BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.154 Germline Genetic Testing for Hereditary Diffuse Gastric Cancer (CDH1, CTNNA1)

Annual Effective Policy Date: April 1, 2024

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Related Policies:

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

Germline Genetic Testing for Hereditary Diffuse Gastric Cancer (CDH1, CTNNA1)

Description

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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.

OBJECTIVE

The objective of this evidence review is to evaluate the clinical validity and clinical utility of germline genetic testing of individuals with or at high-risk of HDGC and to determine if its use improves the net health outcome.

POLICY STATEMENT

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 the following criteria (see Policy Guidelines):

- A diagnosis of diffuse gastric cancer (DGC) before age 50 years; OR
- A diagnosis of DGC at any age in individuals of Maori ethnicity, or with a personal or family history of cleft/lip palate; OR
- A diagnosis of bilateral lobular breast cancer before age 70 years; OR
- Personal or family history of both DGC and lobular breast cancer, one diagnosed before age 70 years; OR
- Two 1st- or 2nd-degree relatives (see Policy Guidelines) with a diagnosis of gastric cancer at any age, one DGC; OR
- Two 1st- or 2nd-degree relatives (see Policy Guidelines) with a diagnosis of lobular breast cancer before 50 years of age.

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

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

POLICY GUIDELINES

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing. The National Comprehensive Cancer Network (NCCN) guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v3.2023 recommend testing for high-penetrant breast cancer susceptibility genes including *CDH1* for individuals diagnosed at any age with lobular breast cancer with personal or family history of diffuse gastric cancer and state, "See NCCN Guidelines for Gastric Cancer". Thus, these two NCCN guidelines' criteria conflict as to the age of lobular breast cancer. Plans with legislative mandated coverage of biomarkers might need to use the broader criteria for coverage determination.

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, NCCN advises testing a close relative (see above) who has cancer related to hereditary diffuse gastric cancer (HDGC) 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.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology- "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"- to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG-AMP: American College of Medical Genetics and Genomics and the Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Some Plans may have contract or benefit exclusions for genetic testing, or have state mandates for biomarker testing coverage.

FDA 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

Summary of Evidence

For individuals without suspected hereditary diffuse gastric cancer (HDGC) who are at risk for HDGC who receive germline genetic testing for cadherin 1 **(***CDH1)* variants, the evidence includes retrospective observational studies. Relevant outcomes are overall survival (OS), disease-specific survival, test validity, morbid events, functional outcomes, health status measures, quality of life, treatment-related mortality, and treatment-related morbidity. 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 prophylactic total gastrectomy (PTG) to reduce risk of gastric cancer. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with suspected HDGC who receive germline genetic testing for *CDH1* variants, the evidence includes retrospective observational studies. Relevant outcomes are OS, disease-specific survival, test validity, morbid events, functional outcomes, health status measures, quality of life, treatment-related mortality, and treatment-related morbidity. 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. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with suspected HDGC, or without suspected HDGC who are at risk for HDGC who receive germline genetic testing for catenin alpha 1 (*CTNNA1)* variants, the evidence includes a small number of case reports of *CTNNA1* variants identified in individuals from families with HDGC. Relevant outcomes are OS, disease-specific survival, test validity, morbid events, functional outcomes, health status measures, quality of life, treatment-related mortality, and treatment-related morbidity. There is no direct evidence of the clinical utility of testing for *CTNNA1* variants in individuals with suspected HDGC or at risk for HDGC. The evidence is insufficient to demonstrate clinical validity and therefore a chain of evidence cannot be established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

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.

REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Stomach Cancer. https://seer.cancer.gov/statfacts/html/stomach.html. Accessed June 22, 2023.
2. Lee K, Krempely K, Roberts ME, et al. Specifications of the ACMG/AMP variant curation guidelines for the analysis of germline CDH1 sequence variants. Hum Mutat. Nov 2018; 39(11): 1553-1568. PMID 30311375
3. Guilford P, Hopkins J, Harraway J, et al. E-cadherin germline mutations in familial gastric cancer. Nature. Mar 26 1998; 392(6674): 402-5. PMID 9537325
4. National Comprehensive Cancer Network. Gastric Cancer. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed June 23, 2023.
5. Hansford S, Kaurah P, Li-Chang H, et al. Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. JAMA Oncol. Apr 2015; 1(1): 23-32. PMID 26182300
6. Roberts ME, Ranola JMO, Marshall ML, et al. Comparison of CDH1 Penetrance Estimates in Clinically Ascertained Families vs Families Ascertained for Multiple Gastric Cancers. JAMA Oncol. Sep 01 2019; 5(9): 1325-1331. PMID 31246251
7. DiBrito SR, Blair AB, Prasath V, et al. Total Gastrectomy for CDH-1 Mutation Carriers: An Institutional Experience. J Surg Res. Mar 2020; 247: 438-444. PMID 31685251
8. Ithurralde-Argerich J, Rosner L, Rizzolo M, et al. Laparoscopic Prophylactic Total Gastrectomy for Hereditary Diffuse Gastric Cancer in CDH1 Mutation Carriers. J Laparoendosc Adv Surg Tech A. Jul 2021; 31(7): 729-737. PMID 34097461
9. Mastoraki A, Danias N, Arkadopoulos N, et al. Prophylactic total gastrectomy for hereditary diffuse gastric cancer. Review of the literature. Surg Oncol. Dec 2011; 20(4): e223-6. PMID 21872467

10. van der Post RS, Vogelaar IP, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. J Med Genet. Jun 2015; 52(6): 361-74. PMID 25979631
11. Benesch MGK, Bursey SR, O'Connell AC, et al. CDH1 Gene Mutation Hereditary Diffuse Gastric Cancer Outcomes: Analysis of a Large Cohort, Systematic Review of Endoscopic Surveillance, and Secondary Cancer Risk Postulation. Cancers (Basel). May 26 2021; 13(11). PMID 34073553
12. Asif B, Sarvestani AL, Gamble LA, et al. Cancer surveillance as an alternative to prophylactic total gastrectomy in hereditary diffuse gastric cancer: a prospective cohort study. Lancet Oncol. Apr 2023; 24(4): 383-391. PMID 36990610
13. Kluijt I, Siemerink EJ, Ausems MG, et al. CDH1-related hereditary diffuse gastric cancer syndrome: clinical variations and implications for counseling. Int J Cancer. Jul 15 2012; 131(2): 367-76. PMID 22020549
14. Blair VR, McLeod M, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical practice guidelines. Lancet Oncol. Aug 2020; 21(8): e386-e397. PMID 32758476
15. Lobo S, Benusiglio PR, Coulet F, et al. Cancer predisposition and germline CTNNA1 variants. Eur J Med Genet. Oct 2021; 64(10): 104316. PMID 34425242
16. Benusiglio PR, Colas C, Guillerm E, et al. Clinical implications of CTNNA1 germline mutations in asymptomatic carriers. Gastric Cancer. Jul 2019; 22(4): 899-903. PMID 30515673

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2022	New policy - Add to Genetics section	Policy created with literature review through July 11, 2022. Germline genetic testing for CDH1 variants to identify individuals with or at risk for hereditary diffuse gastric cancer (HDGC) may be considered medically necessary with criteria. Germline genetic testing for CTNNA1 variants to identify individuals with or at risk for HDGC is considered investigational.
December 2023	New policy	Policy updated with literature review through June 23, 2023; references added. Policy statements unchanged. FEP 2024 Benefit update. FEP new policy