LEARN ABOUT **GENE THERAPY** FOR HEART CONDITIONS

TENAYA™ THERAPEUTICS

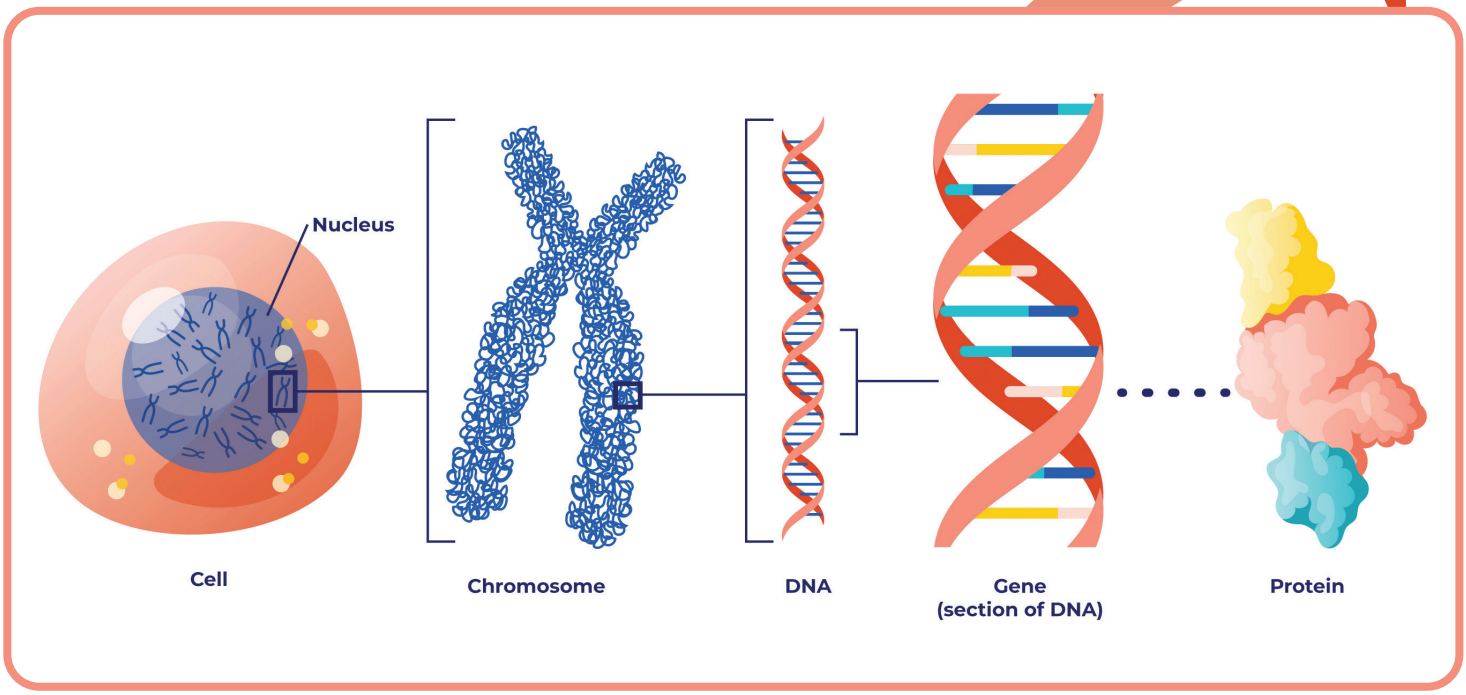
Tenaya Therapeutics (Tenaya) is a biotechnology company using knowledge of genetics to discover and develop new medicines that may transform and extend the lives of people with heart disease.

The role of genetics

To understand how gene therapy may be a potential treatment for some heart conditions, it helps to know some basic information about genetics.

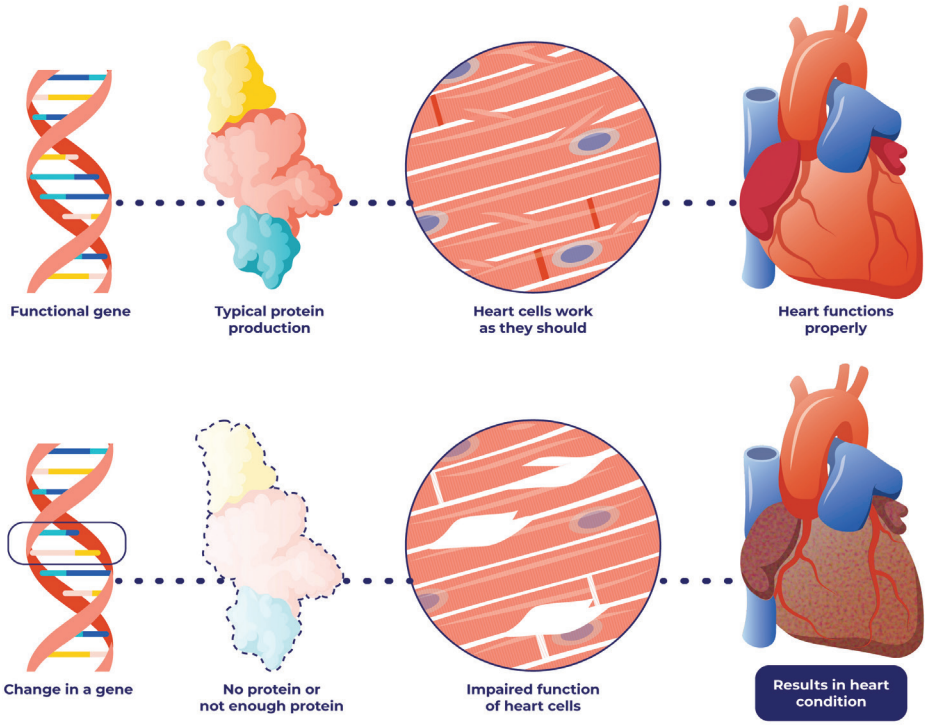
Many types of heart conditions are passed down within families (inherited). Changes in genes that lead to these conditions can come from one or both parents.

Your body is made up of **cells**.[1] Cells, in turn, contain different parts, like **chromosomes**. Chromosomes are long strands of **DNA**.[2] Within DNA are **genes**. Genes contain the instructions to make **proteins.** There are thousands of proteins that work together to tell your body how to grow, develop and function.[3,4] For example, proteins are involved with making your organs, like your liver, lungs, and heart work.[4]



How changes in a gene cause genetic conditions

Mutations (also known as variations or changes) in a gene can affect that gene's ability to make a protein the way it should or can affect whether that protein is made at all. For example, a gene mutation can prevent the heart muscles from making a protein needed for the heart to function as expected. Some genetic conditions that affect the heart include hypertrophic cardiomyopathy (HCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC).[5]



Learn if you have gene variations through genetic testing

Genetic tests are usually performed by taking a sample of blood, saliva, or cells from inside of your cheek to identify changes in your genes. The results can help you understand your risk of developing a genetic condition. They can also help you and your doctor make decisions about your medical care.

As part of the genetic testing process, you may see a genetic counselor. This is a healthcare professional who can help you and your family understand the entire genetic testing process, including the possible outcome of the test and your test results. They can also explain how a genetic condition is inherited and your chance of passing it onto your children.

Did you know that genetic testing is recommended for people who have inherited heart conditions such as HCM and ARVC?[6] Ask your cardiologist about genetic testing for heart conditions.

Gene therapy for heart conditions

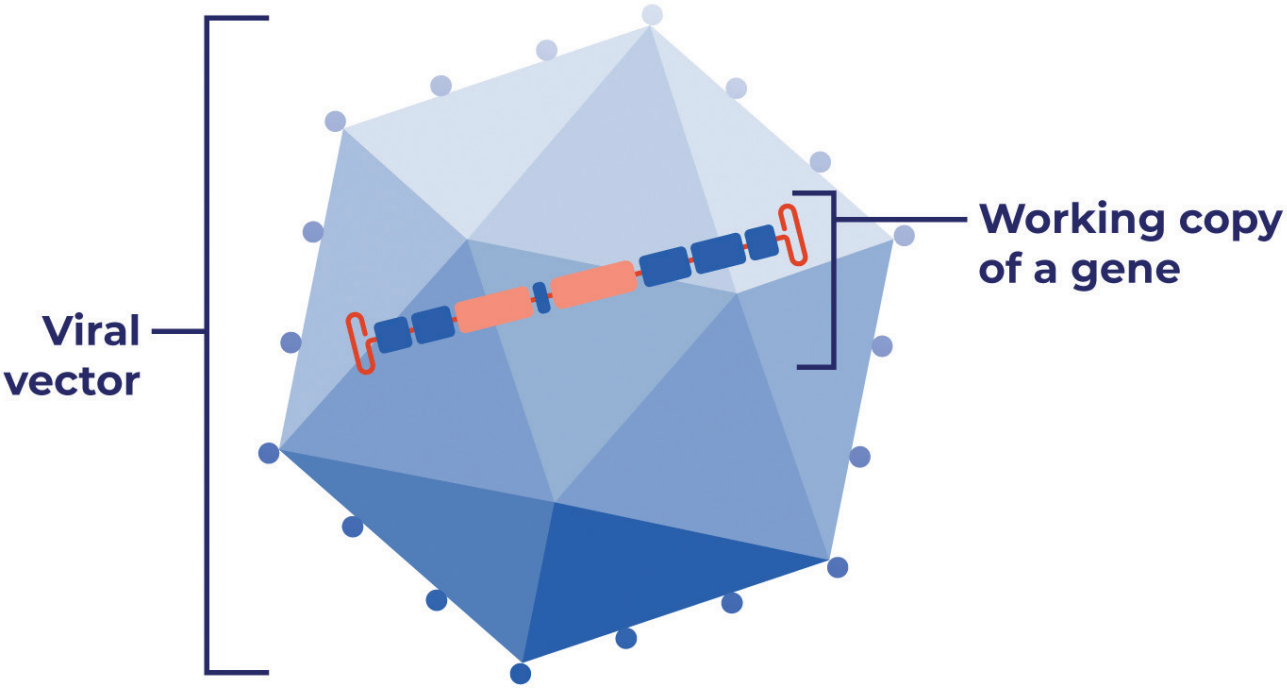
What is gene therapy?

Gene therapy is a way of treating or preventing conditions caused by genetic mutations. Gene therapy delivers a working copy of a gene into a cell to help the cell build the necessary protein to restore the expected function.[7]

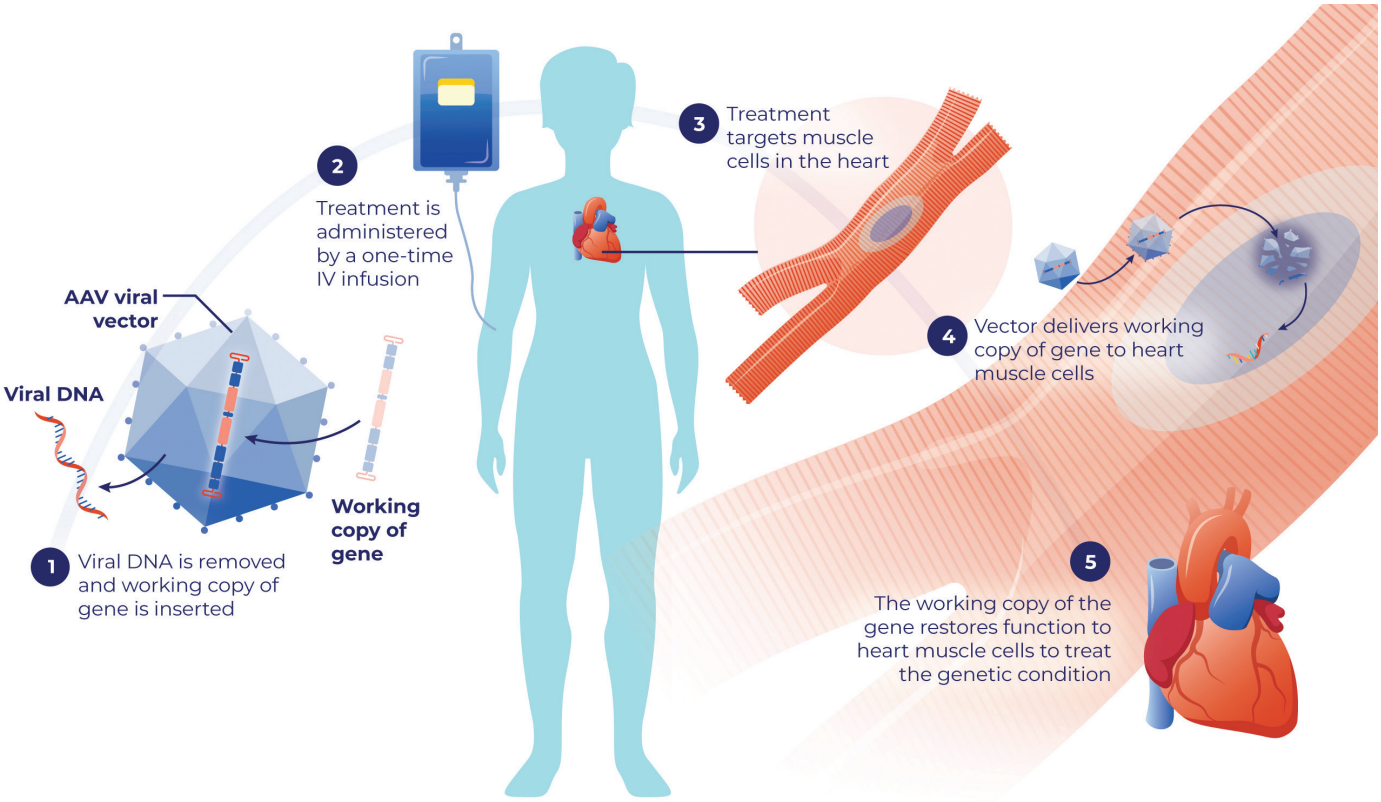
What is AAV gene therapy?

AAV gene therapy is an approach that uses an adeno-associated virus (AAV) as a vehicle (called a vector) to deliver a working copy of a gene into cells. AAV gene therapies have been studied in thousands of people for the treatment of many different genetic conditions for over 20 years.[8-11] Research on AAV gene therapies is ongoing, and there are currently several FDA-approved products that use AAV for the treatment of genetic conditions.[12]

An **adeno-associated virus (AAV)** is a naturally occurring virus that does not cause symptoms or diseases in people. AAV is one type of virus commonly used in gene therapy.[13] It is modified to be used as a vector, or vehicle, to carry genes into the body's cells.[2]



Viruses are used because they are good at entering cells. When a virus is made into a vector, all viral genes are removed and replaced with a working copy of a human gene.[14] Once inside the body, the vector can deliver the working gene into target cells, such as heart muscle cells. The goal of this approach is to address the underlying genetic condition and correct the problem, rather than only treating symptoms.



What is Tenaya's approach?

Tenaya is researching AAV gene therapies for genetic heart conditions.

Tenaya's AAV gene therapies are intended to

- be delivered via a one-time intravenous (IV) infusion
- target specific types of muscle cells in the heart

Tenaya's gene therapies are investigational and have not been approved by the U.S. Food and Drug Administration (FDA) or any other countries' health authority or regulatory agency.

Common questions about gene therapy

What are the goals and potential benefits of AAV gene therapy for genetic heart conditions?

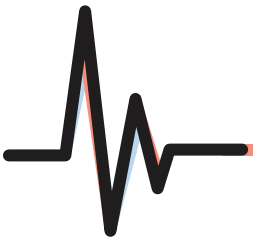
The goals of gene therapy for genetic heart conditions are:

- To address the underlying genetic cause or root cause of the condition
- To prevent or reverse the condition
- To demonstrate meaningful improvements in heart rhythm, heart pump function, symptoms, and quality of life
- To be administered as a single (one time) IV dose, with a long-lasting response

While gene therapy for inherited heart disease is still under investigation, it has several potential benefits:

- To stop or reverse genetic heart disease progression
- To stop or decrease the need for other medications and devices
- To increase quality of life
- A one-time therapy

How long will AAV gene therapy work?



AAV gene therapy is designed to achieve permanent or long-lasting effects in the body. The FDA recommends that developers of gene therapies conduct long-term follow-up studies of at least five years. During this time, researchers will monitor patients for safety and to understand how well the gene therapy is working.

What are the potential risks of AAV gene therapy?

Researchers are studying the potential risks of AAV gene therapy, which may include:

- The immune system may recognize the gene therapy as a harmful intruder. AAVs do not cause diseases in people. However, the immune system is designed to remove anything it does not recognize as part of a person's body. The immune system may react by attacking the treatment before it has a chance to work.[9,15]
  - Some studies of AAV and other forms of gene therapy show that immune system reactions may affect a person's liver[15]
  - Medicines that suppress or subdue the immune system are typically given before a person receives AAV gene therapy to help prevent or reduce this reaction[16]
- Currently, a person can receive AAV gene therapy only once; it cannot be re-dosed or administered in a larger dose at a later time[9,15]
  - After the first treatment with AAV gene therapy, a person's immune system makes antibodies to the AAV vector. If the body sees the same AAV again, it will attack it before it has a chance to work[18]
- AAV gene therapy may deliver a working gene to the incorrect cell[9,18]
- Participation in an AAV gene therapy clinical trial may prevent an individual from participating in clinical trials for other AAV gene therapies in the future
- Although many clinical trials of AAV gene therapies have been completed to date, other clinical trials of AAV gene therapies are still ongoing and not all of the risks are known

If a person receives AAV gene therapy, will they pass the new working gene to their children?

AAV gene therapy does not make changes to genes in a person's reproductive cells (i.e., sperm or eggs).[19] The working gene cannot be passed from a parent to a child and so receiving AAV gene therapy will not change the risk of potentially passing on a genetic condition to children.

Will AAV gene therapy protect a person's children from having their genetic heart condition?

Are there any approved AAV gene therapies?

As of March 2023,

The U.S. FDA has approved three AAV gene therapies:[12]

- A treatment for people with inherited retinal disease (IRD)
- A treatment for children less than two years old with spinal muscular atrophy (SMA)
- A treatment for adults with hemophilia B

The European Medicines Agency has granted conditional approval or approval in the European Union for two AAV gene therapies:

- A treatment for adults with severe hemophilia A[20]
- A treatment for adults and children aged 18 months and older with severe aromatic L-amino acid decarboxylase (AADC) deficiency[21]
- A treatment for children with spinal muscular atrophy (SMA)[22]

Where can I find more information about gene therapy?

These organizations can provide educational information about gene therapy:

American Society of Gene & Cell Therapy (ASGCT): www.asgct.org
HealingGenes: www.healinggenes.org
MedlinePlus Genetics: www.medlineplus.gov/genetics
National Human Genome Research Institute: www.genome.gov
Global Genes: www.globalgenes.org
National Organization for Rare Disorders (NORD): www.rarediseases.org

Gene therapy - words to know

AAV (adeno-associated virus): A naturally occurring virus that does not cause illness, infections, or diseases in people. It can be modified to carry genes into a person's cells.[2]

DNA (deoxyribonucleic acid): Genes are composed of segments of DNA. DNA carries the genetic information in cells.[2,3]

Gene: A segment of DNA that carries a cell's genetic information. Genes provide instructions for the structure and function of cells in the body. Some genes include instructions to make molecules called proteins.[3]

Gene therapy: A way to treat or prevent a disease or medical disorder using functional genes.[6]

Genetics: The scientific study of genes and inheritance.[23]

Genetic condition: A disease or disorder caused in whole or in part by a change in the typical DNA sequence of a gene, also called a gene mutation or variation.[5]

Immune response: The process by which a person's immune cells, also called white blood cells, find and fight an infection or a foreign substance in the body.[24]

Immune system: An organization of cells, tissues, and organs that work together to protect a person from infection, other diseases, or a foreign substance that it does not recognize as part of the body.[25]

Protein: A large molecule made from the instructions of genes. Proteins are crucial to almost all the work done by cells in a person's body, and are required for the structure, function, and regulation of a person's tissues and organs.[4]

Variation: A change or mutation in the typical DNA sequence of a gene.[23]

Vector: A vehicle or carrier used in gene therapy for delivering a working gene to target cells.[14]

We encourage you to talk with your doctor if you have any questions about gene therapy. You may also share the information in this brochure with your doctor.

References: [1]U.S. Department of Health and Human Services, National Institutes of Health, National Institute of General Medical Sciences; 2020. https://www.nigms.nih.gov/education/fact-sheets/Pages/studying-cells.aspx. Accessed March 30, 2023. [2]American Society of Gene + Cell Therapy; 2023. https://asgct.org/education/more-resources/glossary. Accessed March 30, 2023. [3]U.S. Department of Health and Human Services, National Institutes of Health, National Human Genome Research Institute; 2023. https://www.genome.gov/genetics-glossary/Gene. Accessed March 30, 2023. [4]U.S. Department of Health and Human Services, National Institutes of Health, National Human Genome Research Institute; 2023. https://www.genome.gov/genetics-glossary/Protein. Accessed March 30, 2023. [5]U.S. Department of Health and Human Services, National Institutes of Health, National Human Genome Research Institute; 2018. https://www.genome.gov/For-Patients-and-Families/Genetic-Disorders. Accessed March 30, 2023. [6]Musunuru K., et al. Genetic testing for inherited cardiovascular diseases: a scientific statement from the American Heart Association. *Circ Genom Precis Med*. 2020;13:e000067. [7]Department of Health and Human Services, National Institutes of Health, National Human Genome Research Institute; 2023. https://www.genome.gov/genetics-glossary/Gene-Therapy. Accessed: March 30, 2023. [8]Kuzmin DA, et al. The clinical landscape for AAV gene therapies. *Nat Rev Drug Discov*. 2021;20:173-174. [9]Au HKE, et al. Gene therapy advances: a meta-analysis of AAV usage in clinical settings. *Front Med*. 2022;8:809118. [10]George LA, et al. Long-term follow-up of the first in human intravascular delivery of AAV for gene transfer: AAV2-HFIX16 for severe hemophilia B. *Mol Ther*. 2020;28:2073-2082. [11]Novartis. Q3 2022 Results. https://www.novartis.com/news/novartis-financial-results-q3-2022. Accessed March 29, 2023. [12]U.S. Food and Drug Administration (FDA); 2022. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products. Accessed March 30, 2023. [13]Naso MF, et al. Adeno-Associated Virus (AAV) as a vector for gene therapy. *BioDrugs*. 2017;31:317-334. [14]American Society of Gene + Cell Therapy. 2021. https://patienteducation.asgct.org/gene-therapy-101/vectors-101. Accessed March 30, 2023. [15]Delire B, et al. Immunotherapy and gene therapy: new challenges in the diagnosis and management of drug-induced liver injury. *Front. Pharmacol*. 2022;12:786174. [16]Xiang Z, et al. The effect of rapamycin and ibrutinib on antibody responses to adeno-associated virus vector mediated gene transfer. *Hum Gene Ther*. 2022;33:614-624. [17]Meliani A, et al. Determination of anti-adeno-associated virus vector neutralizing antibody titer with an in vitro reporter system. *Hum Gene Ther Methods*. 2015;26:45-53. [18]Mayo Foundation for Medical Education and Research; 2022. https://www.mayoclinic.org/tests-procedures/gene-therapy/about/pac-20384619. Accessed March 30, 2023. [19]Goswami R, et al. Gene therapy leaves a vicious cycle. *Front. Oncol*. 2019;9:297. [20]European Medicines Agency; 2022. https://www.ema.europa.eu/en/news/first-gene-therapy-treat-severe-haemophilia. Accessed March 30, 2023. [21]European Medicines Agency; 2022. https://www.ema.europa.eu/en/medicines/human/EPAR/upstaza. Accessed March 30, 2023. [22]European Medicines Agency; 2022. https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma. Accessed March 30, 2023. [23]U.S. Department of Health and Human Services, National Institutes of Health, National Institute of General Medical Sciences; 2022. https://nigms.nih.gov/education/fact-sheets/Pages/genetics.aspx. Accessed March 30, 2023. [24]U.S. Department of Health and Human Services, National Institutes of Health, National Institute of General Medical Sciences; 2022. https://nigms.nih.gov/education/pages/glossary.aspx#letter-I. Accessed March 30, 2023. [25]U.S. Department of Health and Human Services, National Institutes of Health, National Library of Medicine; 2020. https://medlineplus.gov/immunesystemanddisorders.html. Accessed March 30, 2023.

For more information about Tenaya and Tenaya's investigational gene therapies for genetic heart conditions:

Visit www.TenayaTherapeutics.com
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