Hereditary Diffuse Gastric Cancer (HDGC) is caused by pathogenic (harmful) variants in the CDH1 gene, and are linked to an increased risk for a specific type of stomach cancer called diffuse gastric cancer (also called signet ring cell carcinoma or linitis plastica), as well as lobular breast cancer. There is also some research that suggests that some families with HDGC may also have an increased risk for colon cancer.

CDH1 gene variants are inherited in an autosomal dominant pattern, meaning that children of someone who carries a pathogenic variant each have a 50% risk to inherit the variant and associated cancer risks. Notably, women and men both have the CDH1 gene and have the same chances to inherit and pass down variants in these genes. Therefore, both sides of the family are important when assessing inherited risk. However, the associated cancers and lifetime risks are different between men and women.

Cancer type	Risk in the general population	Risk in CDH1 pathogenic variant carriers
Gastric (stomach)	0.8%	67% (men) 83% (women)
Female breast	12%	60%
Colon	5.5%	undetermined

Genetic testing for CDH1

Genetic testing for pathogenic variants in CDH1 are currently available, but there are a few different ways to approach testing:

- *Single site analysis*: Testing specific to a known pathogenic variant in the family
- Full gene sequencing and rearrangement analysis: Comprehensive testing to search for all currently detectable pathogenic variants in the gene
- Gene panels: Newer, more broadly based gene tests that would include not only the CDH1 gene, but other genes known or suspected to be associated with increased cancer risks

Who should be offered testing for CDH1?

Other than someone's personal history of cancer, another piece of information that we can use to help determine if someone is at a higher risk to have a pathogenic variant in the CDH1 gene is you family history. The National Comprehensive Cancer Network (NCCN) is a group of medical professionals that regularly meet to look over any updates in research studies and determine recommendations for who should be considered at a higher risk for

one of these gene variants, and thus should be offered genetic testing.

Some of the things in the family history (make sure to include yourself in your family history if you have been diagnosed with cancer) that may put someone at a higher risk for a CDH1 pathogenic variant are:

- A family history of two people on the same side of the family diagnosed with gastric cancer, with one person being diagnosed before age 50
- A family history of three people on the same side of the family with diffuse gastric cancer at any age
- A family history of someone diagnosed with diffuse gastric cancer before the age of 40
- A family history of diffuse gastric cancer and lobular breast cancer, with one being diagnosed before age 50

These are some loose guidelines for who may be an increased risk, but a medical professional, such as a genetic counselor, will be able to meet with you to further review your family history and help determine if you meet criteria for genetic testing.

Cancer Screening & Management for CDH1

If you are tested and found to have a pathogenic variant in the CDH1 gene, it is recommended to discuss your management plan with your healthcare team, and if available, to seek consultation through a specialized high-risk clinic. General recommendations are included here based on updated guidelines of the NCCN, but may be tailored to your specific medical and family history.

If someone is found to have a CDH1 pathogenic variant and has also been diagnosed with gastric cancer, the recommendation is to have a total gastrectomy (surgical removal of the stomach) for treatment and prevention.

If someone is found to have a CDH1 pathogenic variant and has *not* been diagnosed with gastric cancer, the recommendation is to consider prophylactic (preventative) gastrectomy between ages 18-40. Preventative surgery is recommended at this time because screening for diffuse gastric cancer does not always detect cancer at an early enough stage for it to be easily treatable. There are, however, significant health consequences associated with a prophylactic gastrectomy. Because of this, it is important to carefully consider all options, and to discuss the risks and benefits of the surgery with your healthcare team (which usually includes a gastroenterologist, surgeon, nutritionist, etc) to make the decision that is right for you.

If, after consideration of all of this information, the individual decides not to have the prophylactic surgery (or decides to put it off for the time being), then the recommendation would be to do an upper endoscopy with multiple random stomach biopsies every 6-12 months to look for signs of gastric cancer.

To address the higher risk of breast cancer associated with CDH1 pathogenic variants, the screening recommendations are:

- *Beginning at age 18*: Breast self exam to facilitate awareness and familiarity with breast tissue
- *Ages 25-29*: Clinical breast exam (every 6-12 months) and breast MRI (every 12 months)
- *Ages 30-75*: Clinical breast exam (every 6-12 months), breast MRI (every 12 months) and mammogram (every 12 months)
- *Age 75+*: Individualized management; patients should work with their doctor or healthcare provider to determine the most appropriate plan

Prophylactic (preventative) mastectomies may also be considered for breast cancer prevention.

If there is a family history of colon cancer, early and more frequent colon cancer screening should be considered. Individuals with a CDH1 pathogenic variant and a family history of colon cancer should work with their doctor or healthcare provider to determine the most appropriate plan for colon cancer screening.

Click here to learn more about scheduling a genetic counseling appointment for questions about hereditary cancer predisposition.