Vol 4 / Issue 2

LGMD News

Uniting the Limb-Girdle Muscular Dystrophy Community

ML BIO SOLUTIONS

Biomarkers: Tiny Detectives in the World of Clinical Trials

SAREPTA THERAPEUTICS

Sarepta is Conducting Non-Interventional Research Studies

LGMD SCIENTIFIC WORKSHOP

Moving Drug Development Forward for LGMD

ACCELERATED APPROVAL OF NEW DRUGS BASED ON SURROGATE ENDPOINTS

An Explanation and LGMD Community Perspective

Matters of the Heart

A "Silent and Invisible Threat" in Limb-Girdle Muscular Dystrophy

The Speak Foundation hosts Sarepta Therapeutics with important updates on EMERGENE

LIVE COMMUNITY WEBINAR

LGMD R4/2E

April 10 2024

Begins 12 PM EST

Scan the QR Code to Register!

Hosted by The Speak Foundation

Do you or does someone you know have LGMD2I/R9?

AskBio will be conducting a clinical study of an investigational gene therapy for individuals with a confirmed genetic diagnosis of LGMD2I/R9.

- This is a one-time intravenous infusion of gene therapy designed to produce fukutin-related protein (FKRP) in the body, primarily in muscle.
- Part 1 of the study will assess the safety of LION-101 only in adults (ages 18 and 65 years).
- This is a randomized, placebo controlled, double-blind study.
- The study is designed to investigate at least two different doses of LION-101 versus placebo.
- The initial phase of this first-in-human dose-finding study will be conducted in the US.
- Travel to study sites may be reimbursed; local and home-based testing will be used when possible.
- Information on the clinical trial can be found on clinicaltrials.gov.

To learn more, please visit AskBio.com, email AskFirst@AskBio.com or go to clinicaltrials.gov (NCT05230459)

AskBio™

LGMD News

Vol 4 / Issue 2

How To Donate

Visit **TheSpeakFoundation.com** and select "Donate" to support our mission and programs. The Speak Foundation is a 501(c)(3) nonprofit charity. All donations are secure and tax deductible.

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.

Contents

Departments

Feature Articles

Connect with Us

Comments, Questions, or Suggestions?
ContactUs@TheSpeakFoundation.com

TheSpeakFoundation.com

Facebook.com/TheSpeakFoundation

Instagram.com/TheSpeakFoundation

Twitter.com/SpeakFoundation
Twitter.com/LGMDFoundation

Exciting Progress at the LGMD Scientific Workshop

As we move forward, we will need to work collaboratively with all stakeholders and LGMD organizations in our space.

Connect with Us

ContactUs@TheSpeakFoundation.com

TheSpeakFoundation.com

On February 8, 2024, The Speak Foundation convened a multi-stakeholder LGMD Scientific Workshop in Rockville, Maryland. The workshop brought together academic medical experts, senior leaders from the U.S. FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), highly experienced drug developers, and other specialists. The workshop's focus was answering important questions on how to drive momentum to fulfill the unmet, critical need of the patient community to accelerate drug development for LGMDs. The meeting focused on six LGMD subtypes: R1/2A, R2/2B, R5/2C, R3/2D, R4/2E, and R9/2I.

We are thrilled that the workshop advanced a collaborative dialogue and brought people together from every facet of the drug development process to drive progress for patients. Please continue to help us advance the science by supporting efforts of this kind. As we move forward, we will need to work collaboratively with all stakeholders and LGMD organizations in our space.

In this issue, we are also grateful to Dr. Kan Hor of Nationwide Children's Hospital for bringing attention to the critical issue of cardiac function and the importance of MRI. In recent years, cardiac magnetic resonance imaging (CMR) has become the gold standard to diagnose early scar formation before it begins to show up on an echocardiogram. In the Duchenne community, CMR has become more routinely used, yet this is still not a common standard of practice for LGMDs.

We highlight in this issue the urgent need to update methodology to include CMR for many subtypes to assess cardiac function, versus relying on echocardiograms alone. This area is clearly understudied, as is respiratory function in LGMDs. In future issues, we plan to discuss issues relating to pulmonary function testing and regular screening with end tidal capnography to assess for elevated CO2. ■

Kat Bryant Knudson

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

International Consortium of LGMD Organizations

United States

The Speak Foundation
Uniting the entire LGMD community
TheSpeakFoundation.com

Beyond Labels & Limitations
Funding research for LGMD R1/2A 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 R19/2S
CamronsCure.com

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

Cure LGMD2i
Funding research for LGMD R9/2i
CureLGMD2i.org

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

LGMD Awareness Foundation
Raising awareness of and advocating for the LGMD community
LGMD-Info.org

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

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

LGMD2i Research Fund
Funding research for LGMD R9/2i and educating the patient community
LGMD2iFund.org

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

Team Titin
Strengthening the titin community: LGMD R10/2J
TitinMyopathy.com

The Jain Foundation
Funding research for LGMD R2/2B 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 R1/2A 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 D2/1F
ConquistandoEscalones.org

"GFB ONLUS"/ Family Group of Beta-Sarcoglycanopathy
Representing the LGMD R5/2C Gamma Sarcoglycan-related, LGMD R3/2D Alpha Sarcoglycan-related, LGMD R4/2E Bèta-Sarcoglycan-related, and LGMD R6/2F 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 R1/2A Calpain 3-related community
AICA3.org

Japan

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

Netherlands

Stichting Spierkracht
Raising awareness and supporting the LGMD R3/2D Alpha Sarcoglycan-related community
StichtingSpierkracht.com

South Korea

Korean Dysferlinopathy Patients Association
Providing patients with LGMD R2/2B information and research updates
Cafe.Naver.com/UniteDsyferlinopathy

Spain

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

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

Richard Roxburgh, MB ChB, FRACP, PhD

Consultant Neurologist and Associate Professor, Auckland City Hospital

Meet the Expert

Associate Professor **Richard Roxburgh, MB ChB, FRACP, PhD** is a consultant neurologist with expertise in neurogenetics and an interest in neuromuscular disorders at Auckland City Hospital in New Zealand. His medical training was at the University of Otago (MBChB), with specialist training (FRACP) in Wellington and Manchester, Cambridge and Queens Square, London. He completed a PhD at Cambridge. Upon returning to New Zealand, Dr. Roxburgh established the country's only neurogenetics service, based at Auckland City Hospital. As well as a wide adult neurogenetic clinical practice including neuromuscular conditions, he, with a team of dedicated clinicians and scientists, has established Pūnaha Io, the New Zealand NeuroGenetic Registry & BioBank, the NZ Motor Neurone Disease Registry, and the University of Auckland Centre for Brain Research Neurogenetics Clinic where he runs natural history studies and clinical trials.

Q

My son was diagnosed with LGMD R1/2A at age 4 due to high CPK levels. At a young age, he was suffering from muscle cramps with strenuous activity, which he no longer has now at 13. He does have discrete contractures, but he still practices boxing and doesn't have any noticeable muscle weakness. We stopped him from playing football. Do you think he might stay like this for a long time?

A

Great to hear that your son is doing well. I would characterize your son as being pre-symptomatic — i.e., just a positive CK — so yes, until actual weakness starts (e.g., difficulty with running), I think that this state can continue for years. From the natural history studies that have been conducted in LGMDs, there can be a lot of variability in onset of muscle weakness and rate of progression even among patients having the same subtype, so it's hard to give a prognosis. It may be worth considering stretching to avoid contractures becoming worse and interfering with function.

Q

I have LGMD R1/2A and have severe hip pain at night (lying on my side), which wakes me every 2-3 hours. Nothing seems to help, but I recently heard a physiotherapist say that a cortisone injection is the only remedy for this type of severe pain. What is your view and have you heard about this problem from other patients?

A

We do know that pain can be a major issue in genetic muscle diseases. In some cases, it is so common that it seems to be an integral part of the disease. We surveyed the population of New Zealand with muscle disease with regard to pain and found that it was a common feature. When we looked specifically at people with LGMDs, we found that around 75% experienced pain. Unsurprisingly, the presence of pain contributes to a poorer quality of life.

However, when the pain is as specific as what you describe, it is most likely due to a local mechanical problem, a bursitis, a nerve root entrapment, or a ligament under strain. I would recommend consulting with a musculoskeletal specialist.

Q

Changes in the *TTN* gene can result in a form of LGMD R10 (formerly 2J). Can you provide advice for people with weakness whose genetic testing comes back with a variant of unknown significance (VUS) in the *TTN* gene? What advice do you have for families who are working to determine if these VUS are the cause of their disease or not? Is there anywhere you can refer families for long-reads genetic testing or RNAseq testing?

A

When a gene panel or whole exome is done to look for the cause of a muscle disease, all of us will have variants that are not the same as the "reference" sequence. When a particular variant occurs, which has been found before in other families with the same disease or has a clearly deleterious effect on the gene, then it is easy to characterize the variant as "pathogenic" (or disease causing). Similarly, when the variant is common in healthy populations, it is easy to characterize it as "benign." Then there are variants that fall somewhere in the middle. It is these variants that are called "variants of uncertain significance" (VUS). Any variant that has never been observed before will automatically be labeled a VUS, and many (if not most) of these will not be disease causing.

The *TTN* gene is huge and codes for the largest human protein, titin. It is not surprising that variants turn up in the *TTN* gene, and many will be benign. In fact, many people in the general population (who don't have muscular dystrophy) have VUS in the *TTN* gene. I would look at whether there were any other affected family members and see if the condition and the gene variant run together in the family. Then, as you say, there are ways of looking at the messenger RNA — for example the variant may have changed the way the messenger RNA has been put together (spliced).

I think, though, that it comes down to the neuromuscular specialist assessing whether the specific variant in the *TTN* makes clinical sense as the cause of the condition. Because these conditions are rare, getting external advice could help with this. For *TTN*, there are certainly internationally-renowned specialists whom your neurologist would be able to identify and who would be happy to advise. In other words, bioinformatics combined with the evaluative techniques of a skilled clinician can help determine the possible significance of a variant.

Q

What can we do as LGMD patients to be proactive while we experience progression — is there any special diet or medications you would recommend?

A

Exercise is probably the most useful thing to do and is great for your mental health too. Also, stretching to avoid joint contractures and maintain flexibility can be very valuable. You are more than your muscles, and a healthy diet for your heart is a healthy diet for your brain as well. Maintaining a healthy BMI is helpful to preserving mobility. I tell everyone to avoid calcium supplements (the calcium goes straight to your heart and can cause heart attacks), zinc (it causes your body to excrete copper and copper deficiency is bad for your spinal cord) and vitamin B6, which can be toxic to your nerves. It's hard to be deficient in these things if you are on a balanced diet.

> *We do know that pain can be a major issue in genetic muscle diseases. In some cases, it is so common that it seems to be an integral part of the disease. We surveyed the population of New Zealand with muscle disease with regard to pain and found that it was a common feature. When we looked specifically at people with LGMDs, we found that around 75% experienced pain.*

Question

CK or creatine kinase is a naturally-occurring enzyme that is present in all muscle cells. When people have conditions like LGMDs, the muscle cells are leaky, which is why we find higher levels in the blood than in people with healthy muscle cells.

Connect with Us

TheSpeakFoundation.com

Have a Question for Our Experts?

Send Questions To:
ContactUs@TheSpeakFoundation.com

Q

Is it unusual for CK levels to drop over time?

A

No, it is not unusual. CK or creatine kinase is a naturally-occurring enzyme that is present in all muscle cells. When people have conditions like LGMDs, the muscle cells are leaky, which is why we find higher levels in the blood than in people with healthy muscle cells. Over time, the number of muscle cells declines as the disease progresses, so there are fewer cells to leak the enzyme; thus, it is normal for CK to drop over time.

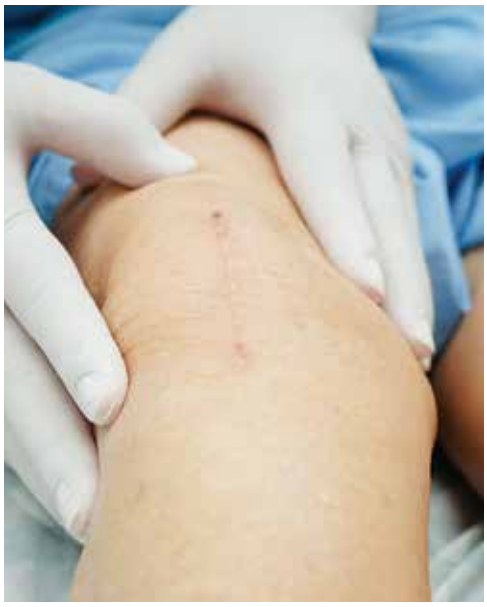
Q

Do you know of any clinical trials that could help someone with myofibrillar myopathy, dominantly inherited? I have what used to be termed LGMD 1E-desmin mutation.

A

I am unaware of any such clinical trial at the moment. There are cell-based studies looking at CRISPR (a type of gene editing) in one of the myofibrillar myopathies caused by mutations in the *BAG3* gene. CRISPR approaches are beginning to be used in clinical trials especially where the effect of the disease-causing variant is to create a toxic protein. CRISPR is quite good for turning off such genes.

On a disease-management note, myofibrillar myopathies can often affect the heart, especially the electrical conduction system (see the article by Dr. Kan Hor in this issue). It is very important that someone with myofibrillar myopathy have regular heart monitoring.



Q

I live with LGMD R12/2L ANO5. Can you speak at all to recovery from a knee replacement? Can I expect to be able to walk normally? I have avascular necrosis in the knee from taking steroids for over 15 years (bone is dying from poor blood supply).

A

Avascular necrosis is a nasty but fortunately rare complication of steroid use, and the usual treatment is indeed joint replacement. Knee replacement success depends on early mobilization, which favors a good range of motion at the knee. How well you recover depends quite a lot on what your muscle power is like, particularly in the thighs. I suspect that the avascular necrosis may have led to a degree of disuse atrophy on top of your condition, so the concerns would be the possibility of a long road or limited recovery. You will need a lot of physiotherapy input, especially soon after your operation, to get the best outcome. ■

fortify

Fortify is a Phase 3 clinical trial evaluating if an investigational oral therapy (BBP-418) is safe and effective for treating Limb Girdle Muscular Dystrophy type 2I / R9, FKRP-related (LGMD2I/R9)

About Fortify

Fortify is a 36 month randomized, double-blind, placebo-controlled trial for individuals with genetically confirmed LGMD2I/R9 measuring patient response to treatment by measuring both biomarkers and clinical assessments. For every three study participants, two will receive BBP-418 and one will receive placebo.

About the Therapy

In patients with LGMD2I, the enzyme FKRP does not work properly. FKRP is responsible for a critical step in a process called "glycosylation", whereby a crucial string of sugars are added to alpha dystroglycan (α-DG). Without this string, α-DG does not work correctly in its role as a "shock absorber" for muscle fibers. BBP-418's theoretical mechanism of action supplements the FKRP enzyme by adding more of the molecule that FKRP normally reacts with to drive residual activity of FKRP and helping it to stabilize muscle cells and act as a shock absorber. BBP-418 is an investigational therapy and is not yet approved by any health authorities for the treatment of LGMD2I/R9.

Who Can Participate

You may be eligible to participate in Fortify if you:

- Have a genetically confirmed diagnosis of LGMD2I/R9
- Are 12 to 60 years of age
- Have not used ribose or systemic corticosteroids prescribed for the treatment of LGMD or other investigational therapies for the treatment of LGMD within 90 days of screening

There are other requirements to participate in Fortify. A physician or study team member will help determine if you are eligible to participate and if this study is a good fit for you. Speak with your physician about your ability to participate in Fortify.

Fortify Locations:

The trial will be conducted at clinical sites in the United States and Europe.

Additional information about our BBP-418 study is available at **www.clinicaltrials.gov** and at **www.mlbsolutions.com**.

Scan to visit our website

ML Bio Solutions

Team Titin:

A Pillar of Support for the LGMD R10/2J Community

Changes in the TTN gene are known to cause a range of both skeletal muscle and heart conditions.

Team Titin, Inc., a 501(c)(3) nonprofit organization founded in 2022, is eager to share with the rest of the LGMD community information about our mission, goals, and activities. Our advocacy efforts focus specifically on subtype R10/2J, as well as a spectrum of other disorders caused by mutations in the TTN (titin) gene. Changes in the TTN gene are known to cause a range of both skeletal muscle and heart conditions.

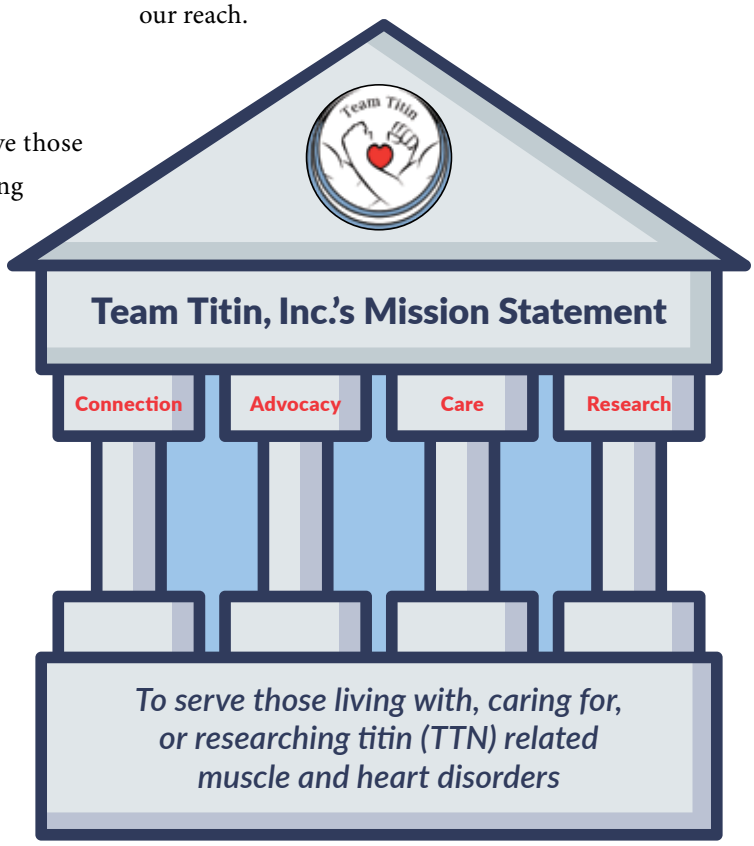
Mission

Team Titin, Inc.'s mission is to serve those living with, caring for, or researching titin-related muscle and heart disorders across the globe. To achieve this mission, we focus on four key pillars: Connection, Advocacy, Care, and Research.

As an organization, we are committed to strengthening the titin community through these four pillars, serving as a catalyst to advance understanding of the disease process and supporting efforts leading ultimately to treatments.

Connection

Connection is a key pillar of our mission. We aim to connect with and support affected individuals, parents, and caregivers, helping them navigate the complexities of TTN-related LGMD. In addition, we strive to connect with organizations, such as the Speak Foundation, and stakeholders that support our mission, fostering a larger community and expanding our reach.



Team Titin pillars supporting our mission

Our efforts to connect also include providing information about titinopathy and sharing the latest research with the affected community. We understand that knowledge is power, and we want to empower our community with the most up-to-date, accurate information about these disorders.

We use various tools to foster connections within our community. These include newsletters, online forums such as social media, webinars, YouTube videos, and our website **TitinMyopathy.com**.

We also host conferences, such as SciFam, which provide a platform for individuals to share their experiences, learn from experts, and feel less alone in their journey.

Advocacy

Advocacy forms another crucial pillar of our mission. We serve as advocates for our community, amplifying and projecting our collective voice. We believe in the power of unity and strive to ensure the needs and concerns of our community are heard and addressed.

Among policy makers and legislators, we push for changes that can help advance our mission. This includes pursuing more specific codes for the International Classification of Diseases (ICD codes) to facilitate better recognition and treatment of TTN-related disorders.

Care

While we seek treatment for tomorrow, we are committed to helping affected individuals access the best care today. This commitment to care is the third pillar of our mission. We work towards creating and disseminating care guidelines for TTN-related muscle and heart disorders, providing a valuable resource for those dealing with these conditions.

Research

The final pillar of our mission is research. We support, fund, and connect with researchers, clinicians, and other stakeholders in the field of TTN-related disorders. We aim to support the search for treatments and a better understanding of titinopathy.

Our research efforts include clinical trial readiness, funding research through a peer-reviewed request for proposals process, and connecting with researchers globally. We invite affected individuals with TTN-related LGMD to enroll in our registry, the Congenital Muscle Disease International registry: **CMDIR.org**. We also co-host biannual titin case conference/research update meetings (virtual), which allow us to stay at the forefront of scientific advancements and share these developments with our community of experts. We attend international conferences focused on neuromuscular disease, including the 2023 International LGMD Conference held in Washington, DC, last year. In addition, we support recruitment for future natural history studies and clinical trials, underscoring our commitment to advancing research in this field.

As an organization, we are committed to strengthening the titin community through these four pillars, serving as a catalyst to advance understanding of the disease process and supporting efforts leading ultimately to treatments. ■

Written by Sarah Foye
President/Treasurer, Team Titin

Above: Team Titin's Sarah Foye at the 2023 International Limb Girdle Muscular Dystrophy Conference

Connect with Us

TitinMyopathy.com
CMDIR.org

LIVE

COMMUNITY WEBINAR

EMERGENE Study (SRP-9003, Study 301)

The Speak Foundation is Excited to Host Sarepta this Spring!

Sarepta will be giving a presentation to the community to provide a study update on the LGMDR4/2E program. This is an opportunity to hear directly from Sarepta and engage in a live Q&A on their EMERGENE study.

LGMDR4/2E	April 10 2024	Begins 12 PM EST		Hosted by The Speak Foundation

Scan the QR Code to Register Today!

Questions? *ContactUs@TheSpeakFoundation.com • Advocacy@Sarepta.com*

You do not have to have LGMDR4/2E to register and attend. This webinar is open to ALL members of the LGMD community.

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 July 1, 2024 through July 31, 2024, please visit **TheSpeakFoundation.com/grant-programs-1**.

The HOPE Project
A Program of The SPEAK Foundation

TheSpeakFoundation.com/grant-programs-1

Accepting applications from July 1, 2024 through July 31, 2024.
Available to US residents only.

Join the NEW Patient-Powered LGMD 2A/Calpainopathy Registry

Coalition to Cure Calpain 3 (C3) recently launched a new initiative with global reach to research calpainopathy (genetic mutations in the CAPN3 gene), including limb-girdle muscular dystrophy (LGMD) type R1/2A and LGMD type D4/1I.

The central feature of this initiative, the LGMD2A/Calpainopathy Registry, is that it creates a platform to bring the calpainopathy community together and collect patient data that is required for policy makers, academic researchers, and therapeutics companies working to advance treatments for this disease. Additionally, the study will help identify individuals with calpainopathy who might be eligible to participate in other research studies or clinical trials.

C3 is partnering with the National Organization for Rare Disorders (NORD) to utilize their cutting-edge, cloud-based platform that is easy to use and prioritizes data security. "This new study has tremendous promise as a strong partnership that engages the patient community and addresses current knowledge gaps for calpainopathy. NORD is thrilled to be a part of driving research and innovation-based outcomes for all the families in the calpainopathy community," says Aliza Fink, Director of Research Programs, NORD.

The LGMD2A/Calpainopathy Registry replaces C3's original patient registry. While the original registry served primarily to contact calpainopathy patients, the new registry incorporates the capability to collect data about symptom progression by having participants periodically update their information. This information is vital to help us understand the progression of symptoms over time, which will inform patient care, drug development, and clinical trial design. Additionally, the registry will identify and contact potential participants for research studies. "Our goal is to enroll as many patients, or their parents or legal guardians, as possible," notes Jordan Boslego, C3 President. "The success of the registry is dependent upon community participation, and it's essential that the 1000+ patients in our original registry take the time to register on this new platform."

"The LGMD2A/Calpainopathy Registry will provide a complete picture of each patient's experience with this disease," shares Dr. Jennifer Levy, C3 Scientific Director. "We are launching this initiative to help fill in the missing information researchers and medical experts need to advance research and, one day, find a cure." ■

Written by Jennifer Levy, PhD
Scientific Director, Coalition to Cure Calpain 3

The success of the registry is dependent upon community participation, and it's essential that the 1000+ patients in our original registry take the time to register on this new platform.

Connect with Us

LGMD2A.iamrare.org

LGMD2A/Calpainopathy Registry
www.LGMD2A.iamrare.org

Preparing for Clinical Trials

These types of studies inform us about the course of these diseases, the rate of progression, and which individuals are best suited for early clinical trials.

On February 8, 2024, the Speak Foundation hosted a Scientific Drug Development Workshop in Rockville, Maryland that included individuals living with LGMDs, patient advocacy groups, clinicians, industry, and members of the FDA. One of the take-home messages from this meeting was the continued need to use natural history studies to build the foundation for clinical trials. These types of studies inform us about the course of these diseases, the rate of progression, and which individuals are best suited for early clinical trials.

We, in the GRASP-LGMD consortium, are pleased to have support from the National Institutes of Health (NIH) to build this foundation for individuals living with LGMD R1/2A (CAPN3). The NIH has supported the consortium to enroll ambulatory individuals (patients who are still able to walk) with LGMD R1/2A in GRASP-003. This study will measure muscle function, record lived experience, and detect the amount of lean muscle by using magnetic resonance imaging (MRI). Participants will have visits annually for two years. This study builds on prior work within the consortium that was previously supported by the NIH and the Coalition to Cure Calpain-3. We need your support and

UPDATED: APRIL 1, 2024

Active GRASP-LGMD Natural History Studies

Recruiting: Defining Clinical Endpoints in Limb-Girdle Muscular Dystrophy (LGMD) (GRASP-01-001)

Inclusion Criteria

- Ages 4–65
- Clinically affected (defined as weakness on bedside evaluation in either a limb-girdle pattern or in a distal extremity)
- Genetic confirmation of one of the LGMD subtypes listed below

Exclusion Criteria

- Any other illness that interferes with subject safety or data integrity
- Positive pregnancy test at any timepoint of the study

Subtypes

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

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

Inclusion Criteria

- Ages 8 and older
- Clinically affected (defined as weakness on bedside evaluation consistent with BMD)
- Genetic confirmation of a dystrophin mutation

Exclusion Criteria

- >16 hours of ventilatory support
- Any other illness that interferes with subject safety or data integrity

Note: Subjects ages 8-16 must be ambulatory and their dystrophin mutation must be in-frame.

Note: Subjects 17 and older may be non-ambulatory, but must not have lost ambulation prior to the age of 16.

For Additional Information on Active GRASP-LGMD Natural History Studies, Contact:

participation in this study at a site close to you. You can learn more about the criteria for participation in the sidebar below.

You may be thinking: Another natural history study? Where are the treatment trials? Please know that we agree with these sentiments and that we are also eager to embark on therapeutic trials. Here the old saying from carpentry, "Measure twice and cut once" applies. One of the worst things to happen in our field would be to reject a promising drug because a clinical trial was not properly designed to detect its effect. We hope that continuing to refine our trial design through studies like GRASP-003 will help reduce this chance. We were heartened to hear members of the FDA acknowledge that the information collected in studies like GRASP-003 may help lessen the need for placebo in clinical trials, or potentially allow them to be shorter. So, while we work with our partners in industry to speed the development of drugs, your participation in this study can help move the process forward. Please reach out to our network coordinators listed below to help find a study site near you. ■

Written by Nicholas Johnson, MD, MSci, FAAN
Professor and Vice Chair of Research
Virginia Commonwealth University

Connect with Us

Questions?
Ruby.Langeslay@VCUHealth.org
Jennifer.Raymond@VCUHealth.org

ClinicalTrials.gov

Recruiting: Trial Readiness and Endpoint Assessment in LGMD R1/2A (GRASP-01-003)

Inclusion Criteria

- Ages 12–50
- Clinically affected (defined as weakness on bedside evaluation in a pattern consistent with LGMD R1/2A)
- Genetic confirmation of LGMD R1/2A (presence of homozygous or compound heterozygous pathogenic mutations in CAPN3)

Exclusion Criteria

- Have contraindications to MRI
- Non-ambulatory, defined as unable to safely walk 10 meters without assistive devices (ankle foot orthotics allowed)
- Positive pregnancy test at any timepoint during the trial
- Have dominantly inherited CAPN3 mutations (i.e. LGMD D4)
- Any other illness that would interfere with subject safety or data integrity

Active Sites

- **Virginia Commonwealth University**
  Richmond, VA
- **Nationwide Children's Hospital**
  Columbus, OH
- **The University of Kansas Medical Center**
  Kansas City, KS
- **Washington University**
  St. Louis, MO
- **University of Colorado**
  Denver, CO
- **UC Irvine**
  Irvine, CA
- **Community Health Clinic**
  Shipshewana, IN
- **University of Minnesota**
  Minneapolis, MN
- **University of Iowa**
  Iowa City, IA

Ruby Langeslay *Network Coordinator*
(804) 828-8481 | *Ruby.Langeslay@vcuhealth.org*

Jennifer Raymond *Network Coordinator*
(804) 828-6318 | *Jennifer.Raymond@vcuhealth.org*

SPONSORED CONTENT

Sarepta is conducting non-interventional research studies

Overview

Non-interventional (non-treatment) studies provide an opportunity for people living with an LGMD to share their unique experiences and perspectives. “Patient Voice” studies are one form of non-interventional studies.

When you participate in non-interventional studies, such as interviews and surveys, you are contributing to research that helps people understand the impact of LGMDs on daily life and what matters to people living with an LGMD.

Your input can help healthcare professionals and researchers:

Gain a deeper understanding of LGMDs from your perspective as someone living with an LGMD. This can potentially help researchers develop investigational drugs to address unmet medical needs

Advance drug development: Researchers and regulators often rely on patient-reported data to make decisions regarding drug development

Evaluate the effectiveness of current disease management and assess the impact of interventions. This information can help enable better patient-centric care

Our non-interventional research studies are currently focused on LGMD sarcoglycanopathies (2E/R4, 2D/R3, 2C/R5) but we may conduct research on other LGMD subtypes in the future.

Please note: *Participation in these types of studies will not impact your ability to enroll in future clinical trials for investigational drugs.*

If you are eligible and participate in a non-interventional research study, you will be compensated for your time.

SPONSORED CONTENT

Sarepta's non-interventional research studies will collect data about your experience living with an LGMD

The types of studies include:

Surveys

Surveys are typically web-based and may include questions on topics such as symptoms of your LGMD, the condition's impact on activities of daily living, caregiver experience, or how you manage your LGMD. They may also seek to understand your perspective on investigational drugs to treat LGMDs, including hypothetical benefits and risks.

Interviews

Interviews, conducted via a phone or video call, may cover the same topics as web-based surveys. In addition, interviews provide opportunities for the interviewer to ask follow-up questions and you to elaborate and provide valuable context.

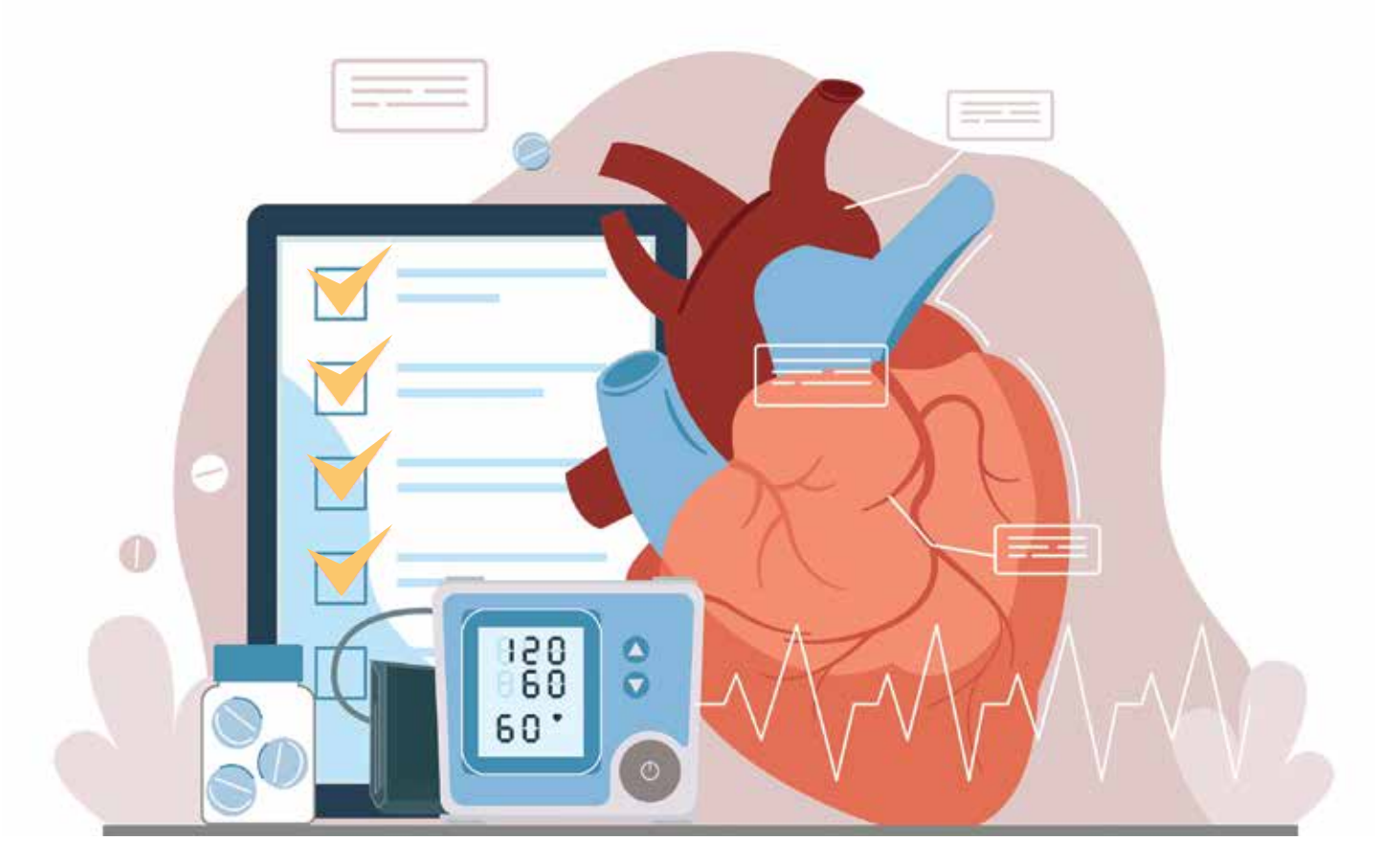
Medical chart review

Chart reviews provide insight into your medical history with LGMD, including before and after genetically confirmed diagnosis. Chart reviews require consent from patients for researchers to be able to access medical charts. Individuals who are eligible and choose to participate may receive a consolidated summary of their charts. All data are kept confidential.

Visit **limbgirdle.com/stay-connected** to receive email updates about new non-interventional study opportunities.

SAREPTA THERAPEUTICS

Written By Kan N. Hor, MD
Director, Advanced Cardiovascular Imaging and Fellowship Program, Cardiology
Associate Division Chief for Research, Cardiology
Professor of Pediatrics
The Heart Center, Nationwide Children's Hospital and The Ohio State University



Matters of the Heart in Limb-Girdle Muscular Dystrophy:

A "Silent and Invisible Threat"

Both in general and even in the neuromuscular community, the impact of LGMD on the heart is not well understood, given that it does not necessarily correlate with skeletal muscle weakness. Cardiac involvement is much more variable in progression, varies widely between genetic subtypes, and is not well studied.[1]

In contrast to skeletal muscle, heart muscle involvement in LGMD can be quite variable and frequently without obvious symptoms. For patients, skeletal muscle weakness is overt and affects everyday aspects of their lives.[2] For health care professionals, assessing problems related to skeletal muscle, though sometimes challenging, is more apparent and is commonly based on observations of gait issues and generalized weakness to loss of ambulation with a recognizable pattern.[3] However, the heart—which is pumping blood throughout the body, never resting, and responding constantly to meet the demands of the body—also needs assessment. Patients

can present with heart rhythm issues and palpitations involving the heart's electrical system. These conduction issues can present as the heart beating too slow (bradycardia), too fast (tachycardia) from either the top (atrial) or bottom (ventricular) chamber, or the feeling of skipped beats.[1] Arrhythmias can be "silent" (not being noticed by the patient), but some patients may have the feeling that their heart is beating too rapidly, which may lead them to seek medical care. In some patients, the conduction abnormalities are mild, while in other patients the symptoms are severe enough to require medical treatment, as in the case of heart block where a pacemaker is necessary (Figure 1).[2,4]

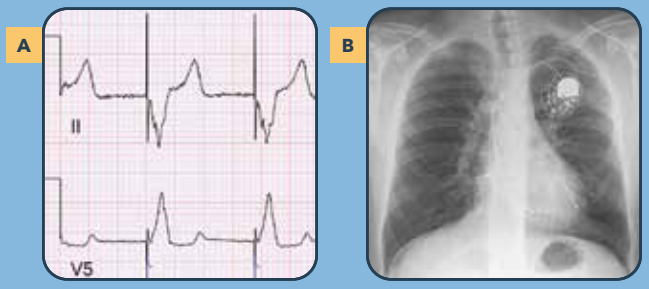


Figure 1: EKG and Chest X-Ray (A) EKG of two leads showing pacemaker spike (blue vertical line) in a patient with complete heart block and (B) chest X-Ray of a pacemaker in the left upper chest for complete heart block

Unlike arrhythmia due to conduction issues, heart muscle disease known as cardiomyopathy, which can lead to abnormal heart function and sometimes heart chamber enlargement and eventually heart failure, tends to be silent and not as well understood. Cardiomyopathy is associated with various muscular diseases. Review papers have looked at the implications of cardiac involvement in other diseases, such as Duchenne Muscular Dystrophy (DMD), but there is a paucity of evidence describing this in LGMDs.[4] The diagnosis of cardiomyopathy from heart muscle disease leading to poor heart function (where the heart no longer squeezes normally, and ultimately heart failure when the heart can no longer keep up with the body's demands) is much harder to grasp.

There is a general recommendation for patients with high-risk LGMD subtypes to be referred for a cardiology evaluation regardless of symptoms.[2,4] However, many general practitioners and patients do not have a robust understanding of who is in the high-risk group (see box-out below) and many patients have a delayed cardiology referral or have not been referred at all. Once referred, cardiologists who are unfamiliar with neuromuscular disease may not perform the appropriate tests and follow-up plans. In addition to an electrocardiogram to evaluate the patient's conduction system, an echocardiogram (ultrasound of the heart) is often the only test used. While echocardiograms are a useful tool, they typically assess for cardiac chamber enlargement and global heart function by left ventricular ejection fraction, which is frequently normal. It is not uncommon for LGMD patients in the high-risk category to only receive a single evaluation with no follow-up plans.

Cardiac magnetic resonance imaging (CMR) is more precise and accurate than an echocardiogram in detecting cardiac involvement. CMR allows for a comprehensive evaluation and offers a one-stop shop to assess the

The Heart of the Matter

Subtypes Commonly Associated with Heart Conduction Issues

- **LGMD 1B** (dominant EDMD–Lamin A/C)
- **LGMD R4/2E** (beta–Sarcoglycan)

Subtypes Commonly Associated with Cardiomyopathy

- **LGMD R3/2D** (alpha–Sarcoglycan) – *less likely than other sarcoglycanopathies*
- **LGMD R4/2E** (beta–Sarcoglycan)
- **LGMD R5/2C** (gamma–Sarcoglycan)
- **LGMD R6/2F** (delta–Sarcoglycan)
- **LGMD R9/2I** (FKRP)
- **LGMD R10/2J** (Titin) – *depending on particular mutation*

Subtypes Not Commonly Associated with Heart Involvement

- **LDMD D1/1D** (DNAJB6)
- **LGMD R1/2A** (Calpain–3)
- **LGMD R2/2B** (Dysferlin)
- **LGMD R12/2L** (ANO5)

** This is not a comprehensive list. Current knowledge of cardiac involvement in LGMDs is not complete. Patients should discuss their cardiac risk and appropriate monitoring with their medical team.*

patient's heart in multiple ways.[5] In addition, like many ultrasound techniques, echocardiogram assessment becomes more limited as patients age, restricting the ability to see the heart as clearly. It is not uncommon for patients to have serial echocardiograms that indicate normal heart function only to undergo a CMR study showing evidence of scar formation on the heart muscle or significantly abnormal heart function.[6] The use of CMR has improved the understanding of DMD-associated cardiomyopathy and has been used clinically for both patient management and clinical trials.[7-10] Cardiac assessment by CMR is now common in DMD patients but remains limited in LGMD patients.[11] With an improved understanding of the value of CMR, its use is improving in the LGMD population but is frequently limited to larger medical centers with experience caring for LGMD patients. Improved diagnostic techniques can allow LGMD patients to undergo appropriate treatment earlier, including more aggressive therapy depending on disease severity and better follow-up plans. Serial CMR in at-risk LGMD patients has shown more rapid progression of cardiac involvement than what was previously published in the medical literature (Figure 2). As such, for LGMD patients falling into the high-risk category, the use of CMR assessment should be considered. Currently, however, there are no clear guidelines in the US for recommended screening or follow-up testing for even the high-risk cardiac LGMD group.[4]

Previous literature suggests no cardiac follow-up or evaluation is needed for patients in the low-risk cardiac category.[12] There have been no recommendations for initial screening for LGMD patients in this group because the level of cardiac risk for this group has relied on outdated diagnostic testing such as echocardiogram.[1,4,12] In our experience, with the use of a more accurate technique such as CMR, some low cardiac-risk groups have been shown to have a higher prevalence of cardiac disease than previously published. This certainly has been the case for DMD, where the use of CMR has altered follow-up and management plans[11] and is now part of the cardiac care consideration guidelines.[13] There is a need for larger observation studies in the low-cardiac risk group when patients present with electrocardiogram abnormalities or any cardiac symptoms (including chest pain, fainting, palpitations, or activity intolerance not attributable to the skeletal muscle system). However, it is important to note that due to skeletal muscle weakness, the use of a traditional heart failure assessment tool, which requires normal ambulation, may underestimate the extent of cardiac disease in an individual and its prevalence in the general LGMD population.

Traditional heart failure assessment tools (for example, the NYHA classification)[14] may be of limited utility in neuromuscular patients, including those with LGMD, due to skeletal muscle weakness. For example, symptoms such as shortness of breath upon exertion may not be apparent in non-ambulatory patients, or they may be masked by skeletal muscle disease. Even at advanced stages of cardiac involvement, patients may present with vague and non-specific symptoms due to muscle weakness and limited ambulation. In clinical practice with patients with neuromuscular disorders, cardiac therapy initiation and titration are rarely based on heart failure symptoms and NYHA classification.

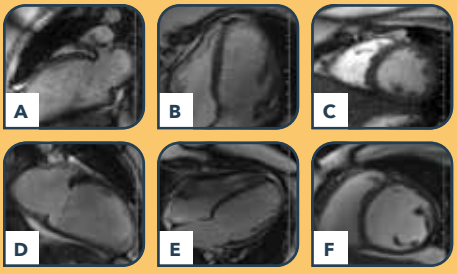


Figure 2: Cardiac Magnetic Resonance Images. (A–C) Cardiac MRI images showing normal size and function (A = 2 chamber, B = 4 chamber, and C = Mid-ventricle short axis). (D–F) One year later, showing severe enlargement and decline in heart function (D = 2 chamber, E = 4 chamber and F = Mid-ventricle short axis).

The use of CMR in DMD and some LGMD patients has improved evidenced-based treatment, especially the early evidence of cardiomyopathy when myocardial fibrosis (scar in the heart muscle) is seen but the global heart function, a late finding of cardiomyopathy, remains normal (Figure 3). Beyond the implications of LGMD cardiac risk stratification, the incidence of cardiac disease is generally increased due to aging, lack of physical activity, and associated diseases, such as diabetes, hypertension, and obesity. Each of these factors can increase the risk of heart disease. It is important for *all* LGMD patients in both high and low-cardiac risk groups to be aware of these issues.

The following are take-home messages for patients living with LGMDs: (1) "high risk" patients should seek active care from a cardiologist knowledgeable about muscular dystrophy; (2) "low risk" patients should not assume there is no risk, and also realize that our knowledge of cardiac risk in LGMDs is incomplete and continues to evolve; (3) a negative test result does not mean you are "clear," but rather that your heart appears okay for the foreseeable future; periodic follow-up testing is still indicated.

Both health professionals and patients alike are frequently in the dark. We only know what we know, but there is much that we do not. The advent of CMR and its use in monitoring patients with DMD and BMD has significantly improved management of cardiac involvement for those diseases. The same should be possible for LGMDs with better monitoring and more proactive treatment approaches. ■

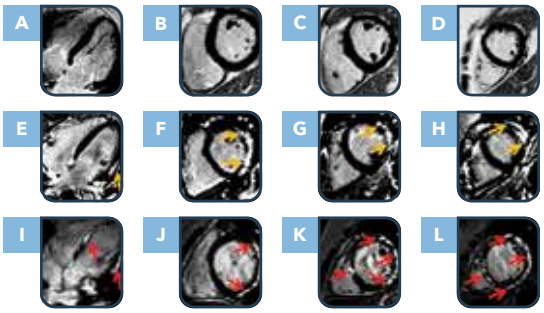
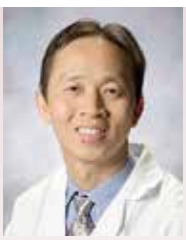


Figure 3: Cardiac Magnetic Resonance Images. Late Gadolinium Enhancement for Scar Assessment in a 4-chamber view and 3 Short Axis Views. (A–D) Cardiac MRI images showing the heart muscle without scars (all black). (E–H) Images showing small areas of scars (white with yellow arrows). (I–L) Images showing more areas with scars in later stages, caused by declining heart function.

References

1. Nallamilli BRR, Chakravorty S, Kesari A, Tanner A, Ankala A, Schneider T, da Silva C, Beadling R, Alexander JJ, Askree SH, et al. Genetic landscape and novel disease mechanisms from a large LGMD cohort of 4656 patients. *Ann Clin Transl Neurol*. 2018;5:1574-1587. doi: 10.1002/acn3.649
2. Georganopoulou DG, Moisiadis VG, Malik FA, Mohajer A, Dashevsky TM, Wuu ST, Hu CK. A Journey with LGMD: From Protein Abnormalities to Patient Impact. *Protein J*. 2021;40:466-488. doi: 10.1007/s10930-021-10006-9
3. Angelini C. LGMD. Identification, description and classification. *Acta Myol*. 2020;39:207-217. doi: 10.36185/2532-1900-024
4. Feingold B, Mahle WT, Auerbach S, Clemens P, Domenighetti AA, Jefferies JL, Judge DP, Lal AK, Markham LW, Parks WJ, et al. Management of Cardiac Involvement Associated With Neuromuscular Diseases: A Scientific Statement From the American Heart Association. *Circulation*. 2017;136:e200-e231. doi: 10.1161/CIR.0000000000000526
5. Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU, Pennell DJ. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol*. 2002;90:29-34. doi: 10.1016/s0002-9149(02)02381-0
6. Soslow JH, Xu M, Slaughter JC, Stanley M, Crum K, Markham LW, Parra DA. Evaluation of Echocardiographic Measures of Left Ventricular Function in Patients with Duchenne Muscular Dystrophy: Assessment of Reproducibility and Comparison to Cardiac Magnetic Resonance Imaging. *J Am Soc Echocardiogr*. 2016;29:983-991. doi: 10.1016/j.echo.2016.07.001
7. Hor KN, Kissoon N, Mazur W, Gupta R, Ittenbach RF, Al-Khalidi HR, Cripe LH, Raman SV, Puchalski MD, Gottliebson WM, et al. Regional circumferential strain is a biomarker for disease severity in duchenne muscular dystrophy heart disease: a cross-sectional study. *Pediatr Cardiol*. 2015;36:111-119. doi: 10.1007/s00246-014-0972-9
8. Hor KN, Taylor MD, Al-Khalidi HR, Cripe LH, Raman SV, Jefferies JL, O'Donnell R, Benson DW, Mazur W. Prevalence and distribution of late gadolinium enhancement in a large population of patients with Duchenne muscular dystrophy: effect of age and left ventricular systolic function. *J Cardiovasc Magn Reson*. 2013;15:107. doi: 10.1186/1532-429X-15-107
9. Raman SV, Hor KN, Mazur W, Cardona A, He X, Halnon N, Markham L, Soslow JH, Puchalski MD, Auerbach SR, et al. Stabilization of Early Duchenne Cardiomyopathy With Aldosterone Inhibition: Results of the Multicenter AIDMD Trial. *J Am Heart Assoc*. 2019;8:e013501. doi: 10.1161/JAHA.119.013501
10. Raman SV, Hor KN, Mazur W, Halnon NJ, Kissel JT, He X, Tran T, Smart S, McCarthy B, Taylor MD, et al. Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2015;14:153-161. doi: 10.1016/S1474-4422(14)70318-7
11. Lee S, Lee M, Hor KN. The role of imaging in characterizing the cardiac natural history of Duchenne muscular dystrophy. *Pediatr Pulmonol*. 2021;56:766-781. doi: 10.1002/ppul.25227
12. Moore U, Fernandez-Torron R, Jacobs M, Gordish-Dressman H, Diaz-Manera J, James MK, Mayhew AG, Harris E, Guglieri M, Rufibach LE, et al. Cardiac and pulmonary findings in dysferlinopathy: A 3-year, longitudinal study. *Muscle Nerve*. 2022;65:531-540. doi: 10.1002/mus.27524
13. Buddhe S, Cripe L, Friedland-Little J, Kertesz N, Eghtesady P, Finder J, Hor K, Judge DP, Kinnett K, McNally EM, et al., Cardiac Management of the Patient With Duchenne Muscular Dystrophy. *Pediatrics*. 2018 Oct;142(Suppl 2):S72-S81. doi: 10.1542/peds.2018-0333I.
14. Caraballo C, Desai NR, Mulder H, Alhanti B, Wilson FP, Fiuzat M, Felker GM, Pina IL, O'Connor CM, Lindenfeld J, et al. Clinical Implications of the New York Heart Association Classification. *J Am Heart Assoc*. 2019;8:e014240. doi: 10.1161/JAHA.119.014240



Kan N. Hor, MD, pediatric cardiologist, is the director of Cardiac MRI at The Heart Center at Nationwide Children's Hospital and an associate professor of Clinical Pediatrics at The Ohio State University College of Medicine. Dr. Hor received his medical degree from University of Illinois-COM, Chicago and completed his pediatric internship and residency at Children's Hospital of Wisconsin, Milwaukee. Dr. Hor continued his training and completed his pediatric fellowship training at Cincinnati Children's Hospital Medical Center. Dr. Hor completed an additional advanced cardiac imaging fellowship at Cincinnati Children's Hospital with a focus on cardiac MRI. Dr. Hor's clinical interests include cardiac MRI, cardiac CT angiography, echocardiography (TTE and TEE), and congenital heart disease. His academic research interest includes cardiac MRI and echocardiography and its application for analysis of cardiac strain and synchrony in Duchenne Muscular Dystrophy, heart failure and congenital heart disease. Dr. Hor collaborates with many other researchers around the globe and is board certified in both pediatrics and pediatric cardiology.

F R E E E V E N T

1st European LGMD R9/2I Community Conference

A gathering of individuals affected by Limb-Girdle Muscular Dystrophy Type R9, to meet, share experiences, and learn about trials and research.

This in-person event is for individuals in the LGMD R9/2I community living in Europe and the United Kingdom. Recordings will later be shared with the wider global community. The LGMD R9/2I Community Conference is free to attend and will include refreshments and dinner. The cost of travel and hotel accommodation is not included.

Booking details will be shared at Registration.

May 25, 2024 ▪ 9AM to 5:30PM

DoubleTree by Hilton ▪ Amsterdam Centraal Station

To attend the 1st European LGMD R9/2I Community Conference, scan and complete the interest form >

For additional information, please contact the organising team at: ***fkrpregistry@newcastle.ac.uk***

GLOBAL FKRP REGISTRY · LGMD2iFund · Myopathies des Ceintures LGMD · The SPEAK Foundation · CURELGMD2i · MUSCULAR DYSTROPHY UK · John Walton · NHS The Newcastle upon Tyne Hospitals · Newcastle University

Moving drug development forward for Limb-Girdle Muscular Dystrophy

LGMD SCIENTIFIC WORKSHOP

On February 8, 2024, The Speak Foundation, the first patient-led organization for Limb-Girdle Muscular Dystrophy (LGMD), assembled a multi-stakeholder group of leading academic medical experts, patients and caregivers, patient advocates, senior leaders of the U.S. Food & Drug Administration's drug and biologic centers including Peter Marks, M.D., Ph.D., Peter Stein, M.D., Nicole Verdun, M.D., and Michelle Campbell, Ph.D., and experienced commercial drug developers for a scientific drug development workshop focused on LGMD.

WORKSHOP SPEAKERS AND PANELISTS

Lindsay Alfano, PT, DPT
Principal Investigator, Assistant Professor
The Abigail Wexner Research Institute at Nationwide Children's Hospital
Center for Gene Therapy

Michelle Campbell, PhD
Associate Director,
Stakeholder Engagement and Clinical Outcomes,
Office of Neuroscience
United States Food and Drug Administration (FDA)

Joanne Donovan, PhD, MD
Chief Medical Officer
Edgewise Therapeutics

Keith Flanagan
Consultant
Flanagan Strategies, LLC

Nicholas Johnson, MD
Associate Professor, Division Chief of Neuromuscular, and Vice Chair of Research, Department of Neurology
Virginia Commonwealth University
Head, GRASP LGMD Consortium

Peter Kang, MD
Professor and Vice Chair of Research
Department of Neurology
University of Minnesota Medical School

Annie Kennedy
Chief of Policy, Advocacy, and Patient Engagement
EveryLife Foundation for Rare Diseases

HISTORY WAS MADE AT THE LGMD SCIENTIFIC WORKSHOP AS ALL STAKEHOLDERS CONVENED TO FURTHER DRUG DEVELOPMENT

(L to R): Peter Marks, MD, PhD, **The Speak Foundation's CEO** and **Founder, Kathryn Bryant Knudson**, and **Peter Stein**, MD

The scientific workshop built upon the momentum of the October 2020 FDA Patient Listening Session and the September 23, 2022, Externally Led Patient-Focused Drug Development meeting, which focused on the health effects, daily impacts, and decision factors considered when seeking out or selecting a treatment for symptoms and burdens associated with LGMD.

As a practical next step, the workshop provided scientific leadership with the opportunity to illuminate a pathway to regulatory approval for LGMD treatments informed by disease context.

The following key themes emerged:

- With no available treatment options, people living with LGMDs urgently need therapies that slow down or stop the natural progression of this severely debilitating disease and do not consider a cure as the only clinically meaningful outcome of successful drug development.
- LGMDs are exceptionally rare, slow, and variable (even within the same subtype) in progression from the perspective of clinical researchers, while for patients and their families the effects appear faster-moving, pervasive, and irreversible with far-reaching ramifications on the lives of those impacted by the disease. Together, this presents significant challenges to traditional drug development approaches that rely on clinical measures insensitive to progression within a typical clinical trial time frame.
- LGMD pathophysiology is well understood, and science has advanced to provide an opportunity to develop tailored approaches directly targeting the causal pathway of each of the subtypes discussed at the workshop: R1/2A, R2/2B, R5/2C, R3/2D, R4/2E and R9/2I.

Kathryn Bryant Knudson
Founder and CEO
The Speak Foundation

Jennifer Levy, PhD
Scientific Director
Coalition to Cure Calpain 3 (C3)

Peter Marks, MD, PhD
Director of the Center for Biologics Evaluation and Research (CBER)
United States Food and Drug Administration (FDA)

Katherine Mathews, MD
Professor of Pediatrics — General Neurology
University of Iowa Health Care,
Carver College of Medicine

Jerry R. Mendell, MD
Former Attending Neurologist
Nationwide Children's Hospital
Senior Advisor, Medical Affairs
Sarepta Therapeutics

Anh Nguyen, MD
Vice President, Therapeutic Sector Leader
AskBio Therapeutics

Sophie Olivier, MD
Chief Medical Officer
Atamyo Therapeutics

- Innovative drug development approaches are needed to improve the feasibility and efficiency of LGMD clinical trials considering the challenges presented by smaller population size, heterogeneity of the population, and irreversible effects of the disease; FDA acknowledges its long-standing commitment to apply regulatory flexibility in the context of diseases like LGMD and the importance of leveraging its "toolbox" to address the unmet need, to include consideration of:
  - > surrogate endpoints and Accelerated Approval, with biological plausibility as a cornerstone to its use.
  - > case studies highlighted the use of muscle biopsy biomarkers as potential surrogate endpoints in LGMD R9/2I (glycosylated αDG) and LGMD R4/2E (β-sarcoglycan protein expression).
  - > clinical endpoints that are adequately sensitive to progression and reflect meaningful benefits for patients.
  - > single arm studies, supported by natural history data.
  - > platform approaches that may be applied across LGMD subtypes.
  - > totality of evidence, looking at all available science and data as a package.
  - > patient perspectives on what constitutes a meaningful benefit, willingness to accept uncertainty, and tolerate risk.

Patient Preferences in Drug Development

SOME VIEWS EXPRESSED IN PATIENT PRESENTATIONS IN THE WORKSHOP

Use the Accelerated Approval pathway and consideration of the totality of evidence for LGMDs—all serious diseases with no available treatments.

Consider using natural history and clinical trial data to inform clinical trial design, the development of clinically meaningful endpoints, and the use of external controls. Requiring placebos in long randomized trials will impede recruitment and retention of patients who will continue to irreversibly decline on placebo.

WORKSHOP SPEAKERS AND PANELISTS

Louise Rodino-Klapac, PhD
Executive Vice President, Head of R&D, Chief Scientific Officer
Sarepta Therapeutics

Laura Rufibach, PhD
Co-President
Jain Foundation

James Signorovitch, PhD
Managing Principal
Analysis Group

Douglas Sproule, MD
Chief Medical Officer
ML Bio Solutions

Peter Stein, MD
Director of CDER's Office of New Drugs (OND)
United States Food and Drug Administration (FDA)

Nicole Verdun, MD
Director,
Office of Therapeutic Products (OTP)
CBER, U.S. FDA

Matthew Wicklund, MD
Professor of Neurology
University of Texas San Antonio

By bringing the brightest scientific minds and patients in the LGMD community together with regulators, the workshop provided a productive forum to find solutions focused on advancing therapies that will improve the lives of LGMD patients, and serve as a model to facilitate engagement and progress for other disease communities. Researchers, clinicians, and drug developers shared disease expertise and preclinical and clinical perspectives; patients underscored their treatment preferences; and regulators conveyed a balance of rigor, feasibility, and flexibility.

(L to R): EveryLife Foundation for Rare Diseases' Chief of Policy, Advocacy, and Patient Engagement, Annie Kennedy, with **Peter Marks**, MD, PhD, and **Peter Stein**, MD

Throughout the day, repeated calls were made for early, frequent, and continued conversation and collaboration between FDA, patients, and industry to efficiently address the full range of challenges and opportunities to bring the first therapies to LGMD patients as rapidly as possible while creating a viable blueprint for more therapies to follow. In-depth documentation of the workshop's findings and next steps is in progress and will be shared when available. ▪

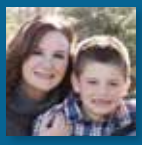
Collaboration between regulators and industry (analogous to steps taken during COVID-19 vaccination development) is needed to expedite safe and effective treatments.

It is critical to incorporate patient input into the FDA risk/benefit assessment framework.

Patients are willing to take reasonable risks and accept a degree of uncertainty to improve quality of life, but there is a need to further educate the patient population on the potential risks, benefits, and uncertainties associated with LGMD therapies.

PATIENT PANEL

Kelly Brazzo
(Mom & Caregiver of Sammy)
Subtype: LGMD R9/2I (Dystroglycanopathy)
Age of Onset: Age 2



Rachel DeConti
(Mom & Caregiver of Jacob)
Subtype: LGMD R3/2D (Sarcoglycanopathy)
Age of Onset: Age 5

Brooklyn Garza
Subtype: LGMD R1/2A (Calpainopathy)
Age of Onset: Age 9

Patrick Moeschen
Subtype: LGMD R4/2E (Sarcoglycanopathy)
Age of Onset: Age 11

Joshua Thayer
Subtype: LGMD R2/2B (Dysferlinopathy)
Age of Onset: Age 18

SCAN ME

VIEW THE FULL VIDEO RECORDING OF THE WORKSHOP

Written By Joshua Thayer

Accelerated Approval of New Drugs Based on Surrogate Endpoints

An Explanation and LGMD Community Perspective

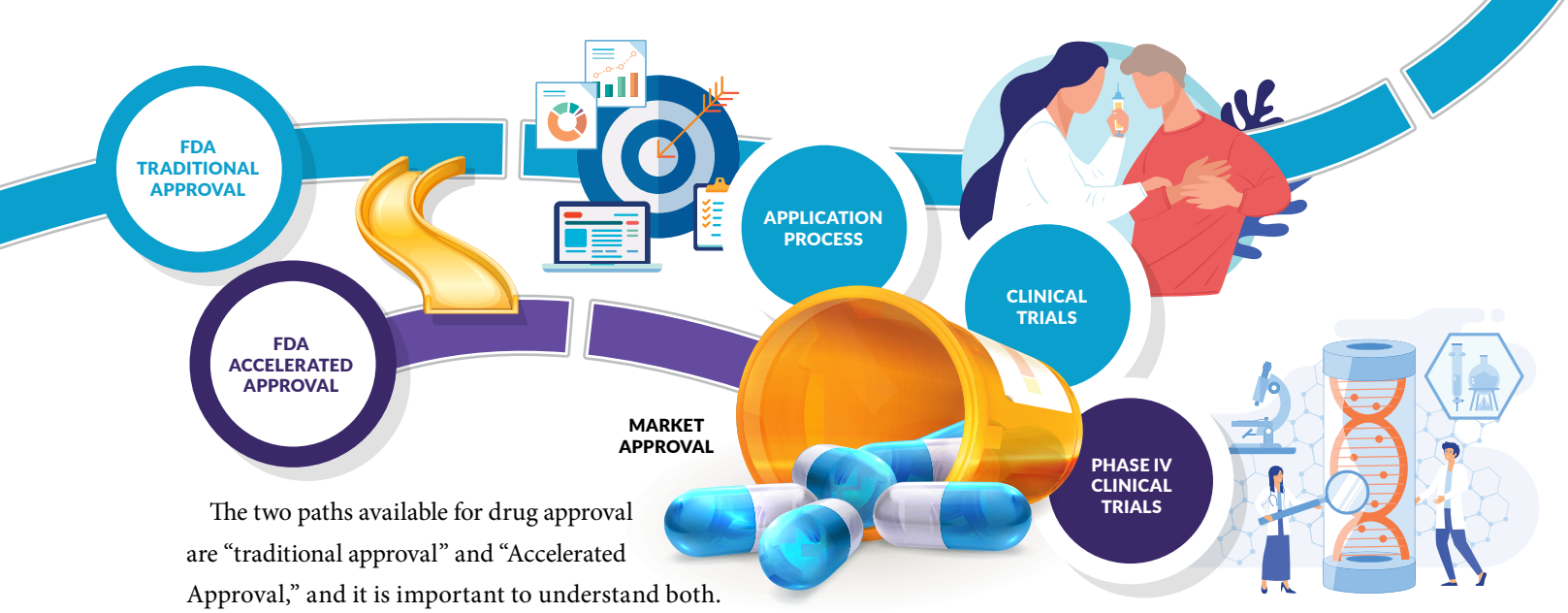
In US news coverage of drug development for rare genetic disorders, such as LGMDs, it's hard to miss references to "Accelerated Approval" and "surrogate endpoints." That's an exciting development for our community because the Accelerated Approval program offers faster access to drugs to treat our diseases, and for us, each day counts.

However, understanding regulatory terminology can be challenging. This article explains that terminology, as well as how the Accelerated Approval program works and how it fits in the broader framework of drug approval in the United States. We then look at a recent, well-publicized case of Accelerated Approval, and why Accelerated Approval seems particularly appropriate for LGMDs.

First, what does the FDA require to approve a new drug?

To sell any new drug, the drug's developer must apply for market approval after conducting clinical trials. In the United States, this application, filed with the Food & Drug Administration (FDA), is called a New Drug Application (NDA) for "traditional" drugs, and a Biologics License Application (BLA) for biologics, which includes gene therapies.[1]

To approve a drug, the FDA must conclude that the drug's benefits to the relevant patient population outweigh its risks.[2] That is, data from research studies and clinical trials must demonstrate that the drug is sufficiently safe, well tolerated, and likely to be an effective treatment for the targeted disease.[3] The FDA seeks input from patients on this risk/benefit analysis by mechanisms such as Patient-Focused Drug Development (PFDD) meetings. This risk/benefit analysis is subjective and can vary for different diseases. For serious or life-threatening diseases, such as LGMDs, the FDA may accept a higher risk profile and less established efficacy data, especially if no other treatments are available.[4]



The two paths available for drug approval are "traditional approval" and "Accelerated Approval," and it is important to understand both.

Customarily, with the route of traditional approval, the FDA has required clinical trials to show either "clinically meaningful benefits" or "well-validated surrogate endpoints." The first concept is what everyone hopes to see in any clinical trial. These benefits prolong life, improve function, or improve the way a patient feels and are measurable during the trial or by the end of the study's data review.[5] For example, if a patient is pain-free at the end of a clinical trial for a pain medication, that would be a clinically meaningful benefit.

For some diseases, the FDA will accept a change in certain *biomarkers as surrogates* of near-term functional benefits. The FDA defines biomarkers as "characteristics that are objectively measured as indicators of health, disease, or a response to an intervention, including therapeutic interventions."[6] Perhaps without realizing it, most of us are quite familiar with certain biomarkers used as clinical trial endpoints. For example, diabetes drugs may be approved based on their capacity to lower blood sugar, and heart disease drugs based on their capacity to reduce cholesterol or blood pressure, without either showing an immediate impact on the patients' quality of life.[7] The biomarkers are accepted as "well-validated surrogate endpoints" because the medical and scientific communities have come to recognize their value based on extensive experience treating and monitoring patients.[8]

But where does traditional approval leave people living with LGMD today?

Imagine a gene therapy clinical trial that includes non-ambulatory LGMD participants. And suppose that within one year after dosing, each participant can stand up and walk, even if with some difficulty. One could reasonably assume that the FDA would consider such results to be clinically meaningful and grant the drug traditional approval.

But would the same be true if the patient remained non-ambulatory, but could bathe and dress more independently? And what if the patient showed no clear improvement but remained stable? How does one determine what is "clinically meaningful," and who gets to decide, especially in a disease like an LGMD that progresses slowly and has varied rates of progression?

The FDA can turn to biomarkers as surrogate endpoints, but what if all surrogate endpoints for the applicable LGMD were still being discovered and validated? Where do the traditional "well-validated surrogate endpoint" criteria leave emerging therapies for serious diseases, such as the LGMDs?

Fortunately, the FDA decided to address these types of scenarios in its regulations governing Accelerated Approval.

Accelerated Approval, "reasonably predictive" surrogate endpoints, and post-approval confirmatory clinical trials

Under FDA's Accelerated Approval program,[9] a drug or biologic may receive market approval without showing either a clinically meaningful benefit or a well-validated surrogate endpoint, provided the drug is intended to treat serious conditions and fills an unmet medical need. Where such criteria are met, the drug must only have an

effect on a surrogate endpoint deemed *reasonably likely* to predict clinical benefit.[10]

For example, the FDA has said it could approve a cancer drug that shrinks tumors, which it considers to be a biomarker that is "reasonably likely to predict a real clinical benefit" even without waiting to see if the drug "will actually extend survival for cancer patients."[11]

The FDA has described its rationale for adopting the Accelerated Approval program as follows:

> "Mindful of the fact that it may take an extended period of time to measure a drug's intended clinical benefit, in 1992 the FDA instituted the Accelerated Approval regulations. These regulations allowed drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint. *Using a surrogate endpoint enabled the FDA to approve these drugs faster* (emphasis added)."[12]

In cases where the FDA approves the marketing of a drug under Accelerated Approval, the sponsor must continue to research the drug to verify its clinical benefit, which must include adequate and well-controlled clinical trials. Such trials are referred to by the FDA as "confirmatory trials," "post-marketing trials," or "Phase IV Clinical Trials."[13] If Phase IV Clinical Trials establish safety and clinical efficacy, the FDA may waive any further conditions resulting in unconditional approval of the drug. However, if the trials fail to show clinical benefit or reveal toxicity over long-term use, the FDA may withdraw approval outright.[14]

Heroic predecessors spurred the FDA to adopt Accelerated Approval

We would like to pause here to note the debt of gratitude our community of LGMD patients owes to AIDS patients and their advocates for their role in pushing for Accelerated Approval in the 1980s and 1990s. Their very public and relentless campaign for faster approvals of HIV treatments, all while fighting stigma, death, and loss of loved ones, has been credited for leading to the FDA's adoption of the Accelerated Approval regulations.[15]

Accelerated Approval of a muscular dystrophy gene therapy in the news

On June 22, 2023, the FDA approved the BLA for SRP-9001, Sarepta Therapeutics' gene therapy for the treatment of Duchenne Muscular Dystrophy in ambulatory children between the ages of four and five years old.[16] The decision made headlines in mainstream media outlets as well as scientific and healthcare publications, and it was applauded by patients and rare disease advocacy groups.[17] And for good reason! SRP-9001 (also known as delandistrogene moxeparvovec-rokl and marketed as ELEVIDYS) is the first FDA-approved gene therapy for any type of muscular dystrophy.

But while many were excited, the FDA's Accelerated Approval in this instance was not without critics. Some members of the FDA considered the clinical benefits to be questionable.[18] Some questioned whether the proposed surrogate endpoint — a shortened dystrophin protein designed in a lab — was reasonably predictive of a meaningful clinical benefit. While the drug seems reasonably safe, some expressed concern that patients who receive an AAV gene therapy are usually unable to take it a second time because of the resulting immune reaction to the virus. They worried that if a more robust gene therapy using the same AAV type were later approved, it would not be available to patients already treated with SRP-9001.[19]

The FDA approved the drug following an external advisory committee's vote in favor of Accelerated Approval by a margin of 8-6.[20] While that vote was not binding on the FDA, the agency ultimately agreed with the advisory committee.[21] That decision is not the last step, however: As noted above, Accelerated Approval requires that Sarepta conduct further confirmatory clinical trials to help establish clinical benefits over time.

The clear case for Accelerated Approval of drugs that treat Autosomal Recessive LGMDs . . .

For many reasons, Accelerated Approval is well suited for drugs that treat autosomal recessive LGMDs, or AR LGMDs. (Treatment approaches for dominant LGMDs

are discussed in an article by Andrew Findlay, M.D. in the Winter 2024 issue of *LGMD Magazine).* AR LGMDs are now designated by the letter R followed by a number.

First, all AR LGMDs are serious or life-threatening, robbing those with the disease of strength, mobility, and independence; and in some cases decreasing lung capacity or resulting in heart failure. Second, there are no approved treatments for any LGMD subtype, so any LGMD drug would address an unmet medical need. Consequently, the regulatory conditions for Accelerated Approval are satisfied for these types of LGMDs.

Also, the slow progression of LGMDs and variation of symptoms and progression among patients make demonstrating clinical benefit in a relatively short clinical trial challenging. More time might be necessary to measure any benefit, including a halt in the disease's natural progression. The Accelerated Approval program provides extra time to monitor without delaying patient access to a drug.

But do gene therapy treatments in development for AR LGMDs have biomarkers that can reasonably predict clinical benefit? *The short answer is yes, they do!*

All AR LGMDs are caused by mutations in identified genes and the resulting lack of an adequately functional protein in the muscles. No other biomarker would seem more reasonably predictive of a benefit than restoration of the protein whose deficiency causes the disease in the first place. Protein restoration is in fact the design goal of all gene therapies for AR LGMDs. Unlike current DMD gene therapies, which deliver truncated versions of the missing dystrophin protein, LGMD AAV gene therapies are designed to deliver the full-length transgenes, and hence the full "native proteins" that a person without MD would have.

For this reason, expression of the protein delivered by the gene therapy drug is a major readout in clinical trials. However, other biomarkers are measured as well, such as creatine kinase (CK) levels, which indicate the rate of muscle breakdown, and which can therefore give an indirect indication that the person's muscles are benefitting from the treatment.

Concluding thoughts

We hope our discussion has helped you understand the meanings of some of the terminology you might come across, including Accelerated Approval vs. traditional approval, and surrogate endpoints vs. clinically meaningful endpoints. We encourage you to lend your voice to your fellow patients and advocates in pressing for liberal use of the Accelerated Approval process for the review of new drugs and biologics designed to treat LGMDs. In future articles, we will address additional clinical trial design elements that we believe require further development and use, such as more advanced functional endpoints than those which are currently used and more attention to existing data from ongoing clinical outcome studies. ■

References

1. *See, e.g.*, Susan J. Schniepp, "The Facts About Filing Drug Applications," *BioPharm International*, June 1, 2021, Vol. 34, Issue 6, Pages: 50, 49, at https://www.biopharminternational.com/view/the-facts-about-filing-drug-applications, and "Allucent, "5 Common FDA Applications for Drugs & Biologics" at https://www.allucent.com/resources/blog/5-common-fda-applications-drugs-and-biologics#:~:text=3.,biologic%20product%20into%20interstate%20commerce.
2. *See, e.g.*, FDA, "*Development & Approval Process / Drugs*," August 8, 2022, at https://www.fda.gov/drugs/development-approval-process-drugs#:~:text=A%20team%20of%20CDER%20physicians,drug%20is%20approved%20for%20sale,
3. *Ibid.*
4. *Ibid.*
5. *See, e.g.*, "FDA Facts: Biomarkers and Surrogate Endpoints" https://www.fda.gov/about-fda/innovation-fda/fda-facts-biomarkers-and-surrogate-endpoints#:~:text=A%20clinical%20trial%27s%20"endpoints"%20are,either%20clinical%20or%20surrogate%20endpoints; and "BEST (Biomarkers, EndpointS, and other Tools) Resource," FDA-NIH Biomarker Working Group, https://www.ncbi.nlm.nih.gov/books/NBK326791/
6. *See, e.g.*, "FDA Facts," at note 5, *above*.
7. *Ibid.*
8. *Ibid.*
9. Code of Federal Regulations Title 21, Sections 314.500 to 314.560, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=314&showFR=1&subpartNode=21:5.0.1.1.4.8
10. *See, e.g.*, FDA, "*Accelerated Approval*," February 24, 2023 at https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval#:~:text=-Section%20901%20of%20FDASIA%20amends,or%20an%20intermediate%20clinical%20endpoint
11. *Ibid.*
12. *Ibid.*
13. *Ibid.*
14. *Ibid.*
15. *See, e.g.*, Lucy Vereshchagina, "Three things to know about the accelerated approval pathway," *Pharma*, December 12, 2022 at https://phrma.org/en/Blog/Three-things-to-know-about-the-accelerated-approval-pathway; and Douglas Crimp, "Before Occupy: How AIDS Activists Seized Control of the FDA in 1988," *The Atlantic*, December 6, 2011 at https://www.theatlantic.com/health/archive/2011/12/before-occupy-how-aids-activists-seized-control-of-the-fda-in-1988/249302/
16. Sarepta Therapeutics, Inc., Press Release, June 22, 2023 https://investorrelations.sarepta.com/news-releases/news-release-details/sarepta-therapeutics-announces-fda-approval-elevidys-first-gene
17. *See, e.g.*, Marco Meglio, "FDA Approves SRP-9001 as First Gene Therapy for Duchenne Muscular Dystrophy," *NeurologyLive*, June 22, 2023 at https://www.neurologylive.com/view/fda-approves-srp-9001-first-gene-therapy-for-duchenne-muscular-dystrophy#;
18. Aditya Samal, "Sarepta slides as FDA about-turn on panel clouds gene therapy approval path," *Reuters*, March 17, 2023 at https://www.reuters.com/business/healthcare-pharmaceuticals/sarepta-slides-surprise-fda-panel-meeting-adds-uncertainty-gene-therapy-2023-03-17/
19. 74th Cellular, Tissue and Gene Therapies Advisory Committee May 12, 2023 https://www.youtube.com/watch?v=k33d4h-CpGU
20. Meg Tirrell, "FDA Advisers Narrowly Vote In Favor Of Experimental Gene Therapy For Rare Muscle Disease," *CNN*, May 14, 2023 at https://www.cnn.com/2023/05/12/health/duchenne-muscular-dystrophy-therapy-fda/index.html
21. *See, e.g.*, Marco Meglio, "FDA Approves SRP-9001," at note 17, *above*.

Biomarkers:

Tiny Detectives in the World of Clinical Trials

By **Douglas Sproule, MD, MSc**. *Chief Medical Officer, ML Bio Solutions*

Just as canaries used to be taken into mines to detect dangerous gases before they affected humans, some biomarkers may act as early warning signs of potential health problems before symptoms appear. They may also offer early information about how an investigational treatment might affect the body. They can serve as an early signal, prompting further investigation and potential intervention.

Signs vs. Symptoms

When understanding our health, medical professionals rely on two key information sources: symptoms and signs. Symptoms are the subjective experiences we feel, like fatigue or pain, while signs are objective observations, like elevated blood pressure or a rash. Another way to think about this is that symptoms are the messages we hear from within, while signs are the external indicators that doctors can observe and measure. Both provide valuable information, but they differ in their perspective.

Biomarkers fall in the category of signs. Imagine tiny detectives within your body, who investigate and send back messages or clues about your health. Biomarkers are just that — biological indicators that can offer invaluable insights into the inner workings of our physiology, from the microscopic level of molecules to the macroscopic functioning of organs. For centuries physicians have used biomarkers to determine disease status, make informed health decisions or guide treatment decisions, and monitor response to treatments.

So, what exactly are biomarkers?

In 1998, the National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[1] A biomarker, short for a "biological marker," a subcategory of medical signs, is an objective measurable indicator that captures what is happening in the body at any given moment. Biomarkers can be anything from pulse and blood pressure to more complex imaging techniques or laboratory tests examining blood or other tissues.

How can biomarkers be used in clinical trials?

In clinical trials, where researchers test new drugs and investigational therapies in clinical trials, biomarkers may come in handy in several ways:

- Finding the right "clinical trial participants": Before even starting a trial, researchers may use genetic testing to identify potential participants. For example, a new drug might be designed to work for patients with specific gene mutations, so scientists use biomarkers to identify these individuals for the trial.
- Understanding the course of disease: At regular doctor's visits, or in a natural history study, doctors may measure biomarkers to track the course of disease.
- Evaluating the impact of an investigational drug: During a clinical trial, researchers may measure biomarkers, when available, to see how the treatment is affecting the disease. Biomarkers can be used as surrogate endpoints and/or clinical endpoints (described in more detail below) and both measures may help to determine whether the investigational treatment is working.

What are clinical endpoints?

Clinical endpoints are carefully chosen measurable outcomes that evaluate the effect of an investigational treatment. They can be simple, like changes in the ability to walk, or more complex, like improved survival rates. Sometimes, clinical endpoints are not sensitive enough to measure the course of a disease over a brief period, resulting in the need for a long clinical trial. Biomarkers can play a crucial role in assessing these endpoints, providing objective and precise measurements to track progress and evaluate the treatment's effectiveness.

What are surrogate endpoints?

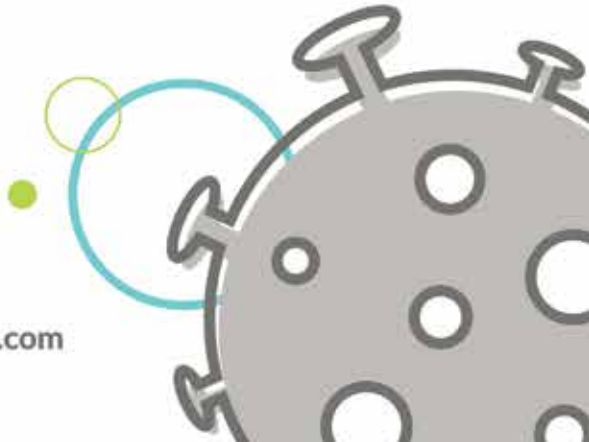
A surrogate endpoint is a biomarker that works as a substitute for a clinical endpoint. Imagine surrogate endpoints as shortcuts on the path to understanding a treatment's efficacy. For example, in Alzheimer's disease research, changes in amyloid plaques in the brain, a known biomarker, might be used as a surrogate endpoint for disease progression, even though directly measuring cognitive decline is the clinical endpoint.

Surrogate endpoints are invaluable for several reasons. They can help speed up clinical trials, requiring fewer patients and shorter durations. They can also be more sensitive than traditional clinical endpoints, detecting subtle changes before symptoms manifest. Researchers and patients must work together with regulatory agencies, to ensure that the chosen surrogate and clinical endpoints reflect the overall clinical picture and provide reliable information about a treatment's long-term benefits.

Biomarkers are crucial signs, revealing valuable information about our biology. Working with symptoms, and the patient's perspective, they form an integral part of the medical landscape, acting as objective signals for both diagnosis and treatment evaluation. While their relationship with clinical endpoints can be multifaceted, their power as potential surrogate endpoints holds immense promise for revolutionizing medical research and improving patient care.

So, next time you hear about a promising new drug in a clinical trial, remember the tiny detectives working behind the scenes — the remarkable biomarkers. They are helping scientists develop safe, effective treatments, more quickly, leading to better healthcare for everyone.

[1] Strimbu K, Tavel JA. What are biomarkers? Curr Opin HIV AIDS. 2010 Nov;5(6):463-6. doi: 10.1097/COH.0b013e32833ed177. PMID: 20978388;



Health Equity Grant for Access to Excellent Care

At the Speak Foundation, we believe that every person deserves excellent healthcare and that financial struggles should not prevent anyone from world-class care.

Connect with Us

Jessica@TheSpeakFoundation.com

TheSpeakFoundation.com/grant-programs1

Those living with physical health conditions often face a myriad of barriers to full inclusion and flourishing wellness. These challenges, faced by many in our limb-girdle muscular dystrophy community, include those relating to the physical environment, legislation or policy, stigma and discrimination, and even lack of access to excellent institutions for medical care.

It is not uncommon for individuals with rare diseases to struggle with finding physicians who are truly knowledgeable about their diagnosis. For many, lack of proximity to major cities where there are large hospitals and teaching universities with cutting-edge research taking place creates yet another burden. The reality is that not everyone is in a financial position to afford the cost of travel for appropriate services, creating a disconcerting disparity in healthcare equity.

At the Speak Foundation, we believe that every person deserves excellent healthcare and that financial struggles should not prevent anyone from world-class care. Our Health Equity Grant program seeks to address this critical gap to obtaining quality medical treatment by removing financial barriers. This program will provide travel grants for qualified LGMD patients living in the United States to visit approved, leading centers of excellence for LGMD.

Approved centers include:*

- UCI Health ALS & Neuromuscular Center–Orange, CA
  ucihealth.org
- University of Florida Health Center for Pediatric Neuromuscular and Rare Diseases, Gainesville, FL
  ufhealth.org/locations/uf-health-center-for-pediatric-neuromuscular-and-rare-diseases
- University of Iowa Health Care and Carver College of Medicine–Iowa City, IA
  uihealthcare.org
- University of Minnesota Medical School–Minneapolis, MN
  med.umn.edu
- University of Texas San Antonio–San Antonio, TX
  uthscsa.edu
- Virginia Commonwealth University–Richmond, VA
  vcu.edu
- Washington University School of Medicine in St. Louis–St. Louis, MO
  medicine.wustl.edu

* If you have another center in the USA that you would like to be seen at for LGMD, please connect with us.

Eligibility criteria:

- US residency
- Suspected or confirmed diagnosis of LGMD
- Lacking access to an excellent facility for medical care/in need of multidisciplinary care
- In need of financial assistance
- Must be able to travel

This program opens July 1, 2024. To find out if you are eligible for a travel grant, please contact **Jessica@TheSpeakFoundation.com** after this date. The program will involve reimbursement of travel expenses and recipients must cash the check within 90 days of receipt. Visit **TheSpeakFoundation.com/grant-programs-1** for more information. ■

Written by Jessica Evans, Psy.D.

Thank you to Sarepta Therapeutics for providing this grant to the Speak Foundation.

University of Iowa Carver College of Medicine
University of Iowa Health Care

2024 Iowa Wellstone Dystroglycanopathy Patient & Family Conference

The 2024 Iowa Wellstone Dystroglycanopathy Patient & Family Conference will be held at the Hyatt Regency Coralville Hotel and Conference Center in Coralville, Iowa on Friday and Saturday, July 12–13, 2024. The conference is free, and anyone interested in the dystroglycanopathies is welcome to attend.

Questions? Contact Carrie Stephan at *Carrie-Stephan@uiowa.edu*

Registration will open in the spring 2024.

The SPEAK Foundation
3551 Blairstone Road #105-62
Tallahassee FL 32301

TOGETHER WE ARE STRONGER

SEPTEMBER
30
2024

Mark your calendar for the 10th Annual LGMD Awareness Day!

Join the LGMD Awareness Foundation in our mission to elevate global awareness for limb-girdle muscular dystrophy. Together we advocate for better access to diagnosis, care, and treatment for those affected.

In celebration of the 10th anniversary, we're rolling out an awareness toolkit!

Be the first to receive updates to your inbox when you join our mailing list.

LGMD AWARENESS FOUNDATION

lgmd-info.org