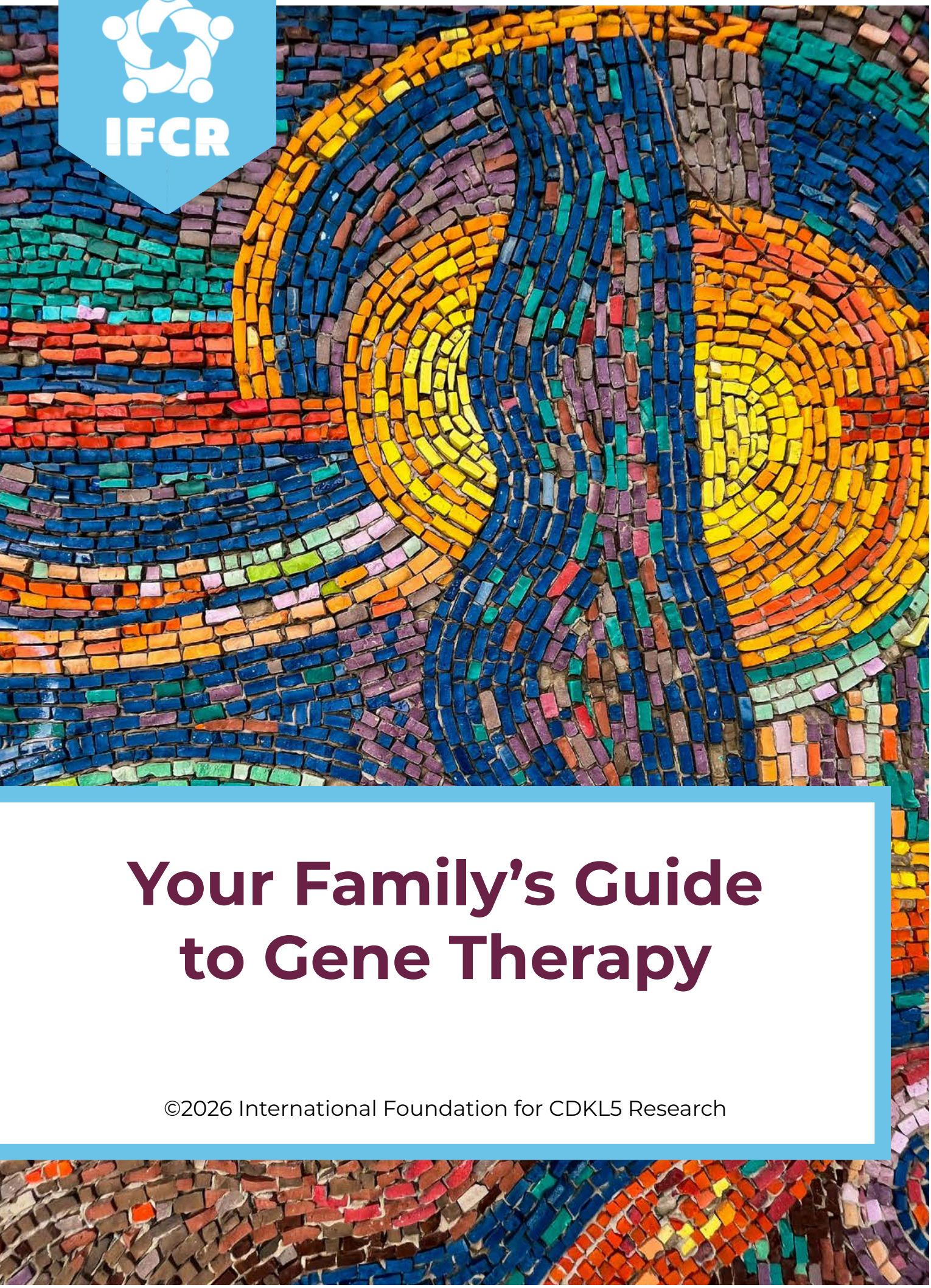


Your Family's Guide to Gene Therapy

WELCOME

YOU MAY BE HEARING ABOUT GENE THERAPY FOR THE FIRST TIME. IT'S COMPLETELY NORMAL TO FEEL UNSURE, OVERWHELMED, OR EVEN HOPEFUL ALL AT ONCE. THIS GUIDE IS HERE TO SUPPORT YOU.

Research on gene therapy for CDKL5 is still very new. It offers hope, but there is also a lot we do not know yet. You don't need to understand everything all at once. Take it step by step, go at your own pace, and remember you're not alone!

Why gene therapy matters

Today, most epilepsy medications focus on symptoms, like seizures. These treatments can help, but they don't fix the underlying cause of the condition.

Gene therapy is a new area of medicine that scientists are studying to help people with genetic conditions like CDKL5. Instead of only treating symptoms, it aims to fix the root cause of the disease. Genes act like instructions for the body. **Gene therapy aims to give cells new or corrected instructions so they can work better.**

This guide will walk you through the basics of gene therapy and how it's being studied for CDKL5. Along the way, we'll share important topics for families to think about as you learn more and make decisions that feel right for your family.

CONTENTS

UNDERSTANDING GENES AND CDKL5

Our bodies are made of trillions of tiny cells. Inside most cells are genes.

Genes are like instruction books. They tell your body how to grow, work, and stay healthy. Genes help decide things like your hair color and control important jobs like how your heart beats. Scientists think humans have more than 20,000 genes!

Genes give instructions to make proteins. Proteins do many important jobs. They help build muscles, fight infections, carry oxygen and help the brain work.

Sometimes, a gene doesn't work the way it should. When that happens, the body might not make the right protein, or might not make enough of it.

Children with CDKL5 have a change in the CDKL5 gene. As a result, their bodies don't make enough of an important protein for brain development.

You can think of it like a missing page in an instruction book. Without that page, brain cells may not grow or connect the way they should. This can lead to seizures and challenges with learning, movement, speech and vision.

WHAT IS GENE THERAPY?

Gene therapy is a new area of medicine that scientists are studying to help people with genetic conditions like CDKL5. Most current treatments focus on managing symptoms. Gene therapy is different. It aims to treat the root cause.

It may:

- Help slow how the condition changes over time
- Help the body work better
- Keep some symptoms from getting worse, or help them go away

It's important to know, though, that ***gene therapy is not a cure***.

Think of the CDKL5 gene as part of an instruction manual. If a page is missing, the body can't follow the directions. Gene therapy tries to add that missing page back. For children with CDKL5, this means helping brain cells make the protein they need.

Scientists are studying different approaches to gene therapy. For CDKL5, the main approach is called **gene replacement**, which adds a working copy of the CDKL5 gene.

Other approaches that may be explored include:

- Gene editing—fixing the gene directly
- Targeted X-reactivation—turning on a silent copy of the gene

How gene therapy works

Gene therapy gives cells new instructions to make the proteins they need. There are three main parts:

PART ONE

VECTOR

A vector carries the new instructions into cells. Scientists often use viruses because they are good at getting inside cells. These viruses are changed so they can't make you sick.

Many gene therapies for other conditions use a type of virus called AAV (adeno-associated virus) as the vector.

For CDKL5, scientists also plan to study AAV. Researchers are also developing new and improved virus shells (called capsids) to help gene therapies reach the right cells more effectively and safely.

PART TWO

TRANSGENE

This is the new, working copy of the gene. It has the correct instructions.

PART THREE

PROMOTER

Like a light switch, the promoter turns the transgene on at the right time and place.

You can think of gene therapy like sending a package:

- The **vector** is the delivery truck
- The **transgene** is the package
- The cell uses the **package** to make the missing protein

What this means for your child: *For CDKL5, this means brain cells get the instructions they need to make the protein that helps the brain develop properly.*

How gene therapy is given

Gene therapy can be given in different ways.

- **In vivo** means the therapy is given directly into the body
- **Ex vivo** means cells are taken out of the body, changed in a lab, and put back

For conditions that affect the brain, like CDKL5, **in vivo** is being researched.

Common delivery methods for in vivo gene therapy include:

- An injection into spinal fluid, called **intrathecal** (IT)
- An injection into fluid-filled spaces in the brain, called **intracerebroventricular** (ICV)
- An injection near the base of the brain, called **intracisternal** (ICM)
- An infusion into the bloodstream, called **intravenous** (IV),through a small needle and tube in the arm

Aside from an IV, these procedures are usually done under anesthesia, so your child is asleep. Each method has its own risks and benefits. Researchers study these carefully in clinical trials.

Why gene therapies can be different

Not all gene therapies are the same. Scientists can change:

- Vectors (delivery trucks)
- Transgenes
- Promoters (power on/off)
- Doses
- Delivery methods

It's a bit like cooking. Small changes in a recipe can lead to different results. Clinical trials help researchers learn which approaches are safe and work best.

Potential benefits and goals

Gene therapy is still being studied, but it may offer new possibilities. **The main goal is to fix the root cause of disease by giving cells the right instructions so they can work more normally.**

Other possible benefits include:

- **New options for rare diseases**—Many genetic conditions, including CDKL5, have few treatment options. Gene therapy may offer a new approach to care
- **Changing how a disease develops**—In some cases, gene therapy may help slow down or change how a condition progresses
- **Building on progress from other diseases**—Some gene therapies have been approved by the Food and Drug Administration (FDA) for other

conditions, such as spinal muscular atrophy and Duchenne muscular dystrophy. These advances help guide research for CDKL5

What this means for your child: *These are goals researchers are working toward, not guarantees. Some children may benefit, and others may not.*

Limitations and challenges

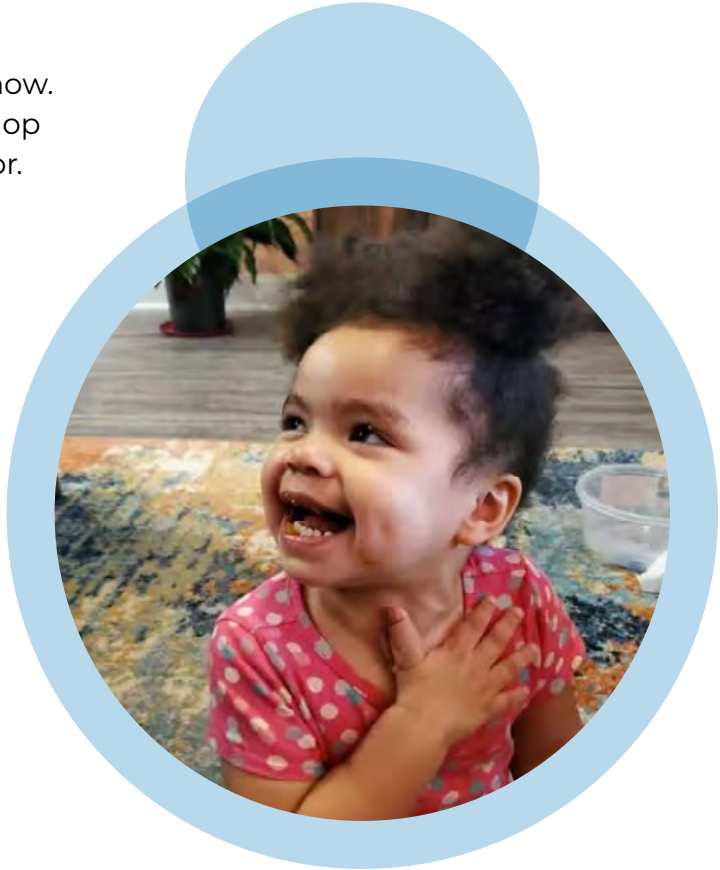
Gene therapy offers hope, but it also comes with challenges:

- It takes many years to develop new treatments. Some may stop in early trials if they don't work well or are unsafe
- Not every child responds the same way
- Most gene therapies are given one time—and may limit the ability to participate in other clinical trials
- Repeat dosing is not possible right now. After treatment, the body may develop antibodies against the delivery vector. This may make the treatment less safe or less effective if it is given again. Scientists are studying ways to overcome this challenge
- Side effects can happen

Side effects may include:

- Immune reactions
- Inflammation (swelling) in organs like the liver
- Effects on the nervous system

In rare cases, serious harm or death has occurred. Reading this may feel scary. That is completely understandable. Because of these risks, children are closely monitored during and after treatment.



UNDERSTANDING CLINICAL TRIALS

You may wonder how a scientific idea becomes a treatment doctors can use. This happens through clinical trials.

Clinical trials help answer:

- Is the treatment is safe?
- How does the body respond?
- Does it help the condition?

These studies are only possible because of the people and families who choose to take part.

Before a new treatment can be approved, it must go through several phases. The typical drug development process is outlined below, but the steps may be a little different depending on the treatment being researched.

CLINICAL TRIALS

PHASE 1

Focuses on safety in a small group of people, usually healthy volunteers. Researchers study how the body responds, what dose is safest, and what side effects might happen

CLINICAL TRIALS

PHASE 2

Looks at how well the treatment works while **continuing to monitor safety**

CLINICAL TRIALS

PHASE 3

Studies the treatment in a larger group of people to see how well it works and how it **compares to current care**

In rare diseases like CDKL5, clinical trials may look a little different. Because fewer people have the condition, researchers often combine study steps. This means they can find the right dose and also look for early signs that the treatment is working at the same time. Even when steps are combined, studies must still meet strict safety standards.

Researchers may also use natural history data, which shows how a disease changes over time without treatment. This can help compare outcomes in people who receive a treatment, especially when it is difficult to include a placebo group (no active treatment at all) in rare disease studies.

Gene therapy trials are often Phase 1–2 studies.

Gene therapy is not tested in healthy volunteers. Because of this, early studies often look at safety and early signs that treatment may work.

Gene therapies can have long-lasting effects, so researchers move carefully. They usually treat small numbers of people and closely monitor each participant. Throughout the study, researchers collect information about safety, side effects and how the therapy impacts the disease.

WHAT A GENE THERAPY TRIAL FOR CDKL5 MIGHT INVOLVE

Every trial is different, but most include these steps:

STEP ONE

Before treatment (screening and eligibility)

Doctors check if your child can take part. This may include:

- Confirming the CDKL5 diagnosis
- Reviewing medical history
- Blood and urine tests
- Imaging, such as MRI scans
- Developmental checks

Some trials have age or health requirements. Others may not allow participation if a child has received certain previous treatments.

A key blood test checks for antibodies to the vector used in gene therapy. Antibodies help the body recognize and fight foreign substances and infections. In gene therapy, antibodies are important.

If your child has high levels of antibodies to the virus used as vector, it may affect safety or how well the gene therapy works. This is something your doctor will discuss with you before joining a clinical trial.

STEP TWO

Preparation

If eligible, families may be asked to track seizures or complete questionnaires. This helps researchers understand your child's starting point (called a baseline). It also makes it easier to measure changes after treatment.

Your child will need to take medications, such as steroids, to reduce the chance of an immune reaction to the treatment. These medications can temporarily weaken the immune system and increase the risk of infections.

During this time families will need to take steps to lower their risk of infection. Your healthcare team will give you clear instructions on how to do this.

STEP THREE

Study design and treatment assignment

Gene therapy trials can be designed in different ways. Before joining a study, it's important to understand how it works and how treatment is assigned. Your healthcare team will explain this and answer questions. There is not just one way these studies are done. A few common ways include:

- **Single-arm studies**—Everyone in the trial receives gene therapy. Researchers compare results to natural history data,

which shows how the disease typically progresses over time without treatment.

Some studies also test different doses of gene therapy. This helps researchers find the safest and most effective dose. In some cases, a lower dose may work as well as a higher dose with fewer side effects.

- **Randomized, placebo-controlled studies**—Participants are randomly assigned (like flipping a coin) to different groups. One group receives gene therapy, while another may receive standard care or a placebo (no active medication).

  In some cases, the placebo may involve a "sham," or fake, procedure that mimics the real one but does not give the gene therapy. All participants receive the same level of care and monitoring. This can be a difficult aspect for families, so it's important to discuss any concerns with your healthcare team.

  In some cases, people who first receive a placebo may be offered the gene therapy later. This is called delayed treatment or a cross-over option. It allows more people in the study to receive the treatment over time.

No matter how the study is set up, it is important to understand the plan and all options before deciding to take part.

STEP FOUR

Treatment day

Gene therapy is usually given **one time** at a specialized hospital. Your child will be given anesthesia to keep them asleep during the procedure. Because the body can develop antibodies after treatment, repeat dosing is not possible at this time.

STEP FIVE

After treatment

Your child will be closely monitored. This may include a hospital stay. Doctors will check:

- Vital signs
- Lab results
- Organ function
- Immune response

Additional medications, such as steroids, may continue to be given to help control inflammation and reduce immune responses. Your child may need to be monitored for several weeks after treatment. It's important to attend all follow up appointments.

STEP SIX

Long-term follow-up

Follow-up can last 5–15 years. Families return for regular visits and stay in contact with the study team. You will not go through this alone—the care team supports you every step of the way.

IMPORTANT CONSIDERATIONS FOR FAMILIES

Joining a clinical trial is a big decision. It's normal to have questions or mixed feelings.

Before joining, families go through a process called informed consent. The study team explains:

- The purpose of the trial
- What will happen
- Possible risks and benefits

This is your time to ask questions and decide what feels right for your family.

Participation in a gene therapy trial also requires a meaningful commitment. Families may need to:

- Travel to specialized hospitals, especially in the months after treatment
- Stay near the treatment center for an extended time period. For some families, temporary relocation may be necessary
- Track health information at home, such as seizures or daily activities
- Stay in regular contact with the study team for long-term follow-up

Choosing to participate is extremely personal. Some families join to help advance research, while others decide that a trial is not the right step for them. Both choices are valid.

While families can leave a clinical trial at any time, it's important to remember that gene therapy has long-lasting effects and **cannot be reversed**. Staying in the study, when possible, is very important. It helps:

- Closely monitor your child's safety
- Provide information about how the therapy works
- Support research that may help other families in the future

Factors to consider

There is no one "right" choice. There's a lot to think about, and every family is different. Talking with your child's healthcare team can help you decide what matters most. Things to think about:

- **Treatment options**— Consider all available options and whether gene therapy may offer meaningful benefits. Remember, gene therapy is long-lasting and cannot be reversed
- **Trial setup**—Learn how the trial is organized. Some studies use random assignment, placebo or sham procedures. Participation may also affect whether your child can join other trials or receive certain treatments in the future

- **Medications**—Many trials require medicines, like steroids, to lower the chance of an immune response. These can temporarily increase infection risk and may lead to behavioral issues
- **Risks and side effects**—Side effects can happen, and some may be serious. That's why careful monitoring is so important
- **Time and travel**—Studies may last months or years and often require travel to specialized hospitals. Think about how this fits into your daily life, school, work and family commitments
- **Family impact**—Consider the time, routine changes, and potential costs that may not be covered by the study

Take your time. Ask questions. Revisit your decision as you learn more.

QUESTIONS TO ASK A TRIAL TEAM

If your family is considering a gene therapy trial, asking questions can help you feel more informed and prepared. You may want to bring a list and take notes during your conversations. Here are some questions to get you started:

About the therapy

- What is the goal of the trial?
- How does this therapy work?
- How will it be given?

About the trial

- How many people will take part?
- Who can take part? Are there age or health requirements?
- What tests are needed to qualify?
- Is there a chance my child could receive placebo or a sham procedure?
- If receiving placebo, will there be a chance to receive the gene therapy later?

Safety

- What side effects have been seen so far?
- How will my child be monitored?
- What happens if there is a serious reaction?

Logistics

- Where is the trial located?
- How long will hospital stays last?
- How often are follow-up visits?
- Are travel or lodging costs covered?

Long-term participation

- How long is follow-up?
- What happens if the therapy doesn't work?

Communication

- Who is our main contact?
- Will we receive updates or results during the trial?

KEY TAKEAWAYS AND HOPE FOR THE FUTURE

Gene therapy is a fast-growing area of research. It may offer new possibilities for families affected by CDKL5.

Gene therapies often:

- Deliver a working copy of a gene into the body
- Are **one-time treatments**
- Require careful screening before treatment and long-term monitoring afterward

It is important to remember that gene therapy is still being studied.

Researchers cannot guarantee results. Some participants may see benefits, while others may not.

There is still much to learn, including how long effects may last and how treatment may impact development over time.

Staying informed, asking questions and talking with your child's healthcare team can help you make the decision that feels right for your family. No matter what you decide, you are doing your best for your child. And you don't have to figure it out alone.

RESOURCES FOR FAMILIES

Learning about gene therapy can feel like a lot. That's completely normal. You don't have to learn everything all at once. Take your time and go step by step.

You might find it helpful to:

- Start with one simple resource
- Write down questions as they come up
- Talk through what you learn with your healthcare team

Here are some trusted resources to help you get started:

Gene therapy basics

A simple, easy-to-read overview of how gene therapy works and what it means for rare diseases
Gene Therapy Fact Sheet (NORD)

Resources and videos that explain gene therapy in a simple way
ASGCT Cell and Gene Therapy Basics

Understanding clinical trials

A visual guide that explains how clinical trials work
Clinical Trials Infographic (ASGCT)

An explanation of the different phases of clinical trials and what each one means
Clinical Trial Phases Explained (ASGCT)

Real-life examples

An example of how gene therapy is already being used for another rare condition
Gene Therapy for Spinal Muscular Atrophy (SMA)—Children's Hospital of Philadelphia

Gene therapy research in CDKL5

A guide to gene therapy webinar. This explores ELJ-101 being studied in CDKL5
Gene Therapy Webinar (IFCR)

Another visual guide to learn more about gene therapy in CDKL5
Gene Therapy in CDKL5

Information from UltraGenyx about their work in gene therapy
UltraGenyx's Patient Advocacy website

Information from Elaaj Bio about their work in gene therapy
Elaaj Bio website

GLOSSARY

AAV (Adeno-Associated Virus)
A virus that has been changed so it cannot cause disease, used as a delivery tool (vector) in many gene therapies

Antibodies
A protein made by the body to fight germs. It helps the immune system recognize and remove viruses, bacteria, or other foreign substances

Anesthesia
A state of controlled unconsciousness using medication. The person is asleep, does not feel pain and remains still during procedures

Baseline
A person's starting point prior to taking a medication. It's used to measure changes in health or development after treatment

Capsid
The capsid is the outer shell of a virus. In gene therapy, scientists can change the capsid to help the virus safely deliver new genetic instructions to the right cells in the body

Clinical trial
A research study that tests new treatments in people to see if they are safe and how well they work

Crossover
When a participant switches from one group to another, usually from the placebo group to receiving therapy later in the study

Developmental assessments
Tests that measure a child's skills and growth, such as movement, speech, or learning abilities

Dose
The amount of treatment given to a person

Effectivenes
How well a treatment works

Eligibility
Whether a person meets the rules or requirements to take part in a clinical study

Exclusion criteria
Rules that prevent someone from joining a clinical trial, often for safety reasons

Ex vivo
A method where cells are removed from the body, changed in a lab, and then returned to the body

Food and Drug Administration
The regulatory authority that reviews and approves medicines for the United States

Gene
A small section of DNA that gives instructions for how the body grows and functions

Gene editing
A technique that makes precise changes to a gene to fix it

Gene replacement
Adding a working copy of a gene into a person's cells to replace a non-working one

Gene silencing
Turning off a gene that is causing problems so normal proteins can work

Genetic change (sometimes referred to as mutation or variant)
A change in a gene that affects how it works

Immune response or reaction
The body's reaction to something it sees as harmful, like infections or gene therapy. In gene therapy, the body might attack the viral vector thinking it is a germ

Inclusion criteria
Rules that determine who is allowed to join a clinical trial

Informed consent
The process of learning about a study and agreeing to take part

In vivo
A method where the therapy is given directly into the body

Intracerebroventricular (ICV)
An injection into a fluid-filled space in the brain

Intracisternal (ICM)
An injection near the base of the brain

Intrathecal (IT)
An injection into the fluid around the spinal cord

Intravenous (IV)
Treatment given into the bloodstream through a small needle and tube in the arm

Long-term follow-up
Ongoing monitoring after treatment to track safety and effects over many years

Natural history
Information collected from earlier studies that show how a disease typically changes over time in people who have not received treatment. This helps researchers understand what usually happens and provides a comparison when studying therapies

Phase 1 clinical trial
A study that primarily looks at safety, dosage, and side effects usually in healthy volunteers

Phase 2 clinical trial
A study that looks at how well a treatment works while continuing to monitor safety

Phase 3 clinical trial
A study in a larger group of people to understand effectiveness and compare the new treatment to current care

Placebo
A treatment with no active medicine, used in clinical trials for comparison

Promoter
A part of a gene that acts like a switch, telling the transgene when and where to turn on

Protein
A molecule in the body that does important jobs, like building muscles, carrying oxygen, fighting illness, and helping the brain work

Random assignment / randomization
When participants are assigned to different groups in a study by chance to ensure fair comparison

Single-arm study
A type of study where everyone in the trial receives the same treatment; there is no comparator

Screening
The process of checking eligibility for a clinical trial through tests, medical history, and assessments

Sham procedure
A “fake” treatment given in a trial to compare with the real therapy. It looks like the real treatment but has no active therapy

Steroids / immune-suppressing medications
Medicines sometimes given before or after gene therapy to lower the chance of the body reacting to treatment

Transgene
The new or corrected instructions delivered to cells in gene therapy

Vector
A delivery tool, often a virus, used to carry a working gene into the body’s cells. The parts of the virus that can make you sick have been removed

Vital signs
Key measurements of essential body functions, including body temperature, pulse rate, breathing rate and blood pressure

ABOUT IFCR

IFCR
International Foundation for CDKL5 Research

Our mission is to treat and cure CDKL5 Deficiency Disorder by funding scientific research, while helping affected individuals and their families to thrive.

We have chosen the starfish as our symbol, based on the story “The Star Thrower” by Loren Eiseley.

In the story, a man sees a young boy walking along a beach, picking up starfish that had washed ashore and throwing them safely back into the sea.

“Young child,” the man commented, “do you not realize that there are miles and miles of beach, and there are starfish all along every mile? You can’t possibly make a difference.”

The little boy throws another starfish back into the ocean and replies, “I made a difference to that one!”

We believe this story serves as a powerful reminder of how, by supporting one another and learning together, we can make a difference in the lives of everyone affected by CDKL5 Deficiency Disorder.

We are here to help. Please sign up for our newsletter and follow us on social media.

Additional CDKL5 guides and resources are available in the "Resource Library" of our website at www.CDKL5.com.