Vol 2 / Issue 4

LGMD News

Uniting the Limb-Girdle Muscular Dystrophy Community

An Interview with Dr. Jerry R. Mendell

Progress for the Sarcoglycanopathies

GRASP CONSORTIUM

More Natural History Studies Lead to More Clinical Trials

A CONVERSATION WITH DIANE BERRY, PhD

Senior VP, Global Health Policy; Government and Patient Affairs, Sarepta Therapeutics

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Participate in the First EL-PFDD for Limb-Girdle Muscular Dystrophies

September 23, 2022 | Find out more at **www.lgmdpfdd.com**

LGMD AWARENESS DAY

September 30, 2022

- Advocate
- Educate
- Celebrate

2022
Girdie Sticker Campaign
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"I AM LGMD"

A time to celebrate:

- **individuals** living with LGMD
- **caregivers**
- **parents** of children with LGMD
- **doctors, therapists, and other healthcare professionals,** who treat our community.
- **researchers, pharmaceutical companies, and the scientific community** focused on LGMD.
- **families and friends**

LGMD is what brought us all together.
Together We Are Stronger!

Take a moment to shine a light on yourself and the importance of LGMD Awareness! Be proud to say, "I AM LGMD".

There is great strength in awareness, understanding, and unity. The LGMD community demonstrates global connectivity each year when we campaign together and gain recognition for limb-girdle muscular dystrophy.

Join us as we Advocate - Educate - Celebrate LGMD

I AM LGMD Celebrate

- Request your Girdie Sticker to share
- Wear Lime Green for LGMD Awareness
- Take the TikTok Girdie "Lime" Dance Challenge
- Share on social media #LGMDawareness
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LGMD News

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Thank you for your support!

The Speak Foundation
Uniting the entire LGMD community to make a difference together in future treatments for this rare disease.

The origin of The Speak Foundation's name comes from Proverbs 31:8. It is: "Speak up for those who have no voice." Living with a rare disease means many of us wait years to have a voice in areas that impact our daily lives personally. The Speak Foundation helps our voices to be heard.

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The First EL-PFDD for LGMDs!

Remember, this is just the first group of LGMDs going before the FDA, and other subtypes can pursue EL-PFDDs in the future.

Many of you have heard about the Externally-Led Patient-Focused Drug Development (EL-PFDD) meeting and have wondered why it is so important. The Food and Drug Administration (FDA) does not offer many opportunities for patients with rare diseases to interact directly with their agency while treatments are being developed. With many clinical trials coming up for certain forms of limb-girdle, it is important for us to take full advantage of this platform, to explain why we need these treatments reviewed quickly.

The EL-PFDD is a structured program of the FDA, created to allow patients to share directly with the reviewing body while certain treatments are in development. Other stakeholders from around the world attend, too, including researchers, industry, clinicians, and other disease communities.

If you have been diagnosed with one of the six subtypes going to the EL-PFDD meeting in September (LGMD2A/R1, 2C/R5, 2D/R3, 2E/R4, 2F/R6, or 2I/R9), you can actively participate in the live, online meeting. Patient participants will be directly interacting with the meeting's moderators during this dynamic, all-day event.

If you do not have one of these subtypes, you are still invited to watch the event. Remember, this is just the first group of LGMDs going before the FDA, and other subtypes can pursue EL-PFDDs in the future. Note, too, that there have been other efforts made on behalf of all forms of LGMD, such as the Patient Listening Session that occurred in October 2020, as well as the 2022 Global Advocacy Summit. (You can learn more about these advocacy efforts at **TheSpeakFoundation.com**.)

The EL-PFDD will be livestreamed at **lgmdpfdd.com** on September 23rd, starting at 10:00am Eastern Daylight Time (EDT), but you will need to pre-register to participate. Once you sign up, you will receive updates from our EL-PFDD Coalition on how you can be involved. (The Coalition is made up of six nonprofit organizations who have united to represent the subtypes appearing in this first-ever LGMD EL-PFDD.) Pre-register at **lgmdpfdd.com** today, so that you do not to miss this momentous event for our community! ▪

Kat Bryant Knudson

Kathryn Bryant Knudson
Editor In Chief
Founder & CEO, The Speak Foundation

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lgmdpfdd.com

Our Mission

The Speak Foundation was based on the principle of "Speak up for those who have no voice." *Speak up for those who cannot speak for themselves.* — Proverbs 31:8

LGMD News is a program of the Speak Foundation. In order to help individuals and families living with limb-girdle muscular dystrophy receive critical and life-saving information, the Speak Foundation began publishing this resource in 2021.

International Consortium of LGMD Organizations

United States

The Speak Foundation
Uniting the entire LGMD community
TheSpeakFoundation.com

Beyond Labels & Limitations
Funding research for LGMD 2A/R1 and educating on its disease course
BeyondLabelsLimitations.com

Breathe with MD
Educating and raising awareness about breathing muscle weakness in neuromuscular disease
BreatheWithMD.org

CamronsCure
Funding research for LGMD 2S/R18
CamronsCure.com

Coalition to Cure Calpain 3
Funding research for LGMD 2A/R1
CureCalpain3.org

Cure LGMD2I
Funding research for LGMD 2I/R9
CureLGMD2I.org

Kurt + Peter Foundation
Funding research for LGMD 2C/R5
KurtPeterFoundation.org

LGMD Awareness Foundation
Join us for LGMD Awareness Day
LGMD-Info.org

LGMD-1D DNAJB6 Foundation
Representing LGMD 1D/D1 and DNAJB6 subgroup
LGMD1D.org

LGMD2D Foundation
Funding research for LGMD 2D/R3 and educating patients and physicians
LGMD2D.org

LGMD2I Research Fund
Funding research for LGMD 2I/R9 and educating the patient community
LGMD2IFund.org

LGMD2L Foundation
Representing the LGMD 2L/R12 Anoctamin5-related community
LGMD2L-Foundation.org

Team Titin
A consortium of scientists and affected community members for LGMD2J/R10 Titin-related
TitinMyopathy.com

The Jain Foundation
Funding research for LGMD 2B/R2 and educating the patient community
Jain-Foundation.org

Argentina

ADM Argentina Muscular Dystrophy LGMD Group
Funding research for neuromuscular diseases
ADM.org.ar

Australia

Daniel Ferguson LGMD2A Foundation
Funding research for LGMD 2A/R1 and educating the patient community
DFFoundation.com.au

France

"GI LGMD"/LGMD Patient Group of AFM-Telethon
Focusing on all subtypes of LGMD, supporting research and educating the patient community
LGMD.AFM-Telethon.fr

Italy

Conquistando Escalones Association
Funding research for LGMD 1F/D2
ConquistandoEscalones.org

"GFB ONLUS"/ Family Group of Beta-Sarcoglycanopathy
Representing the LGMD 2C/R5 Gamma Sarcoglycan-related, LGMD 2D/R3 Alpha Sarcoglycan-related, LGMD 2E/R4 Bèta-Sarcoglycan-related, and LGMD 2F/R6 Delta-Sarcoglycan-related communities
Beta-Sarcoglicanopathy.org

Gruppo Cingoli of UILDM – Unione Italiana Lotta alla Distrofia Muscolare
Focusing on all subtypes of LGMD, raising awareness and providing support for the entire Italian community.
UILDM.org

Italian Association Calpain 3
Funding research for the LGMD 2A/R1 Calpain 3-related community
AICA3.org

Japan

Patients' Association for Dysferlinopathy Japan
Representing the Japanese and International LGMD 2B/R2 Dysferlin-related and Miyoshi Muscular Dystrophy 1 (MMD) communities
PADJ.jp/index.html

Netherlands

Stichting Spierkracht
Raising awareness and supporting the LGMD2D/R3 Alpha Sarcoglycan-related community
StichtingSpierkracht.com

Spain

Conquistando Escalones Association
Funding research for LGMD 1F/D2
ConquistandoEscalones.org

Proyecto Alpha
Funding research for LGMD 2C/R5 Gamma Sarcoglycan-related, LGMD 2D/R3 Alpha Sarcoglycan-related, LGMD 2E/R4 Bèta-Sarcoglycan-related, and LGMD 2F/R6 Delta-Sarcoglycan-related
ProyectoAlpha.org

Nicholas Johnson, MD, MSci, FAAN

Virginia Commonwealth University

Meet the Expert

Nicholas Johnson, MD, MSci, FAAN is Associate Professor and Vice Chair of Research at Virginia Commonwealth University. After medical school at the University of Arizona, he completed a residency and fellowship in neuromuscular experimental therapeutics at the University of Rochester. His research program includes a translational laboratory and coordinating center for the GRASP-LGMD Consortium. He is one of the co-founders of the Consortium, formed to improve diagnosis in LGMD and accelerate therapeutic development. He has led multi-center natural history studies to develop and refine clinical endpoints. These include the GRASP-LGMD study and ML Bio studies on page 9 of this issue, as well as studies in myotonic dystrophy. His clinical practice in Richmond, VA, focuses on inherited nerve and muscle diseases.

Q

At what stage are the treatment studies on LGMD2D/R3 α-sarcoglycan-related? Is there a gene study for this subtype that will be happening soon?

A

There are efforts underway in the GRASP-LGMD Consortium to better understand how the disease progresses and develop the tools needed for approaching gene replacement trials. Previous trials have evaluated an AAV gene replacement trial for LGMD2D/R3 in a single limb. Unfortunately, I do not have an exact date on when pharmaceutical companies may begin gene therapy trials.

Q

When will clinical trials for LGMD2A/R1 calpain 3-related start, and how long will it take for those trials to reach the next stage?

A

Like LGMD2D/R3, there are efforts underway in the GRASP-LGMD Consortium to better understand how the disease progresses and develop the tools needed for approaching gene replacement trials. There are several promising treatment approaches for LGMD2A/R1. It typically takes at least 12 months, and more typically two to three years, to move a potential therapy through the pre-clinical safety studies in other mammals, in order to ensure humans are not exposed to unnecessary risk. Unfortunately, it is difficult to predict when clinical trials might start.

Q

I have LGMD2N/R14 POMT2-related. Is there a gene therapy for this pathology planned? If so, when will it be available?

A

Unfortunately, I am not aware of any current gene therapy program for this subtype. One of the main barriers for a gene therapy would be to know if the gene was small enough to put in the viruses we use. If this is the case, this subtype would be amenable to a potential gene replacement therapy.

Q

Why did the animal model switch from a mouse to a zebra fish?

A

Different model systems (mice, zebrafish, human cells) are used in different ways to understand the disease, identify treatments, and test the safety of these treatments. It is common that, during the course of a project, multiple systems will be used.

Q

I have LGMD2L/R12 anoctamin5-related and I would like to know why it is so difficult to introduce the missing ANO5 protein in the muscles in order to make up for the deficient cells.

A

Like so many other forms of LGMD, the technology is available to use an AAV gene replacement approach for ANO5. The challenge is working together to fill all of the missing gaps, including: What is the disease progression? What happens in a mouse model if you have too much of the protein? Can you manufacture the gene therapy for a large enough population? Much of those answers need to come from researchers in academic medical centers or pharmaceutical companies. But you can help by participating in available natural history studies and continuing to motivate researchers like myself to work as quickly as possible.

Q

I have LGMD2G/R7 telethonin-related, which I hear very little about regarding research or potential treatments. Is there anything to share for this subtype?

A

This is a rare subtype. Because of the design of our natural history studies in the GRASP-LGMD Consortium, our intention is that information gained across multiple subtypes may be transferred into more rare ones like LGMD2G/R7. Clinically, it appears to affect similar muscles to other LGMDs and is unfortunately progressive. Given the size of the gene, it is possible that this form would be amenable to gene replacement therapy.

Q

Does LGMD get carried by the children of an affected male parent?

A

LGMD is passed either in a dominant or recessive fashion. For those subtypes that are abbreviated with a "D/1," there is a 50/50 chance either parent will pass it to their children. For those subtypes abbreviated with a "R/2," there is a 50% chance their children will be carriers. For their children to have the condition, they would need to have children with someone else who is a carrier, and then there is a 25% chance their child would be affected.

Q

What is the biggest challenge in being able to recommend endpoints to measure progression of LGMD for use in clinical trials? Do you look at endpoints on a spectrum of objective versus subjective? If so, how do you determine the degree of subjectivity in an endpoint?

A

We like to think about endpoints like a toolbox. Sometimes you need to measure a protein in the muscle, sometimes you measure muscle function, and sometimes you measure how a person feels. All of these are important to capture during a clinical trial, with quantitative measures often used early in the trial, and more subjective measures used later. We do try to choose endpoints that are as precise as possible. The biggest challenge is that LGMD is a slowly progressive disease, so you need tools that can see small changes. This is a primary focus of our current studies.

We do try to choose endpoints that are as precise as possible. The biggest challenge is that LGMD is a slowly progressive disease, so you need tools that can see small changes. This is a primary focus of our current studies.

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Question

In almost every form of muscular dystrophy that has been studied, regular, moderate intensity exercise promotes endurance and improves quality of life. Overdoing it with high intensity exercise or heavy weights may cause injury.

Have a Question for Our Experts?

Send Questions To:
ContactUs@TheSpeakFoundation.com

Q

I have LGMD D1 DNAJB6-related. I would like information on exercise. How do I find the correct balance to keep the muscle I still have at its best performance, without taxing my muscles too much or causing more damage?

A

In almost every form of muscular dystrophy that has been studied, regular, moderate intensity exercise promotes endurance and improves quality of life. Overdoing it with high intensity exercise or heavy weights may cause injury. But, in general, you will benefit from moderate intensity aerobic exercise, if you are able to do so.

Q

When therapies become available for LGMD, will they reverse my disease or just keep me from getting worse?

A

That is hard to know without starting these treatment trials. The first objective is always to make sure the therapy is safe for you to take. In many cases, the trial is designed to show that it will slow progression. Of course, we can always hope for more benefit.

Q

Are prolonged calf muscle cramps connected to LGMD? If so, why do they happen and what can I do to prevent them?

A

Individuals with muscle disease are susceptible to muscle cramps. There is no perfect way to prevent them, but stretching before and after exercise and staying hydrated may help. If these efforts do not work, you may ask your muscular dystrophy specialist about medications to treat your muscle cramps.

Q

Can you shed some light on stem cell therapy and its effectiveness on LGMD2A/R1 calpain 3-related? A lot of doctors here in India claim to have been successfully treating LGMD through this therapy method. Do you agree?

A

It depends on whether the stem cells are manufactured appropriately, are known to go to the muscle, and how many stem cells are infused. In addition, infusion of stem cells may prevent someone from qualifying from future clinical trials. It would be important to get some of this information on the quality of the stem cell infusion prior to proceeding. In general, it would not be something I would recommend.

Q

My daughter has LGMD1B (LMNA). I am interested to hear about any therapeutic advances for this disease, as well as any supplements that you might recommend.

A

There have not been supplements that have been shown to be beneficial in LGMD. In fact, there is probably more information to suggest exercise may be beneficial. Right now, there are not active treatment trials in LGMD1B. ▪

JOURNEY

We welcome you to join our Journey...

Journey is a clinical outcomes assessment study, also referred to as a natural history study. Journey studies the natural progression of the disease and how it affects the muscles, lungs, and heart over a period of time (~3 years). The study does not involve the use of an investigational study drug. Individuals affected with Sarcoglycan Limb-girdle muscular dystrophy are invited to participate.

The Journey to uncover your potential treatment options

Currently there are no therapies for individuals with Limb-girdle muscular dystrophy. Participation will provide you access to highly experienced clinical trial physicians and clinicians with expertise in your condition and knowledge about future drug therapy research. Your participation in Journey will not hinder your ability to participate in future clinical studies, including those with investigational study drugs.

Who may be eligible

- Male or Female
- Age 4 years and older
- Genetic diagnosis of LGMD2E/R4, LGMD 2D/R3, or LGMD2C/R5

*Other inclusion/exclusion may apply and will be discussed with a study doctor at screening.

Journey Participation

Study participants will undergo medical and functional procedures during the screening visit, and at scheduled study visits throughout the lifetime of the study.

On-site visits: For screening and every 6-month visit:
- meet with the study doctor and research team
- complete motor assessments.

In between on-site visits: For every 3-month visit:
- study research team will contact you every 3 months by phone
- ask you questions on your health and wellbeing.

Journey Locations

The Journey study is currently enrolling at research centers in the United States and Europe, and is planned to be active in Canada, and parts of South America and Asia.

To learn more about the study and how you can join the Journey, go to journeyLGMD.com

You can also find more information about this study and participating locations, by visiting ClinicalTrials.gov and searching NCT04475926.

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SAREPTA THERAPEUTICS

More Natural History Studies Lead to More Clinical Trials

GRASP-LGMD studies go hand-in-hand with the numerous new therapies at various stages of the drug development pipeline.

The abbreviation GRASP-LGMD stands for Genetic Resolution and Assessments Solving Phenotypes in Limb-Girdle Muscular Dystrophy, and the GRASP-LGMD Consortium is led by Dr. Nicholas Johnson at Virginia Commonwealth University.

The genetics of LGMD are exceptionally complicated, as there are over 30 different genes linked to different subtypes of LGMD, far more than other categories of muscular dystrophy. During the process of seeking a genetic diagnosis for LGMD, it is important to remember that there is no single, perfect, or universal genetic test; each one is good at detecting certain genetic changes and often not as good at detecting others. For example, genetic test panels with specific lists of genes that are examined may miss changes in genes that have not yet been linked to LGMD. And exome sequencing is excellent at detecting small changes in DNA, but not always good at detecting larger changes. Therefore, the work of the GRASP-LGMD Consortium and participation in studies for LGMDs are so important.

I am thrilled to lead a site at the University of Minnesota for the Consortium, as it has extensive geographic reach in the United States and other countries, and explores key, unanswered questions in the study of LGMD while implementing human clinical trials of novel therapies. I am excited about all GRASP-LGMD studies, among them, "Defining Clinical Endpoints in LGMD," as it prepares multiple subsets of individuals affected by LGMD for interventional clinical trials, including children and adults with LGMDD1/1D (*DNAJB6*), LGMDR1/2A (*CAPN3*), LGMDR2/2B (*DYSF*), LGMDR3/2D (*SGCA*), LGMD R4/2E (*SGCB*), LGMDR5/2C (*SGCG*), LGMDR6/2F (*SGCD*), and LGMDR12/2L (*ANO5*). It is particularly impressive that this one study will help set the stage for clinical trials in eight different subtypes of LGMD, and that children are being included.

GRASP-LGMD studies go hand-in-hand with the numerous new therapies at various stages of the drug development pipeline. In the future, I would like to see even more subtypes of LGMD to be studied in this manner, and the GRASP-LGMD Consortium is the ideal home for such investigations. ■

Written by Peter B. Kang, MD, FAAN, FAAP
University of Minnesota Medical School

UPDATED: AUGUST 20, 2022

Active GRASP-LGMD Natural History Studies

Recruiting:

Defining Endpoints in Becker Muscular Dystrophy (GRASP-01-002)

Inclusion Criteria

Ages 8 and older:

- Clinically affected (defined as weakness during evaluation consistent with Becker Muscular Dystrophy)
- Genetic confirmation of an in-frame dystrophin mutation
- Willing and able to give informed consent and follow all protocol instructions

Ages 8–16:

- All of the above and must be ambulatory

Exclusion Criteria

Ages 8–16:

- Out-of-frame dystrophin mutation
- Inability to walk 10 meters without assistive devices
- >16 hours of ventilatory support
- Other illness that would interfere with participation or results

Ages 17 and older:

- Loss of ambulation prior to age 16
- >16 hours of ventilatory support

Recruiting:

Defining Clinical Endpoints in Limb-Girdle Muscular Dystrophy (LGMD) (GRASP)

Inclusion Criteria

- Age between 4–65 at enrollment
- Clinically affected (defined as weakness on bedside evaluation in either a limb-girdle pattern, or in a distal extremity)
- A genetically or functionally confirmed mutation in ANO5, CAPN3, DYSF, DNAJB6, or SGCA-G
- Ambulatory

Exclusion Criteria

- Non-ambulatory at the time of enrollment
- Any other illness that would interfere with the ability to undergo safe testing or would interfere with interpretation of the results in the opinion of the site investigator

Subtypes

- CAPN3 (LGMD 2A/R1)
- DYSF (LGMD 2B/R2)
- ANO5 (LGMD 2L/R12)
- DNAJB6 (LGMD 1D/D1)
- Sarcoglycan (LGMD 2D/R3, LGMD 2E/R4, LGMD 2C/R5, LGMD 2F/R6)

Not Recruiting:

Biomarker Development in LGMD 2I/R9 (MLB-01-001)

Inclusion Criteria

- Age between 10–65 at enrollment
- Clinically affected (defined as weakness on bedside evaluation in either a limb-girdle pattern, or in a distal extremity)
- A genetically confirmed mutation in FKRP (LGMD 2I/R9)
- Up to 60 participants will complete the 10-meter walk test in greater than 4 seconds
- Up to 40 participants will complete the 10-meter walk test in over 12 seconds
- Up to 20 participants may be non-ambulatory

Exclusion Criteria

- Any other illness that would interfere with the ability to undergo safe testing or would interfere with interpretation of the results in the opinion of the site investigator
- History of a bleeding disorder, platelet count <50,000, current use of an anticoagulant
- Positive pregnancy test at start or at any time during the trial

Subtype

- FKRP (LGMD 2I/R9)

Contact: **Jessica St. Romain** | Project Manager, Grasp-LGMD Consortium | (804) 828-7887 | *Jessica.Stromain@vcuhealth.org*

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Tahseen Mozaffar, MD, FAAN | University of California Irvine


Urvi Desai, MD | Atrium Health


Volker Straub, MD, PhD | Newcastle University


Monkol Lek, PhD | Yale University, Non-Clinical Site

GRASP-LGMD Researcher Spotlight

Dr. Peter B. Kang | University of Minnesota Medical School

Dr. Peter B. Kang is the Director of the Paul and Sheila Wellstone Muscular Dystrophy Center, and Professor and Vice Chair of Research in the Department of Neurology at the University of Minnesota Medical School. A pediatric neuromuscular neurologist and physician-scientist, he has treated patients with LGMD and studied LGMD for over 15 years, focusing on genetic and clinical questions. His laboratory studies genetic diagnostic dilemmas in muscular dystrophy and mechanisms of rare muscle diseases, with an overall goal of developing novel therapies for these disorders. He welcomes inquiries from individuals with LGMD who have unresolved genetic diagnoses and may be interested in study participation. He has been the site PI for several multi-center, clinical research studies on muscular dystrophy. He is the Medical Editor of *LGMD News* magazine and has started a site for the GRASP-LGMD Consortium in Minnesota.

By Rachel DeConti
LGMD2D Foundation

Progress for the Sarcoglycanopathies:

An Interview with Dr. Jerry R. Mendell

The honorable Dr. Jerry R. Mendell is a clinician-scientist with decades of experience studying and treating limb-girdle muscular dystrophy.

Currently, Dr. Mendell is an attending neurologist at Nationwide Children's Hospital, the Dwight E. Peters and Juanita R. Curran Endowed Chair in Pediatric Research at the Abigail Wexner Research Institute at Nationwide Children's Hospital, and Professor of Pediatrics and Neurology at Nationwide Children's and The Ohio State University. He was the principal investigator (PI) on the first gene therapy trials for DMD and LGMD, and was the PI on the SMA gene therapy trial that was FDA-approved for systemic delivery for infants with SMA Type 1 in 2017. His life's work has emphasized clinical translation. Dr. Mendell has published more than 370 articles with a focus on neuromuscular disease, and authored books on muscle disease, peripheral nerve disorders, and most recently, gene therapy for muscle disease.

The following interview is comprised of Dr. Mendell's answers to questions from members of the LGMD2D/R3 community through the LGMD2D Foundation.

What findings from previous LGMD2D/R3 or current sarcoglycan clinical trials (such as 2E/R4) are being applied for future trials and treatments for these subtypes?

Dr. Mendell: Gene therapy has an accumulative effect. Work has been done for over 20 years to get to where we are today and it will continue to evolve in the future. Every time we do a clinical trial, we learn something new and very important for the next trial. The first clinical gene therapy trial done for muscular dystrophy was in 1999 for limb-girdle muscular dystrophy, type 2D/R3. At that time, little was known about safety or if a gene could even be expressed in the muscle. That trial was completed in two patients, both of whom were injected with the gene in a small foot muscle. We learned from that trial that we could achieve gene expression in the muscle.

Gene therapy has an accumulative effect. Work has been done for over 20 years to get to where we are today and it will continue to evolve in the future. Every time we do a clinical trial, we learn something new and very important for the next trial.

— Dr. Jerry R. Mendell

We took that experience and reinitiated another trial in 2007, again for LGMD2D/R3. Taking a similar design approach from the 1999 trial, we injected six patients (versus two). From this trial, a critical learning experience was the immune response to the adeno-associated virus (AAV) used as the vector for transfer. One of the patients had pre-treatment exposure to AAV and had antibodies circulating in their blood, blocking the gene delivery to muscle. From that point forward, we learned to test for pre-existing antibody to AAV in every patient before gene therapy is initiated. This has been a guide for every trial we do now.

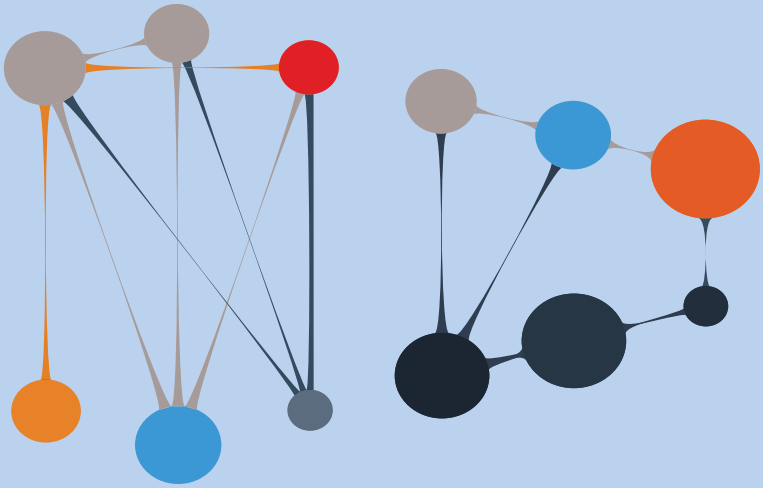
In 2009, we took another step forward, applying outcomes from the previous trials to another LGMD2D/R3 trial. This time, we took an intermediate step to reach more muscles than we could achieve by intramuscular delivery. We injected AAV carrying the alpha-sarcoglycan gene into the femoral artery of the patients' lower extremities (versus just the foot muscle). This is called "isolated limb perfusion" or ILP. We found through this trial that once the corrective gene is put into the circulatory system, it went beyond the isolated limb and improved muscle strength in the arm muscles. It was a good learning experience but the gene delivery in an isolated

limb was difficult for patient and provider. It was a valuable lesson, showing that we could achieve gene expression by delivering the gene into the circulation. We also learned that delivering the gene to the circulation did not result in any major side effects.

The LGMD2E/R4 trial that we have done recently with Sarepta, which has demonstrated good results, uses the principles from prior studies. Now the virus carrying the gene is delivered intravenously (a vein in the arm), permitting the gene to reach muscles through the entire body. Without the previous years of research and trials, we would not be where we are today for trials like this and future ones.

In addition to the actual trials, we have developed methods for producing AAV that we use in the clinical trials. We first started producing virus in a small, converted laboratory in the Center for Gene Therapy at Nationwide Children's. As the demand for clinical trials has grown, so has the need for greater virus production. If we wanted to make an impact on gene therapy, we needed to develop a vector manufacturing facility at Nationwide Children's. As a result, a new facility, Adelyn Biosciences, was opened in 2020, which is now a commercial resource and has helped with many gene therapy trials.

What we have learned in advances in vector usage, manufacturing, and safety have been applied to our studies at Nationwide Children's Hospital and will continue to support future clinical trials with the intention of reaching more patients and other forms of LGMD.



What is the biggest challenge in developing an effective, manufactured treatment for LGMD2D/R3?

Dr. Mendell: The biggest challenge is the overall speed in getting projects to the market and to patients. The process in developing a gene therapy treatment takes time. For example, we have data from previous LGMD2D/R3 clinical trials, and now from the recent 2E/R4 trial. To apply what we have learned from previous trials to another form of LGMD, we need to go back to the laboratory and prove that we have a safe and effective AAV carrying the gene to the patient. We need to treat an animal model that simulates the human disease. This applies to moving forward for treating LGMD2D/R3 or LGMD2B/R2. Experiments in the laboratory must be done in animals with proven safety. Complete autopsies of the animals receiving the gene must include careful examination of every major organ to be sure there are no hidden toxicities. All steps done to prove safety and efficacy in the laboratory are packaged and presented to the U.S. Food & Drug Administration (FDA) in an Investigational New Drug (IND) application. These steps need to be done for every clinical trial proposed, which takes considerable time.

Have the natural history research studies shown any new trends that were previously unknown for the sarcoglycanopathies? How can we enhance participation in these studies?

Dr. Mendell: The natural history study data has shown a number of new things that are relevant for sarcoglycanopathies. We are seeing a wider spectrum of patients living with this disease than we initially anticipated. There are patients as young as five years old and others that are over 40 being relatively newly diagnosed. We are learning more about the similarities and differences within the sarcoglycans as well. These natural history studies are teaching us more about age distribution and muscle weakness. From early diagnosis to follow-up appointments, we use this data to determine the best outcomes for the disease to apply to clinical trials.

Participation can be enhanced by raising awareness of the studies through the work of the LGMD foundations. These foundations are key to bringing in new patients to these research studies so we can learn more. The foundations can help patients understand more about LGMD and the resources available to them. The more awareness raised on critical information like genetic testing, the more individuals can be accurately diagnosed within an LGMD subtype, and then encouraged to participate in these studies if one is available.

Are other forms of treatment being explored for LGMD2D/R3 and the sarcoglycan subtypes? We have heard of success with other treatments in trials for different forms of LGMD and DMD.

Dr. Mendell: There are only a few forms of treatment for gene replacement therapy, and we are doing them now with the LGMD2E/R4 clinical trial and the work being done for Duchenne muscular dystrophy. This includes using different AAV serotypes to better promote gene expression in muscle. These alternative AAVs are being tested in the laboratory and will be applied to clinical trials. These forms of treatment could be tested and applied to LGMD2D/R3 or other sarcoglycanopathies in the future. There are also issues related to immunity to the virus that are relevant to patient outcomes, and these are being explored in clinical trials as well. Other advances are taking place in this rapidly growing field. Gene editing is planned for clinical trial for muscular dystrophies and holds great promise. The method, called CRISPR, allows the gene to be edited in its place. The editing allows restoration of the gene's function and should allow for correction for the lifetime of the patient.

Are there exercises you can recommend (isometric or others) that will help sustain muscle strength and flexibility while treatments are being developed?

Dr. Mendell: We have tried experimenting with various muscle exercises in the past in numerous ways and have never achieved a program that would strengthen muscle based solely on exercise. Passive extremity stretching can help range in motion so the muscles do not get contracted — mainly in the hips and ankles — which can help muscles function, but muscles afflicted with dystrophy do not respond well to deliberate attempts like weight training.

Do you have any updates that you can share on the LGMD2E/R4 trial that would benefit the 2D/R3 and broader sarcoglycan community?

Dr. Mendell: So far, there is very good expression of the gene upon delivery by AAV through circulation. This has been shown in the muscle biopsies of LGMD2E/R4 patients participating in the clinical trial sponsored by Sarepta Therapeutics with delivery of SRP-9003. This shows that the treatment is working. We have also seen improvement in functional outcomes including the modified LGMD North Star assessment (NSAD), time to rise, and 100-meter walk. What has been learned in this trial has implications for LGMD2D/R3.

What advice do you have for patients waiting for a treatment or cure, to offer them hope?

Dr. Mendell: I have been doing gene therapy for 20+ years and every year, we have gotten better and better and have seen greater opportunities of significantly improving muscle function using gene therapy as a mode of treatment. We are very hopeful that we can make major improvements in LGMD with treatments offered in the future. ▪

We Offer HOPE.

Are you an individual living with limb-girdle muscular dystrophy who needs assistance covering the costs of mobility and durable medical equipment (DME)? The SPEAK Foundation is here to help.

Through **The HOPE Project**, we are able to award a one-time stipend of up to $250 to qualified applicants living in the United States who have a diagnosis of limb-girdle muscular dystrophy and need assistance affording DME expenses for mobility.

For additional information or to submit an application from August 1, 2022 through October 28, 2022, please visit **TheSpeakFoundation.com/grant-programs**.

The HOPE Project

A Program of The SPEAK Foundation

TheSpeakFoundation.com/grant-programs

Accepting applications from August 1, 2022 through October 28, 2022.
Available to US residents only.

A Conversation with Diane Berry, Ph.D.

Senior VP, Global Health Policy, Government and Patient Affairs, Sarepta Therapeutics

Diane, what is your current role, and in which ways do you focus on Limb-girdle muscular dystrophy (LGMD)?

I joined Sarepta over a decade ago after serving in the U.S. government. As part of Sarepta's executive leadership team, I help guide and shape our strategy. My work cuts across all of the programs in our pipeline, including gene therapies for LGMD, as they share common challenges and opportunities in development, approval and patient access. Today's policies were established in a world that had not yet envisioned gene therapy. Our team works to tackle barriers and advance critical policies to enable cutting-edge science to reach patients in the fastest, most responsible ways possible. To do this, we engage federal and state policymakers, patient advocates, physicians, industry peers, and other thought leaders.

How can policy support faster drug development timelines?

Progress in policy is often not visible or measured in days or months. It can take years before new policies are fully embraced and put into practice resulting in speedier development timelines. That's why we started laying the groundwork a decade ago to ensure regulators, like the FDA, have the authority and tools they need to address challenges presented by rare and ultra-rare, slowly progressing diseases. For example, in Congress' 21st Century Cures Act, a process which kicked off in 2013 and led to a new law passed in 2016, Sarepta drove the inclusion of language that provided clear authority to FDA allowing them to leverage data across programs that share commonalities – much like our LGMD programs – to facilitate drug development for serious rare, and subsets of rare, diseases.

What are the policy challenges and opportunities facing LGMD drug development?

LGMD is a great example of how regulatory innovation (e.g., biomarkers, novel trial designs, etc) could be applied to more efficiently respond to the urgent unmet needs of the community. The pathway to approval in LGMD is unprecedented and requires navigating complexities of the disease and gene therapy manufacturing process that challenge our shared goal to hasten the availability of new treatments. The good news is that FDA has the necessary tools and authority to enable creative and flexible approaches to gene therapy development and manufacturing. And importantly, FDA has an open door for patients and caregivers to share first-hand experiences and insight into the needs of those living with LGMD such that regulators can apply appropriate flexibility and make informed decisions. Working together, there is an opportunity for developers, regulators, and the scientific and patient community to address the key scientific and regulatory challenges and illuminate a path forward for treatments for LGMD.

By Jennifer R. Levy, PhD
Scientific Director, Coalition to Cure Calpain 3

Make Your Voice Heard

Participate in the First EL-PFDD for Limb-Girdle Muscular Dystrophies

On September 23, 2022, an Externally-Led Patient-Focused Drug Development (EL-PFDD) meeting will be held with representatives from the Food and Drug Administration (FDA) and other key stakeholders. This meeting, which will focus on LGMD subtypes 2A/R1, 2C/R5, 2D/R3, 2E/R4, 2F/R6, and 2I/R9, will facilitate the integration of patients' perspectives into the development and approval of LGMD therapies.

9/23/22 LIVE EVENT 10:00AM (EDT)

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You must pre-register in order to participate by signing up at:
www.lgmdpfdd.com

Q

What is the goal of an EL-PFDD meeting?

A

This meeting is devoted to listening to and learning from caregivers and people living with the six subtypes of LGMD listed on page 16. The goal of this meeting is to provide the FDA, clinicians, medical product developers, patient advocates, and academic researchers an opportunity to hear perspectives from individuals with LGMD on the health effects and daily impacts of living with the disease. The goal is also to communicate patients' viewpoints when it comes to seeking out or selecting a treatment.

Q

Why is the EL-PFDD meeting important?

A

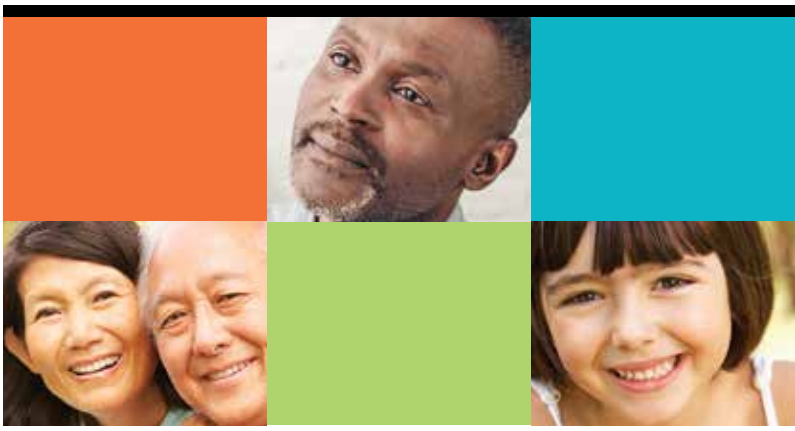
Nobody knows more about what it means to live with LGMD than you! The meeting is a unique opportunity for patients and families to share their stories with the FDA and other key stakeholders. The patient perspective is critical in helping the FDA understand the context in which regulatory decisions are made during the approval process for new therapeutics. It can also help pharmaceutical companies better design clinical trials that have a low burden on participants and outcome measures that align with what matters most to us.

Q

Why is this meeting being held now?

A

In the past, the patient's voice has not been central to the drug development process. That is beginning to change, thanks in part to the FDA's EL-PFDD initiative, a commitment under the fifth authorization of the Prescription



Drug User Fee Act (PDUFA V) to systematically gather patients' perspectives. Patient and caregiver engagement is now a priority to the FDA and other stakeholders such as pharmaceutical and biotechnology companies. The sarcoglycanopathies, LGMD2A, and LGMD2I all have treatments in clinical or late-preclinical stages. We are on the cusp of an exciting period of progress for LGMDs, and we want to arm drug developers, the FDA, and other key stakeholders with our perspectives so that future treatments meet the needs and expectations of our community.

Q

What topics will be covered?

A

The meeting will begin with a brief welcome message, an overview of LGMD from a clinical expert, and a statement from an FDA representative.

The first session will focus on the sarcoglycanopathies: disease symptoms, health effects, and the toll on daily life. The session will begin with four panelists sharing their stories: the initial emergence of symptoms, how they were diagnosed, what their most significant symptoms are, and the overall impact of their condition on their daily life and relationships. After panelist statements, a live discussion will be held via videocast. Patients and caregivers are encouraged to call or write in

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9/23/22 LIVE EVENT **10:00AM (EDT)**

with comments. The second session will follow a similar format as the first, but will include individuals living with LGMD2A and LGMD2I, as well as their caregivers.

The third session includes individuals with all six subtypes sharing their perspectives on current and future treatments for LGMDs. These panelists and discussion participants will discuss the effectiveness and drawbacks of current approaches to managing their symptoms, their willingness to participate in research, their experiences participating in clinical trials, and their perspectives on what they would look for in future treatments for LGMD.

At the end of the meeting, there will be closing remarks that summarize some of the topics of the day, as well as a discussion of next steps.

Q

What happens after the meeting?

A

A recording of the meeting will be made publicly available online. A report titled the "Voice of the Patient" (VOP) will summarize the ideas and information shared at the meeting and be sent to the FDA and other key stakeholders, as well as posted on the websites of the organizations in the LGMD Coalition. This report will serve as a resource to help drug developers and regulators understand patient/caregiver perspectives when developing and approving new treatments.

Q

Who is organizing the event?

A

Representatives from Coalition to Cure Calpain 3, Cure-LGMD2i, the Kurt + Peter Foundation, the LGMD2D Foundation, the McColl-Lockwood Laboratory for Muscular Dystrophy Research, and the Speak Foundation have joined together to organize this event. Jointly referred to as the LGMD Coalition, these nonprofit organizations are encouraging members of the global patient community to make their voices heard.

Q

Who should participate?

A

Great attendance from the LGMD community will show the FDA and others that we are mobilized and ready for a cure! It will also help us get a wide range of perspectives from people with very different experiences. Individuals living with LGMD subtypes 2A/R1, 2C/R5, 2D/R3, 2E/R4, 2F/R6, and 2I/R9, and those who are caring for them, are encouraged to participate by partaking in live polling and by calling and writing in with comments. Your voice is critical to a successful meeting! Academic investigators, clinicians, regulators, industry representatives, and the general public are welcome to watch the meeting. ▪

How Can I Participate?

Visit **www.lgmdpfdd.com** to pre-register for the meeting and to submit pre-meeting comments on your experiences living with LGMD.

Mark your calendar to attend the meeting live on **September 23, 2022**, from **10am–3pm EDT**. A link to join the meeting will be emailed in September to people who pre-register.

On the day of the meeting, join us live. You can participate in live polling, call in, and submit written comments. **We need to hear from you!**

9/23/22 **LIVE EVENT** **10:00AM (EDT)**

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Meet the LGMD Coalition

By Carol Abraham and Michele Wrubel
Coalition to Cure Calpain 3

The LGMD Coalition is a group of six 501(c)(3) nonprofit organizations, including Coalition to Cure Calpain 3, CureLGMD2i, the Kurt+Peter Foundation, the LGMD2D Foundation, the McColl-Lockwood Laboratory for Muscular Dystrophy Research, and the Speak Foundation. They are collaborating to host the LGMD EL-PFDD focused on limb-girdle subtypes 2A/R1, 2C/R5, 2D/R3, 2E/R4, F/R6, and 2I/R9.

Coalition to Cure Calpain 3 (C3) has a pinpoint focus: to drive research to treat and ultimately cure limb-girdle muscular dystrophy type 2A (LGMD2A), also referred to as LGMDR1 and calpainopathy. C3 was founded in 2010 by patients frustrated at the lack of funding for, and awareness of, this muscle-wasting disease, caused by genetic changes in the calpain 3 gene. Scientific Director Dr. Jennifer Levy directs the C3 grant program, with a portfolio focused on gene and cell therapy, novel approaches, tool creation, and clinical trial readiness. For the last decade, C3 has been the U.S.-based, nonprofit leader of LGMD2A/R1 funding, with over $2 million committed to innovative research undertaken by international leaders in the muscular dystrophy field. Importantly, C3 maintains the Global LGMD2A/R1 Patient Registry to improve the accuracy of the estimated number of people with LGMD2A/R1; to draw attention to the disorder; to keep patients updated on advances in the field; to allow researchers to better understand the progression and manifestations of the disease; and to help researchers locate participants for clinical trials. C3 is proud to partner with the organizations that comprise the LGMD Coalition.

CureLGMD2i was founded by the Brazzo family when their daughter, Samantha, was diagnosed with LGMD2I/R9 at the age of two. At that time, there were no available treatment options for this rare and progressive disease, so they decided to create this 501(c)(3) nonprofit organization (formerly known as the Samantha Brazzo Foundation). CureLGMD2i is focused on advocating for patients living with LGMD2I/R9, funding cutting-edge research programs, and partnering with the biotech industry to facilitate the development of successful treatments for LGMD2I/R9. To date, CureLGMD2i has provided over $890,000 in grants to support research, awareness programs, and patient/family conferences focused on the dystroglycanopathies. We are thrilled to be participating in the EL-PFDD with our LGMD partner organizations. This is such an exciting time in treatment development for our LGMD community and we feel that the FDA will be compelled by the participation and stories of our passionate patients and their caregivers.

The **Kurt+Peter Foundation** was founded by the family of Kurt and Peter Frewing, two boys living with limb-girdle muscular dystrophy type 2C (also referred to as type R5). The Kurt+Peter Foundation primarily focuses on raising funds for research that applies available scientific techniques to treat or potentially cure LGMD2C/R5. Research that the Kurt+Peter Foundation has funded includes preclinical research for exon skipping conducted at Northwestern University and the University of Chicago, use of low-dose steroids to mitigate muscular dystrophies, as well as preclinical gene therapy research conducted at Nationwide Children's Hospital in Columbus, Ohio. The Kurt+Peter Foundation also seeks to raise awareness of LGMD2C/R5 and to connect patients. The Kurt+Peter Foundation has worked with other muscular dystrophy organizations to communicate with regulators about the patient experience, including with the U.S. Food and Drug Administration.

Founded in September 2013, the **LGMD2D Foundation** is a registered 501(c)(3) nonprofit foundation whose mission is to expedite the development of an effective therapy or cure for limb-girdle muscular dystrophy type 2D/R3. We, too, saw there was a gap in providing information and resources to those living with this rare disorder. In addition to educating patients and physicians, the foundation maintains a patient registry, funds research and monitors progress, provides financial support to accelerate clinical trials, and encourages scientific collaboration. Our International Patient Registry is free to join and is currently the only database for patients affected with LGMD2D/R3. The purpose of this registry is to help assist in the development of treatments for LGMD2D/R3 by showing a true representation of those impacted by the disease globally. This registry helps researchers identify patients who qualify for future clinical studies and trials, allows researchers to study disease progression, helps us to raise awareness of LGMD2D/R3, and assists patients in finding appropriate clinical trial information. The LGMD2D Foundation is a proud member of the LGMD Coalition. We are excited to collaborate with our partner organizations and be a part of this monumental event for the LGMD community.

The **McColl-Lockwood Laboratory for Muscular Dystrophy Research** focuses on developing novel therapies for muscular dystrophy, specifically limb-girdle muscular dystrophy (LGMD). The laboratory is funded with the support from the Carolinas Muscular Dystrophy Research Endowment, which was created by the McColl and Lockwood families. Additional funding is from Atrium Health Foundation as well as federally funded grants. Directed by Qi Long Lu, MD, PhD, the lab is a division of the Carolinas Neuromuscular/ALS MDA Center, part of Atrium Health Musculoskeletal Institute and Atrium Health Neurosciences Institute. The McColl-Lockwood Laboratory has established cell cultures, specific reagents, and animal models specific and critically important to therapeutic development for muscular dystrophies. The laboratory continues to make milestone achievements in experimental therapies by its research team of scientists and technicians with specialized training and experience in drug design, pharmacology, cell, and molecular biology. The McColl-Lockwood Laboratory has successfully created a small molecule drug that is in Phase 2 of an FDA clinical trial – the dosing of LGMD2I/R9 patients with ribitol, led by ML Bio Solutions/BridgeBio Pharma. If approved by the FDA, it will be the first and only proven drug therapy for LGMD patients.

Founded in 2008, the **Speak Foundation** is a 501(c)(3) nonprofit organization that seeks to improve the quality of life of those living with limb-girdle muscular dystrophy and other rare neuromuscular diseases. It was founded by Kathryn Bryant Knudson, who lives with LGMD2I/R9. The foundation's name comes from Proverbs 31:8: "Speak up for those who cannot speak for themselves."

Since its founding, the Speak Foundation has been a pioneer for the LGMD community, creating vital programs and resources, including the International LGMD Conference, the Personal Care Attendant Stipend Program, the C.A.R.E. Program for newly diagnosed patients, *LGMD News* magazine, the HOPE Project, the LGMD Global Advocacy Summit, educational webinars, and more. The organization continues to provide ongoing support and resources to the community while also establishing important relationships with physicians, pharma, biotechs, and now the FDA. For the upcoming EL-PFDD meeting for the first group of LGMDs, the Speak Foundation is honored to represent the LGMD2E/R4 community, which does not have an established organization in the USA. Speak is prepared to assist more subtypes in future EL-PFDD meetings.

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9/23/22 LIVE EVENT **10:00AM (EDT)**

Meet the Panelists

By Carol Abraham and Michele Wrubel
Coalition to Cure Calpain 3

The LGMD Coalition is grateful to the EL-PFDD panelists for sharing their stories. We hope they inspire you to reflect upon the issues you would like to share about living with LGMD and encourage you to participate. By writing in with comments (before or during the meeting), responding to live polling, and/or phoning in during the September 23rd livestream event, our united voices will make a difference!

SESSION 1

Rania

Age: 35 ▪ LGMD2E/R4
Orlando, Florida

"It's a remarkable feeling to have the reach and influence to speak with a governing body that could drastically change the quality of my life."

- **First Symptoms:** I waddled when walking, had difficulty climbing steps, tired easily, and needed a chair to lean on to get up from the floor.
- **If I Were Cured Tomorrow…** I would pack my suitcase, go to the airport, and take the next available, international flight.
- **Fun Fact:** I have been on a hot air balloon ride!

Kurt

Age: 16 ▪ LGMD2C/R5
Menlo Park, California

"I am excited to participate in the EL-PFDD to provide insight about what it's like living with LGMD2C."

- **First Symptoms:** I would army crawl (age 2).
- **If I Were Cured Tomorrow…** I would get a job working in a professional kitchen.
- **Fun Fact:** I am obsessed with cooking.

Peter

Age: 14 ▪ LGMD2C/R5
Menlo Park, California

"I am excited about the opportunity to share my experience with LGMD2C with other patients and the FDA."

- **First Symptoms:** I tired more easily than my classmates.
- **If I Were Cured Tomorrow…** I would go to Disneyland!
- **Fun Fact:** I like to code and build giant LEGOs.

Elizabeth

Age: 42 ▪ LGMD2C/R5
Holland, Michigan

"If sharing my story of living with a rare neuromuscular disease helps in future research that may lead to finding treatment or a cure, I am happy to take part."

- **First Symptoms:** I was a toe-walker, had difficulty getting up from the floor, and easily fatigued (age 7).
- **If I Were Cured Tomorrow…** I would love to be able to live independently!
- **Fun Fact:** I love crafting, coffee, and books!

Donavon

Age: 59 ▪ LGMD2D/R3
Andover, Kansas

"I want to tell the FDA my family's story."

- **First Symptoms:** I was not able to run very fast (age 10).
- **If I Were Cured Tomorrow…** I would drive.
- **Fun Fact:** I was the first person in the world to undergo gene therapy for any form of MD.

SESSION 2

Dan

Age: 57 ▪ LGMD2I/R9
Longmont, California

"There is an urgent and unmet need to find effective treatments and therapies for LGMD."

- **First Symptoms:** I was a toe-walker (toddler).
- **If I Were Cured Tomorrow…** I would hike into my old, secret fishing spot and fish all day long.
- **Fun Fact:** I learned to fly sailplanes when I was 15.

Jane

Age: 25 ▪ LGMD2I/R9
Charlotte, North Carolina

"This is something all patients should be excited about, as it is a huge step for the LGMD community. I am honored to have been chosen to represent our close-knit community in front of the FDA and am hopeful for our future."

- **First Symptoms:** I had trouble keeping up with friends on the playground and consistently used the same leg to climb stairs instead of alternating (age 4-5).
- **If I Were Cured Tomorrow…** I would start by taking my dog for a run. Then, I would go out with friends without stressing about accessibility or the daunting task of transferring out of my chair to use the restroom.
- **Fun Fact:** My eyes are two different colors.

9/23/22 **LIVE EVENT** **10:00AM (EDT)**

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Brooklyn

Age: 15 ▪ LGMD2A/R1
Pflugerville, Texas

"I'm very excited to share my story and hope it will make a difference."

- **First Symptoms:** I could not support my weight with my arms and kept falling while trying to learn to do a cartwheel (age 9).
- **If I Were Cured Tomorrow…** I would go on a hike at Yellowstone National Park.
- **Fun Fact:** I LOVE listening to music and going to concerts!

Carol

Age: 61 ▪ LGMD2A/R1
Twin Lakes, Wisconsin

"I am grateful to have this opportunity to share my LGMD journey with the FDA and other key stakeholders. No one knows the effect of how these progressive neuromuscular diseases impact our lives better than those who live with these conditions."

- **First Symptoms:** I walked on my toes and had difficulty keeping up with my peers (age 5).
- **If I Were Cured Tomorrow…** I would run up to my husband, wrap my arms tightly around him, and give him a huge hug and kiss! Then, I would go running on a sandy beach.
- **Fun Fact:** In 2001, I received the "Female Waterskier of the Year" Award from Rehabilitation Institute of Chicago!

SESSION 3

Patrick

Age: 49 ▪ LGMD2E/R4
Salem, New Hampshire

"I am happy and excited to share my story and meet others!"

- **First Symptoms:** I displayed weakness while running in gym class, ran on my toes, and lost balance while jumping and running (age 11).
- **If I Were Cured Tomorrow…** I would play my drums again.
- **Fun Fact:** I have driven across the U.S. twice, visiting 38 different states. My bucket list is to visit all 50.

Paul

Age: 65 ▪ LGMD2C/R5
Napa, California

"Once I realized God has my back, I was no longer depressed about having this disease."

- **First Symptoms:** I had symptoms at birth, like choking and paralysis. My parents thought I was going to die as an infant.
- **If I Were Cured Tomorrow…** I would RUN!
- **Fun Fact:** I love cooking. I'm a big foodie!

Jacob

Age: 6 ▪ LGMD2D/R3
Newington, Connecticut

Jacob's mom (Rachel):

"As a caregiver, I am honored to be a part of the LGMD Coalition and this meeting for the LGMD community. My hope is with events like these, more treatment options will be available for patients like my son, sooner."

- **First Symptoms:** Jacob was diagnosed after a case of rhabdomyolysis (which causes dark urine when overly active) and his legs hurt and are sore (age 5).
- **If I Were Cured Tomorrow…** We would let Jacob be as active as he wanted – running, jumping, climbing – for as long as he wanted, with a little less worry.
- **Fun Fact:** Jacob LOVES Spider-Man! For his Kindergarten graduation, he said that he wants to be him when he is older!

Samantha

Age: 14 ▪ LGMD2I/R9
Lancaster, Pennsylvania

Sammy's mom (Kelly):

"It is important for us to show the FDA how our lives have been affected on so many levels by this progressive disease. I am excited for the FDA to see the strength of our amazing LGMD community, and I pray that this will help to successfully bring treatments to the market more efficiently."

- **First Symptoms:** Sammy had trouble keeping up with peers, fell often, had difficulty getting up from the ground, and she had a waddling gait/hip sway (age 2).
- **If I Were Cured Tomorrow…** I would want to go to the beach, run through the sand and into the ocean, jump in the waves, and not worry about falling over or getting sea legs when I get out. That would be amazing.
- **Fun Fact:** I really love watching basketball (my dad is a coach), and I love cooking all kinds of savory foods and sweets.

Kathryn

Age: 49 ▪ LGMD2I/R9
Tallahassee, Florida

"Be joyful in hope, patient in affliction, and faithful in prayer." – Romans 12:12

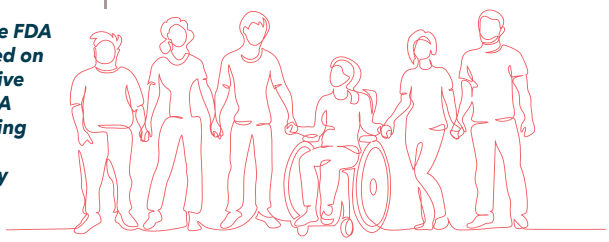
- **First Symptoms:** I had rhabdomyolysis starting at six years of age.
- **If I Were Cured Tomorrow…** I would go to the beach and spend all day at the ocean. Then I would go to Italy and hike everywhere!
- **Fun Fact:** I competed as "Miss Chesterfield County" in the Miss Virginia pageant!

Andrew

Age: 41 ▪ LGMD2A/R1
Canterbury, U.K.

"It's a real honor to be involved in this project."

- **First Symptoms:** I struggled to get up from the floor (age 19).
- **If I Were Cured Tomorrow…** I would walk with my son on the beach.
- **Fun Fact:** My tongue has grown quite large because of my muscle disease. Try sharing an ice cream with me now!



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9/23/22 LIVE EVENT **10:00AM (EDT)**

Externally-Led Patient-Focused Drug Development Meeting

SCHEDULE

SEPTEMBER 23, 2022 ▪ ALL TIMES ARE IN EASTERN DAYLIGHT TIME (EDT) (UTC-4)

10:00AM Welcome
Kathryn Bryant Knudson
Founder/CEO, The Speak Foundation
Living with LGMD2I/R9

10:05AM FDA Speaker
Wilson Bryan, MD, OTAT, CBER

10:15AM LGMD Clinical Overview
Katherine Mathews, MD
University of Iowa

10:30AM Introduction & Meeting Overview
James Valentine, JD, MHS
Co-moderator
Jennifer Levy, PhD
Coalition to Cure Calpain 3
Co-moderator

10:35AM Demographic Polling
Includes all 6 LGMD subtypes

10:40AM Session 1: Living with Sarcoglycanopathies (LGMD2C, 2D, 2E, 2F) — Symptoms, Health Effects, and Impacts on Daily Life
- *Includes Patient Panelists and Discussion Starters*
- *Patient/caregiver audience remote polling*
- *Moderated audience discussion (telephone and written comments)*

11:40AM Session 2: Living with LGMD2A and LGMD2I — Symptoms, Health Effects, and Impacts on Daily Life
- *Includes Patient Panelists and Discussion Starters*
- *Patient/caregiver audience remote polling*
- *Moderated audience discussion (telephone and written comments)*

12:40PM Lunch

1:20PM Session 3: Current and Future Treatments (all 6 subtypes)
- *Includes Patient Panelists and Discussion Starters*
- *Patient/caregiver audience remote polling*
- *Moderated audience discussion (telephone and written comments)*

2:45PM Summary Remarks
Larry Bauer, RN, MA

2:50PM Closing Remarks & Next Steps
Charlotte Drew, MD
Co-Founder, The Kurt+Peter Foundation
Caregiver of two sons living with LGMD2C/R3

3:00PM Adjourn

9/23/22 **LIVE EVENT** **10:00AM (EDT)**

DON'T MISS YOUR CHANCE!
You must pre-register in order to participate by signing up at:
www.lgmdpfdd.com

It Is Not Too Late!

By Kelly Brazzo
Co-Founder and CEO, CureLGMD2i Foundation

It is not too late to sign up to participate in the Externally-Led Patient-Focused Drug Development (EL-PFDD) meeting with the FDA

Do you want the FDA to hear your voice on September 23rd? It is not too late to participate in this monumental, LIVE, and INTERACTIVE event for our LGMD community. We encourage you to SIGN UP TODAY on our website at **www.lgmdpfdd.com**.

Do not miss this opportunity to share your voice with the FDA!

Your voice matters and the more involvement we have from our LGMD community, the better! The EL-PFDD is a meeting hosted, led, and presented by our LGMD leaders. We welcome and encourage you to actively participate from the comfort of your own home if you are a patient diagnosed with, or a caregiver for one of the following subtypes: LGMD2A/R1, LGMD2C/R5, LGMD2D/R3, LGMD2E/R4, LGMD2F/R6, or LGMD2I/R9. We will cover a range of topics, including symptoms, health effects, struggles, impact on daily living, and perceptions on existing and future treatments. ▪

How Can You Get Involved?

Go online to register your information at **www.lgmdpfdd.com.** Once you are registered, a team member from our EL-PFDD Coalition will send you detailed information regarding the schedule for the EL-PFDD meeting and how you can be an active participant throughout the event.

What are some ways you can participate?

- **Remote Polling:** During the EL-PFDD meeting on September 23rd, there will be opportunities for you to respond, via your computer or phone, to a variety of different polling questions that will let the FDA know who is in attendance from our LGMD patient and caregiver community. For example, these could include questions about where you live, what LGMD subtype you are living with, and more.

- **Ask questions or make comments during our LIVE call-in.** We will have time throughout the EL-PFDD meeting for an interactive audience discussion specifically for the six LGMD subtypes listed above. You will be prompted by the meeting moderator to call in or submit your written comments online. You may also submit your written comments in advance of the event at the **www.lgmdpfdd.com** website.

Why is it important for me to participate?

The EL-PFDD meeting is the perfect opportunity for you to let the FDA know what matters most to you as someone whose life is affected by LGMD. Your voice will have an impact on future clinical trial designs, outcome measures that are more meaningful to patients, and increased awareness of the hardships and challenges of living with LGMD. After our EL-PFDD meeting, a "Voice of the Patient" (VOP) report will be compiled and kept on file. The "Voice of the Patient" report is a meeting summary and will be used as a reference document by the FDA, medical product developers, health care providers, federal partners, and our patient community. This educational resource will be available to the FDA when reviewing potential, new drug therapies or treatments. It will also be beneficial to the other LGMD subtype groups who are planning for future EL-PFDD meetings.

Do not wait. Sign up today!

Go to our website at **www.lgmdpfdd.com** or use the QR Code below to sign up to participate today! Mark your calendars for September 23rd so that you can join our live discussion and engage with the FDA to share your thoughts about living with LGMD. After you are registered, our team will keep you informed of all the details pertaining to our EL-PFDD meeting. We appreciate your support and look forward to this vitally important opportunity for our LGMD family.

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9/23/22 LIVE EVENT **10:00AM (EDT)**

By Charlotte Drew, MD
Kurt + Peter Foundation

I Want to Be Involved,
but My Subtype Was Not Included!

If you live with a form of LGMD that is not included among the six subtypes that will be discussed at the September 23, 2022 Externally-Led Patient-Focused Drug Development (EL-PFDD) meeting with the Food and Drug Administration (FDA), it does not mean that an EL-PFDD will not happen for your subtype or that you do not have an opportunity to participate in an EL-PFDD. Indeed, if you or someone you care about has a form of LGMD that is not scheduled for the September 23rd event, you have an opportunity to play a key role in the next LGMD-focused EL-PFDD.

The purpose of patient-focused drug development is to hopefully incorporate patients' experiences, perspectives, needs, and priorities into the development of treatment drugs. Patients are experts in living with their condition and are best positioned to inform the FDA of their understanding of what they want from drug development. EL-PFDDs are led by patients and patient organizations who want to share their experiences with the FDA and other stakeholders, such as clinicians and pharmaceutical companies.

The September 23, 2022 EL-PFDD came about because 16 representatives from ten LGMD organizations met to discuss how best to move forward with the EL-PFDD process. Those participants agreed that patients living with one of the sarcoglycanopathies, LGMD2A/R1, or LGMD2I/29 would request the first EL-PFDD because those types of LGMD have similar symptoms and ages of symptom onset. Additionally, various drug companies have programs in clinical or late-preclinical stages of development for those forms of LGMD. The fact that these forms of LGMD have similarities and hopefully treatments close to submission to the FDA made them appropriate to group together. Because the science has demonstrated that the differences among the various subtypes of LGMD disease vary by genetic subtype, and because most therapies in development today target specific subtypes rather than all LGMDs, regulators such as the FDA are likely to consider each subtype as a distinct disease when reviewing targeted treatments for approval. As a result, the September 23rd EL-PFDD meeting will highlight information specific to each of these six genetic subtypes.

Patients and advocacy organizations focused on other LGMD subtypes can have an opportunity in the future to organize and participate in their own EL-PFDDs. Meetings with the FDA and other stakeholders are optimal when the patient community for a particular subtype, or group of subtypes, feels the preclinical or clinical work has progressed sufficiently enough that it makes sense

9/23/22 LIVE EVENT 10:00AM (EDT)

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for that community to engage to elicit the patient perspective. The patients who organized the September 23rd EL-PFDD made clear to the FDA that the meeting will only focus on this small number (six) of the many LGMD subtypes. Consistent with those representations, patient advocacy organizations that represent other forms of LGMD, or individual patients, may submit Letters of Intent (LOIs) for future EL-PFDDs focused on their forms.

If you are a patient with a form of LGMD that will not be discussed on September 23rd, or a representative of an organization focused on another form of LGMD, you can have the opportunity to organize an additional EL-PFDD meeting. Before organizing, you should consider the following:

1. **Are you interested in collecting patient perspectives to inform the FDA and other stakeholders about the specific disease subtype or subtypes?**

2. **Are you prepared to identify the target patient population, including the disease subpopulations or patient characteristics that should be represented in an EL-PFDD?**

3. **Have there been other recent interactions with the FDA by other relevant patient stakeholders?**

4. **How will you collaborate with other relevant patient stakeholders, such as other advocacy organizations that represent LGMD subtypes similar to your own?**

5. **Is there another scientific or FDA-related meeting for the specific LGMD subtype that should be coordinated with an EL-PFDD?**

Once you have considered these issues, you can submit an LOI to the FDA. The LOI should be a short (approximately three pages) explanation of what your group hopes to gain from a meeting with the FDA and should be submitted approximately one year prior to the date that you wish to hold the meeting. Guidelines for developing a LOI are provided by the FDA at **FDA.gov/industry/prescription-drug-user-fee-amendments/externally-led-patient-focused-drug-development-meetings**.

Finally, it is important to note that this first EL-PFDD for LGMDs can offer substantial insight to other subtype groups in the future. This meeting will be virtual. As a result, any person, including patients with other forms of LGMD, can watch the meeting live, access the recorded footage later, and download the meeting's Voice of the Patient (VOP) report. With these resources, you can consider how your subtype might wish to be represented in a future LGMD EL-PFDD. ■

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9/23/22 LIVE EVENT **10:00AM (EDT)**

Kathryn Bryant Knudson

Advocating for the Future: The Mission of The Speak Foundation

It is crucial that we work together to build new programs and create new projects that help build paths to treatment.

Connect with Us

Send Questions To:
ContactUs@TheSpeakFoundation.com

TheSpeakFoundation.com/grant-programs

As Founder and CEO of The Speak Foundation, I am routinely asked certain questions and I am happy to address them in this and future issues of *LGMD News*. It is an honor to have this platform to reach more people in our growing community.

Q

What projects by the Speak Foundation directly help patients?

A

As we have grown from our founding in 2008, we have tried to help patients in many direct ways. We are a small charity, with a small staff, and our mission is patient-focused always. We work tirelessly for *all* forms of LGMD through advocacy programs like the International LGMD Conference, the Global Advocacy Summit, educational webinars, this magazine with a global reach, and the upcoming LGMD EL-PFDD.

Additionally, over the last two years alone, the Speak Foundation has given out thousands of dollars directly to families or individuals living with LGMD, in the form of grants or durable medical equipment (DME) through our COVID relief programs, HOPE Project, CARE Program, PCA Stipend Program, Christmas giveaways, and more. The new cycle of our HOPE Project, which started August 1st, will offer thousands more in needed grants to individuals living in the USA, by providing up to $250 per approved applicant to cover DME expenses.

Q

What do you think is the biggest hurdle for LGMDs?

A

I believe there is a lack of information about how we can really impact the overall process of drug development in a positive manner. I also think there is a lack of understanding in the broader LGMD community of what efforts each organization is undertaking.

We need every single tool in our toolbox to get treatments to market. People living with the disease, like myself, who have founded these organizations with the mutual goal of finding treatment, are working tirelessly. Your encouragement and support makes such a difference, as it can be exhausting, especially when you have limited physical resources. Let us continue to focus our efforts on fighting this disease together, not each other, and I believe we will accomplish so much more, and faster.

It is crucial that we work together to build new programs and create new projects that help build paths to treatment. Building versus division is how we are going to get there.

If you have a question for the Speak Foundation, I invite you to reach out to us at **ContactUs@TheSpeakFoundation.com**. ■

A Family of Faith and Fortitude

I hope the FDA can see what families have done to find a cure for LGMD, and I think they need to see our faces and hear our voices … My family members are dying as we keep waiting for treatments to be approved.

Donavon Decker, living with LGMD2D/R3, and his family have been significantly impacted by limb-girdle muscular dystrophy. His mother suffered emotionally as five of her eight children, and two of her granddaughters, were diagnosed with LGMD. In time, two of those five children died from complications related to their disease. Donavon's sister, Jolene Harms (also with LGMD2D/R3), says of their mother, "She worries about losing more." Until treatments can be approved, that is a valid concern.

While the family waits for approved therapies, daily living is a struggle. Jolene, diagnosed in 1978, says, "Dystrophy colors every single thing we do. The impact MD has had on me personally can be stated in one word — loss." Most significantly, Jolene has lost the ability to breathe without her ventilator for much of the time — through the night and a good portion of the day. Donavon's other sister, June Burney (LGMD2D/R3), shares, "My muscles are getting weaker by the day, causing aching. My neck muscles tighten to the point where I can't turn my head."

June believes the patient voice is vital in approving treatments. She says, "Since we're the ones dealing with the disease, we're the best ones to push. We know what it means if there is not treatment. When researchers say it's coming and another five years pass and nothing has been done, it's difficult to believe it will be done in time for our family. While my faith is not in doctors, it's still important for us to push treatments forward. If not for us, for others. Some of us don't have time to wait five to ten years."

Still, Donavon's family remains positive, leaning on each other and their faith in God. His niece, Stephanie Wipf, living with LGMD-2I/R9, says, "I may not understand or like MD, but I trust God and His sovereign plan for me." Jolene adds, "I'm thankful that I can still do computer work. I can still study and teach Sunday School. I can still plan events. I can go to our grandkids' activities. I can pray. I can read. I can encourage and counsel folks who need it. I can solve problems. I can share Jesus. This list can go on. I'm grateful."

Donavon's subtype, and his niece's, are two of the six going in front of the FDA and other stakeholders this September for the first EL-PFDD meeting for LGMDs. This is a monumental and historical opportunity for the LGMD community. Donavon says, "I hope the FDA can see what families have done to find a cure for LGMD, and I think they need to see our faces and hear our voices … My family members are dying as we keep waiting for treatments to be approved." Thankfully, Donavon will get that opportunity, as he is one of the LGMD Panelists selected to share his voice on September 23rd. ■

Written by Rachel Sapp, *The Speak Foundation*

Above: Pictured **(From left)** June Burney, Jolene Harms, Donavon Decker, and Stephanie Wipf.

ML Bio Solutions is developing an oral therapy for Limb-Girdle Muscular Dystrophy Type 2I (LGMD2I/LGMDR9).

We will soon be announcing next steps for our development program for BBP-418. Additional information about our BBP-418 studies will soon be available on www.clinicaltrials.gov and at www.mlbiosolutions.com and will be shared with LGMD patient advocacy organizations. Check with your physician about participation and eligibility. Stay tuned!

Scan to visit our website.

ML Bio Solutions (ML Bio) is a biotechnology company founded by a family whose child was diagnosed with LGMD2I. ML Bio Solutions is a member of the BridgeBio family — a team of experienced drug discoverers, developers, and innovators working to create life-altering medicines that target genetic diseases.

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ML Bio Solutions
a bridgebio company

The SPEAK Foundation
PO BOX 600062
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Your Voice Will Make a Difference!

The LGMD community will be leading an Externally-Led Patient-Focused Drug Development (EL-PFDD) meeting on September 23, 2022.

What will happen at this EL-PFDD meeting? This important, monumental effort will give individuals diagnosed with limb-girdle muscular dystrophy types 2A, 2C, 2D, 2E, 2F, and 2I an opportunity to share with the FDA and other stakeholders about the experiences and challenges of living with LGMD.

What do we hope to gain? The EL-PFDD meeting is designed to engage patients and elicit their unique perspectives. With this information, our goal is to enable knowledgeable development and review of LGMD therapies that meet the needs and expectations of our patient community.

Coalition to Cure Calpain 3 — Overcoming Weakness With Strength
kurt+peter Foundation
LGMD2D Foundation
The SPEAK Foundation
CURELGMD2i
McColl-Lockwood Laboratory for Muscular Dystrophy Research

www.lgmdpfdd.com