

A woman with a shaved head, wearing a yellow knit sweater, is sitting at a desk and looking at a laptop. The room has a white wall decorated with several framed photographs. On the desk, there are two potted plants, a pen holder, and some papers. The overall atmosphere is calm and focused.

# **CBCN Advocacy Guide: Increasing Research on HER2-Low Breast Cancer**

# **HER2 Proteins and Breast Cancer**

In healthy cells, HER2 proteins on breast cells maintain normal growth, division, and repair. However, very high levels of HER2 proteins on the cell surface causes uncontrolled cell growth and division. Breast cancers that show very high levels of HER2 proteins are referred to as HER2-positive breast cancers<sup>1</sup>.

Determining whether breast cancers are HER2-positive or not is based on an immunohistochemistry (IHC) score which can range from 0 to 3+. IHC is a diagnostic test that uses tissue from a biopsy to differentiate between certain types and subtypes of cancer by looking at the molecules, also known as markers, in the cell tissue<sup>2</sup>. The current standardized HER2 scores are either positive or negative, where an IHC score of 3+ is defined as HER2-positive breast cancer and all scores below IHC 3+ (that is, IHC 0 to 2+) are defined as HER2-negative breast cancer<sup>3,4</sup>. In borderline IHC 2+ cases, confirmatory tests are done with a different technique (FISH, fluorescent in situ hybridization).

## **What is HER2-Low Breast Cancer**

There has been a shift in classifying breast cancer cells that have some HER2 proteins but not enough to be HER2-positive, as HER2-low breast cancer. It might be easier to consider HER2-positive breast cancer as being amplified by the HER2 protein, while in HER2-low breast cancer the HER2 protein is still there, but it does not drive the cancer in the same way as in cases of HER2-positive breast cancer.

The concept of HER2-low breast cancer is very new, originating in 2020. It is important to be aware that there is no standard definition of HER2-low breast cancer, but the commonly recognized meaning of this subtype of breast cancer is an IHC score of 1+ or 2+ with a negative FISH<sup>5,6</sup> test. For clarity, the remainder of this guide will consider HER2-negative breast cancer as having an IHC score of 0, HER2-low as an IHC score from 1+ to 2+ (FISH negative), and HER2-positive as an IHC score of 3+.

Many studies agree that between 50-55% of breast cancer patients are HER2-low, including 35% of metastatic breast cancer patients, and 44% of triple negative breast cancer (TNBC) patients. HER2-low expression has also been found to be higher among patients with hormone receptor (HR)-positive breast cancer. Furthermore, an individual's HER2 status can change throughout the course of treatment, so recognizing variability in HER2 status rather than viewing it as only negative or positive is important<sup>7,3</sup>.

## ***Benefits of Reclassifying HER2***

One of the biggest benefits and reason for reclassifying HER2-negative breast cancer into HER2-negative and HER2-low is that it allows for new treatment paths for patients

with HER2-low breast cancer<sup>7</sup>. HER2 targeted therapies have been around since 1998 and dramatically improved the prognosis for individuals diagnosed with HER2-positive breast cancer<sup>6</sup>. Researchers now recognize that HER2-low patients may also benefit from therapies that target the HER2 protein because they still have HER2 proteins, just at low level<sup>4</sup>. In fact, the 2022 Destiny Breast-04 clinical trial became the first clinical trial to show significant therapeutic advances for HER2-low targeted therapies<sup>7</sup>.

Additionally, TNBC, a subtype of breast cancer defined by a lack of estrogen (ER), progesterone (PR) hormones, and HER2 proteins, has fewer treatment options than HER2-positive breast cancer. For TNBC, chemotherapy is the standard of care in all lines of treatment and combined with some newer targeted therapies in the second- and third-line setting<sup>8</sup>. Reclassifying HER2-negative breast cancer into either HER2-negative or HER2-low could mean that some TNBC will no longer be defined as such. This would mean potentially more treatment options for individuals diagnosed with TNBC. Therefore, HER2-low targeted therapies are especially important for patients diagnosed with TNBC and metastatic breast cancer (mBC) where there are fewer treatment options or resistance to therapies<sup>6</sup>.

## ***Finding Your HER2 Status***

HER2-low breast cancer is not a new diagnosis; it is just a reclassification of the existing HER2-status. Therefore, finding out your HER2 status and IHC score should be fairly accessible. You can find this information through the following:

- In your pathology report
- Generated from assays
- Your medical team can explain your IHC score as it is part of standard pathology testing

[1] [Sub-Types of Breast Cancer](#) Canadian Breast Cancer Network. Accessed June 5, 2023

[2] [Immunohistochemistry \(IHC\)](#) City of Hope. Accessed June 5, 2023

[3] [Landscape of HER2-low metastatic breast cancer \(MBC\): results from the Austrian AGMT MBC-Registry](#) Breast Cancer Research. Accessed June 5, 2023

[4] [Current Biological, Pathological and Clinical Landscape of HER2-Low Breast Cancer](#). Cancers Journal. Accessed June 5, 2023

[5] [FISH \(Fluorescence In Situ Hybridization\) Test](#) BreastCancer.org. Accessed June 5, 2023

[6] [HER2-Low Breast Cancer Explained](#) Breast Cancer Research Foundation. Accessed June 5, 2023

[7] [DESTINY-Breast04 Establishes Trastuzumab Deruxtecan As a New Standard of Care for HER2-Low Metastatic Breast Cancer](#). ASCO. Accessed June 5, 2023

[8] [My Treatment Plan](#). Canadian Breast Cancer Network Accessed June 5, 2023

# Self-Advocacy for Standardizing HER2-Low Scores

Currently, IHC testing is only meant to tell the difference between HER2-positive scores and everything below HER2-positive. This means that although current IHC tests will generate a score between 0 to 3+, more sensitive tests are needed to pick up HER2-low scores with greater accuracy. For the same reason, it is difficult to adopt a standard definition of HER2-low or to develop more treatment for HER2-low targeted therapies<sup>4,6,7</sup>. Therefore, advocacy to increase research into HER2-low breast cancer and standardizing it as a new classification is needed. The steps on this are discussed below.

## Understand Your HER2 Status

Speak with your healthcare team to understand how your HER2 status and IHC score might impact your treatment. This could include going over your pathology report to identify your IHC score and monitoring your IHC score to see if it changes. If your report shows a score of IHC 1+ to 2+, ask your doctor about appropriate targeted therapy options and if they consider HER2-low scores in treatment paradigms.

## Participate in Clinical Trials

Once you receive your pathology report and speak with your healthcare team to understand your HER2 score, you can find and participate in clinical trials exploring HER2-low targeted therapies. You can learn more about clinical trials, and begin your clinical trials search using the links below:

- Read about what a clinical trial is and where to find them [here](#)
- Learn more about participating in clinical trials [here](#)
- Read CBCN's clinical trial facts sheet [here](#)

## Share Your Experience and Input

If you were diagnosed with HER2-negative breast cancer after 2018, participate in our [HER2-low survey](#) to share your experience. CBCN can use your feedback as evidence to push for a standardized definition of HER2-low and to call for more research into HER2-low breast cancer.