What is Hereditary Diffuse Gastric Cancer (HDGC)?

**Hereditary Diffuse Gastric Cancer (HDGC)** is a rare cancer syndrome that leads to a higher-than-average risk of developing two types of cancer: diffuse gastric cancer (DGC) and lobular breast cancer (LBC). The word “hereditary” means that the syndrome is passed down from a parent to their child.

**Diffuse gastric cancer** is a type of cancer that grows and spreads within the lining of the stomach. Because it does not typically cause a bulky tumor to develop, it is more difficult to find and more likely to be found at a later stage when it can be very difficult to treat successfully.

How does a person get HDGC?

HDGC is inherited, meaning the syndrome (a set of symptoms or signs that occur together and suggest the presence of a disease or increased chance of developing a disease) is passed down from a parent to a child. Most families with HDGC have a mutation (a change in the genetic code) in a gene called *CDH1*. When it functions correctly, *CDH1* acts as a tumor suppressor, preventing cancers from growing. However, mutations in *CDH1* could possibly lead to the development of cancer. Mutations in a gene that contribute to the development of a disease are known as **pathogenic variants**.

Everyone has two copies of the *CDH1* gene, one from their mother and one from their father. Because of the nature of *CDH1*, you only need one of your two copies to have a pathogenic variant to be affected by HDGC. When you have a parent with HDGC caused by a pathogenic variant in the *CDH1* gene, you have a 50 percent chance of also having that same mutation.

In a small number of cases, HDGC is caused by a mutation in a different gene called *CTNNA1*. This gene functions similarly to *CDH1*.

HDGC is diagnosed when a person or family tests positive for a pathogenic variant in the *CDH1* or, more rarely, the *CTNNA1* gene. For more information on genes and genetic testing, see “**Genetic Testing and HDGC.**”

**What should I do if I suspect my family has HDGC?**

It is important to learn about the health of your family members, especially any diagnosis of cancer. If you can, try to gather information on the types of cancer
your family has experienced, pathology reports from doctors, the age of the family member at diagnosis and, if it applies, the age that they died.

Tell this information to your primary care provider. If you think your family might have HDGC syndrome, you can request a referral to a genetic counselor to discuss this and consider genetic testing (see “Genetic Testing and HDGC” for more details).

**What does it mean to have HDGC?**

If you are diagnosed with HDGC syndrome, it does not necessarily mean that you have or will develop cancer — you just have a **higher risk**. People with HDGC may develop none, one or more than one cancer. Being diagnosed with one type of cancer does not mean that the risks for other cancers no longer apply.

Though it can be difficult to estimate your exact risk of cancer:

- Some studies show that individuals with a pathogenic CDH1 gene variant and a strong family history of stomach cancer have up to a 70 percent risk of having diffuse gastric cancer in their lifetime; however, it is generally accepted that the risk is in the 30 to 40 percent range.
- Women with HDGC have an estimated 40 to 55 percent risk of having lobular breast cancer in their lifetime.
- People with HDGC and little or no family history of stomach cancer may have a lower risk of diffuse gastric cancer, but family history may not be a completely reliable factor in determining cancer risk.

These cancers can affect adults of all age groups.

**Know Your Risk and Management Options**

Knowing that you are at a higher risk for certain cancers and understanding the signs and symptoms of those cancers could save your life.

**Gastric Cancer**

The symptoms of gastric cancer can be vague and are not specific to gastric cancer, but you should still **know the symptoms of gastric cancer:**

- Abdominal pain
- Decreased appetite
- Weight loss
- Indigestion
- Heartburn
- Excessive burping
- Feeling full or bloated easily
- Difficulty swallowing
- Nausea
- Vomiting
- Changes in bowel movements
- Blood in your stool

If you are at risk of gastric cancer due to a *CDH1* mutation, consider your options.

**Screening:** If you are diagnosed with a *CDH1* mutation, you should have an upper endoscopy (a procedure done to visually examine your upper digestive system) and stomach biopsies (the removal of samples of stomach tissue for examination).

If you choose to use screening as your management strategy for HDGC, you will likely have an upper endoscopy every 6 to 12 months.
- This method is not very sensitive for detecting very early stages of stomach cancer but is important to be certain that there isn't an obvious problem.
- About 30 to 40 percent of the time, stage I cancer cells are identified on biopsies that are examined by a pathologist after endoscopy.
- Because these cells may or may not progress to later stages of cancer, individuals found to have stage I cancer cells on upper endoscopy are encouraged to partner with healthcare providers who have HDGC expertise to discuss personalized options for next steps.

**Total Gastrectomy:** It is recommended that individuals who have a *CDH1* mutation and a family history of gastric cancer have a total gastrectomy, or removal of the stomach, to eliminate the risk of developing an advanced gastric cancer. This procedure is also referred to as a *prophylactic total gastrectomy*.
- You should discuss this option with your health care providers as well as a health care team that specializes in HDGC and total gastrectomy.
- Because gastrectomy can lead to long-term health and nutrition problems, when considering total gastrectomy your health care team should include providers with expertise in nutrition, gastric surgery and gastroenterology.
- The timing of this surgery will depend on many factors

**Find a team with HDGC expertise:** No matter what option you choose, a team with genetic counselors, gastroenterologists, surgical oncologists, pathologists and nutritionists will be indispensable to help develop the care plan that is right for you.
- It may be helpful to talk to a psychologist or therapist about the difficult decisions ahead of you and the emotions that come with a diagnosis of HDGC.
Breast Cancer

Know the symptoms of breast cancer:
• A lump in your breast
• Skin changes or dimpling of your breast
• Breast asymmetry
• Nipple pain or discharge
• Breast pain

If you are at risk of lobular breast cancer (LBC) due to a *CDH1* mutation, consider your options.

• **Screening:** Recommended screening procedures include mammograms and MRIs of the breasts on a regular basis starting at age 30.

• **Bilateral Mastectomy:** Having a bilateral mastectomy (surgery to remove both breasts) to decrease breast cancer risk may be an option.
  • You should discuss these options with your health care providers as your decision will depend on many factors
  • Note that even with bilateral mastectomy, there is still a very small possibility that breast cancer will develop at a later point because not all at-risk breast tissue can be removed

• **Find a team who is familiar with HDGC and LBC:** This may include breast oncologists, surgical oncologists and pathologists who can help you develop a care plan that is right for you.
  • It may be helpful to talk to a psychologist or therapist about the difficult decisions ahead of you and the emotions that come with a diagnosis of a *CDH1* mutation.

Other Risk Factors
Many factors can influence the risk of cancer. Modifiable factors, meaning factors that you can control, associated with an increased risk of stomach cancer include drinking three or more alcoholic drinks per day, eating foods high in salt or salt-preserved foods and having a high intake of processed or red meat. However, in the setting of *CDH1* mutations it is not clear if these factors play a role in the development of cancer.

Diet and nutrition guidelines that may reduce the risk of stomach cancer in the absence of a *CDH1* mutation include the following:
• Maintain a healthy weight
• Keep physically active
• Eat a variety of whole grains, vegetables, fruit (especially citrus fruits) and beans
Avoid salt-preserved and high-salt (high sodium) foods
Avoid sugar-sweetened beverages
Limit processed and red meat consumption
Limit your alcohol intake
Avoid tobacco

To learn more about diet and nutrition guidelines to reduce the risk of stomach cancer, you can refer to evidence-based resources such as the American Cancer Society (ACS) and the American Institute for Cancer Research (AICR).

Keep in mind that diet and lifestyle recommendations to reduce the risk of stomach cancer do not guarantee cancer prevention. People who have an inherited risk of stomach cancer need to follow additional guidelines from their health care team. Talk to your health care team about additional recommendations specific to you. You may find it useful to print this page and take notes on those recommendations in the blank space below.