Gene Therapy 101

Produced by Sarepta Therapeutics

Over the course of 2023, Sarepta published a four-part educational series in the *LGMD News Magazine* on the science of gene therapy.

All four parts are compiled in this booklet.

Members of the U.S. community can sign up at limbgirdle.com/stay-connected to receive information on community resources, news, and research on LGMD.

Have more gene therapy science questions, comments, or want to connect with a member of the Sarepta Patient Affairs team? Please email us at Advocacy@Sarepta.com.

SAREPTA THERAPEUTICS

Intended for US audiences

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Sarepta Therapeutics is a biotech company headquartered in Cambridge, Massachusetts. We have over 20 gene therapy programs in development, including for limb-girdle muscular dystrophy types 2E/R4, 2D/R3, 2C/R5, 2B/R2, 2L/R12, and 2A/R1.

The science of gene therapy is complicated—Sarepta is committed to providing educational resources for rare disease communities to improve understanding of this investigational treatment approach. To do this, we're kicking off a four-part educational series, where we'll delve into questions and topics the community has asked about, such as:

What is the goal of gene therapy?

Why is gene therapy currently a one-time treatment?

How is gene therapy evaluated in clinical trials?

How long are the therapeutic effects of gene therapy expected to last?

Look for more Gene Therapy 101 in the next few issues.

If you're interested in learning more, here are a few additional ways to connect with us:

TEST YOUR KNOWLEDGE

Scan the QR code to visit limbgirdle.com and quiz yourself on the topics featured in this article

FIND MORE INFORMATION

Visit our YouTube channel to watch our GT-FAQ series, featuring short videos on gene therapy science

ASK A QUESTION

Have more gene therapy science questions? Have comments, or just want to connect? Email us at Advocacy@Sarepta.com

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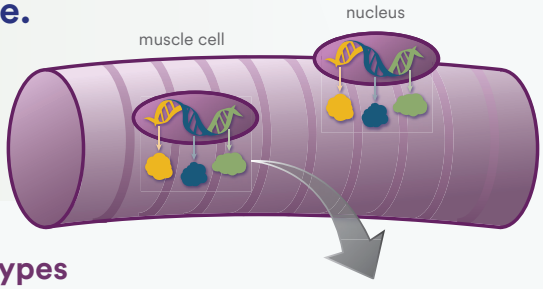
What is the goal of gene therapy?

Gene therapy aims to slow or stop progression of a specific genetic disease.

HOW? To begin, let's first look at what may cause a genetic disease.

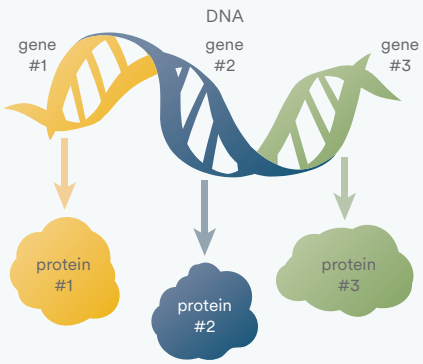


A person's body is made up of different types of cells, like muscle cells.

"DNA at Work"

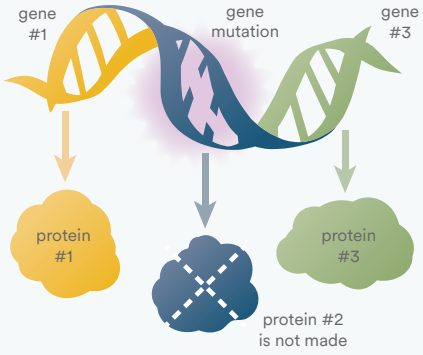
Inside the nucleus of muscle cells is a set of the person's own DNA. DNA is divided into segments called genes, which provide the instructions for making proteins.

Proteins are considered the building blocks for how the body functions. Simply put, they do important jobs that help keep cells, and therefore a person's body, healthy.



Genetic Disease

Sometimes a person may have a gene mutation, or change, which can result in not enough of an important muscle protein being made. If this happens, there may not be enough protein to do its job correctly. A person's muscles may not function properly as a result, and a person may be diagnosed with a genetic disease through genetic testing.

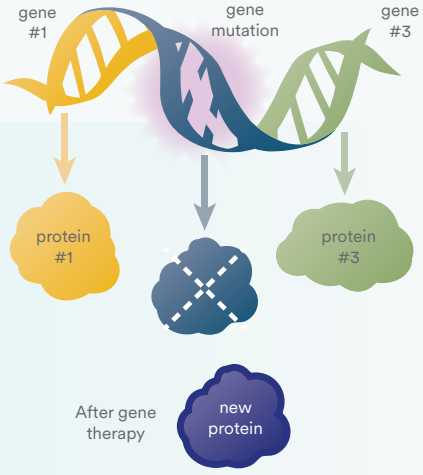


So, how does gene therapy aim to slow or stop progression of a disease?

After Gene Therapy

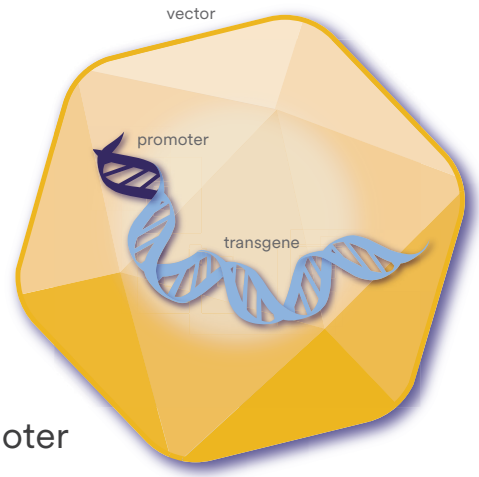
Gene therapy has the potential to help the cell to make a new protein, which is designed to do the job of the missing protein.

With the new protein now doing the important job in the cell, the hope is that the disease's progression would be slowed or stopped.



What are the key components of gene therapy?

There are three main components of gene therapy:



1. **Vector** – the vector aims to deliver the promoter and transgene to the disease-impacted cells

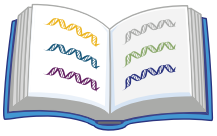
2. **Promoter** – the promoter aims to tell the cell to begin making the new protein if it's been delivered to the right place in the body

3. **Transgene** – the transgene is a functioning copy of a gene that aims to give the cell instructions to make a new, therapeutic protein

Not all gene therapies are the same.

The vector, promoter, and transgene may differ across investigational gene therapies, even if they are being developed to treat the same disease.

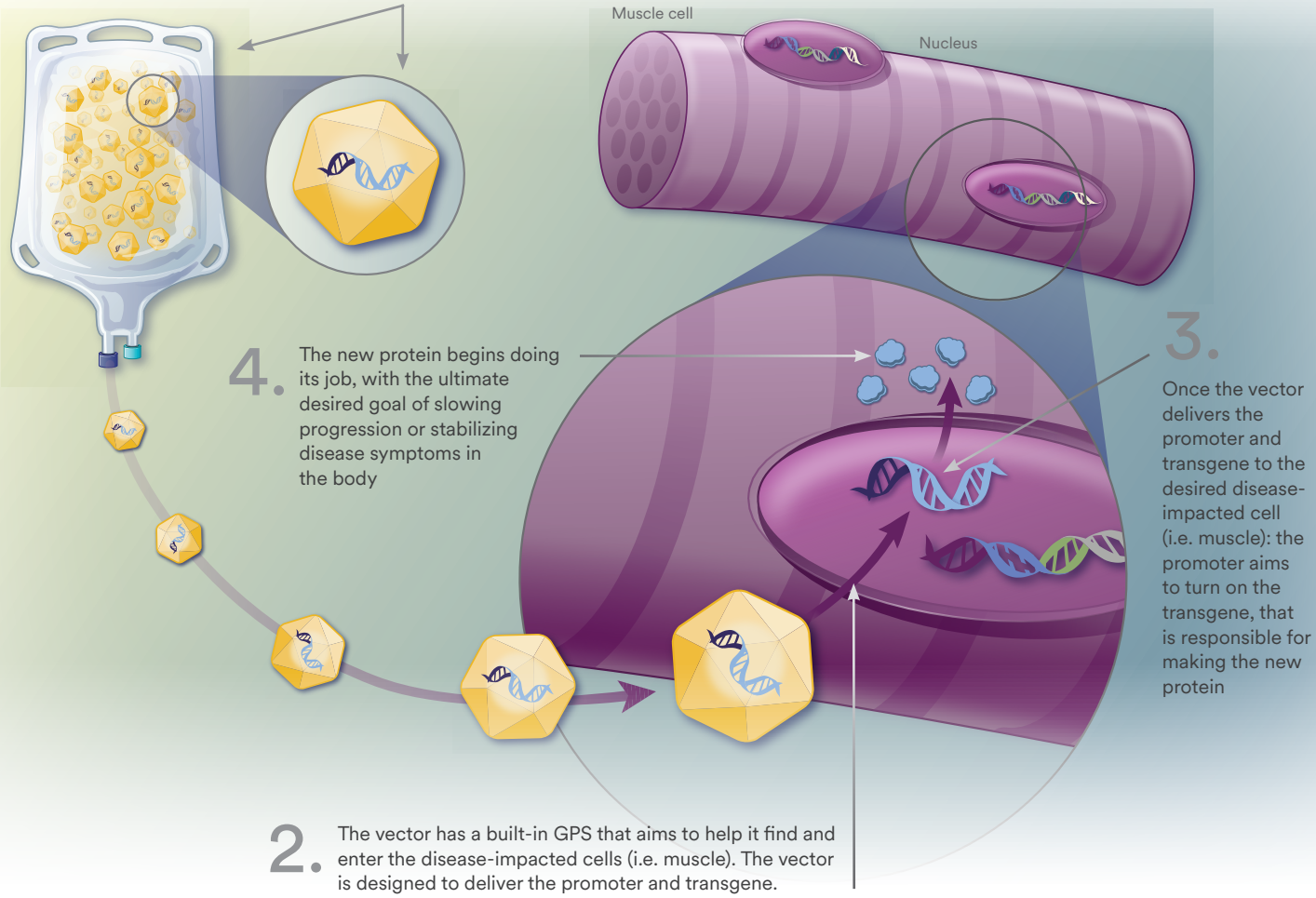
How does gene therapy work?



Gene therapy aims to deliver the right instructions to cells so that they can make the new protein.

The vector, promoter, and transgene work together to help accomplish the intended goal:

1. Gene therapy may be delivered as an intravenous infusion



2. The vector has a built-in GPS that aims to help it find and enter the disease-impacted cells (i.e. muscle). The vector is designed to deliver the promoter and transgene.

3. Once the vector delivers the promoter and transgene to the desired disease-impacted cell (i.e. muscle): the promoter aims to turn on the transgene, that is responsible for making the new protein

4. The new protein begins doing its job, with the ultimate desired goal of slowing progression or stabilizing disease symptoms in the body

Want to test your knowledge?

Scan the QR code to take a short gene therapy quiz on limbgirdle.com.
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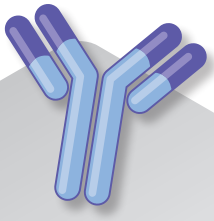
Due to its potential to treat serious diseases, gene therapy is the focus of much scientific research.

Learning more about gene therapy science will help individuals have informed discussions with their doctors.

Gene therapies have unique features which may affect who is eligible for treatment.

Certain tests may help clarify eligibility for gene therapy clinical trials or treatment. Tests that may be required include:

Genetic testing
that confirms the disease diagnosis



Antibody testing
to confirm that the body doesn't have elevated antibodies that recognize the gene therapy vector

Sarepta is committed to providing educational resources to rare disease communities to improve understanding of this investigational treatment approach.

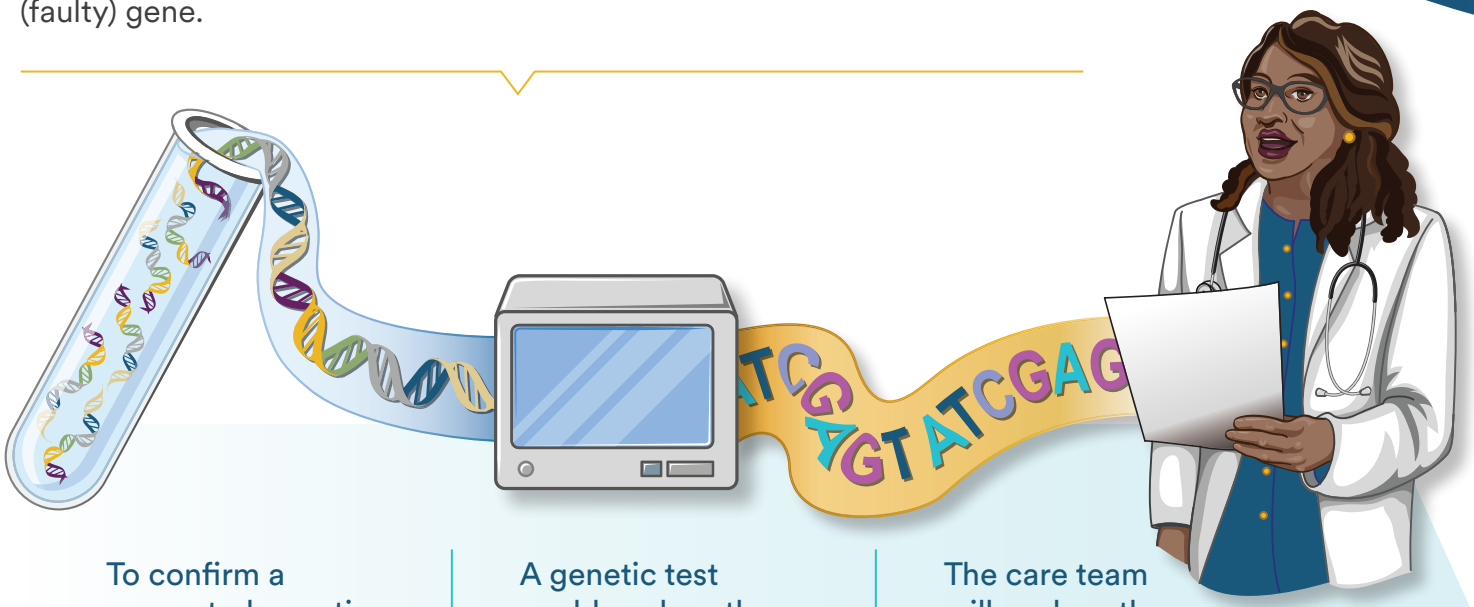
In case you missed it, in Chapter 1, we explored the goal of gene therapy and how it's intended to work. Check out the January 2023 issue of the *LGMD News Magazine* or contact us at Advocacy@Sarepta.com

Intended for US audiences

Why is genetic testing important for gene therapy?

CHAPTER 2
OF A FOUR-PART SERIES

There are different ways that a doctor may diagnose a disease. However, genetic testing is required to determine if a disease is caused by a mutated (faulty) gene.



To confirm a suspected genetic muscle disease, a person may have to give a DNA sample, usually via blood or saliva.

A genetic test could analyze the sequences of dozens of muscle-related genes (DNA).

The care team will analyze the sequencing results and will determine if the person has a genetic diagnosis.

Gene therapy is intended to address the underlying cause of a genetic disease. Therefore, it is necessary to confirm a diagnosis through genetic testing to determine if a gene therapy may be appropriate.

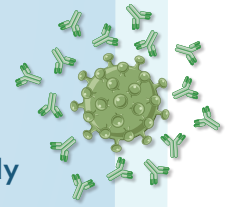
Several programs in the US offer free genetic testing for LGMD and other muscle diseases.
Learn more at limbgirdle.com/genetic-testing

What are antibodies and why do they matter to gene therapy?

First, some background about antibodies:

Antibody

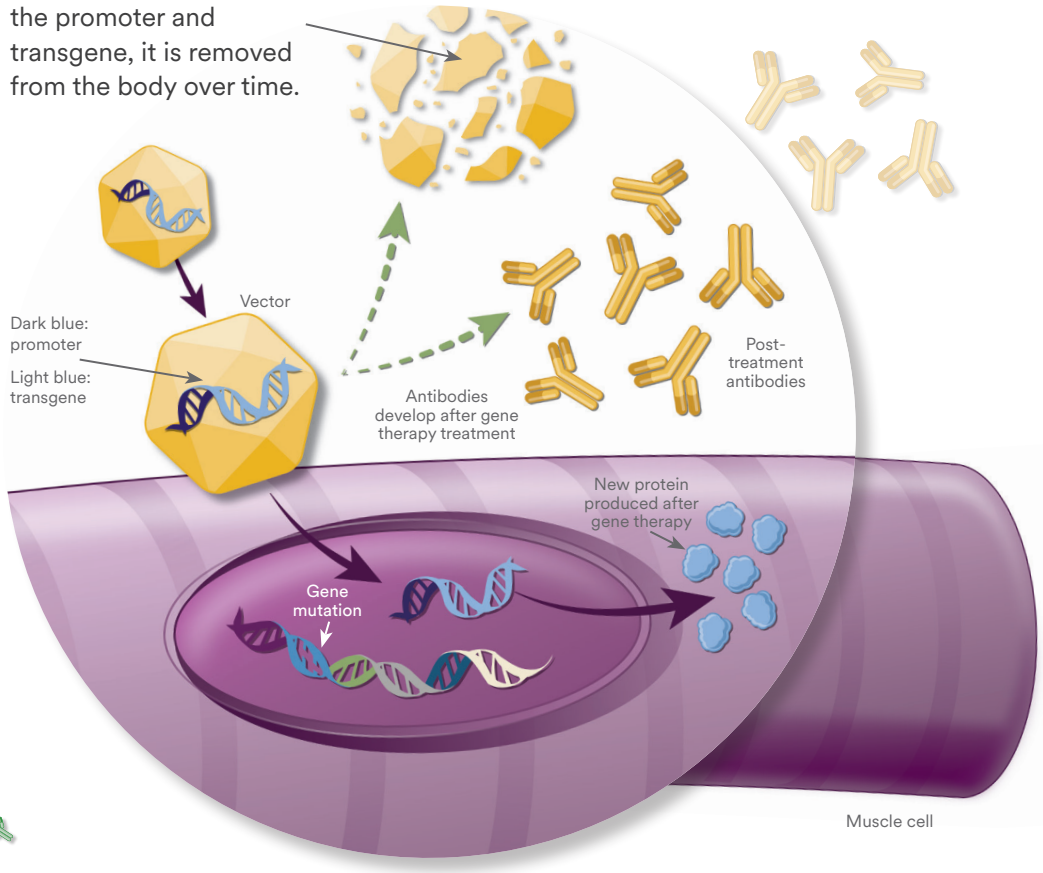
- Antibodies are an important part of the immune system, which aim to protect the body from foreign invaders, like viruses
- When a person has a virus, the immune system may help them recover, in part by developing antibodies that specifically try to fight it

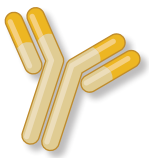


- Antibodies can exist in the body for a long time. This could help the body fight the same or similar virus if it is infected again

Antibodies form after vector exposure

The vector aims to deliver the promoter and transgene to the target cell, with the goal of producing a new protein that may slow the disease progression.



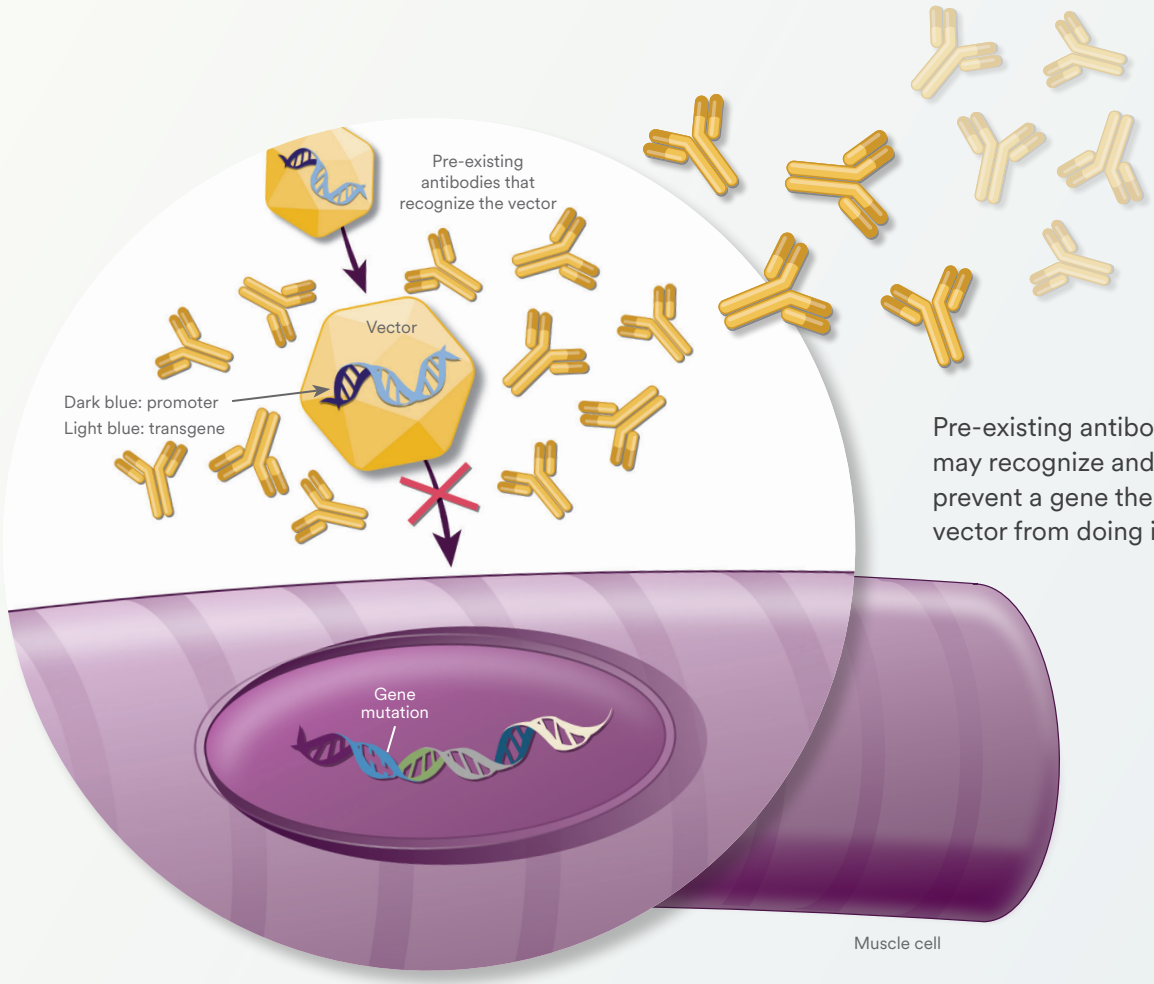


After gene therapy, the body will produce antibodies that recognize the vector. For this reason, gene therapy is currently a one-time treatment.

Even if a person has never received a gene therapy before, they might have pre-existing antibodies that recognize the vector.

This could happen if they were exposed naturally to viruses similar to the gene therapy vector. Some viruses naturally present in the environment are similar to vectors used in gene therapy.

Pre-existing antibodies could prevent gene therapy from working as intended



Pre-existing antibodies may recognize and prevent a gene therapy vector from doing its job.

Pre-existing antibodies that recognize the vector may prevent a gene therapy from working as intended. Therefore, antibody testing is an important part of determining eligibility.

Want to test your knowledge?

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DISCOVERY

Development begins with years of research, with scientists designing and testing the proposed gene therapy—the vector, promoter, and transgene—that aims to determine the best way to deliver a functional gene to the right cells.

MANUFACTURING

Manufacturing is a key part of gene therapy development and regulatory review and approval. In the US, the regulatory body is the Food and Drug Administration (FDA).

CLINICAL TRIALS

Studies focus on the safety of the gene therapy and test to see if it addresses the disease it is meant to treat.

Trials can take years to collect and analyze enough data to meet regulatory requirements.

PRE-CLINICAL STUDIES

The potential gene therapy is tested to see if it works as intended in the laboratory.

The FDA generally requires the manufacturing process to be in place prior to starting clinical trials. This process is comprised of several complex steps and components.

CHAPTER 1 CHAPTER 2

Sarepta is committed to providing gene therapy educational resources to rare disease communities

Check out more GT 101 in the previous 2023 issues of the *LGMD News Magazine* or email Advocacy@Sarepta.com

How is a gene therapy developed?

CHAPTER 3
OF A FOUR-PART SERIES

As part of the FDA's review, they may also perform inspections of the manufacturing facility and processes to help ensure a high-quality product.

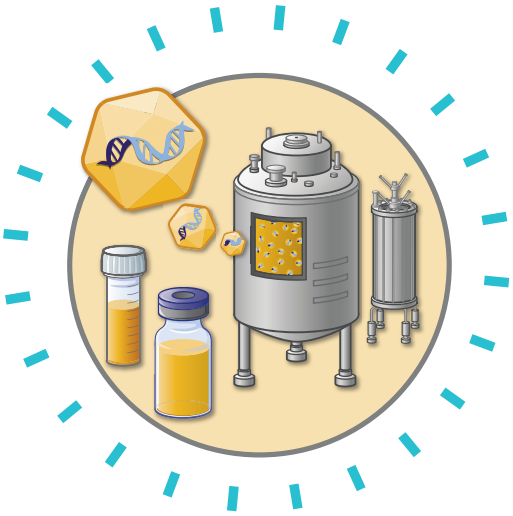
CONTINUING STUDIES

Additional follow-up studies may be required to collect more information on the gene therapy even though the gene therapy is available on the market.

REGULATORY REVIEW & APPROVAL

Once the clinical trials are complete, an application is submitted to the FDA for the gene therapy to be approved for commercial use in patients.

The FDA review process can typically take up to one year.



What can I do?

→ Learn about trials by talking to your doctor and knowing your genetic subtype

→ Join advocacy groups, registries and natural history studies

Intended for US audiences

SAREPTA THERAPEUTICS

More on manufacturing gene therapy vectors

Once the manufacturing process is defined, making a single batch of gene therapy vector can take several months.

Gene therapy vectors containing the promoter and the transgene are made in living cells. Many vectors are needed when targeting a disease that affects cells throughout the body, such as a neuromuscular condition.

Gene therapy manufacturing involves multiple phases with dozens of steps, each of which must meet the strictest quality measures and involve:

- Growing living cells into sufficient quantities to produce the gene therapy vector
- Multiple purification steps to remove impurities
- Numerous tests to help ensure the quality and safety of the product

Once a batch is complete, the product is packaged, stored and shipped to where it's needed.

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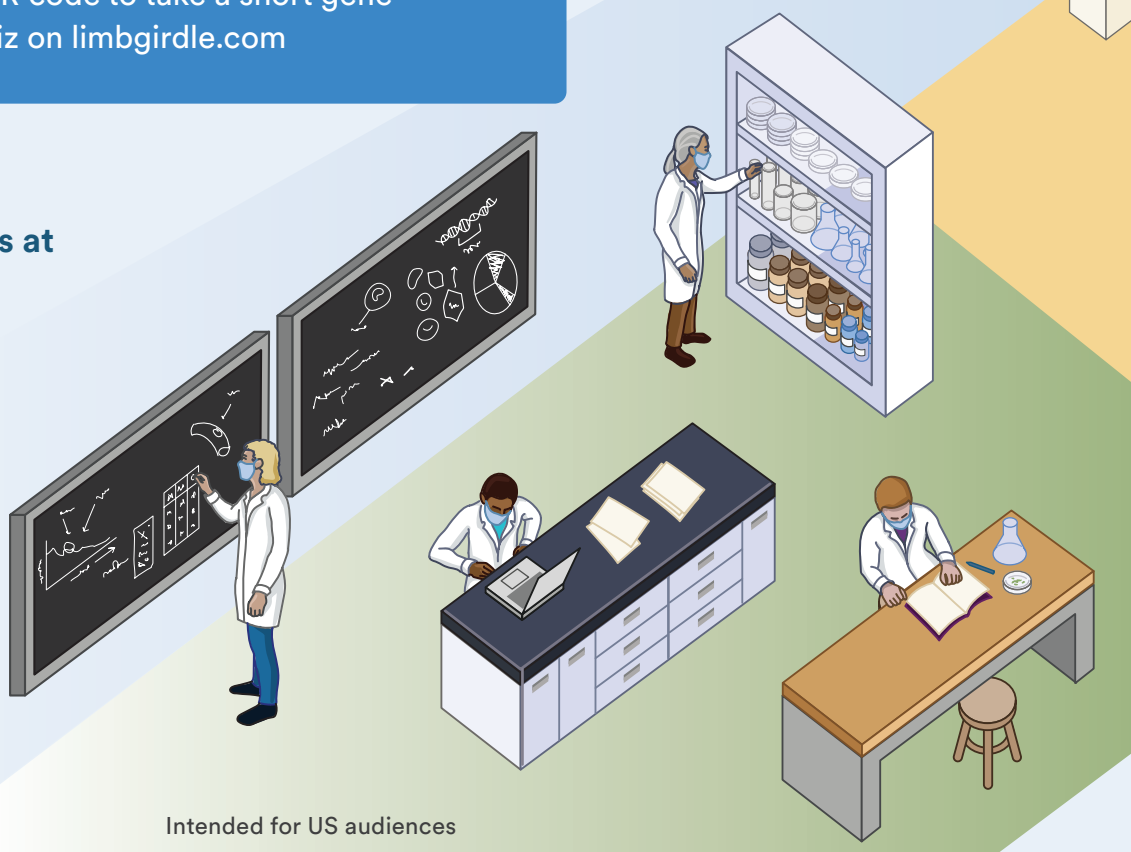

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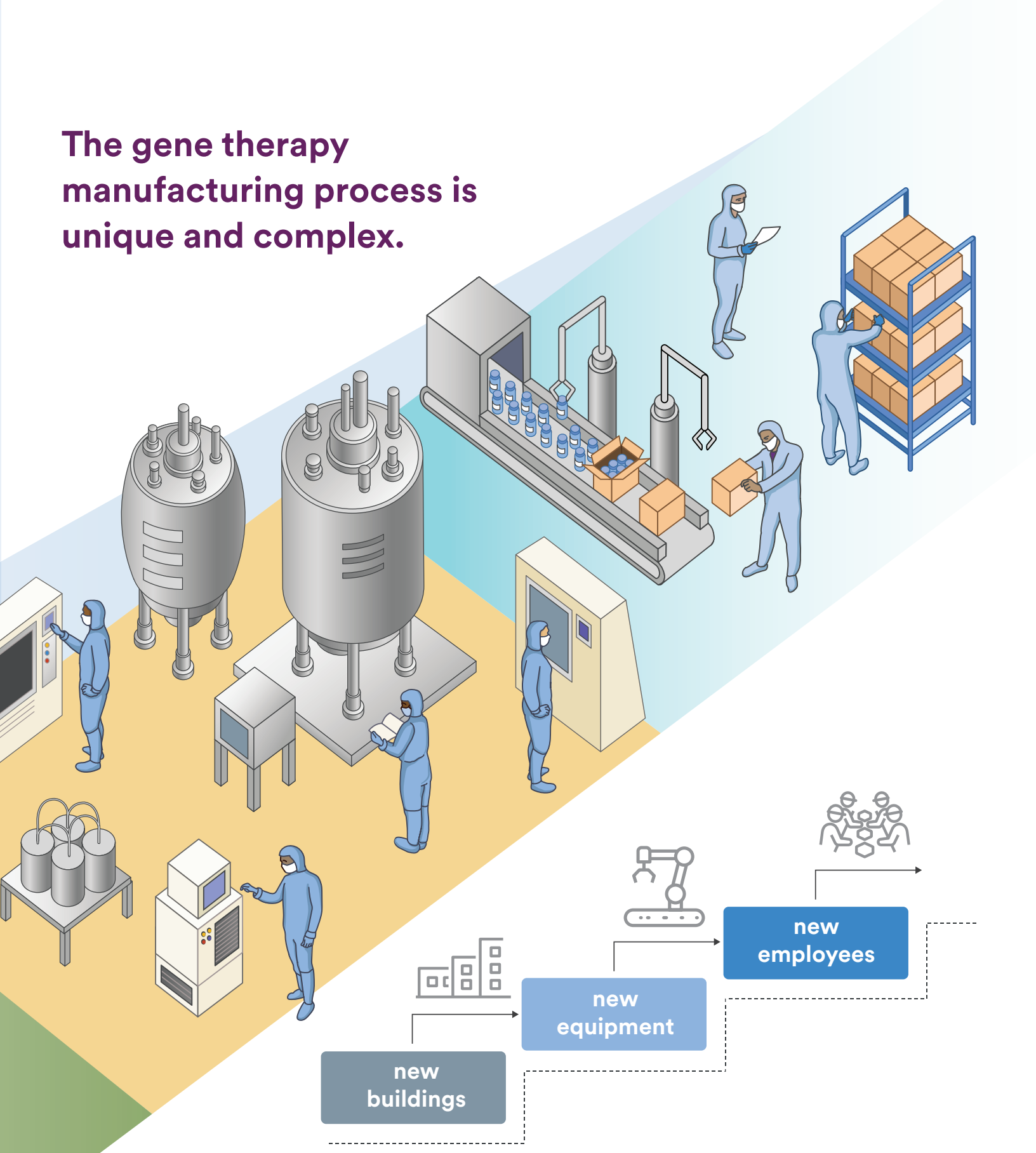
The gene therapy manufacturing process is unique and complex.



Scientists and engineers may have to design, test and build new equipment, instruments and processes. This may mean adding new buildings and hundreds of specially trained employees.

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What is assessed in gene therapy clinical trials?

3 primary categories may include :

Safety

First is safety. During a clinical trial, participants are closely monitored. Doctors look for and record side effects – which may also be called adverse events. This helps protect the overall health and well-being of the participants and may also help researchers potentially adjust treatment plans for future clinical trials.

Participants in gene therapy clinical trials are also monitored long-term—often for years. This provides information on the long-term effects of gene therapy.

If you are considering gene therapy for yourself or a loved one, speaking with your doctor is the best way to learn more.

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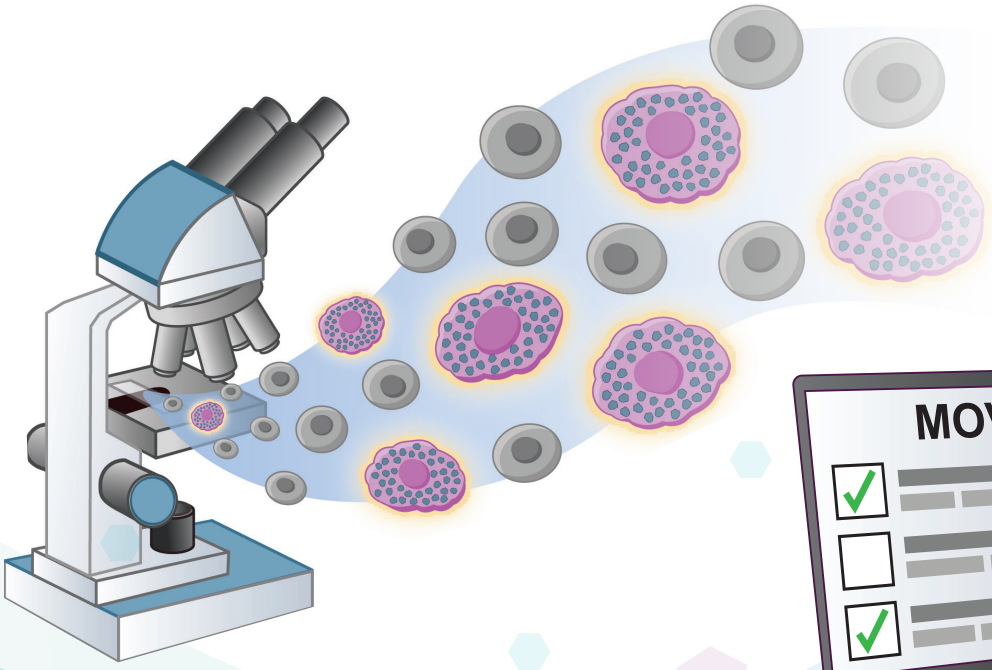
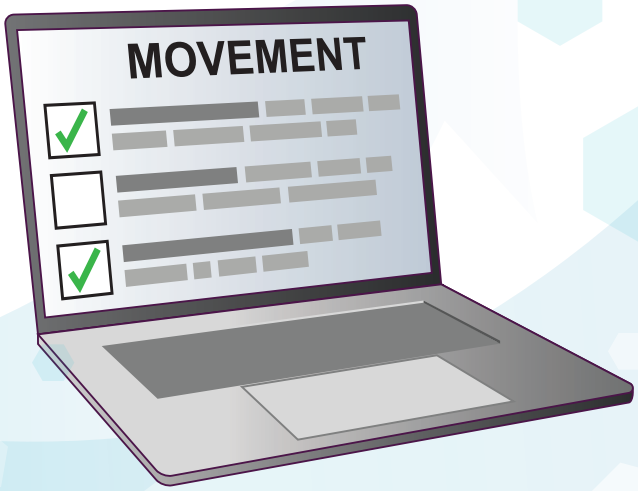
CHAPTER 4

OF A FOUR-PART SERIES





Protein Expression

Next is protein expression. Gene therapy is designed to produce a new protein inside disease-impacted cells. Expression is the measurement of how much protein has been produced in a collection of cells. Knowing whether the disease-impacted cells are producing the intended protein helps researchers understand if the gene therapy is working as intended.

Impact on Disease

Finally, remember that the goal of gene therapy is to slow or stabilize the disease. Therefore, researchers may ask clinical trial participants to perform tests before and after the treatment to help determine any impact on their disease. For gene therapies that aim to address muscular dystrophy, this could include tests examining a person's muscle movement and function.

CHAPTER 1 CHAPTER 2 CHAPTER 3

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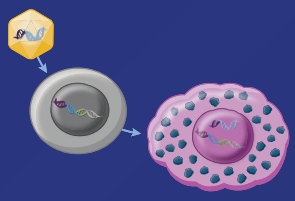
Gene Therapy 101

is a four-part educational series featured in the 2023 issues of the *LGMD News Magazine*.

Throughout this series, we have explored common questions and areas of interest regarding investigational gene therapy research and development.

What have we covered in Chapters 1-3?



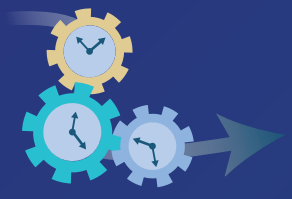
Chapter 1

Investigational gene therapy's goal is to slow or stabilize disease by delivering the right instructions to cells to make a new protein.

Chapter 2

Gene therapy has unique features that may affect treatment eligibility. Two tests to determine eligibility are:

- Genetic diagnosis of the disease, including subtype
- Vector antibody testing to confirm that the body doesn't have elevated antibodies that could prevent the gene therapy from working as intended



Chapter 3

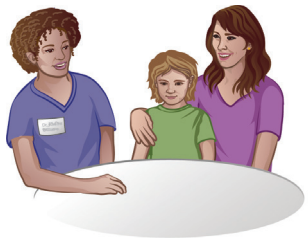
Gene therapy development takes place over the course of years, with significant investment required to manufacture the product once it's been designed.

If you are considering gene therapy for yourself or a loved one, speaking with your doctor is the best way to learn more.

How can the LGMD community help further research?

There are many ways to be involved. A few suggestions are detailed below.

Connect with a Neuromuscular Specialist



Understand your LGMD subtype with a Genetic Test

and get your genetic test report which may help inform your care plan

Participate in Registries, Natural History Studies, and Surveys

which can provide information that may help research in rare diseases

Ask your Doctor about Potential Clinical Trials

for your subtype. You can also search for trials on clinicaltrials.gov

Engage with Patient Advocacy Organizations

to access community news, support, education, and events

Sarepta is the proud sponsor of

LimbGirdle.com

a U.S. educational website.

Members of the U.S. community can sign up at **limbgirdle.com/stay-connected** to receive information on community resources, news, and research on limb-girdle muscular dystrophy.

U.S. community members may also choose to follow Sarepta on our social media platforms (Facebook, LinkedIn, Instagram, Twitter).

If you wish to speak directly to a member of the Sarepta Patient Affairs team and share about yourself and hear about community resources, we encourage members of the U.S. and international communities to connect with us by emailing **Advocacy@Sarepta.com**.

ELIJAH
Living with limb-girdle muscular dystrophy

Sarepta is advancing the science behind limb-girdle muscular dystrophy research.

Sarepta Therapeutics is a global biotechnology company on an urgent mission to engineer precision genetic medicine to reclaim futures otherwise impacted or cut short by rare diseases, including limb-girdle muscular dystrophy (LGMD).

Sarepta currently has 6 LGMD development programs: sarcoglycanopathies (LGMD2C/R5, LGMD2D/R3, LGMD2E/R4), dysferlin (LGMD2B/R2), anoctamin-5 (LGMD2L/R12), and calpain-3 (LGMD2A/R1).

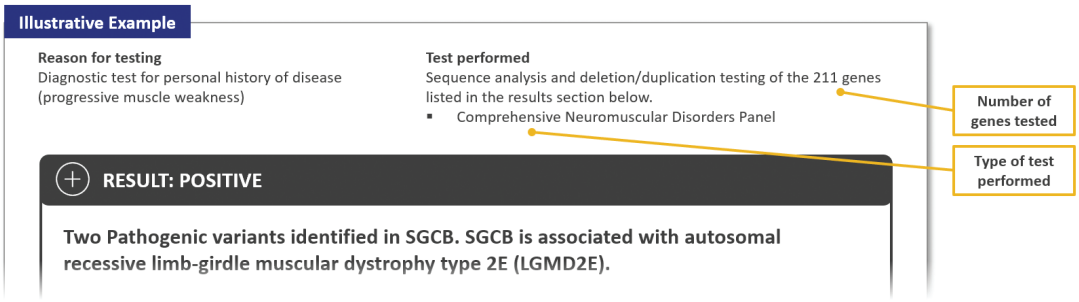
Do you have your genetic test report?

You are an important member of your care team.

While all subtypes of LGMD share some common features, each has unique characteristics that may impact your care team composition and clinical management decisions.

Some clinical trials may require a genetic diagnosis, or may only be available for people with specific subtypes of LGMD caused by a variant(s) in a certain gene. Therefore, if you have not had a genetic test, or your genetic test was done years ago, it may be time to pursue genetic testing.

What information can you learn from a genetic test report?



Possible results from a genetic test:

Positive	Uncertain	Negative
2 Pathogenic or Likely Pathogenic variants in the same gene associated with an autosomal recessive LGMD subtype	1 Pathogenic or Likely Pathogenic Variant and 1 Variant of Uncertain Significance (VUS) identified in the same gene, OR >1 VUS detected in the same gene*	No Pathogenic, Likely Pathogenic, or VUS detected in any of the tested genes
▸ This is a definitive diagnosis of LGMD and your LGMD subtype can be determined	▸ This is not a definitive diagnosis. Discuss next steps with a healthcare provider, such as variant reclassification or family testing, and ask questions to clarify results	▸ The test did not identify any of the subtypes of LGMD caused by genes that were screened for in the specific genetic test. To see which genes were screened for, visit the laboratory website and search for the name of the genetic test on the report

- Uncertain results do not offer a clear and final diagnosis, and additional efforts may be undertaken to clarify the diagnosis
- Negative results do not rule out the possibility of LGMD, if not all LGMD genes were tested or if the subtype has not been discovered yet
- Always discuss questions and results with a healthcare provider

*Some LGMD subtypes are characterized by a dominant inheritance pattern and require only one Pathogenic or Likely Pathogenic variant to cause disease. However, these subtypes are more rare.

What are My Next Steps?

If you do not have a **copy of your genetic test report**, contact your doctor and ask for a copy.

If your result is negative or uncertain, ask your healthcare provider (neurologist or genetic counselor) if getting a new test or reclassification could be an option for you.