

Hereditary Diffuse Gastric Cancer [1]

What is hereditary diffuse gastric cancer?

Hereditary diffuse gastric cancer (HDGC) is an inherited condition associated with an increased risk of [gastric \(stomach\) cancer](#) [2]. The stomach is located in the upper abdomen and plays an important role in digesting food. When food is swallowed, it is pushed down the muscular tube that connects the throat with the stomach, called the esophagus, and enters the stomach. The muscles in the stomach mix the food and release gastric juices that help break down and digest the food. The food then moves into the small intestine for further digestion. Some people commonly refer to the stomach as the entire abdomen. However, doctors make a distinction between the stomach, which is an organ, and the abdomen, which is the area of the body between the chest and pelvic bones that holds many organs.

Diffuse gastric cancer is a specific type of stomach cancer, sometimes also called “signet ring cell gastric cancer” or “linitis plastic.” It tends to affect much of the stomach rather than staying in one area of the stomach. Approximately 20% of all stomach cancers are diffuse gastric cancers, and a small number of these are due to HDGC. The average age for someone with HDGC to be diagnosed with stomach cancer is 38, although it can be diagnosed much earlier or later than that. Gastric cancers not associated with this syndrome tend to occur in individuals older than 60. Women with HDGC also have an increased risk of lobular [breast cancer](#) [3]. People with HDGC may also have some increased risk of [colorectal cancer](#) [4], although this has not been firmly established.

What causes HDGC?

HDGC is an inherited, genetic condition. This means that the cancer risk and other features of HDGC can be passed from generation to generation in a family. The gene most commonly associated with HDGC is called *CDH1*. A mutation (alteration) in the *CDH1* gene gives a person

an increased risk of developing gastric cancer and other cancers associated with HDGC. Researchers believe that other genes including *CTNNA1* may be associated with HDGC, and studies are ongoing to learn more about these genes.

How is HDGC inherited?

Normally, every cell has two copies of each gene: one inherited from the mother and one inherited from the father. HDGC follows an autosomal dominant inheritance pattern, in which a mutation happens in only one copy of the gene. This means that a parent with a gene mutation may pass along a copy of their normal gene or a copy of the gene with the mutation. Therefore, a child who has a parent with a mutation has a 50% chance of inheriting that mutation. A brother, sister, or parent of a person who has a mutation also has a 50% chance of having the same mutation.

Options exist for couples interested in having a child when they know that one of them carries a gene mutation that increases the risk for this hereditary cancer syndrome. Preimplantation genetic diagnosis (PGD) is a medical procedure done in conjunction with in-vitro fertilization (IVF). It allows people who carry a specific known genetic mutation to have children who do not carry the mutation. A woman's eggs are removed and fertilized in a laboratory. When the embryos reach a certain size, one cell is removed and is tested for the hereditary condition in question. The parents can then choose to transfer embryos that do not have the mutation. PGD has been in use for over two decades, and has been used for several hereditary cancer predisposition syndromes. However, this is a complex procedure with financial, physical, and emotional factors to consider before starting. For more information, talk with an assisted reproduction specialist at a fertility clinic.

How common is HDGC?

The specific number of families with HDGC is unknown. The overall incidence of gastric cancer varies in different parts of the world. In the United States, it is estimated that less than 1% of the population will develop stomach cancer of any kind; only a small fraction of these will be due to HDGC. The highest rates of gastric cancer in the world are in China, Japan, and other countries in Southeast Asia, as well as in Central and South America.

How is HDGC diagnosed?

Guidelines for the diagnosis of HDGC syndrome have been proposed, but may change over time as more is learned about this condition. Currently, the diagnosis of HDGC is suspected and *CDH1* genetic testing should be considered if a person or family meets any of the criteria listed below:

- Families with 2 or more cases of stomach cancer, with at least 1 being diffuse gastric cancer

- A person diagnosed with diffuse gastric cancer before age 40
- Personal or family history of both diffuse gastric cancer and lobular breast cancer, if at least 1 person was diagnosed before age 50
- Families with 2 or more cases of lobular breast cancer diagnosed before age 50
- A person diagnosed with multiple different lobular breast cancers before age 50

Genetic testing for mutations in the *CDH1* gene is available. However, only about 20% to 30% of families that appear to have HDGC will have a mutation found in the *CDH1* gene. Therefore, both clinical and genetic aspects must be considered in counseling individuals about the potential for their family to have HDGC. Talking with a specialist who has training in genetic diseases and conditions, called a genetic counselor or geneticist, who is familiar with the syndrome is recommended.

What are the estimated cancer risks associated with HDGC?

Not everyone who inherits a gene mutation for HDGC will develop cancer. In people who have a mutation in the *CDH1* gene, the lifetime risk for diffuse gastric cancer is estimated to be 70% to 80% for men and 56% to 83% for women by age 80. Women with a mutation in the *CDH1* gene have about a 39% to 52% risk of developing lobular breast cancer by age 80. It remains unclear if people with HDGC are at an increased risk for colon or rectal cancer.

What are the options for reducing cancer risks associated with HDGC?

Given the increased risk of cancers associated with germline mutations in *CDH1*, it is recommended that people found to have this genetic mutation (called carriers) discuss with their doctors the most appropriate strategies to reduce cancer risks:

- **Stomach cancer:** Although a baseline upper endoscopy exam (esophagogastroduodenoscopy or [EGD](#) [5]) is recommended for people with a *CDH1* mutation carriers, previous studies have shown that screening endoscopy exams often miss early-stage diffuse gastric cancers.

Therefore, since endoscopic surveillance can be ineffective for preventing or detecting early-stage diffuse gastric cancers, individuals with germline *CDH1* mutations are advised to consider having their stomach surgically removed, also known as prophylactic total gastrectomy, even if their endoscopy is normal, as surgery is the most effective way to prevent diffuse gastric cancers. It is important to know, however, that surgical removal of the stomach results in permanent changes to the digestive tract and can be associated

with long-term side effects. It is very important for each patient to talk with his or her doctor about what tests and procedures would be appropriate for their individual care.

People who decide not to undergo surgery to remove the stomach may consider intensive surveillance with an annual EGD with multiple (more than 30) mucosal biopsies. This is best performed in centers with expertise in care of people at risk for HDGC.

- **Additional screening for women:** Women at risk for HDGC are at high risk for lobular breast cancer and should talk with their doctor about breast cancer screening options at the age of 30, or ten years before the age of the youngest breast cancer diagnosis in the family. It is not yet clear what the best breast cancer screening strategy is for women with *CDH1* mutations. Screening options include:
 - Monthly breast self-examinations
 - Clinical breast examinations performed by a doctor or nurse every 6 months
 - Regular breast imaging with [mammograms](#) [6], [ultrasound](#) [7], and/or [magnetic resonance imaging](#) [8] (MRI)

Since lobular breast cancers can be difficult to detect with mammograms, breast MRI is recommended for breast cancer screening for women with *CDH1* mutations. Surgical removal of the breasts, called prophylactic mastectomy, is sometimes recommended to reduce a woman's risk of breast cancer. Women should discuss options for reducing their [breast cancer risk](#) [9] with their doctors.

- **Other screening:** [Colonoscopy](#) [10] should be considered in families where both stomach cancer and colorectal cancer have been diagnosed, although it remains unproven whether people with *CDH1* mutations have an increased risk for colon or rectal cancer. Colonoscopy is the examination of the body's large intestine, meaning the colon and rectum. Colorectal cancer screening should begin 10 years earlier than the youngest diagnosis of colorectal cancer in the family or by age 50, whichever is sooner.

Learn more about [what to expect when having common tests, procedures, and scans](#) [11].

Questions to ask the doctor

If you are concerned about your risk of cancer, talk with your doctor. Consider asking the following questions of your doctor:

- What is my risk of developing stomach cancer?
- What is my risk of developing other types of cancer?
- What can I do to reduce my risk of cancer?
- What are my options for cancer screening and cancer prevention?

If you are concerned about your family history and think you or other family members may have HDGC, consider asking the following questions:

- Does my family history increase my risk of stomach cancer?
- Does it suggest the need for a cancer risk assessment?
- Will you refer me to a genetic counselor or other genetics specialist?
- Should I consider [genetic testing](#) [12]?

More Information

[The Genetics of Cancer](#) [13]

[Genetic Testing](#) [12]

[What to Expect When You Meet With a Genetic Counselor](#) [14]

[Collecting Your Family Cancer History](#) [15]

[Sharing Genetic Test Results with Your Family](#) [16]

Additional Resources

No Stomach for Cancer, Inc.

<http://www.nostomachforcancer.org> [17]

Facing Our Risk of Cancer Empowered (FORCE)

www.facingourrisk.org [18]

National Cancer Institute

www.cancer.gov [19]

American Cancer Society

www.cancer.org [20]

CancerCare

www.cancercare.org [21]

To find a genetic counselor in your area, ask your doctor or visit these websites:

National Society of Genetic Counselors

www.nsgc.org [22]

National Cancer Institute:

www.cancer.gov/cancertopics/genetics/directory [23]

Links

[1] <http://www.cancer.net/cancer-types/hereditary-diffuse-gastric-cancer>

[2] <http://www.cancer.net/node/31376>

[3] <http://www.cancer.net/node/31322>

[4] <http://www.cancer.net/node/31317>

[5] <http://www.cancer.net/node/24731>

[6] <http://www.cancer.net/node/24584>

[7] <http://www.cancer.net/node/24714>

[8] <http://www.cancer.net/node/24578>

[9] <http://www.cancer.net/node/18621>

[10] <http://www.cancer.net/node/24481>

[11] <http://www.cancer.net/node/24959>

[12] <http://www.cancer.net/node/24895>

[13] <http://www.cancer.net/node/24897>

[14] <http://www.cancer.net/node/24907>

[15] <http://www.cancer.net/node/30761>

[16] <http://www.cancer.net/node/24906>

[17] <http://www.nostomachforcancer.org/>

[18] <http://www.facingourrisk.org/>

[19] <http://www.cancer.gov/>

[20] <http://www.cancer.org/>

[21] <http://www.cancercare.org/>

[22] <http://www.nsgc.org/>

[23] <http://www.cancer.gov/cancertopics/genetics/directory>