

# CDH1 gene

## Associated Syndrome Name: Hereditary diffuse gastric cancer (HDGC) syndrome

### CDH1 Summary Cancer Risk Table

CANCER	GENETIC CANCER RISK
Breast	High Risk
Gastric	High Risk

### CDH1 gene Overview

Hereditary diffuse gastric cancer (HDGC) syndrome <sup>1, 2, 3, 4, 5, 6, 7</sup>

- Individuals with mutations in *CDH1* have hereditary diffuse gastric cancer syndrome (HDGC).
- Patients with HDGC have a high risk for the diffuse form of gastric cancer, which is less common than intestinal type gastric cancer. Diffuse gastric cancer is more difficult to detect with endoscopic screening because it typically forms without a distinct mass. The majority of gastric cancers in individuals with HDGC are diagnosed under age 40, with some diagnoses occurring in the mid-teens.
- Nearly all individuals with mutations in *CDH1* have small superficial lesions in their stomach called intramucosal signet-ring cell carcinoma (SRCC), typically stage 1. The likelihood of these lesions progressing to advanced stage (stage 2 or higher) diffuse gastric cancer is uncertain. Risks for gastric cancer in the published literature may include individuals with early stage SRCC and advanced stage diffuse gastric cancer.
- Women with HDGC have a risk for lobular breast cancer that is significantly increased over the 12.5% lifetime breast cancer risk for women in the general population of the United States. The risk for male breast cancer is not thought to be increased.
- There have been reports of an increased risk for colorectal cancer in patients with HDGC, but recent studies have not shown an increased risk. Currently, most experts in HDGC do not provide any recommendations for medical management of colorectal cancer risk.
- Individuals with mutations in *CDH1* should have the opportunity to engage in shared-decision making regarding the option of risk-reducing gastrectomy versus endoscopic surveillance, taking into account the pros and cons of surveillance versus gastrectomy, patient preference, and family history.
- Guidelines for the medical management of patients with HDGC have been developed by the International Gastric Cancer Linkage Consortium (IGCLC) and the National Comprehensive Cancer Network (NCCN). These are summarized below. These groups differ in the details of their recommendations, including whether gastrectomy or screening is the best choice for some patients. Due to the complexity of this condition, it is recommended that patients with *CDH1* mutations be managed by a multidisciplinary team with expertise in medical genetics, gastric surgery, gastroenterology, pathology and nutrition.

### CDH1 gene Cancer Risk Table

CANCER TYPE	AGE RANGE	CANCER RISK	RISK FOR GENERAL POPULATION
Gastric (male)	To age 80 <sup>2, 7, 8</sup>	Any stage: 19%-70% Advanced stage: 10% or higher	0.6%
Gastric (female)	To age 80 <sup>2, 7, 8</sup>	Any stage: 13%-56% Advanced stage: 7% or higher	0.6%
Female Breast	To age 50 <sup>2, 7, 8</sup>	11%	2.1%
	To age 80 <sup>2, 7, 8</sup>	37%-42%	10.8%

### CDH1 Cancer Risk Management Table

The overview of medical management options provided is a summary of professional society guidelines. The most recent version of each guideline should be consulted for more detailed and up-to-date information before developing a treatment plan for a particular patient.

This overview is provided for informational purposes only and does not constitute a recommendation. While the medical society guidelines summarized herein provide important and useful information, medical management decisions for any particular patient should be made in consultation between that patient and his or her healthcare provider and may differ from society guidelines based on

a complete understanding of the patient's personal medical history, surgeries and other treatments.

CANCER TYPE	PROCEDURE	AGE TO BEGIN	FREQUENCY (UNLESS OTHERWISE INDICATED BY FINDINGS)
Gastric	Gastrectomy, after baseline endoscopy <sup>1,4</sup>	Individualized. May be considered for those with stage 1b or higher, symptoms, and/or high risk endoscopic findings.	NA
	Surveillance with endoscopies including targeted and random biopsies is recommended for patients delaying or declining gastrectomy, and may be appropriate for those with no family history of diffuse gastric cancer <sup>1,4</sup>	Individualized. May be considered for those who decline or postpone gastrectomy.	Every 6 to 12 months
	Treat <i>Helicobacter pylori</i> infection if present <sup>1</sup>	Individualized	NA
Female Breast	Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider. Periodic, consistent breast self-examination (BSE) may facilitate breast awareness. <sup>1,5</sup>	18 years	NA
	Clinical encounter, including clinical breast exam, ongoing risk assessment and risk-reduction counseling <sup>1,5</sup>	25 years, or 5 to 10 years younger than the earliest age of breast cancer diagnosis in the family	Every 6 to 12 months
	Mammogram <sup>1,5</sup>	30 to 40 years, or 5 to 10 years younger than the youngest diagnosis in the family, whichever comes first	Annually
	Consider breast MRI with and without contrast <sup>1,5</sup>	30 years, or 5 to 10 years younger than the youngest diagnosis in the family, whichever comes first	Annually
	Consider risk-reducing mastectomy. <sup>1,5</sup>	Between 30 and 60 years	NA

## Information for Family Members

The following information for Family Members will appear as part of the MMT for a patient found to have a mutation in the CDH1 gene.

This patient's relatives are at risk for carrying the same mutation(s) and associated cancer risks as this patient. Cancer risks for females and males who have this/these mutation(s) are provided below.

Family members should talk to a healthcare provider about genetic testing. Close relatives such as parents, children, brothers and sisters have the highest chance of having the same mutation(s) as this patient. Other more distant relatives such as cousins, aunts, uncles, and grandparents also have a chance of carrying the same mutation(s). Testing of at-risk relatives can identify those family members with the same mutation(s) who may benefit from surveillance and early intervention.

There is an increased risk for children who inherit a *CDH1* mutation to be born with blepharocheilodontic syndrome or isolated cleft lip/palate. This risk may be higher in families in which clefts have occurred previously.<sup>3,9,10</sup>

Parents who are concerned about the possibility of passing on a *CDH1* mutation to a future child may want to discuss options for prenatal testing and assisted reproduction techniques, such as pre-implantation genetic diagnosis (PGD).<sup>1</sup>

## References

1. Blair VR, et al. Hereditary diffuse gastric cancer: updated clinical practice guidelines. *Lancet Oncol.* 2020 21:e386-e397. PMID: 32758476.
2. Hansford S, et al. Hereditary Diffuse Gastric Cancer Syndrome: *CDH1* Mutations and Beyond. *JAMA Oncol.* 2015 1:23-32. PMID: 26182300.
3. Kluij I, et al. Dutch Working Group on Hereditary Gastric Cancer. *CDH1*-related hereditary diffuse gastric cancer syndrome: clinical variations and implications for counseling. *Int J Cancer.* 2012 131:367-76. PMID: 22020549.

4. Gupta S, et al. NCCN Clinical Practice Guidelines in Oncology® Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. V 4.2024. Apr 2. Available at <https://www.nccn.org>.
5. Daly M et al. NCCN Clinical Practice Guidelines in Oncology®: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate. V 3.2025. Mar 6. Available at <https://www.nccn.org>.
6. Barbosa-Matos R, et al. Diffuse Gastric and Lobular Breast Cancer Syndrome. 2024 Oct 10. In: Adam MP, et al., editors. GeneReviews® [Internet]. PMID 20301318.
7. Ryan CE, et al. Germline *CDH1* Variants and Lifetime Cancer Risk. JAMA. 2024 Sep 3;332(9):722-729. PMID: 38873722.
8. SEER\*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute. [Cited 2025 Apr 1]. Available from <https://seer.cancer.gov/explorer/>.
9. Figueiredo J, et al. Clinical spectrum and pleiotropic nature of *CDH1* germline mutations. J Med Genet. 2019 56:199-208. PMID: 30661051.
10. Obermair F, et al. Cleft lip/palate and hereditary diffuse gastric cancer: report of a family harboring a *CDH1* c.687+1G>A germline mutation and review of the literature. Fam Cancer. 2019 18:253-260. PMID: 30306390.

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