MEDICAL POLICY

POLICY TITLE	**GERMLINE GENETIC TESTING FOR HEREDITARY DIFFUSE GASTRIC CANCER (CDH1, CTNNA1)**
POLICY NUMBER	**MP 2.384**

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☒ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**2/1/2024**

I. POLICY

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:

- 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 first- or second-degree relatives with a diagnosis of gastric cancer at any age, one DGC; OR
- Two first- or second-degree relatives 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**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure for these indications.

Germline genetic testing for *CTNNA1* variants to identify individuals with or at risk for HDGC is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure for these indications.

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The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat, and manage patients with cancer. The National Cancer Institute's PDQ (Physician Data Query) is NCI's comprehensive source of cancer information, which includes evidence-based summaries on topics that cover adult and pediatric cancer treatment. These guidelines evolve continuously as new treatments and diagnostics emerge, and may be used by Capital Blue Cross when determining medical necessity according to this policy.

II. 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.

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.

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.

Genetic Counseling

Genetic counseling is primarily aimed at patients 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.

III. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO:

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies .

IV. BACKGROUND

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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.

V. RATIONALE

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Summary of Evidence

For individuals without suspected HDGC who are at risk for HDGC who receive germline genetic testing for 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 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.

VI. DEFINITIONS

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N/A

VII. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VIII. DISCLAIMER

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Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

IX. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement. The codes need to be in numerical order.

Covered when medically necessary:

Procedure Codes							
81406	81432	81435	81479				

ICD-10-CM Diagnosis Code	Description
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.029	Malignant neoplasm of nipple and areola, unspecified male breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.129	Malignant neoplasm of central portion of unspecified male breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast

C50.222	Malignant neoplasm of upper-inner quadrant of left male breast
C50.229	Malignant neoplasm of upper-inner quadrant of unspecified male breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast
C50.322	Malignant neoplasm of lower-inner quadrant of left male breast
C50.329	Malignant neoplasm of lower-inner quadrant of unspecified male breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast
C50.422	Malignant neoplasm of upper-outer quadrant of left male breast
C50.429	Malignant neoplasm of upper-outer quadrant of unspecified male breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.529	Malignant neoplasm of lower-outer quadrant of unspecified male breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.629	Malignant neoplasm of axillary tail of unspecified male breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.829	Malignant neoplasm of overlapping sites of unspecified male breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C50.929	Malignant neoplasm of unspecified site of unspecified male breast
D05.00	Lobular carcinoma in situ of unspecified breast
D05.01	Lobular carcinoma in situ of right breast
D05.02	Lobular carcinoma in situ of left breast
Z15.01	Genetic susceptibility to malignant neoplasm of breast
Z15.09	Genetic susceptibility to other malignant neoplasm

Z80.0	Family history of malignant neoplasm of digestive organs
Z85.00	Personal history of malignant neoplasm of unspecified digestive organ
Z85.01	Personal history of malignant neoplasm of esophagus
Z85.020	Personal history of malignant carcinoid tumor of stomach
Z85.028	Personal history of other malignant neoplasm of stomach
Z85.030	Personal history of malignant carcinoid tumor of large intestine
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.040	Personal history of malignant carcinoid tumor of rectum
Z85.040	Personal history of malignant carcinoid tumor of rectum
Z85.048	Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus
Z85.05	Personal history of malignant neoplasm of liver
Z85.060	Personal history of malignant carcinoid tumor of small intestine
Z85.068	Personal history of other malignant neoplasm of small intestine
Z85.07	Personal history of malignant neoplasm of pancreas
Z85.09	Personal history of malignant neoplasm of other digestive organs
Z86.000	Personal history of in-situ neoplasm of breast
Z87.730	Personal history of (corrected) cleft lip and palate

X. REFERENCES

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XI. POLICY HISTORY

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MP 2.384	9/26/2022 New policy.

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