecessary and/or ineffective.

To establish a chain of evidence of the clinical utility of an affected individual's germline to benefit family members, evidence is needed from studies demonstrating:

- An association between the genetic variant and clinical disease has been established; and
- Family members are available who may be at risk for the disorder; and
- The individual tested has a clinical diagnosis of the condition (or represents the family member who is most likely to harbor the pathogenic variant), but genetic testing has not been performed; and
- There is a pre-symptomatic phase for the disorder in which interventions are available; and
- Interventions in the pre-symptomatic phase are likely to improve outcomes.

Review of Evidence
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

There are no targeted treatments for HDGC based on *CDH1* variant status. The benefit of genetic testing to affected individuals would be to inform healthcare decisions to reduce risk of other cancers. That is, in individuals diagnosed with lobular breast cancer, a confirmed diagnosis of HDGC could inform decisions about undergoing total gastrectomy to prevent gastric cancer. In individuals diagnosed with DGC, a confirmed diagnosis of HDGC could inform decisions about increased surveillance or prophylactic mastectomy to prevent breast cancer. Additionally, testing would inform decisions about genetic testing for at-risk family members.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

There is no direct evidence of the clinical utility of germline genetic testing for *CDH1* variants in individuals with suspected HDGC.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A chain of evidence can be established from studies demonstrating an association between *CDH1* variant status and increased risk of developing HDGC or lobular breast cancer, and the availability of prophylactic total gastrectomy to reduce risk of gastric cancer.

Section Summary: Genetic Testing for *CDH1* Variants in Individuals With Suspected Hereditary Diffuse Gastric Cancer

There are no targeted treatments for HDGC based on *CDH1* variant status. The benefit of genetic testing to affected individuals would be to inform healthcare decisions to reduce risk of other cancers, and to inform decisions about genetic testing for at-risk family members. A chain of evidence can be established from studies demonstrating an association between *CDH1* variant status and increased risk of developing HDGC or lobular breast cancer, and the availability of PTG to reduce risk of gastric cancer.

Genetic Testing for *CTNNA1* Variants to Identify Individuals With or at Risk for Hereditary Diffuse Gastric Cancer

Clinical Context and Test Purpose

The purposes of *CTNNA1* variant testing to identify individuals with or at risk for HDGC are:
1) to inform decisions about initiating surveillance and, if appropriate, treatment with PTG and/or prophylactic mastectomy, and
2) to inform decisions about testing family members.

The following PICO was used to select literature to inform this review.

Populations

The relevant populations of interest are individuals with suspected HDGC, or who are at risk for HDGC based on family history or clinical factors.

Interventions

The test being considered is genetic testing for *CTNNA1* variants.
Knowledge of variant status in individuals at potentially increased risk of a *CTNNA1* variant may impact healthcare decisions to reduce risk.

Comparators

The comparators of interest are risk assessment without *CTNNA1* genetic testing (e.g., based on family history or *CDH1* testing alone).

Outcomes

The specific outcomes of interest are development of HDGC or lobular breast cancer, OS, disease-specific survival, and harms of treatment including prophylactic gastrectomy and mastectomy.

Study Selection Criteria

Head-to-head studies comparing health outcomes with and without the test provide direct evidence of clinical utility. Randomized controlled trials are preferred but are unlikely to be conducted due to the rarity of the condition.

In the absence of direct evidence, a chain of evidence is needed. To establish a chain of evidence of the clinical utility of a genetic test to benefit an individual with a condition, evidence is needed from studies demonstrating

- The clinical validity of testing AND
- A definitive diagnosis cannot be made based on history, physical examination, pedigree analysis, and standard diagnostic studies/tests alone; AND

A definitive diagnosis:

- Leads to changes in clinical management of the condition that improve outcomes; or
- Eliminates the need for further clinical workup or invasive testing; or
- Leads to discontinuation of interventions that are unnecessary and/or ineffective.

To establish a chain of evidence of the clinical utility of an affected individual's germline to benefit family members, evidence is needed from studies demonstrating:

- An association between the genetic variant and clinical disease has been established; and
- Family members are available who may be at risk for the disorder; and
- The individual tested has a clinical diagnosis of the condition (or represents the family member who is most likely to harbor the pathogenic variant), but genetic testing has not been performed; and
- There is a pre-symptomatic phase for the disorder in which interventions are available; and
- Interventions in the pre-symptomatic phase are likely to improve outcomes.

Review of Evidence

Clinical Validity

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Information on penetrance of *CTNNA1* variants is limited to case reports.[15,] For example, Benusiglio et al (2019) identified 1 family with a CTNN1 variant and diffuse gastric cancer foci in resected tissue from a patient undergoing prophylactic gastrectomy.[16,] Hansford et al (2019) identified *CTNNA1* variants in 2 HDGC families that were *CDH1* negative.[5,]

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

There is no direct evidence of the clinical utility of testing for *CTNNA1* variants in individuals with suspected or at risk for HDGC. The evidence is insufficient to demonstrate clinical validity and therefore a chain of evidence cannot be established.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Genetic Testing for *CTNNA1* Variants to Identify Individuals With or at Risk for Hereditary Diffuse Gastric Cancer

There is no direct evidence of the clinical utility of testing for *CTNNA1* variants to identify individuals with or at risk for HDGC. Evidence of clinical validity is limited to a small number of case reports and is insufficient to establish clinical validity. Therefore, a chain of evidence for clinical utility cannot be constructed.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

International Gastric Cancer Linkage Consortium

In 2020, the International Gastric Cancer Linkage Consortium (IGCLC) updated their guidelines on hereditary diffuse gastric cancer (HDGC), including genetic testing criteria.[14,] The guideline authors noted that, because of the relatively low incidence of HDGC, randomized controlled trial data are lacking and the recommendations relied on consensus expert opinion, expert evidence, and observational studies. Therefore, the evidence level for their recommendations was categorized as "low" to "moderate" according to GRADE definitions (i.e., further research is likely to very likely to have an important impact on confidence in the estimate of the effect addressed by the recommendation). The Guidelines recommended the following criteria for genetic testing:

Family Criteria (family members must be first or second degree blood relatives of each other)

- Two or more cases of gastric cancer in family regardless of age, with at least one diffuse gastric cancer (DGC); or
- One or more case of DGC at any age and 1 or more case of lobular breast cancer before age 70 years in different family members; or
- Two or more cases of lobular breast cancer in family members before age 50 years.

Individual Criteria

- DGC before age 50 years; or
- DGC at any age in individuals of Maori ethnicity; or
- DGC at any age in individuals with a personal or family history (1st degree) of cleft lip/cleft palate; or
- History of DGC and lobular breast cancer, both diagnosed before age 70 years; or
- Bilateral lobular breast cancer, diagnosed before age 70 years; or
- Gastric *in situ* signet ring cells and/or pagetoid spread of signet ring cells in individuals before age 50 years.

The guidelines also note:

Histologically-confirmed intestinal-type gastric and non-lobular breast cancer cases should not be used to fulfil testing criteria as these are not part of HDGC.

Individuals who fulfill criteria for HDGC genetic testing should first have *CDH1* analyzed and, if no variant identified, be considered for *CTNNA1* analysis.

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) Guidelines on Gastric Cancer (v. 1.2023) include the following recommendations:[4,]
Genetic testing for *CDH1* mutations should be considered when any of the following criteria are met:

- Two gastric cancer cases in a family, 1 confirmed DGC regardless of age; or
- DGC diagnosed before age 50 years without a family history; or
- Personal or family history of DGC and lobular breast cancer, one diagnosed before age 70 years; or
- Two cases of lobular breast cancer in family members before 50 years of age; or
- DGC at any age in individuals of Māori ethnicity, or with a personal or family history of cleft lip/cleft palate; or
- Bilateral lobular breast cancer before age 70 years.

Prophylactic total gastrectomy is recommended between ages 18 and 40 for individuals with a *CDH1* variant. Prophylactic gastrectomy prior to 18 years of age is not recommended, but may be considered for certain patients, especially those with family members diagnosed with gastric cancer before 25 years of age.

CDH1 variant carriers who elect not to undergo prophylactic gastrectomy should be offered screening every 6 to 12 months by upper endoscopy with multiple random biopsies.

Individuals with *CDH1* variants should be followed using high-risk guidelines as outlined in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.
For those patients without a strong family history of DGC, genetics counseling with multidisciplinary review is indicated.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

An unpublished trial that might influence this review is listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03030404	Hereditary Gastric Cancer Syndromes: An Integrated Genomic and Clinicopathologic Study of the Predisposition to Gastric Cancer	1150	Dec 2026

NCT: national clinical trial.

References

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Family history, if applicable, particularly related to cancer
  - Reason for test
  - Pertinent past procedural and surgical history
  - Pertinent past and present diagnostic testing and results
  - Treatment plan (i.e., surgical intervention) if applicable
- Consultation and medical clearance report(s), when applicable
- Pertinent Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
- Pertinent Laboratory results

- Other pertinent multidisciplinary notes/reports: (i.e., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management), when applicable

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81406	Molecular Pathology Procedure Level 7
	81432	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
	81435	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
	81479	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
11/01/2022	New policy.
10/01/2023	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to

treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Germline Genetic Testing for Hereditary Diffuse Gastric Cancer (CDH1, CTNNA1) 2.04.154 **Policy Statement:** I. Germline genetic testing for *CDH1* variants to identify individuals with or at risk for hereditary diffuse gastric cancer (HDGC) may be considered **medically necessary** for individuals meeting **any** of the following criteria (see Policy Guidelines section): A. A diagnosis of diffuse gastric cancer (DGC) before age 50 years B. A diagnosis of DGC at any age in individuals of Maori ethnicity, or with a personal or family history of cleft or lip palate C. A diagnosis of bilateral lobular breast cancer before age 70 years D. Personal or family history of both DGC and lobular breast cancer, one diagnosed before age 70 years E. Two 1st- or 2nd-degree relatives (see Policy Guidelines section) with a diagnosis of gastric cancer at any age, one DGC F. Two 1st- or 2nd-degree relatives (see Policy Guidelines section) with a diagnosis of lobular breast cancer before 50 years of age II. Germline genetic testing for *CDH1* variants in individuals not meeting the above criteria is considered **investigational**. III. Germline genetic testing for *CTNNA1* variants to identify individuals with or at risk for HDGC is considered **investigational** (see Policy Guidelines section).	**Germline Genetic Testing for Hereditary Diffuse Gastric Cancer (CDH1, CTNNA1) 2.04.154** **Policy Statement:** I. Germline genetic testing for *CDH1* variants to identify individuals with or at risk for hereditary diffuse gastric cancer (HDGC) may be considered **medically necessary** for individuals meeting **any** of the following criteria (see Policy Guidelines section): A. A diagnosis of diffuse gastric cancer (DGC) before age 50 years B. A diagnosis of DGC at any age in individuals of Maori ethnicity, or with a personal or family history of cleft or lip palate C. A diagnosis of bilateral lobular breast cancer before age 70 years D. Personal or family history of both DGC and lobular breast cancer, one diagnosed before age 70 years E. Two 1st- or 2nd-degree relatives (see Policy Guidelines section) with a diagnosis of gastric cancer at any age, one DGC F. Two 1st- or 2nd-degree relatives (see Policy Guidelines section) with a diagnosis of lobular breast cancer before 50 years of age II. Germline genetic testing for *CDH1* variants in individuals not meeting the above criteria is considered **investigational**. III. Germline genetic testing for *CTNNA1* variants to identify individuals with or at risk for HDGC is considered **investigational** (see Policy Guidelines section).