ASGCT Patient Education

# Huntington's Disease



Huntington's disease is a genetic disorder caused by a breakdown of nerve cells in the brain. The disease affects an individual's ability to move, their mood, and how they think. There's currently no cure for Huntington's disease, but there are types of gene therapy approaches that may offer hope for managing or slowing symptoms.

## About Huntington's Disease

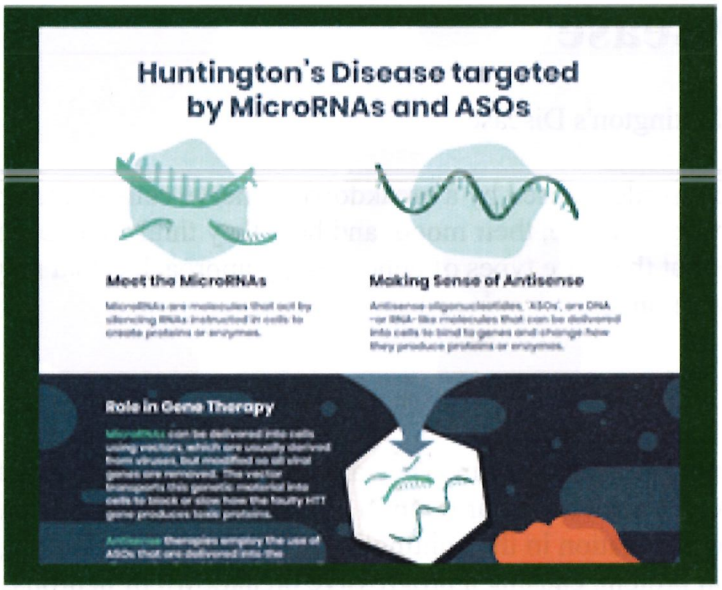
Neurons are the main cell type in our nervous system. They are located in the brain and are in charge of sending messages back and forth from our brain to other tissues such as our muscles. Huntington's disease is caused by a mutation in the huntingtin (HTT) gene. This faulty gene creates too much of the huntingtin protein, causing a progressive breakdown of neurons. As toxic levels of huntingtin protein causes neuron death, individuals face a widespread collection of symptoms that include impaired movement and impaired brain function.

Symptoms of Huntington's disease typically appear between the ages of 30 and 50, and become worse over a 10- to 25-year period. As independence is lost, it can be hard on caregivers to manage both emotional and physical needs. The disease currently has no cure or effective treatment option. However, physical therapy can offer a way to help patients maintain their mobility and prevent falls or other accidents.

## Goal of Gene Therapy

Typically, the concept of gene therapy is to introduce a functional version of a gene into a cell so the cell can produce proteins or enzymes that were missing or defective prior to treatment. However, in the case of Huntington's disease, the goal is to use gene therapy to limit the production of the toxic huntingtin protein. Less toxic protein in the brain would mean a slower breakdown of neurons.

These genetic instructions are delivered to cells using vectors. Vectors are often derived from viruses because they are capable of entering cells to deliver genetic material, such as a working gene. But don't worry, all viral genes are removed and the vector is modified to only deliver therapeutic genes into cells. In this case, the vector's function would be to introduce the new genetic material to block or slow the HTT gene from creating the toxic protein. For example, this could be done by delivering a special type of RNA called microRNAs.




*Download the Infographic: Huntington's Disease targeted by MicroRNAs and ASOs*

Let's talk about microRNA first. As you may be able to guess from the name, they are short RNA molecules. RNA is a molecule that, like DNA, typically encodes information for proteins. This means that RNA translates a gene's genetic information, instructing a cell how to create a protein or enzyme. With this in mind, RNA could then also change how a mutated gene expresses itself. MicroRNAs do not encode information to help cells make proteins. Rather, they help regulate existing RNAs that do create proteins. With gene therapy, a vector would deliver microRNAs into the cell, helping to limit the cell's production of the toxic HTT protein.

Another option being researched is called antisense oligonucleotide therapy. This approach actually blocks or alters how cells express specific genes. Synthetic DNA or RNA strands known as antisense oligonucleotides—also known as ASOs—would be delivered to the cells. The ASOs then bind to the toxic HTT gene, blocking its ability to produce too much of the harmful protein. There are many different types of carriers that can be used to deliver ASOs into the cells, and in some cases it is a vector delivery system, and in other instances, no carrier is needed.

A key difference between these two techniques is that antisense oligonucleotides typically require multiple doses and utilize different carriers, while microRNAs that are delivered by vectors aim to be administered only one time. Although both therapeutic microRNAs and ASOs are designed in the lab, therapeutic microRNAs are based on natural genes found in humans.

# Pathway to Treatment

## Treatment Pipeline

Investigational gene therapies for Huntington's are being researched by uniQure, Spark Therapeutics, Roche, Voyager Therapeutics and Sanofi Genzyme. To find out if there are any active and recruiting gene therapy clinical trials in the US, visit the ASGCT Clinical Trials Finder and search for Huntington's in the "diagnosis" field.

## Eligibility

You may be curious how people with Huntington's disease can participate in clinical trials for gene therapy. These trials offer an opportunity to receive an investigational treatment at no cost, while also benefiting the medical community and others who have the disease. However, for the potential treatments to be successfully researched, individuals must meet strict eligibility criteria to enter a clinical trial, which is based on a variety of factors.

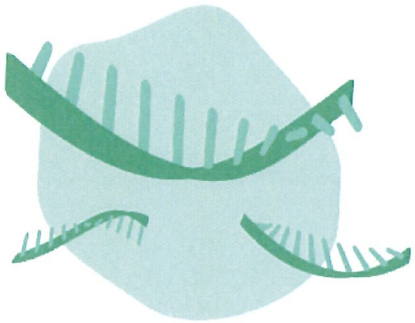
For example, trials may be limited to individuals currently in the early stages of the disease. Also, some trials might require neurosurgery or even monthly lumbar punctures to remove spinal fluid. These invasive procedures come with substantial recovery time and extensive associated care, which may not be feasible for some patients, their families or caretakers. It's important to understand that although clinical trials for Huntington's or approved gene therapies for other diseases can have very beneficial outcomes, they are not like standard off-the-shelf medications that can be applied immediately.

## Genetic Testing

If a child has at least one parent affected by Huntington's disease, there's a 50-50 chance that they might inherit the mutated gene. Even if a potential parent doesn't currently show symptoms of the disease, there's a risk that they may pass it along to their children or may even show symptoms themselves later in life. With this in mind, genetic testing could identify whether a person has the Huntington's gene to help during family planning. .

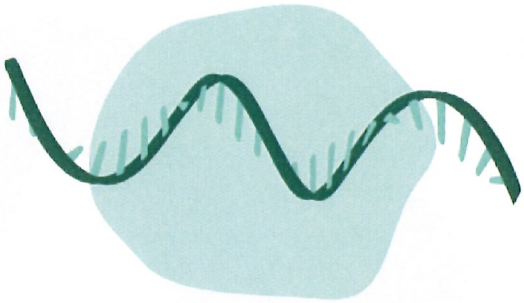
If at-risk individuals want to be tested, the Huntington's Disease Society of America recommends having it done at a genetic testing center that follows the HDSA guidelines. Testing procedures at these centers involve sessions with professionals knowledgeable about the disease, along with local services to connect with. These include patient organizations that work to lower stigma, promote research engagement and provide educational resources.

# Huntington's Disease targeted by MicroRNAs and ASOs



## Meet the MicroRNAs

MicroRNAs are molecules that act by silencing RNAs instructed in cells to create proteins or enzymes.



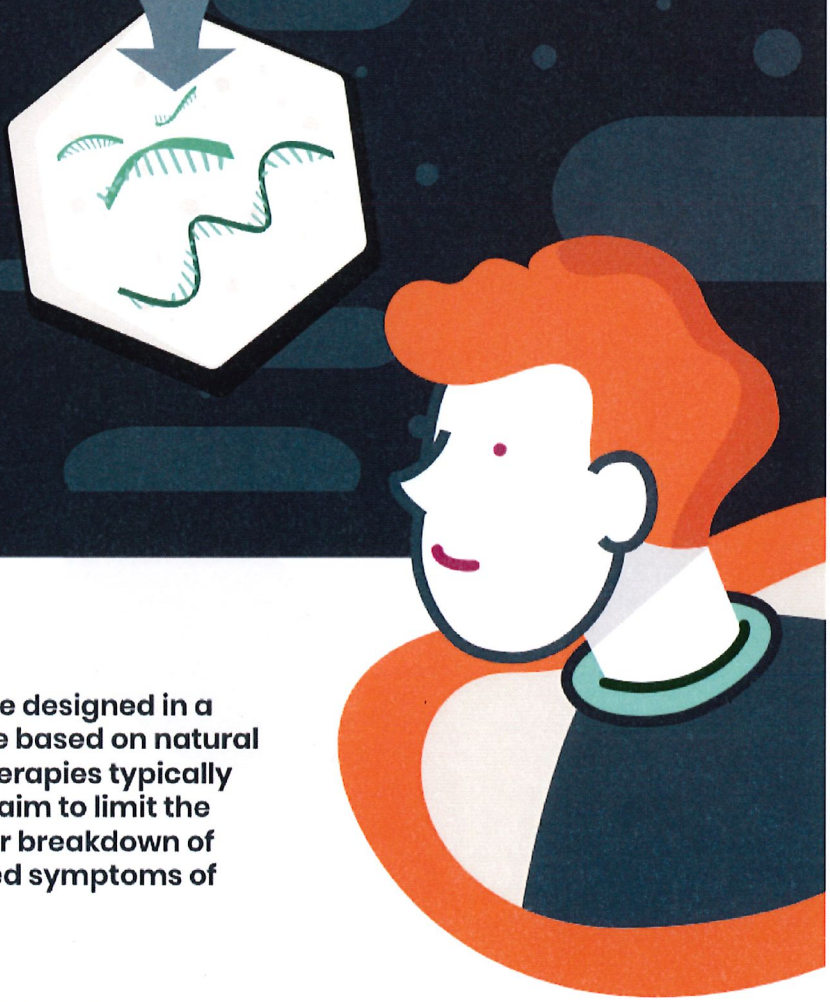
## Making Sense of Antisense

Antisense oligonucleotides, 'ASOs', are DNA -or RNA-like molecules that can be delivered into cells to bind to genes and change how they produce proteins or enzymes.

## Role in Gene Therapy

**MicroRNAs** can be delivered into cells using vectors, which are usually derived from viruses, but modified so all viral genes are removed. The vector transports this genetic material into cells to block or slow how the faulty HTT gene produces toxic proteins.

**Antisense** therapies employ the use of ASOs that are delivered into the diseased cells to block or alter how cells express genes. There, they can modify how target RNAs are processed and expressed to control the faulty HTT gene.



## Different with the Same Goal

Although both the microRNAs and ASOs are designed in a specialized lab, therapeutic microRNAs are based on natural genes found in humans. Also, antisense therapies typically requires multiple doses. Both approaches aim to limit the toxic protein in the brain resulting in slower breakdown of neurons that would lead to better managed symptoms of Huntington's disease.

AMERICAN SOCIETY of GENE & CELL THERAPY

Visit asgct.org/education for more information