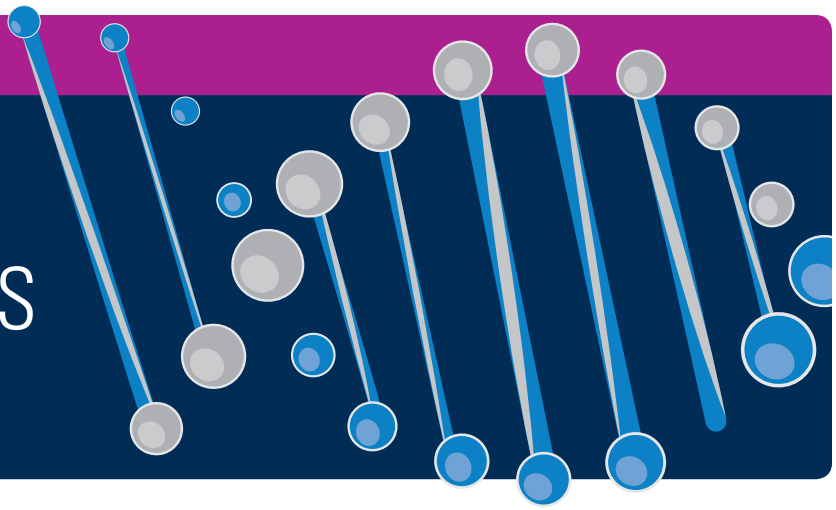
FOR PATIENTS

FREQUENTLY ASKED QUESTIONS

ABOUT GENE THERAPY



What is a gene?

Consisting of segments of DNA, genes primarily provide instructions to the body for making proteins. Proteins are the building blocks of the body and play an important role in functions like repairing tissue and helping blood to clot.

What causes genetic conditions?

Genetic conditions, such as cystic fibrosis and haemophilia, are the result of mutations, or variations, in the structure of a gene. These mutations are most often passed down from biological parents but can sometimes happen spontaneously.

What is gene therapy?

Gene therapy is a method that attempts to use genes to treat or prevent disease. It has been developed to treat several diseases and is currently being evaluated in multiple clinical studies across a wide range of other conditions to determine its potential benefits and risks.

What is gene transfer therapy?

Gene transfer therapy introduces functional, or working, genes into the body with the intent of helping the body create proteins it was previously lacking.

How is gene transfer therapy designed to work?

Gene transfer therapy aims to introduce a functioning gene that can instruct the body to produce a needed protein. A functional gene is created in a lab. It's then placed into a specially created transport vehicle, most often made from the shell of a neutralised virus, called an adeno-associated virus, or AAV. The type of transport vehicle chosen is based on its ability to deliver the functional gene to a particular type of cell. In the case of haemophilia, AAVs that go primarily to the liver are chosen. This newly paired transport vehicle and functional gene are called a therapeutic vector. A large number of vectors are injected into the body, and the functional genes are delivered to their target cells. Once there, the functional gene is meant to instruct the target cells to produce the missing or lacking protein.

What's the difference between gene transfer and gene editing?

Both are methods of gene therapy currently being researched in clinical trials. However, where gene transfer therapy introduces functional genes into the body, gene editing aims to make changes to the original DNA. This technique makes it possible to repair the original DNA or add new DNA in a specific location in the body.

Zinc finger nucleases and CRISPR (clustered regularly interspaced short palindromic repeats) are methods of gene editing currently being researched.

What is a neutralised virus, or AAV?

When we talk about the transport vehicle used in gene transfer therapy, we're really talking about a specific type of virus, AAV, or adeno-associated virus. Occurring in nature, a variety of AAVs have been identified, none of which cause disease in humans. When used in gene therapy, the shell of the AAV is created on its own, without ever having contained viral material.

Who is eligible for AAV gene therapy?

Before a person can be considered a candidate for any gene therapy that uses AAV as the transport vehicle, they'll have to undergo a simple blood test. AAV occurs naturally and some people may have come into contact with it. This blood test will determine whether they already have antibodies to the AAV. Because the presence of antibodies to AAV can affect how gene therapy works, the results of the blood test may affect eligibility for treatment.

How many people have antibodies to AAV?

It can vary greatly. Because AAVs occur in nature, the rate, or seroprevalence, of antibodies is affected by geographic location as well as sex and age. Eleven types of AAV have been identified to date and it's estimated that up to 80% of the human population displays antibodies to at least one type of AAV.

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What if I have an antibody to the AAV in my desired gene therapy?

Over the short term, people with antibodies to AAV may be ineligible to receive their preferred gene therapy. However, studies are ongoing to determine the exact effects an existing antibody to AAV may have on the effectiveness of AAV-based gene transfer therapies. And, with continued research, more gene therapies are entering the market every year.

What are the goals of gene therapy?

Gene therapy aims to address specific mutations in an individual's genes, allowing their body to produce the proteins it needs. Gene therapy treatment may lead to less reliance on currently available medications and may possibly eliminate or reduce routine disease management.

What are the risks of gene therapy?

Gene transfer that uses an adeno-associated virus (AAV) vector to deliver the new genetic material may have several risks:

- As with any virus, the body's immune system could respond to the newly introduced therapeutic vector as if it were an intruder. An immune system reaction can lead to inflammation and other serious risks
- An immune reaction could also make gene therapy work less effectively, or not at all. That is why prospective gene therapy patients are often screened to determine whether they have antibodies against a specific virus
- While the objective of using a particular vector is to direct the new gene to a specific tissue type, viruses can affect other cells that weren't targeted, potentially causing damage or additional illness or disease
- After delivery of the gene therapy, vector particles can be released from the recipient's body. Called vector shedding, this can occur through feces, urine, saliva, and other excreted bodily fluids. Shedding raises the possibility of passing those remaining materials on to untreated individuals through close contact. Its significance is currently being evaluated in gene therapy clinical trials
- Whether gene therapy may have an adverse impact on the health of the organ or tissues targeted is being evaluated with long-term studies
- Gene therapy may result in creation of too much of the protein. The effect of this overproduction, or overexpression, could vary based on the type of protein being created
- For some patients, gene therapy may not work at all. And, it is not yet clear how long the effects of gene therapy may last

Is gene transfer therapy a cure?

Gene transfer therapy is not a cure. While the hope is to allow the body to produce what it needs, gene transfer therapy does not change the makeup of your DNA. Patients with a disease still have that disease even if they show no symptoms. And, that disease can still be passed on to offspring.

Can my gene therapy be passed on to my partner?

While passing along genetic components of gene therapy hasn't been seen in clinical trials, it's best to follow some simple guidelines after you've received a gene therapy treatment:

- Men and/or their female partners should avoid pregnancy and men should not donate semen for a period of 6 months
- And, don't donate blood, or organs, tissues, and cells for transplantation

Are there other health considerations?

Gene therapies are designed to target certain cells within the body. It's possible that alcohol and some forms of medicinal supplements can put additional stress on the body. Consult your physician about follow-up care after treatment with gene therapy.

Is gene therapy safe in children?

Certain gene therapies have been studied in children and were found to be safe and effective. However, not all gene therapies have been studied this way.

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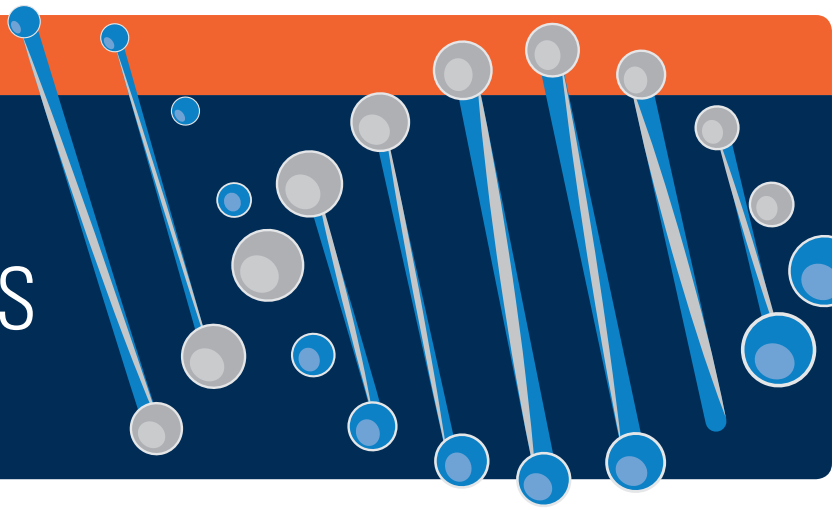

What's the difference between somatic and germ-line gene therapy?

The two major categories of gene therapy, somatic and germ-line, are classified by the nature of the targeted cell.

Germ-line gene therapy involves inserting a working, or functional, gene into reproductive cells (ie, egg or ovum or sperm). This gene will be integrated into the individual genomes and can be passed on to offspring.

With somatic gene therapy, functional genes are transferred into the patient's somatic, or nonreproductive, cells. Therefore, the resulting modifications in the patient's genome cannot be inherited; any effects are restricted to the individual receiving the somatic gene therapy. Somatic gene therapy is also referred to as gene transfer therapy.

How is gene transfer therapy designed to work?

Gene transfer therapy aims to introduce a functioning gene that can instruct the body to produce needed proteins. This method is being investigated in clinical trials in many conditions, and the Food and Drug Administration (FDA) has approved gene transfer therapy for several indications.

The gene transfer process begins when a functional copy of a mutated gene is created in a laboratory. The functional gene is developed to contain the instructions for making a needed protein.

The functional gene then has to be delivered into the body. To protect the gene and allow it to be introduced into the body, a transport vehicle is created from the protein shell of a neutralised virus. Viruses used in gene transfer include adenovirus, adeno-associated viruses (AAV), and lentiviruses.

The functional gene is placed inside the transport vehicle, creating a therapeutic vector, which is designed to target the functional gene toward a preferred tissue. Large numbers of therapeutic vectors are administered via intravenous infusion.

Once introduced in the body, the new gene is designed to work in place of the gene that isn't functioning properly. If successful, the goal for this new gene is to provide instructions for the body to make the protein it needs.

What can affect patient eligibility for gene transfer therapy?

Adeno-associated virus is one type of neutralised virus used in gene transfer therapy. Because AAVs occur naturally and are non-pathogenic, it's possible that some people have already been exposed and developed antibodies against them. Because the presence of antibodies to AAV can affect how gene therapy works, currently, only those who do not have pre-existing antibodies are eligible for AAV gene transfer therapy.

What tests are involved prior to receiving gene therapy?

A simple blood test can determine whether or not a patient already has antibodies to AAV. The results of the blood test may affect eligibility for treatment.

How is gene therapy handled in the office?

Each gene therapy has its own specific handling and administration instructions, but there are some commonalities. Gene therapy arrives at the office or dosing facility frozen at approximately ≤-60°C and should be kept frozen until ready to prepare for administration. The drug should be thawed either within a refrigerator or at room temperature before administering. Once thawed, the product should be used within a certain time frame (typically a few hours) and should not be refrozen.

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