

# HDGC HEREDITARY DIFFUSE GASTRIC CANCER

Understand your risk. Make informed decisions. Advocate for yourself. Support the research.

## WHAT IS HEREDITARY DIFFUSE GASTRIC CANCER (HDGC)?

HDGC is an inherited cancer syndrome that leads to a higher than average risk of developing two types of cancer:

### Gastric (stomach) cancer:

- It is estimated that 1-3% of gastric cancers result from inherited cancer syndromes.
- The type of stomach cancer associated with HDGC is called diffuse gastric cancer (DGC). This cancer tends to grow and spread within the lining of the stomach, making it difficult to find because it does not cause a bulky tumor to develop. Another type of stomach cancer, called intestinal gastric cancer, is not associated with HDGC.
- Doctors sometimes refer to the stomach cancer as *signet ring cell carcinoma* or *linitis plastica*.
- Diffuse gastric cancer is difficult to detect and is usually diagnosed at a late stage when it cannot be cured.

### Breast cancer:

- The type of breast cancer associated with HDGC is called lobular breast cancer (LBC). Another type of breast cancer, called ductal breast cancer, is not known to be associated with HDGC.

## How does a person get HDGC?

- The majority of families with HDGC have a pathogenic variant (mutation) in a gene called *CDH1*, a tumor suppressor gene on chromosome 16. Pathogenic variants directly contribute to the development of disease.
  - This gene mutation was first discovered in a family from New Zealand's Māori population in 1998.
  - Over 150 different pathogenic variants in the *CDH1* gene have been identified.
  - The inheritance pattern is called autosomal dominant, meaning that you only need one mutated copy (from one parent) to be affected by HDGC.
  - Since everyone has two copies of each gene, each person has a 50% random chance of inheriting the mutated copy from their affected parent. This does not mean that 50% of the family members will inherit it – each person's risk is 50%.
  - In a small minority of cases, HDGC is caused by a pathogenic variant in a gene called *CTNNA1*, which is found on chromosome 5 and has a similar function to the *CDH1* gene.
  - In some families, a pathogenic variant in *CDH1* is found, but there is only a family history of breast cancer. In this case, the term Hereditary Lobular Breast Cancer (HLBC) is used. If someone in the family is later diagnosed with diffuse gastric cancer, the diagnosis changes to HDGC.

## How do I know if my family has HDGC?

- HDGC is diagnosed when a person or family tests positive for a pathogenic variant in the *CDH1* or (rarely) the *CTNNA1* gene.
- It is important to learn about the health of your family members, especially any diagnosis of cancer. If possible, gather the types of cancer, pathology reports if available, and age at diagnosis or death.
- Tell your primary care provider about your family health history, and update him/her at every well visit. If you think that your family might have HDGC syndrome you can request a referral to a genetic counselor to discuss this and consider genetic testing.
- Genetic testing is performed on a blood or sputum sample to look for a mutation in the *CDH1* gene. Sometimes, a mutation in the *CDH1* gene is found when someone has panel testing, which is when multiple genes are tested at once.

*continued*

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## How do I know if my family has HDGC? *continued*

- If you or your family fits into any of these categories, you may benefit from genetic counseling and testing:

### Family criteria (1st or 2nd degree blood relatives of each other)

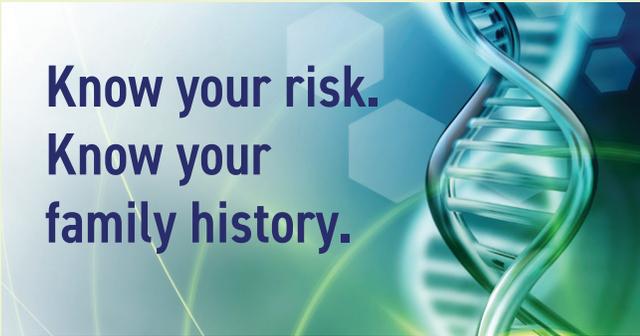
- ≥2 cases of gastric cancer in family regardless of age, with at least one DGC
- ≥1 case of DGC any age and ≥1 case of LBC <70yrs in different family members
- ≥2 cases of LBC in family members <50yrs

### Individual criteria

- DGC <50yrs
- DGC at any age in individuals of Māori ethnicity
- DGC at any age in individuals with a personal or family history (1st degree) of cleft lip/cleft palate
- History of DGC and LBC, both diagnosed <70yrs
- Bilateral LBC (cancer in both breasts), diagnosed <70yrs
- Gastric in situ signet ring cells and/or pagetoid spread (bottom to top) of signet ring cells in individuals <50yrs

## What does having HDGC syndrome mean?

- Exact risks of cancer are difficult to estimate, and may vary between families with HDGC. Some studies have shown that men with a pathogenic *CDH1* gene variant, and a strong family history of stomach cancer, have up to a 70% risk of having diffuse gastric cancer in their lifetime.
- Women with a pathogenic *CDH1* gene variant and a strong family history have up to a 56% risk of having diffuse gastric cancer and a significantly elevated risk of having lobular breast cancer in their lifetime.
- People with pathogenic *CDH1* variants and little or no family history of stomach cancer seem to have a lower risk of this cancer.
- The distinction between HDGC and HLBC acknowledges the likelihood that not all families with pathogenic *CDH1* variants are equally at risk of DGC.
- These cancers can affect all age groups, sometimes as early as the teens or twenties.
- Having HDGC syndrome does not necessarily mean that a person has or will develop cancer – they may just have a higher risk.
  - If you have a mutation in the *CDH1* gene, you have a 50% chance of passing the mutation down to each of your children. Meeting with a reproductive endocrinologist can be helpful to learn about options to eliminate the risk of passing down a *CDH1* mutation.



**Know your risk.  
Know your  
family history.**

### Find current HDGC Clinical Guidelines at:

- [HereditaryDiffuseGastricCancer.org/hdgc-clinical-guidelines](https://HereditaryDiffuseGastricCancer.org/hdgc-clinical-guidelines)

### More information about genetics and *CDH1*

- [HereditaryDiffuseGastricCancer.org/Genetics](https://HereditaryDiffuseGastricCancer.org/Genetics)

### Find a Genetic Counselor

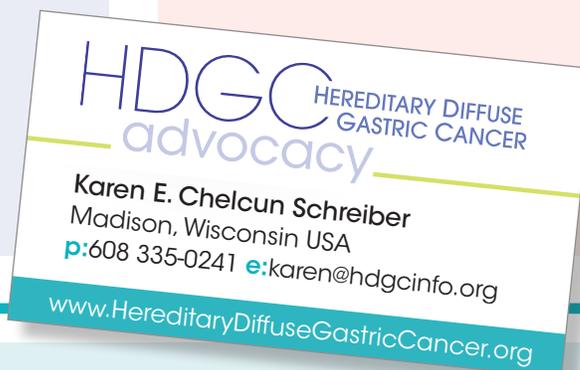
- [NSGC.org/FindAGeneticCounselor](https://NSGC.org/FindAGeneticCounselor)

## What should I do about my risk of gastric cancer?

- Know the symptoms:
  - 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 the stool
- Consider your options:
  - Some people choose surveillance with upper endoscopy and stomach biopsies. Unfortunately, this method is not always able to detect stomach cancer and it is possible that it will miss cancers hiding in the stomach lining.
  - It is recommended that people with HDGC have a total gastrectomy, or removal of the stomach, to prevent diffuse gastric cancer. The timing of this surgery depends on many factors and should be discussed with your healthcare providers.
- Find a team of specialists with HDGC expertise:
  - Genetic counselors, gastroenterologists, surgical oncologists, pathologists, and nutritionists can help you develop a care plan that is right for you.
  - Sometimes it is helpful to talk to a psychologist or therapist about the difficult decisions and how to manage the emotions that come with a diagnosis of HDGC.
- Treatment protocols continue to evolve for HDGC. Ask your provider to review current guidelines and recommendations with you.

## What should I do about my risk of breast cancer?

- Know the symptoms:
  - A breast lump, skin changes or dimpling of the breast, breast asymmetry, nipple pain or discharge, breast pain
- Consider your options:
  - Some people choose surveillance with clinical breast exams, mammograms, and MRIs of the breasts on a regular basis. It is recommended to start breast surveillance at age 30.
  - Taking medications or having a mastectomy to decrease breast cancer risk may be an option. These decisions depend on many factors and should be discussed with your healthcare providers.
- Find a team of specialists who are familiar with HDGC:
  - Breast oncologists, surgical oncologists, and pathologists can help you develop a care plan that is right for you.
  - Sometimes it is helpful to talk to a psychologist or therapist about the difficult decisions and how to manage the emotions that come with a diagnosis of HDGC.
- Treatment protocols continue to evolve for HDGC. Ask your provider to review current guidelines and recommendations with you.



## Thanksgiving is Family Health History Day!

Create a Family Health Portrait:  
[phgkb.cdc.gov/FHH/html/index.html](https://phgkb.cdc.gov/FHH/html/index.html)

## What else can I do?

- Stay healthy by eating a balanced diet, exercising regularly, avoiding smoking, and limiting how much alcohol you drink.
- Find a genetic counselor who can guide you and answer your questions about HDGC.
- Talk to all of your family members about what you learn and how they can stay healthy.
- Advocate for yourself and your family, and find a provider who knows (or is willing to learn) about HDGC.
- Become involved in support groups.

## Overview: Management of individuals & families at risk for Hereditary Diffuse Gastric Cancer

### Abbreviations

GC-Gastric cancer  
 DGC - Diffuse gastric cancer  
 HDGC - Hereditary diffuse gastric cancer  
 LBC - Lobular breast cancer  
 HLBC - Hereditary lobular breast cancer  
 PTG- prophylactic total gastrectomy  
 TG-total gastrectomy  
 BRRM-bilateral risk-reducing mastectomy

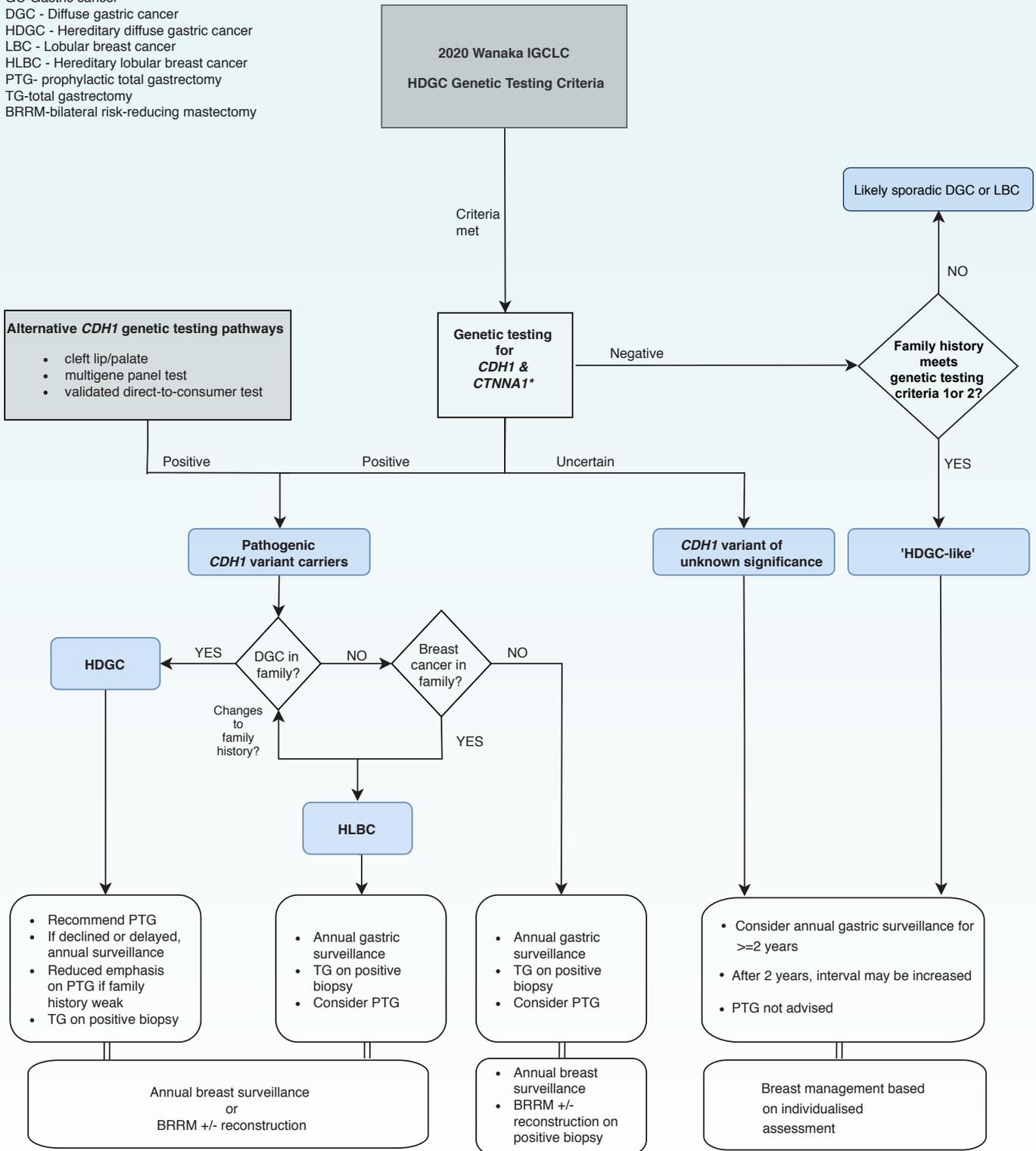


Figure 1: Flow chart for the management of individuals and families who either meet the revised HDGC genetic testing criteria or have had a pathogenic CDH1 variant identified through another route.

\* see text for description of CTNNA1 pathway

Source: Blair VR, McLeod M, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical practice guidelines. *Lancet Oncol* 2020; 21: e385-96.