Future Rare Diseases

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Plain Language Summary of Publication

Future Rare Diseases

A plain language summary of AAV-based gene therapy: challenges and potential solutions for people with antibodies against AAV

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Summary

What is this article about?

This is a summary of a review article about gene therapy. Review articles summarize many previously published scientific articles. The review was about how a common **virus** could change how one type of gene therapy works. It also discussed the importance of antibody testing for people who may receive gene therapy. The original review was published in *Molecular Therapy* in 2023.

Gene therapy is a type of medical treatment. The goal of a specific gene therapy is to treat a specific **genetic condition**. A genetic condition is a health problem caused by a variation (change or mutation) in a **gene** or genes. Genes are instructions that tell the body how to grow and work.

Some genetic conditions can cause rare diseases. A rare disease affects only a very small percentage of people. Gene therapy may help people with some rare diseases because it aims to correct the root cause of the condition instead of just treating symptoms.

Gene therapies work by getting into the **cells** in a person's body. Many gene therapies are modeled after viruses because viruses are good at getting into the body.

One of the viruses used in gene therapy is called **adeno-associated virus** (**AAV** for short). This naturally occurring virus infects many people. People can get infected without realizing it because AAV doesn't typically make a person sick.

After being infected with a virus, people make **antibodies** to fight off that virus. These antibodies can prevent another infection. Antibodies that fight off natural AAV may prevent gene therapy based on AAV from working as it should.

A common reason why people may not be able to receive gene therapy is because they have antibodies against AAV. This means that some people with some genetic conditions or rare diseases may not be able to benefit from gene therapy.

How to say (double click sound icon to play sound)...

- **AAV:** eh-aye-vee
- **Adeno-associated virus:** A-deh-noh-ah-sew-SEE-AYE-ded VY-rus
- **Adenovirus:** add-eh-noe VY-rus
- **Duchenne muscular dystrophy:** dew-SHEN MUS-kyoo-lahr dis-TROH-fee
- **Hemophilia:** HEE-moh-FIH-lee-uh
- **Immunosuppressants:** IH-myoo-noh-suh-PREH·scents
- **Neutralizing:** NOO-troh-LIZE-ng
- **Placenta:** pluh-SEN-tuh
- **Plasmapheresis:** PLAZ-muh-feh-REE-sis
- **Therapeutic:** THAYR-uh-PYOO-tik
- **Thrombotic microangiopathy:** throm-BOH-tik mai-krow-AHNjee-ow-pa-thee

Virus: a type of germ that can enter your body. Some viruses make people sick, but others do not cause any illness.

Genetic condition: health problem caused by a variation (change or mutation) in a gene or genes.

Gene: genetic material that contains the instructions that tell the body how to grow and function properly.

Cell: the basic building block of all living things. Genes are contained inside cells.

Adeno-associated virus (AAV): a small virus that occurs in nature. It is generally considered to not cause illness in people.

Antibodies: proteins produced by the body that recognize and fight specific germs.

Side effects: unwanted or unexpected effects of a medicine or treatment.

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Researchers are trying to understand how antibodies against AAV can prevent gene therapy from working. They are also studying what **side effects** they may cause. This research is important for people with a genetic condition or rare disease that may be treated with gene therapy.

What conclusions did we draw?

- People who have a certain level of antibodies against AAV might not be able to take part in gene therapy clinical trials. They might not be able to receive AAV-based gene therapies that have been approved for commercial use by a regulatory agency such as the FDA (Food and Drug Administration) or EMA (European Medicines Agency).
- For most gene therapies, people need to be tested for antibodies against AAV.
- There are two different types of tests that measure if someone has antibodies against AAV.
- Researchers are looking at ways to lower the effects of antibodies against AAV. This research could allow more people to have gene therapy in the future.

Who sponsored this work?

This work was **sponsored** by Pfizer.

Sponsor: a company or organization that oversees and pays for a clinical research study. The sponsor also collects and analyses the information that was generated during the study.

Who is this article for?

This article is meant for:

- people with a genetic condition or rare disease that may be treatable with AAV-based gene therapy
- their family members and caregivers
- patient advocates
- healthcare professionals who may provide care to people who could be treated with gene therapy

Where can I find the original article on which this summary is based?

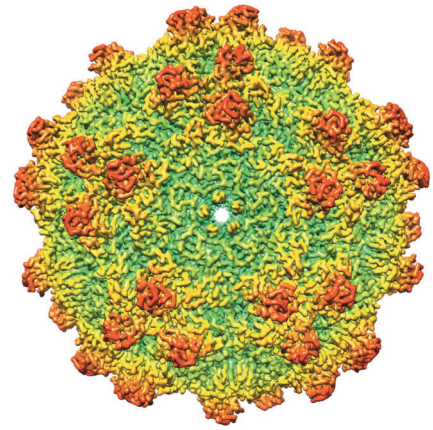
You can read the original article, titled "Binding and neutralizing anti-AAV antibodies: Detection and implications for rAAV-mediated gene therapy", published for free in the journal *Molecular Therapy* at:
https://www.sciencedirect.com/science/article/pii/S1525001623000102

What is adeno-associated virus?

Adeno-associated virus (AAV) is a small virus that occurs in nature. It does not typically cause illness in people. AAV often infects children. Most people do not know when they have been infected. This is because in almost all cases, AAV does not make them feel sick.

Researchers have learned how to use viruses like AAV to deliver a type of treatment called gene therapy. We usually think of viruses as germs that can make a person sick. But in the case of gene therapy, viruses are used to help deliver treatment.

Some gene therapies are made using a changed version of AAV. The focus of this article is on this type of gene therapy. It is called AAV-based gene therapy.



Adeno-associated virus (AAV)

This figure is from an article published in *Acta Crystallographica Section D: Structural Biology* called "Cryo-EM structure of adeno-associated virus 4 at 2.2 Å resolution." You can access the full article for free here:
https://journals.iucr.org/d/issues/2023/02/00/ni5023/index.html

What is gene therapy?

There are different approaches to genetic medicine being studied for different diseases. Some approaches add genes. Other approaches remove or change genes. This article focuses on an approach that transfers (moves into cells) or adds genes, which is referred to here as gene therapy.

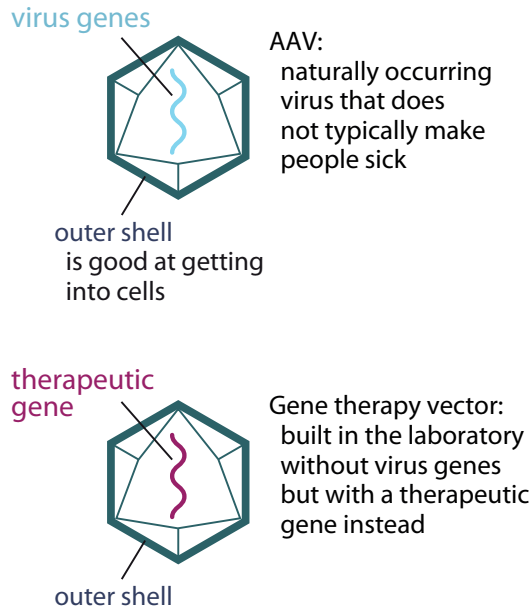
Gene therapy is a new type of medicine that targets the root cause of a genetic condition. Its purpose is to fix the genetic condition at the source instead of only treating symptoms.

The body is made up of billions of cells. Each cell contains a person's genes. Genes are the instructions that tell the body how to grow and work. A variation in a gene or genes can stop some parts of the body from working. This is called a genetic condition.

Genetic conditions caused by variation in a gene can be serious for some diseases, depending on which gene is affected. Some genetic conditions are caused by variation in a single gene. These include many rare diseases. For example:

- hemophilia
- Duchenne muscular dystrophy
- sickle cell disease
- cystic fibrosis
- spinal muscular atrophy

These genetic conditions are a good target for gene therapy because they may be treated by adding a single gene.



Gene therapy adds a working copy of the variant gene into a person's cells. The working copy is called a **therapeutic gene**. It may also be called a healthy, functioning, or working gene. The therapeutic gene has instructions that tell the cells how to work properly again. That means gene therapy targets the cause of the genetic condition instead of targeting only symptoms.

The gene therapy approaches that are currently being developed target somatic cells (all cells in the body except the sex cells, for example, sperm and eggs). They have not been reported to change genes that are passed down to future children.

To work, gene therapy needs to deliver the therapeutic gene into a person's cells. The therapeutic gene cannot be given in an **oral medication** (like a pill) because it would be damaged in the stomach. Instead, the therapeutic gene must be added directly into the blood or tissue. To protect the therapeutic gene in the blood or tissue, gene therapies use a **vector**.

Therapeutic gene: A gene made in a laboratory that is added or transferred into a person's cells to treat a genetic condition caused by a variation in a single gene.

Oral medication: Medicine taken by mouth.

Vector: A tool used to deliver genes into a cell. Vectors are made up of the therapeutic gene plus a protective outer coating.

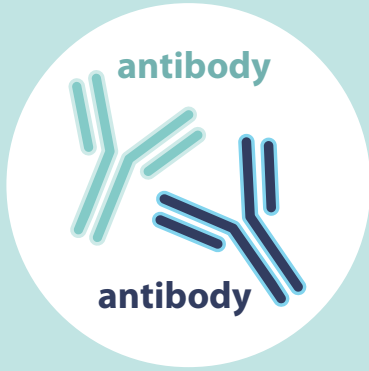
Infuse: A way of delivering a treatment or medicine into the blood.

A vector is a vehicle used to deliver genes directly into a cell. To create vectors, researchers make use of the outer shell of viruses (like AAV). This lets researchers build a therapy that is good at getting into the cells of a person's body because the outer shells of viruses are very good at getting inside cells.

Researchers remove the virus genes so that the vector carries only the therapeutic gene. They then inject or **infuse** the gene therapy vector into a person. The outer shell protects the therapeutic gene and helps deliver it to the right cells so it can work.

Many gene therapies use vectors based on AAV. These vectors are generally good at getting into cells. They have some challenges. For instance, people may have made antibodies against AAV that can eliminate the vector.

What are antibodies?

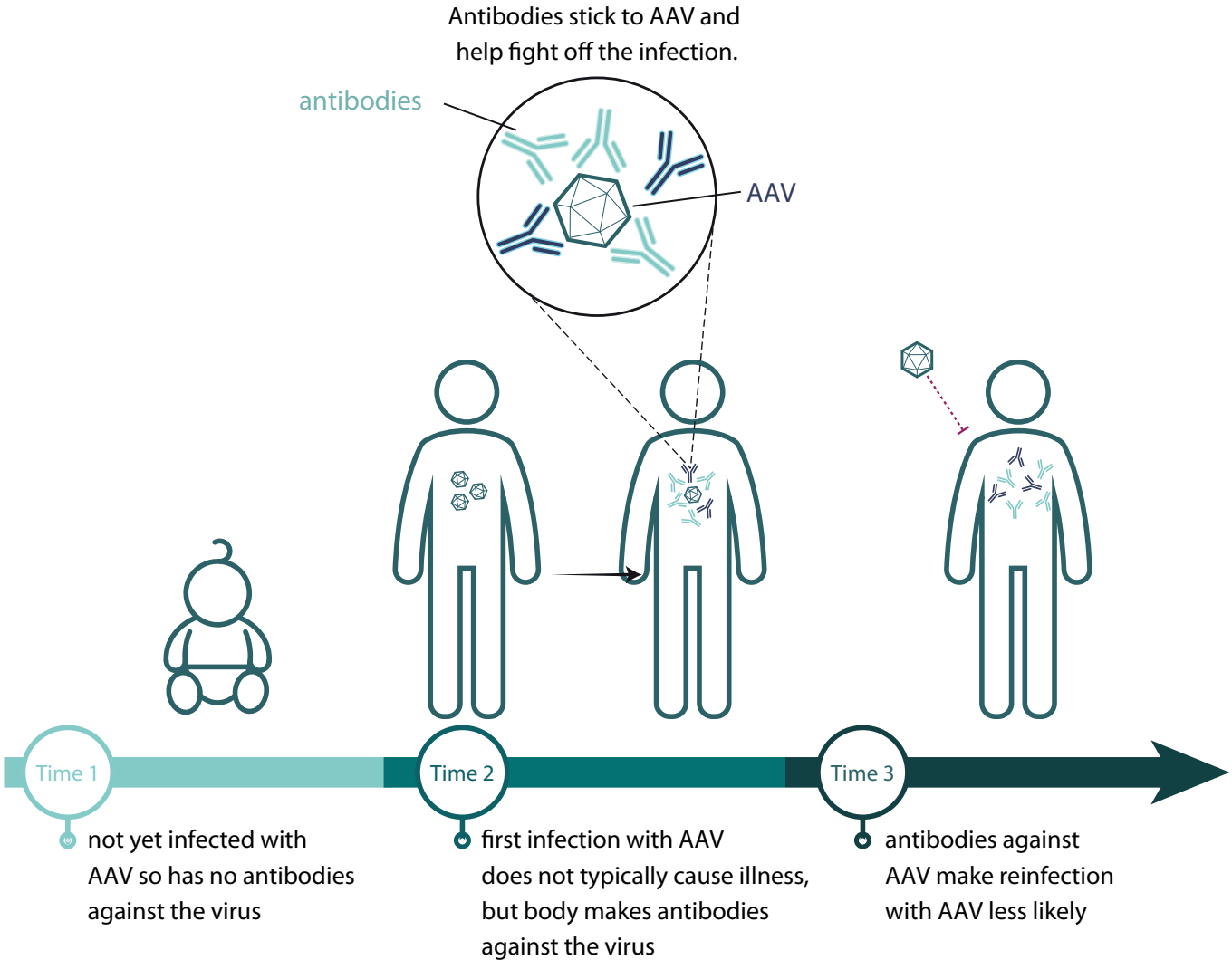


Antibodies are proteins produced by the body to fight germs. Your body can learn to make many different antibodies. They help you fight off many different types of germs.

When a person gets infected by a virus like AAV, their **immune system** learns to make antibodies against the AAV. The antibodies recognize AAV and fight the virus off. After the virus is gone, the immune system can remember it and keep making antibodies against AAV. These antibodies can help protect a person from getting reinfected by AAV again.

Immune system: The body's natural defenses against germs.

This is a timeline showing how a person might develop antibodies against naturally occurring AAV over the course of their life:



How many people have antibodies against AAV?

Between 30% (3 out of every 10 people) to 60% (6 out of every 10 people) of people have antibodies against AAV. The chance that a person has antibodies against AAV can be higher or lower based on:

Age – The number of infections goes up as you get older. Older people are more likely to have antibodies against AAV.

Where people live – AAV is more common in certain parts of the world.

Health – Some health conditions might affect a person's immune system; for example, cancer.

Medications people are taking – Some medications may stop the immune system from working as well. Examples: immunomodulatory drugs, some steroids.

Type of AAV – Different types of AAV may trigger the immune system by different amounts.

How antibodies are measured – Different types of tests may be more or less likely to find antibodies against AAV.

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Are there any other ways that people can develop antibodies against AAV?

Most people develop antibodies against AAV after a natural infection. Researchers are studying other ways that people might develop antibodies against AAV. These include:

- Passing antibodies from mother to baby via the **placenta** and in breast milk. These antibodies last for a short time.

- AAV-based vaccines – Some vaccines use viral vectors. These teach the immune system how to make antibodies against a virus. This protects the person from catching the virus in the future. Although possible, developing antibodies against AAV after receiving an AAV-based vaccine has not been proven. Right now, AAV-based vaccines are only studied in **clinical trials**.

- Previous treatment with gene therapy that used an AAV-based vector.

* Important: Adeno-associated virus (AAV) is different from **adenovirus**.

Some COVID-19 vaccines are based on adenovirus, for example:

- Johnson & Johnson (J&J)/Janssen COVID-19 vaccine, called Jcovden
- Oxford/AstraZeneca COVID-19 vaccine, called Vaxzevria or Covishield

People who have received these adenovirus-based vaccines can still potentially get AAV-based gene therapy if they do not have antibodies against AAV. They would still need to meet other eligibility criteria.

Vaccines based on messenger RNA (mRNA for short) do not affect whether a person may get gene therapy. These include:

- Pfizer–BioNTech COVID-19 vaccine, called Comirnaty
- Moderna COVID-19 vaccine, called Spikevax

Placenta: an internal organ that joins a mother and her unborn baby. It provides food and oxygen to help the baby grow.

Clinical trial: a research study that tests a medical treatment in people.

Adenovirus: a common virus that can cause mild cold- or flu-like symptoms. Adeno-associated virus (AAV) is different from adenovirus.

Can antibodies against AAV change how well gene therapy works?

Antibodies against AAV in a person's blood may also recognize the gene therapy vector as a threat. This is because the outside of the vector "looks like" naturally occurring AAV. The antibodies may then fight off the vector used for gene therapy. This can reduce how well the gene therapy works.

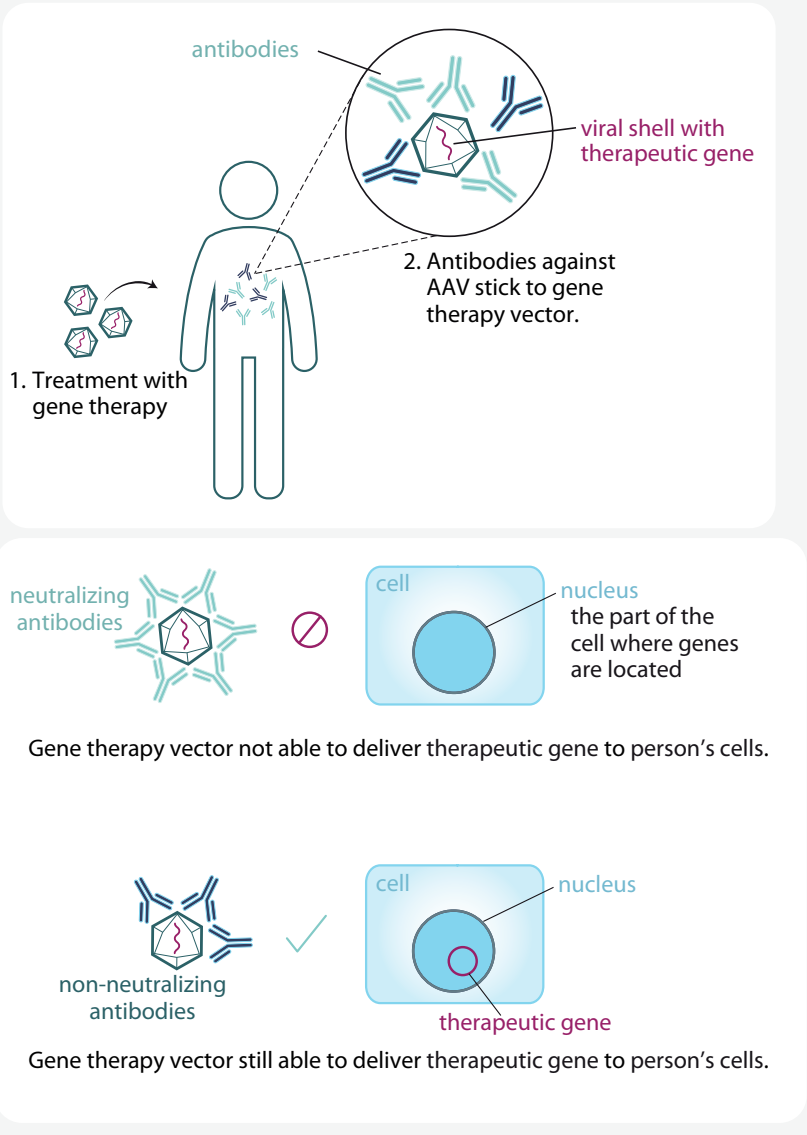
There are two types of antibodies:

Neutralizing antibodies, which stick to the gene therapy vector. They stop it from delivering the therapeutic gene to a person's cells. If the therapeutic gene cannot be delivered, the gene therapy will not work.

Non-neutralizing antibodies, which stick to a different part of the gene therapy vector. This does not stop the vector from delivering the therapeutic gene. This means that the gene therapy could still work.

Neutralizing antibodies: a type of antibody that stops (or neutralizes) its target from having an effect.
Non-neutralizing antibodies: a type of antibody that does not stop (or neutralize) its target from having an effect.

A person can have both types of antibodies against AAV. Sometimes people may have only one or the other type, but this is rare.



Do antibodies against AAV cause any side effects?

Antibodies against AAV may also cause side effects from gene therapy, including:

- Increasing a person's **immune response**. Too much activity in the immune system can make people feel sick. It may cause health problems. An immune response can also cause **inflammation**. Inflammation may cause fever or feeling flu-like. In more severe cases, it can cause injury to the heart or other muscles.
- A specific reaction called thrombotic microangiopathy. This is a condition which can cause **anemia**, kidney injury, and bleeding.

Immune response: activity of the immune system meant to protect the body from germs. Foreign substances like viruses can trigger an immune response.

Inflammation: a normal part of the immune system's response to injury or infection. It can cause symptoms like pain, swelling, and heat.

Anemia: a condition that happens when a person has a low number of red blood cells.

It is important for people to know if they have antibodies against AAV before receiving most gene therapies. This is particularly important for systemic gene therapies. Systemic gene therapies are those administered by an infusion into the bloodstream.

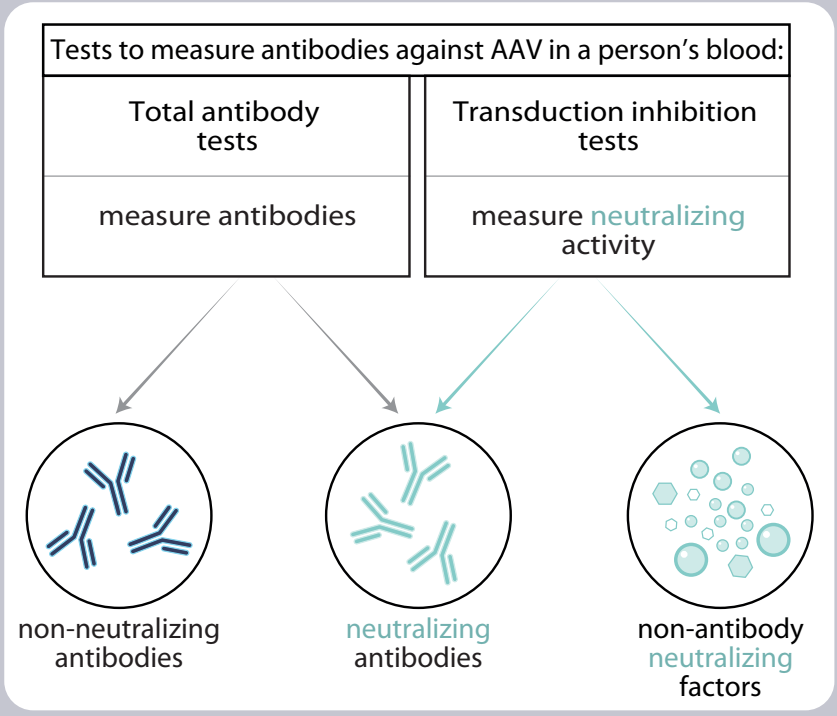
How do people find out if they have antibodies against AAV?

There are two types of blood tests that measure if someone has antibodies against AAV.

Total antibody tests measure antibodies. These tests measure different types of antibodies in a person's blood that stick to the gene therapy vector. That means they will measure both neutralizing and non-neutralizing antibodies.

Transduction inhibition tests measure neutralizing activity. These tests measure how much a person's blood stops the gene therapy vector from working. Transduction inhibition tests will measure neutralizing antibodies. They will not measure non-neutralizing antibodies. These tests also measure any other neutralizing factors in a person's blood, even if they are not antibodies.

Each test measures a different thing. The results of the two tests cannot be compared.



Important things to keep in mind:

- The amount of antibody a person makes can change over time. The same test done at a different time may give different results
- Tests used in clinical trials can be different from tests used in routine healthcare
- Sometimes people will need to take a specific test before they can receive gene therapy. Different gene therapies may require different tests
- Antibody tests are not needed for all gene therapies

Does having antibodies against AAV stop people from getting gene therapy?

Testing positive for antibodies against AAV could have a significant impact on the lives of people with a genetic condition or their families. They may not be able to receive a potentially transformative or life-saving treatment.

Doctors and researchers must balance safety with the availability of treatments. People may be tested for antibodies against AAV before they can receive some approved gene therapies. If their antibodies are too high, they may not be able to receive the gene therapy. Researchers who carry out gene therapy clinical trials may check the levels of antibodies against AAV in a person's blood before they can take part in a clinical trial.

Researchers do not completely understand the link between the presence of antibodies and how well gene therapy might work. For example, some gene therapies seem to work even when tests show that a person has antibodies. This often depends on the levels of antibodies a person has.

- Researchers are trying to understand which people are most likely to experience side effects
- They are also trying to improve antibody tests so the results are more accurate

This research is important because it will help make sure that people are not excluded from getting gene therapy due to the presence of antibodies against AAV unless it would be unsafe for them. This will allow more people to be eligible for gene therapies that could significantly improve their health.

What options are available to people who have antibodies against AAV?

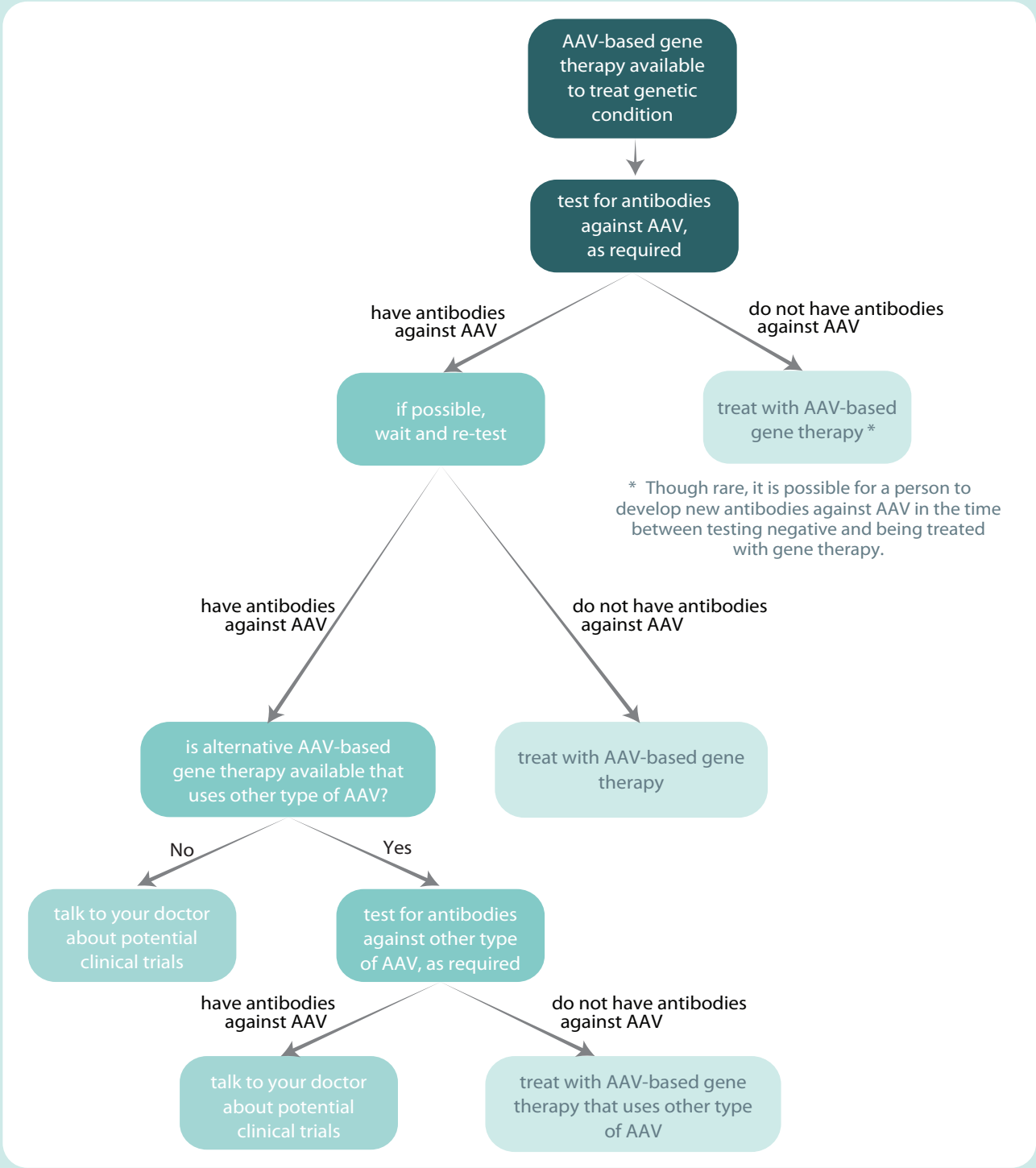
Researchers are trying to find ways to lower the effects of antibodies against AAV. This could allow more people to get gene therapy. Clinical trials are testing treatment options for people with antibodies against AAV. These may include:

- Pre-treatment approaches. These approaches lower antibodies in a person's blood before they get gene therapy.
  - Plasmapheresis is a process that filters a person's blood and removes antibodies
  - Immunosuppressants are a type of medicine that lowers the activity of the immune system
  - Other types of medicine can be used to lower only certain types of antibodies in a person's blood
- Gene therapy vector-related approaches. These approaches change the gene therapy itself so that it is less affected by antibodies.
  - Gene therapies may be delivered in a higher dose
  - Gene therapies may be delivered directly into a target, like the eye
  - The outer shell of the gene therapy vector can be changed. This could stop antibodies against a type of AAV from recognizing the vector

How does having antibodies against AAV affect the patient journey to getting gene therapy?

This is a diagram with information for people who may have antibodies against AAV. It shows how antibody testing may affect potential gene therapy options available to them.

People must also meet any other eligibility criteria before being treated with gene therapy.



What are the key points of this review and what do they mean?

- ✓ Having antibodies against AAV is common. Between 30% (3 out of every 10 people) to 60% (6 out of every 10 people) have antibodies against AAV
- ✓ Having antibodies against AAV could reduce how well some gene therapies work for a person. Having antibodies against AAV may lead to some side effects
- ✓ It is important to know if a person has antibodies against AAV before they are treated with an AAV-based gene therapy
- ✓ Different tests are available to measure the antibodies against AAV in a person's blood. The type of test that is offered will depend on the specific gene therapy
- ✓ Researchers are trying to understand how different antibody levels can affect gene therapy. They are also looking at what side effects they might cause
- ✓ Researchers are coming up with ways to lower the effects of antibodies against AAV. This could allow more people to potentially benefit from gene therapy

Where can I find more information?

This summary is based on the original review article published in *Molecular Therapy* called "Binding and neutralizing anti-AAV antibodies: Detection and implications for rAAV-mediated gene therapy." You can access the full article for free here: https://www.sciencedirect.com/science/article/pii/S1525001623000102

Other sources of information:

Gene & Cell Therapy Education: ASGCT - American Society of Gene & Cell Therapy
https://patienteducation.asgct.org/

EuroGCT
https://www.eurogct.org/

NIH National Human Genome Research Institute
https://www.genome.gov/genetics-glossary/Gene-Therapy

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Competing interests disclosure

Tara Moroz, Martin Schulz, Daniel I. Levy, George Bashirians, Ian Winburn, Matthias Mahn, Suryanarayan Somanathan, and Seng H. Cheng are Pfizer employees, or were Pfizer employees at the time of publication of the original review article. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

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