Vol 4 / Issue 4

LGMD News

Uniting the Limb-Girdle Muscular Dystrophy Community

AN EXPLORATION OF NATURAL HISTORY STUDIES OF RARE DISEASES AND THE LGMD COMMUNITY PERSPECTIVE

How Natural History Studies Can Lead to Improved Care and Facilitate Therapy Development

OUR GOAL: GENETIC DIAGNOSIS FOR ALL LGMD PATIENTS

The Laboratory of Dr. Peter Kang has been Studying Genetic Puzzles in LGMD for Over a Decade

RAREST OF THE RARE

Meet Kristin Salvio, Living with LGMD R14/2N

ACTION NEEDED!

Q&A with Dr. Karen Hoelzer: We Must Reauthorize the U.S. Pediatric Rare Disease Voucher Program

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ORLANDO, FL

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The Importance of the Patient Voice in Advocacy

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The SPEAK Foundation

Empowering the LGMD Community

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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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You are Invited to Represent the LGMD Community!

It is vital for the patient community to make our presence known and to communicate the urgency of our need for treatments at events like the International LGMD Conference.

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The most important goal of advocacy is representing the collective voice of the patient community. Many drug developers, researchers, and clinicians have expressed interest in the International LGMD Conference as a platform for sharing results and scientific breakthroughs with the world. At this strategic event, all stakeholders in the LGMDs will be in attendance. Drug developers new to the LGMD space will be considering our community for drug development, based on factors such as:

- The size and level of engagement of our patient community
- The level of scientific knowledge and natural history data for LGMDs
- The status of advocacy organizations and patient registries for LGMDs

It is vital for the patient community to make our presence known and to communicate the urgency of our need for treatments at events like the International LGMD Conference. Other rare neuromuscular diseases such as spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD) were in our shoes just a few years ago. Now, both of these disease areas have multiple approved treatments. The SMA and DMD communities have shown us the blueprint and steps to take, and now it is our turn to follow suit. When drug developers and leading researchers gather in one place, potential treatments often follow.

The next several years will be critical in new drug development for LGMDs. We must invest in our future as a disease community. Events and programs that highlight and bring awareness to our disease area are one of the most visible ways we can advocate for our community! ▪

Kat Bryant Knudson

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

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.

LET YOUR VOICE BE HEARD!

DAY ON THE HILL 2024

LIMB GIRDLE MUSCULAR DYSTROPHY

LGMD

Delegates living with Limb Girdle Muscular Dystrophy will meet in person with congressional leaders in Washington, DC.

Thank you to all our LGMD representatives!

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September 18, 2024

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 R18/2S
Facebook.com/LGMDCC

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

For additional information about the International Consortium of LGMD Organizations: **ContactUs@TheSpeakFoundation.com**

Conrad Weihl, MD, PhD

Professor of Neurology,
Washington University School of Medicine
in St. Louis, Missouri

Q

Is there any progress towards a therapy for my subtype, LGMD R14/2N (POMT1 related)?

A

Lessons learned from one type of muscular dystrophy can help develop therapies for others. LGMD R14/2N may be amenable to therapies such as Ribitol, which is currently in studies for LGMD R9/2i.

Q

How quickly do you think gene replacement therapy can be extended to other types of muscular dystrophy, specifically LGMD R1/2A (calpain-3 related)?

A

Widespread delivery of viral vectors to skeletal muscle is now feasible and there are current clinical programs in gene transfer therapy for LGMD R1/2A.

Q

Is it common for those with LGMDs to have problems with circulation in their feet? I notice that my feet are often purple.

A

This is a common complaint. It's important to seek medical attention to rule out blood clots, as opposed to being related to muscle loss that causes fluid to accumulate in the feet.

Q

My wife had genetic testing, which showed one pathogenic and one uncertain variant in the GMPPB gene. We are trying to accurately identify the subtype to see if any trials/medications could help her. How do we confirm her subtype?

A

LGMD R19/2T is the subtype associated with GMPPB mutations. Finding variants of uncertain significance is common in genetic testing and resolving them is an active topic in our research. It is incredibly important to have the correct diagnosis to see if the variant is amenable to therapies. Often, supporting evidence such as a muscle biopsy or evaluation by an expert at a Neuromuscle Center can be used to confirm a diagnosis.

Q

Is it common for women with LGMDs to get urinary tract infections (UTIs) often?

A

Although LGMD doesn't affect the involuntary muscles involved in bowel and bladder function, patients with limited mobility often have difficulty using the bathroom (leading them to not drink enough fluids) or have seating issues, making them more susceptible to UTIs. ▪

Meet the Expert

Conrad "Chris" Weihl, MD, PhD is a Professor of Neurology at Washington University School of Medicine in St. Louis, Missouri. He received his MD and PhD from the University of Chicago Pritzker School of Medicine followed by a Neurology Residency and Neuromuscular Fellowship at Washington University. During his post-doctoral fellowship, he began to study the molecular pathogenesis of hereditary myopathies and now has an active clinical and basic science research program focused on genetics and limb-girdle muscular dystrophies. His research has delineated the molecular mechanism of several myopathies and identified the genetic cause of LGMDD1. He has received a number of honors including the Derek Denny-Brown Young Neurological Scholar Award from the American Neurological Association. He is currently a member of the WMS meeting planning committee and is the ANA scientific program advisory committee chair. Dr. Weihl has a strong commitment to the training of future neuromuscular clinicians and myologists.

Have a Question for Our Experts?

Send Questions To:
ContactUs@TheSpeakFoundation.com

Visiting the Labs of AFM-Telethon

The French Association against Myopathies, known as AFM-Telethon, was founded in 1958 by parents of children living with Duchenne muscular dystrophy. AFM-Telethon is an impactful patient-led organization for neuromuscular diseases based in Evry, France, about one hour south of Paris. Currently, 580 employees and 3118 volunteers work for the association. Thanks to generous donations from the annual Telethon TV show, AFM-Telethon has become a significant player in biomedical research for rare diseases. Its three major laboratories involved in developing biotherapies are Genethon, I-Stem, and the Institute for Myology.

Recently, Kathryn Bryant Knudson, founder of the Speak Foundation and editor-in-chief of the *LGMD News* Magazine, was invited to visit the AFM-Telethon headquarters with Mélanie Bordes, a patient advocate who leads AFM's LGMD Patient Interest Group. Together they toured the I-Stem lab with Xavier Nissan, and met with Stephane Degove, CEO of Atamyo Therapeutics, and Professor Isabelle Richard of Atamyo Therapeutics.

With the generous support of donors, AFM-Telethon raised over 92 million Euros (~100 million U.S. Dollars) in 2023 alone, with one main goal: to overcome neuromuscular diseases. The next Telethon will take place on November 29-30, 2024.

Bottom: The members of the LGMD Interest Group of AFM-Telethon, led by Mélanie Bordes (far right)

Right (Top): Kathryn Bryant Knudson, Xavier Nissan, and Mélanie Bordes at the I-Stem Lab

Right (Bottom): Xavier Nissan explains the recent developments and findings to Kathryn Bryant Knudson

The AFM-Telethon LGMD Interest Group

The French LGMD Interest Group was created in 2018 by AFM-Telethon to accompany and support patients and families affected by limb-girdle muscular dystrophies. Led by expert volunteers with different types of LGMDs, the group is a place for patients to be heard. Giving patients a voice is essential for future treatments and adequate medical and social care. The group also provides regular information on medical and scientific developments and advice specific to LGMDs. The creation of the group was based on the simple fact that, at the time, there was no patient advocacy group specifically for LGMDs in France.

The LGMD Interest Group regularly organizes national LGMD meetings to connect patients and families with doctors and researchers in France. The group also collaborates with departmental delegations to improve the quality of life of patients and their family caregivers. There are delegations of AFM-Telethon all over the different regions of France. Members of these delegations advocate for the rights of people with disabilities in various public councils and authorities.

The Mission of the LGMD Interest Group:

- Provide information about LGMDs
- Advocate for the needs of LGMD patients in France and abroad
- Organize regional meetings between patients, their families, doctors, and researchers
- Provide support and advice to patients
- Monitor and inform about scientific developments
- Visit scientific conferences in France and internationally
- Create lasting relationships with international LGMD patient associations

Since November 2023, the group has been led by Mélanie Bordes, a trained patient advocate living with LGMD R9/2i who has considerable experience in national and international advocacy.

Touring the I-Stem Laboratory

Kathryn's tour started at I-Stem, the Institute for Stem Cell Therapy and Exploration of Monogenic Diseases, established in 2005. There, she met Xavier Nissan, research director of the LGMD pharmacology program, and Noëlla Grossi, a pharmacist and PhD student living with LGMD R2/2B.

Xavier Nissan and his team use pluripotent stem cells to study and treat LGMDs by developing high-content/high-throughput screening strategies to identify possible drug candidates. The pharmacological approach consists of identifying drugs that can correct the functional consequences of the mutation to stop or slow down the disease progression. However, this approach does not correct the mutated gene, as in gene therapy. That is why it is essential to identify the specific disease pathways and mechanisms affected by the mutation for the pharmacological approach.

Understanding these pathways is the first step for researchers to develop targeted drugs that can more effectively mitigate the adverse effects caused by the mutation. Once identified, researchers test thousands of pre-existing drugs to avoid creating a new drug from scratch, which is extremely expensive, time-consuming, and restrictive in terms of regulations. This approach, called drug repurposing, is also being followed by other companies involved in LGMD research.

Currently, I-Stem's pharmacological LGMD research program mobilizes six researchers working mainly on:

- Preclinical evaluation (in vivo) of givinostat for LGMD R3/2D and LGMD R5/2C
- Preclinical evaluation (in vitro and in vivo) of a recently discovered molecule for LGMD R2/2B
- Understanding the mechanism of action (in vitro) of new drugs for improving membrane repair in LGMD R2/2B
- Understanding the role of immune cells in LGMD R2/2B pathophysiology
- Understanding dysregulation of pathways involved in LGMD R2/2B
- Identification of new phenotypes and biomarkers for LGMD R9/2i

Discovery of Givinostat for LGMD R3/2D

In 2022, Xavier Nissan's team, in collaboration with Isabelle Richard's team at Genethon, identified a combination of two approved drugs, bortezemib and givinostat, which can treat some mutations in alpha-sarcoglycanopathy (LGMD R3/2D). These findings were published in *Frontiers in Pharmacology*[1] in 2022. This discovery opens new possibilities for treatment of LGMD R3/2D and LGMD R5/2C. Currently, preclinical studies are evaluating the effects of givinostat in an animal model prior to a possible clinical trial in humans.

After the lab tour, Kathryn and Mélanie met Stephane Degove, CEO of Atamyo Therapeutics, and Professor Isabelle Richard, Chief Scientific Officer of Atamyo Therapeutics, at AFM's headquarters.

LGMD Pioneer Award

However, before embarking on the presentation of Atamyo Therapeutics, Kathryn had the great pleasure of awarding Professor Isabelle Richard with the *Fifth Annual LGMD Pioneer Award* for her leadership in the LGMD R9/2i community on behalf of the CureLGMD2i

Foundation. Professor Richard has always been very determined to find treatments for LGMD R9/2i and all of the most common LGMDs. Isabelle Richard was given this award in recognition for her outstanding work and engagement with the LGMD community.

Gene Therapy Approaches by Atamyo Therapeutics

Atamyo Therapeutics is a clinical-stage biopharmaceutical company focused on developing a new generation of effective and safe gene therapies for muscular dystrophies and cardiomyopathies that currently lack treatment options. Its most advanced programs currently target LGMDs, including LGMD R9/2i, LGMD R5/2C (gamma-sarcoglycanopathy), and LGMD R1/2A (calpainopathy).

The name of the company comes from two words: Celtic *atao*, which means "always" or "forever," and *myo*, the Greek root for muscle. Atamyo Therapeutics is fully committed to improving the lives of patients affected by neuromuscular diseases with life-long efficient treatments.

Located in Paris and Evry, Atamyo was founded in 2020 as a subsidiary of Genethon. It leverages unique expertise in AAV-based gene therapy and muscular dystrophies from the Progressive Muscular Dystrophies Laboratory at Genethon, led by Isabelle Richard. Professor Richard is co-founder and Chief Scientific Officer of Atamyo.

Isabelle Richard is an international expert in neuromuscular diseases and a pioneer in researching LGMDs and developing gene therapies targeting LGMDs. She

Opposite: Professor Isabelle Richard receiving the 5th Annual LGMD Pioneer Award from the CureLGMD2i Foundation

Above: Mélanie Bordes and Kathryn Bryant Knudson meeting with Atamyo Therapeutics in the headquarters of AFM-Telethon in Evry, France

Left: Professor Isabelle Richard, Chief Scientific Officer and Stephane Degove, Chief Executive Officer of Atamyo Therapeutics

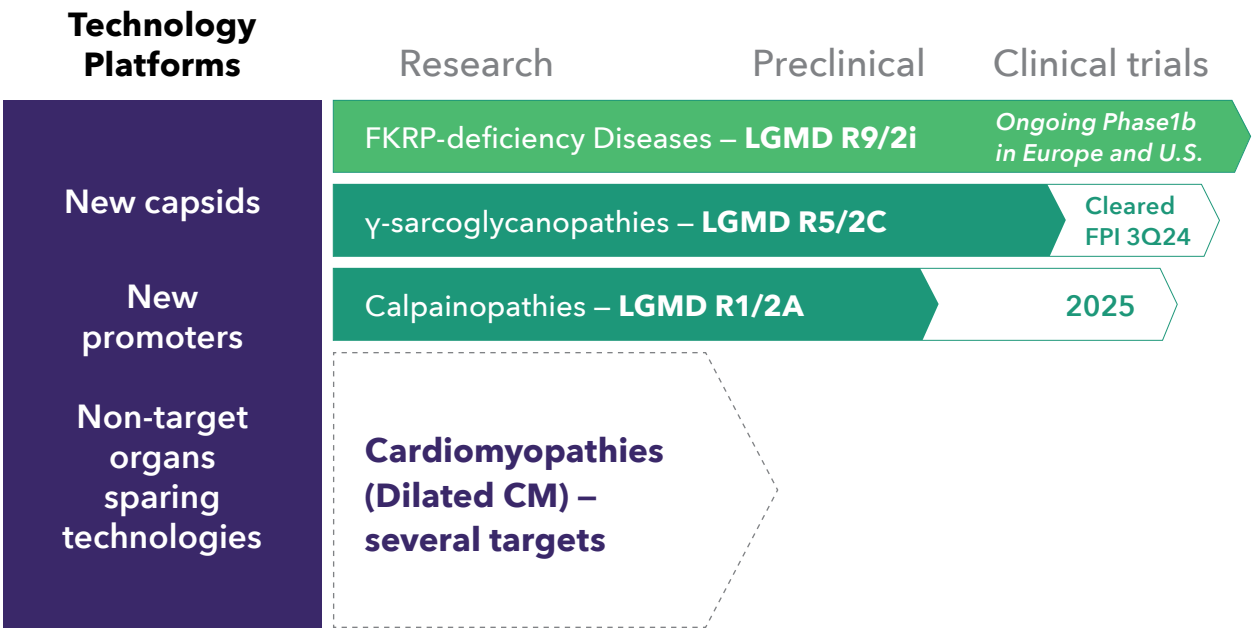


Figure 1: Atamyo Therapeutics pipeline for LGMDs

has published more than 160 scientific papers on muscular dystrophies. Noteworthy highlights of her work include identifying calpain-3 as the first gene implicated in an LGMD, demonstrating the heterogeneity of LGMDs, participating in the identification of the causative genes for all the frequent LGMDs, and proof-of-concept studies of the efficiency of gene therapy for all the most common LGMDs.

Gene therapies developed by Atamyo Therapeutics are single-injection treatments designed to replace the mutated genes that cause LGMDs with functional genes. Atamyo is introducing "first-in-class" technologies that improve the efficacy of gene therapies and prevent adverse effects, such as cardiac or liver toxicity.

ATA-100 for LGMD R9/2i

Atamyo's most advanced gene therapy program, ATA-100, is being developed to treat LGMD R9/2i patients (clinicaltrials.gov ID# NCT05224505). The first clinical results were presented at the Myology Congress in Paris in April 2024. Enrollment of the first low-dose cohort of the study in Europe has been completed with promising initial functional results, and two patients have already been treated in the high-dose cohort. Overall, ATA-100 has been well tolerated to date in all treated patients. In June, Atamyo obtained Fast Track Designation for ATA-100 by the FDA in the USA. Updated results will be presented at the 29th International Annual Congress of the World Muscle Society (WMS) in Prague, October 8-12, 2024.

ATA-200 for LGMD R5/2C

Atamyo's second gene therapy, ATA-200, is cleared to start clinical trials in Europe (France and Italy) for LGMD R5/2C patients (ID# NCT05973630). This phase 1b dose-escalation study will evaluate the safety and efficacy of ATA-200 in children aged 6-11 years at screening. Plans have been made to dose the first patients in the last quarter of 2024. Additionally, Atamyo Therapeutics is in IND-enabling studies (Investigational New Drug) for LGMD R1/2A related to deficiencies in the calpain-3 protein. ■

Written by Mélanie Bordes

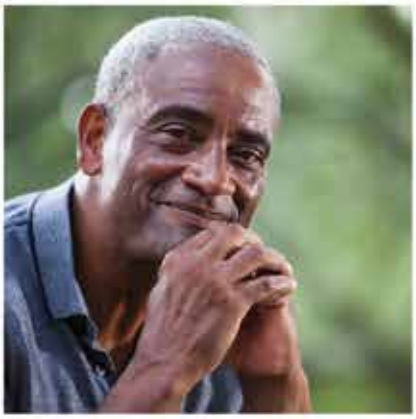
References

1. Hoch, L., Bourg, N., Degrugillier, F., Bruge, C., Benabides, M., Pellier, E., Tournois, J., Mahé, G., Maignan, N., Dawe, J., Georges, M., Papazian, D., Subramanian, N., Simon, S., Fanen, P., Delevoye, C., Richard, I., & Nissan, X. (2022). Dual blockade of misfolded alpha-sarcoglycan degradation by bortezomib and givinostat combination. *Frontiers in Pharmacology*, 13.

We welcome individuals with LGMD2A/R1 to join our journey

JOURNEY

JOURNEY is a clinical outcomes assessment study, also referred to as a natural history study. The study does not involve the use of an investigational study drug, but instead studies the natural progression of LGMD subtypes over a period of time (~3 years). The data collected from JOURNEY will help Sarepta learn more about the condition and how muscle strength, breathing, and heart function can change over time. This information is critically important for researchers to design clinical trials for future therapies. Individuals affected with limb-girdle muscular dystrophy type 2A/R1 (LGMD2A/R1, calpainopathy) are now invited to participate.



The journey to uncover your potential treatment options

Currently there are no treatments approved for individuals with a limb-girdle muscular dystrophy. 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 LGMD2A/R1. Enrollment of individuals with LGMD2E/R4, LGMD2D/R3, or LGMD2C/R5 has been met and is closed for future enrollment

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

JOURNEY Participation

Study participants will have access to highly experienced physicians and 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 and laboratory tests.

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 well being.

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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Muscular Dystrophy UK: Together We are Stronger

Working for better understanding of neuromuscular conditions to speed up referral and improve vital support

Muscular Dystrophy UK is the leading charity for more than 110,000 people in the UK living with one of more than 60 muscle-wasting and weakening conditions, including LGMD. Their mission is to:

- Share expert advice and support people to live well
- Fund groundbreaking research to understand different conditions better and lead to new treatments
- Work with the National Health Service (NHS) to provide universal access to specialist healthcare
- Campaign for people's rights, better understanding, accessibility, and access to treatments

At the start of 2024, Muscular Dystrophy UK published the findings of a survey which revealed that people living with a muscle-wasting or weakening condition in the UK are often misunderstood by non-neuromuscular specialist healthcare professionals and are not referred to specialist services at the earliest opportunity. It highlighted that possible signs of rare and progressive conditions are often missed or not investigated. Speedy referral is essential due to the complex diagnosis process and the urgent need to access healthcare and treatments as quickly as possible (see "Meet Sarah," Page 13).

Some of the Survey Findings:

- Just under half of respondents (47%) faced a misdiagnosis at some point.
- It took four or more meetings with healthcare professionals for the majority (55%) of respondents to get a diagnosis.
- A significant majority of respondents (69%) waited more than a year to receive a diagnosis.

These findings helped inform Muscular Dystrophy UK's "Manifesto for Muscles" in advance of the UK general election in July 2024, in which the charity called for the new government to tackle the barriers and challenges the muscle-wasting community faces so that everyone can get the healthcare, support, and treatments needed to feel good, both mentally and physically.

People must be able to access the right support, management, and where available, treatment. This allows people to remain independent, doing the things they enjoy for longer and more easily.

Part of Muscular Dystrophy UK's mission is to work with the NHS and the muscle-wasting and weakening community to broaden knowledge and understanding of the different conditions, ensure the referral process is quick

and efficient, and improve access to treatments. MDUK also meets with pharmaceutical companies, academics, and regulatory authorities to advise on conditions like limb-girdle muscular dystrophy, and ensure that patients have a voice during research and development projects.

Working with Healthcare Professionals

Muscular Dystrophy UK provides a range of resources and awareness-raising opportunities for non-neuromuscular specialist healthcare professionals across the UK, including an e-learning resource for general practitioners, events, webinars, conferences and connections to local specialist services through its Regional Neuromuscular Networks.

Supporting the Community

In addition to its helpline, which is available to everyone, including parents and carers, Muscular Dystrophy UK organizes regular "Muscle Groups" across the UK, offering a network of support for those living with different conditions. These supportive and confidential spaces provide an opportunity for people to share experiences and meet others affected by muscle-wasting and weakening conditions. The helpline also provides invaluable support and expert advice for those trying to navigate the difficult UK benefits system in order to access their full legal rights to financial support.

Support isn't one-size-fits-all; the charity aims to tailor its support to meet individual needs. There are information days, webinars on specific topics, and support groups on Facebook and WhatsApp with condition-specific groups as well as those tailored to different ages and communities. Through the Joseph Patrick Trust, grants are also available to help with expensive medical equipment such as specialist wheelchairs.

Research

Muscular Dystrophy UK also funds groundbreaking research. In August, the charity announced it is investing £1.7m into 12 new research projects, bringing the total number of funded projects to 51. One of these is Professor Henry Houlden's project at University College London, which will use state-of-the-art genetic sequencing techniques to find more genes that cause limb-girdle muscular dystrophies. ■

> *People must be able to access the right support, management, and where available, treatment. This allows people to remain independent, doing the things they enjoy for longer and more easily.*

Connect with Us

MuscularDystrophyUK.org

Meet Sarah

Sarah Tunnicliffe, 41, from Cardiff in Wales was diagnosed with a probable form of limb-girdle muscular dystrophy in 1999 at the age of 16. Despite the initial diagnosis, it took 11 more years to get a definitive answer.

Sarah explains: "Following various investigations, I was told it might be limb-girdle muscular dystrophy. There were delays as the muscle biopsy was placed in the wrong solution and a second procedure was inconclusive, so my diagnosis remained unconfirmed. In 2010, they conducted further tests, which identified two faults in the calpain-3 (CAPN3) gene, consistent with limb-girdle muscular dystrophy type R1/2A or calpainopathy.

It had been 11 years since my initial diagnosis, but finally I had valuable information on the implications of my condition and the likely prognosis. This was important not only for me, but for my family too. My siblings were at a stage where planning a family was on the cards and they could now be tested for carrier status to fully understand the risks of having an affected child."

Written By Kathryn Bryant Knudson
Founder, The Speak Foundation

and Brad Williams, PhD
Senior Editor, LGMD News

The Importance of the Patient Voice in Advocacy

As we approach our second LGMD Day on the Hill and the 10th anniversary of LGMD Awareness Day, Brad Williams and Kat Bryant Knudson share their thoughts about important priorities for our community's advocacy efforts. As individuals who have lived with LGMD for many years, they know first-hand how devastating the progression can be over time. People living with LGMD must make their voices heard to create change.

Those of us living with LGMDs face extraordinary challenges. As we age, many of us struggle to find help with tasks of daily living, such as bathing, dressing, eating, toileting, and other personal care needs. In many countries, support systems are set up around assisting the young and the elderly. This structure isn't very helpful for people with LGMDs, as our patient population consists largely of young and middle-aged adults. For many LGMD subtypes, onset often occurs in adolescence or young adulthood — precisely when people are establishing independent lives. The needs of a 40-year-old individual who works outside of the home in spite of living with LGMD aren't contemplated in the current support service model. This forces many patients to rely on support from their parents, who should be enjoying retirement, but instead are struggling to help an adult child with a progressive disability.

There is also a tendency to view disability as an all-or-nothing categorization: one is either viewed as disabled, unable to work, and in need of support services; or non-disabled and therefore without need of assistance. But those of us who live with LGMDs understand that these conditions exist on a continuum that changes over time. There is no such thing as a date when we became disabled. The policies that result from this mindset often impede people living with LGMDs from working, lest they risk losing assistance for their care needs, which they cannot afford to pay for on their own, and also to endure bureaucratic nonsense such as periodically proving that they still have muscular dystrophy!

Limb-girdle muscular dystrophies are diseases that often manifest just as someone is beginning their adult life. Many people living

with LGMDs are young adults who want nothing more than to continue working in their career as long as possible, but require personal care support to do so. Those who are no longer physically able to work and need to go on disability should be able to have support at home for activities of daily living. Instead, their partners are often having to find a way to both work outside the home and help their loved one at home. We can and must address these needs in our community.

The LGMD community is in need of legislation to address these shortcomings. It is critical that the voices of patients living with LGMDs play a leading role in educating stakeholders about what we need. Thus far, most of the advocacy initiatives for rare diseases have not been led by patients themselves, yet our patient community is made up of many qualified individuals who are more than capable of speaking on their own behalf. Just as the U.S. Food and Drug Administration has recognized that the patient voice must be a part of drug development, it is critical for those of us living with progressive diseases to make our voices heard regarding legislation that will impact our disease area.

One particular legislative topic discussed in this magazine issue is Rare Pediatric Disease Priority Review Vouchers (RPD PRVs), which is a U.S. program to provide financial incentives (without using any public funds) to encourage drug development for rare diseases affecting children. This important program, which the Speak Foundation stands in support of, requires reauthorization this year, as mentioned in the article on Page 22. Your voice matters; be sure to read more in this issue about how you can make a difference.

PRVs have undeniably encouraged drug development for rare diseases, including LGMDs. However, the benefits of PRVs for LGMD drug development are limited by their being restricted to diseases with pediatric onset. LGMDs can have onset in childhood, adolescence, or adulthood, meaning that only some LGMD subtypes qualify for PRVs. This limitation puts subtypes that don't qualify at a huge disadvantage in terms of drug developers' priorities. An important goal for the future is to broaden the criteria for the program so that more rare diseases can qualify.

This is just one example of the importance of including the voices of patients living with rare diseases in informing legislative priorities. ▪

Thus far, most of the advocacy initiatives for rare diseases have not been led by patients themselves, yet our patient community is made up of many qualified individuals who are more than capable of speaking on their own behalf.

DONATE TODAY!

Support the Movement of Patient-Led Advocacy!

The Speak Foundation is an organization led by individuals living with limb-girdle muscular dystrophy. When you support our organization, you are supporting the efforts of individuals who are working for you and who understand firsthand the challenges you are facing. Did you know *LGMD News* is published entirely by individuals living with LGMDs? Our Design Director, all of our editors, and your Editor In Chief all have LGMD.

The Importance of Multidisciplinary and Specifically Respiratory Care in LGMDs

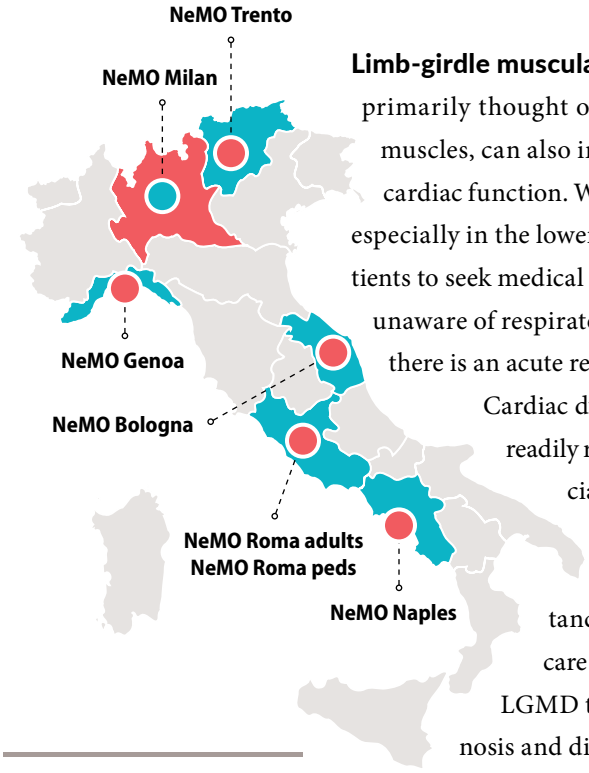

Figure 1: The Milan site in the Italian DMD and BMD network

With our specific focus on neuromuscular conditions, we have a protocol to care for individuals living with LGMDs.

Limb-girdle muscular dystrophies, while primarily thought of as affecting skeletal muscles, can also impact respiratory and cardiac function. While muscle weakness especially in the lower limbs often leads patients to seek medical attention, they may be unaware of respiratory insufficiency until there is an acute respiratory event.

Cardiac dysfunction may not be readily recognized either, especially in nonambulatory patients. This emphasizes the importance of multidisciplinary care for patients living with LGMD to ensure proper diagnosis and disease management.

The Milan NeMO Clinic is a dedicated neuromuscular clinical center where care is provided by a multidisciplinary team of neuromuscular specialists, including three adult neurologists, one pediatric neurologist, four neuromuscular-dedicated pulmonologists, two rehabilitation doctors, four psychologists, and 16 therapists (including physiotherapists, respiratory therapists, occupational therapists, child therapists, nutritionists, and speech therapists) who see patients every six months. There are six other sites across Italy sharing the same protocols and procedures, providing neuromuscular referrals for many patients.

With our specific focus on neuromuscular conditions, we have a protocol to care for individuals living with LGMDs. Patients can be seen as inpatients for a mean of 14 days during which they participate in a full rehabilitation program including: physical endurance and resistance exercise, pulmonary function testing (including being taught air stacking exercises), training for non-invasive ventilation (NIV) or secretion management if needed, and nutritional assessments (e.g., swallowing studies and metabolic investigations). Patients may also be seen as outpatients in daily services in which they receive neuromotor function tests, respiratory function tests, psychological assessments, and nutritional and swallowing studies, as needed. In addition to these individualized care programs, patients can participate in clinical studies — both observational and placebo-controlled clinical trials.

The NeMO site in Milan (Figure 1) is a part of the Italian DMD and BMD network and the Muscular Dystrophy Clinical Research Trial Network led by Virginia Commonwealth University (Dr. Nicholas Johnson), and has recently expanded our existing collaboration in Myotonic Dystrophy and FSHD to include LGMD patients. As part of the GRASP network, the NeMO site in Milan and collaborating NeMO sites in Italy will add clinical data from Becker MD and LGMD patients including neuromotor function, respiratory, nutritional, and psychological test results from retrospective data collected since 2017 and will provide prospective data as part of the GRASP and upcoming protocols in this field. ■

Written by Dr. Valeria Sansone
Professor of Neurology, University of Milan
Director, Centro Clinico NeMO

UPDATED: SEPTEMBER 10, 2024

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 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.

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

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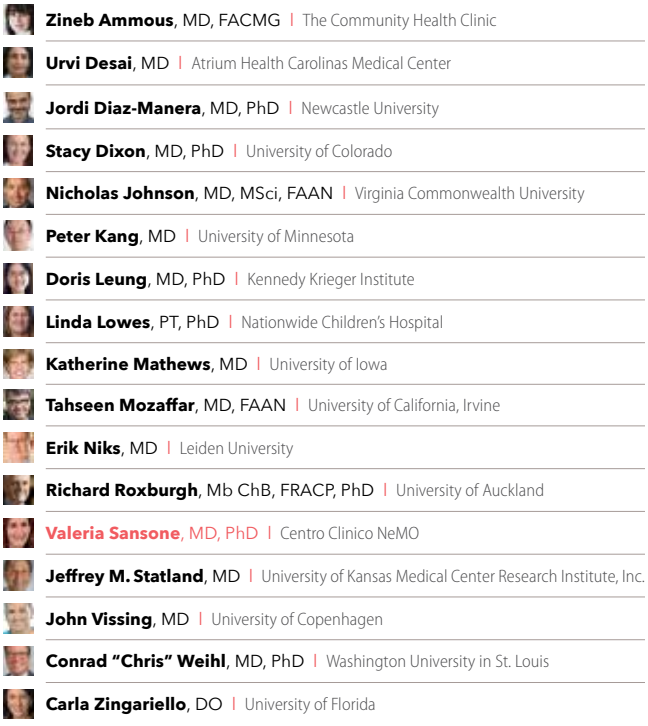

- **Zineb Ammous**, MD, FACMG | The Community Health Clinic
- **Urvi Desai**, MD | Atrium Health Carolinas Medical Center
- **Jordi Diaz-Manera**, MD, PhD | Newcastle University
- **Stacy Dixon**, MD, PhD | University of Colorado
- **Nicholas Johnson**, MD, MSci, FAAN | Virginia Commonwealth University
- **Peter Kang**, MD | University of Minnesota
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- **Linda Lowes**, PT, PhD | Nationwide Children's Hospital
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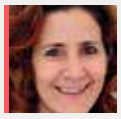


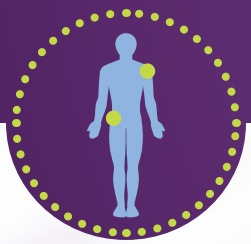
Spotlight:
Dr. Valeria Sansone
Centro Clinico NeMO

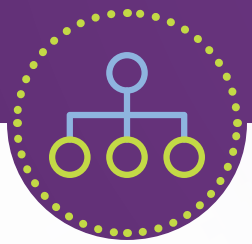
Dr. Valeria Sansone has experience in neuromuscular disorders from both a clinical and a basic science perspective. Dr. Sansone's Ph.D. research project in medical school was focused on studies of ion channel modulation *in vitro* using the patch-clamp technique. For the past 22 years, she has been in charge of inpatients with muscle disorders at the University Department of Neurology in Milan and in charge of the state-run outpatient neuromuscular clinic at the hospital site. Her main field of research is in myotonic disorders, especially the Myotonic Dystrophies (DM). Dr. Sansone is author of several relevant manuscripts dealing with disease progression, natural history, and quality of life. Since 2013, she has been the Clinical Director of a neuromuscular-dedicated multidisciplinary clinic for in- and outpatients with neuromuscular disorders including kids and adults. Dr. Sansone has been a faculty member at the University of Milan since 2006 and the NeMO Center has been a University Teaching Hospital since 2013.

The importance of genetic testing in reaching an accurate diagnosis

In this issue, we invite Brianna Gross, MS, CGC (Certified Genetic Counselor), to share her expertise on the role and importance of genetic testing.

Brianna is a genetic counselor with the Division of Neurology at Children's Hospital of Philadelphia. In her role, she has helped many individuals living with a neuromuscular condition reach a definitive diagnosis to help guide them on a path forward.





Limb-girdle muscular dystrophies (LGMDs) are a group of approximately 30 different subtypes of genetic muscle disease, where the hallmark symptoms are shoulder and hip girdle muscle weakness. LGMD subtypes share many symptoms, such as progressive muscle weakness, but there are subtype-specific features as well. Symptoms can more notably appear at different stages of life; some individuals may show signs early, while others do not experience symptoms until late adulthood. The severity also varies, with some individuals having mild to moderate muscle weakness and others having severe weakness that can cause significant disabilities, such as wheelchair dependence, or can become life-limiting due to heart and lung involvement.

LGMDs are further complicated by the variability within a specific subtype, which may mean that two individuals with the same subtype may experience different symptoms and progression rates.

Many LGMD subtypes also exhibit signs and symptoms that overlap with other non-LGMD conditions such as myositis, Duchenne and Becker muscular dystrophies, spinal muscular atrophy (SMA), and Pompe disease, among others. Given this, and the symptom overlap between subtypes, diagnosing a specific LGMD subtype based solely on an evaluation of symptoms is difficult for a physician. Therefore, the most definitive method for determining an individual's specific LGMD subtype is through genetic testing.

Misdiagnosis is not uncommon for people living with an LGMD. Misdiagnosis can occur in various ways: individuals with a non-LGMD condition may be incorrectly diagnosed with LGMD, while those with LGMD may be inaccurately told they have a different, non-LGMD disorder. To the right are two cases exemplifying how critical it is to receive an accurate and definitive (genetic) diagnosis.

Learn more about genetic testing at LimbGirdle.com/Genetic-Testing

Stay connected to receive updates

This case is about an adult patient who was undergoing treatment for myositis, an immune-related muscle disease.

She had been diagnosed with myositis due to proximal muscle weakness (weakness in the shoulder and hip girdles), which prevented her from daily activities such as getting up from the ground and reaching up to grab items from shelves. She also experienced muscle pain and had an elevated muscle enzyme, creatine kinase (CK), which suggested her muscles were breaking down.

She came to our neuromuscular clinic's attention when her 14-year-old child also began to have proximal muscle weakness. The team was suspicious that she was diagnosed incorrectly with myositis because autoimmune conditions are typically not passed down from parent to child. Following a neuromuscular evaluation and subsequent genetic testing for her child, our suspicions were confirmed that she and her child had an autosomal dominant form of LGMD.

Receiving a confirmed and accurate diagnosis helped enable the patient to better manage her health, avoiding unnecessary interventions. She no longer receives IV immunoglobulin infusions, which is a standard treatment for myositis, and she is now followed regularly by the neuromuscular team. In addition, it provided insight on familial risks and has allowed her and her family members to appropriately plan for expanding their families. Her accurate diagnosis also enabled her to enroll in a subtype-specific patient registry.

This next case is about a 15-year-old who came to our neuromuscular clinic due to having progressive muscle weakness.

He began to struggle with going up the stairs, participating in sports, and getting up from the floor and seated positions. He also fell frequently. Subsequent lab work prior to his visit found that his muscle enzymes were elevated, suggesting his muscles were breaking down. Based on his symptoms and his muscle enzyme elevation, we discussed in detail the likelihood of an LGMD diagnosis.

The family agreed to do genetic testing to confirm a diagnosis. The genetic testing came back negative for all LGMDs tested and the patient was instead confirmed to have SMA. We were able to counsel the patient accordingly. Had he not had genetic testing, he likely would have remained misdiagnosed with an LGMD and missed out on the opportunity to receive treatment for his condition.

Avoiding misdiagnosis is crucial for both the healthcare provider and the patient, as it can significantly impact patient management and treatment. For example, some of the conditions previously mentioned have FDA-approved treatment option(s). It is our priority to ensure that all patients receive the appropriate treatments available to them based on an accurate, definitive (genetic) diagnosis.

Fortunately, genetic testing has become more accessible and allows a timely path to help reach a diagnosis. Correctly identifying a diagnosis is vital for one's health management, and therefore it is important to discuss genetic testing options with your healthcare providers.

SAREPTA THERAPEUTICS

Written By Dan Pope
with Input & Review By Katherine Mathews, MD, FAAN

Rarest of the Rare

Those of us living with LGMD know all too well the challenges and difficulties often encountered when searching for our specific diagnosis. For those of us who do eventually get a confirmed genetic diagnosis, what a relief it is to finally find your "tribe"—those people that truly understand your daily challenges and allow you to draw upon their collective knowledge and experience.

Now, imagine that you have gone through the diagnostic odyssey only to find that your genetic diagnosis is extremely rare and that your tribe consists of just a few people spread out across the globe.

This happened to Kristin Salvio, living with LGMD R14/2N (POMT2-related). Having experienced some developmental delays as an infant, her parents took her to see a neurologist who performed her first muscle biopsy when she was just 18 months old. Unfortunately, the biopsy was inconclusive, leaving her family with more questions than answers.

It was about this time that Kristin's parents also sought out physical, occupational, and speech therapy for their daughter, who was prone to crawling and didn't begin walking and talking until she was almost two years old. Once she did start to walk, it became evident that she had a propensity for toe-walking, and her parents even contemplated having a surgical procedure performed on her Achilles tendons (double tendon-lengthening surgery).

Kristin Salvio (LGMD R14/2N) with her parents

After graduating from high school, Kristin worked with her mom in a medical office and volunteered twice a week working with children with special needs. At this time, she began to notice that her arms, shoulders, and legs were all getting weaker, and she was experiencing more frequent falls, until eventually she was no longer able to get up from the floor on her own.

When Kristin was 21 years old, she had a second muscle biopsy performed, and in April of 2011, she finally received a genetic diagnosis of LGMD R14/2N (POMT2-related).

Feeling relieved to finally have a confirmed diagnosis and a better understanding of the challenges she was facing, Kristin was quite surprised when her neurologist then explained just how rare her condition was. Naturally, she was curious to find others also living with her subtype, but she was only able to locate one other person.

Throughout her twenties, Kristin enjoyed grocery shopping and preparing nightly meals for her large Italian family. However, once she had reached her thirties, she began to experience problems with balance and was no longer able to stand on her own for long, which meant relying more on family members to assist her with the activities of daily living.

Kristin continues to receive physical therapy once a week to treat her chronic neck pain and attends an online exercise class twice a week. She enjoys traveling, cooking with her family, reading, and spending time in the pool. She is also quite active as an advocate for the neuromuscular disease community and is passionate about making air travel more accessible for people with disabilities.

"Of the people enrolled in our natural history study ~7% have POMT2 variants and most of these have congenital muscular dystrophy, not LGMD."

—Dr. Katherine Mathews

What are the dystroglycanopathies?

LGMD R14/2N belongs to a group of conditions called dystroglycanopathies (DGs), which often present as more severe forms of congenital muscular dystrophy (CMD). It is important to note that CMD and LGMD form a continuum without a clear distinction between the two. There are different definitions used to distinguish CMD and LGMD. One definition is that people with LGMD must achieve independent walking and other definitions are based on age at onset of weakness, which can be difficult to define.

The dystroglycanopathies are rare, autosomal, recessively-inherited neuromuscular diseases characterized by reduced glycosylation of α-dystroglycan. There are at least 20 known genes that can cause DG, with POMT1, POMT2, POMGNT1, POMGNT2, GMPPB, ISPD, FKTN, FKRP, and LARGE1 being the most well-known.

Glycosylation adds a series of sugar molecules to α-dystroglycan, allowing it to adhere to structures outside the muscle fiber, providing stability and acting as a shock absorber during muscle contraction. Defects in glycosylation lead to muscle fiber fragility and eventual cell death. POMT1 and POMT2 play critical roles in this process as they contribute to attaching the first sugar molecule to α-dystroglycan. Glycosylation of α-dystroglycan also has an important role in brain development, so some people have learning problems or epilepsy.

Dystroglycanopathies can first come to medical attention in many ways, including developmental delay, weakness, laboratory abnormality, or severe muscle pain and dark urine. Thus, the diagnosis of a dystroglycanopathy has historically been complex and time-consuming; however, the modern era of genetic testing is helping to reduce this time.

Presenting symptoms of LGMD R14/2N can include delayed motor milestones, difficulties in walking, and exercise-related muscle pain, with learning difficulties and cognitive impairment also being common.

Although all LGMDs are considered "ultra rare diseases," dystroglycanopathies (other than LGMD R9/2i) are particularly rare even among LGMDs, and only a minority of patients with mutations in POMT2 and many other DG genes have an LGMD phenotype with the disease presenting after two years old.

Consequently, research into variants in POMT2 and many other DG genes is limited. However, a natural history study entitled *Clinical Trial Readiness for the Dystroglycanopathies* is currently underway at University of Iowa with the intention of learning more about disease progression and developing outcome measures for potential future clinical trials; **Wellstone.medicine.uiowa.edu**. (Contact Carrie Stephan, **carrie-stephan@uiowa.edu**, for more information).

Obtaining a genetic diagnosis of a specific LGMD subtype may be difficult and time-consuming, but it is extremely important. The various subtypes all have subtle differences in presentation and progression, and this knowledge is critical for proper care and disease management, and eventually, treatment. In addition, knowing one's genetic diagnosis is crucial for participating in clinical trials which are all helping to move our community closer to effective cures! ■

Prior to being diagnosed with LGMD in 2003, **Dan Pope** had a career in the field of architectural millwork where he worked in the capacities of design, sales/estimating, and management. He received a genetic diagnosis of LGMD R9/2i in 2013. He currently lives in central Florida and serves as the Vice President and Advocacy Director for the CureLGMD2i Foundation. He loves the outdoors and enjoys hunting, fishing, and exploring his state's parks.

Interviewed By Kelly Brazzo
Co-Founder and CEO, CureLGMD2i Foundation

Q&A

with **Karin Hoelzer**, DVM, PhD

National Organization for Rare Disorders

Action Needed!

Congress Must Reauthorize the U.S. Pediatric Rare Disease Voucher Program by September 30

My name is Karin Hoelzer, DVM, PhD, and I am the Senior Director of Policy and Regulatory Affairs at the National Organization for Rare Disorders (NORD®) in the U.S. In this role, I oversee all of NORD's federal policy work and engage lawmakers, regulatory professionals, and the broader rare disease community on issues that concern all stakeholders.

Growing up, I witnessed the impact of living with a rare condition and the lack of effective treatment options on a family. Fast forward to the COVID-19 pandemic, where I supported the public health response, and I saw the struggles patients with chronic and rare diseases faced when navigating the healthcare system. This experience inspired me to work toward changing that situation.

LGMD News: **NORD has made excellent progress in advocating for our rare disease community. Describe the achievement(s) you are most proud of.**

Dr. Hoelzer: I'm most proud of our community's progress in raising awareness about rare diseases. Rare Disease Day, of which NORD is pleased to be the U.S. sponsor, showcased this. This year we saw unprecedented activity in Washington, D.C. Highlights included a congressional hearing on 18 key policy issues, a White House forum announcing a $48 million project to address the shortage of treatment options, and separate events by the National Institutes of Health (NIH) and Food and Drug Administration (FDA) with community leaders, patients, and advocates.

These activities highlight the growing focus policymakers are placing on rare disease issues thanks to the dedicated advocacy of patient organizations like CureLGMD2i and others. Together, we can amplify the voices of millions of people with rare diseases in the U.S. and worldwide. This collective effort embodies NORD's tagline:

"Alone we are rare. Together, we are strong."

LGMD News: **Can you explain what the Priority Review Voucher is and how it has helped influence the biotech industry to develop approved therapies for rare diseases?**

Dr. Hoelzer: The Rare Pediatric Disease Priority Review Voucher (RPD PRV) program offers hope to the estimated 15 million children with rare diseases by incentivizing the development of therapies for these hard-to-study diseases and patient population. It does this by awarding a voucher to companies that successfully develop a new therapy for a rare pediatric disease.

These vouchers can be redeemed to expedite the FDA review process for a future drug. RPD PRV's, which can be sold for millions of dollars, are a valuable incentive to help offset the significant risks and expenses associated with developing a therapy for a rare pediatric disease. This incentive program has been vital in promoting research and innovation for under-studied pediatric diseases. Congress must vote by the end of September to continue this successful program established 12 years ago.

NORD's report, *Impact of the Rare Pediatric Disease Priority Review Voucher Program on Drug Development 2012–2024*,[1] demonstrates the program's effectiveness. NORD's analysis shows that the RPD PRV has led to more than 50 safe and effective treatments for rare pediatric diseases in its first 12 years offering hope for millions of children. Key findings from the report include:

- **A total of 53 RPD PRVs have been awarded across 39 rare pediatric diseases, many of which are life-threatening and often result in death before adulthood.**
- **Of the 39 rare pediatric diseases granted a PRV, only three had any FDA-approved treatment options prior to the creation of the program.**
- **Success and use of the program has soared over time, with more than half of all RPD PRV designations, awards, and redemptions occurring in the last four years.**

> **Children's lives are dependent on it—it's that simple.**
>
> **—Dr. Karin Hoelzer**

LGMD News: **What could be the potential impact on our rare disease community if the PRV is not renewed on September 30?**

Dr. Hoelzer: Unfortunately, because of the uncertainty about whether Congress will reauthorize the program by the September 30 deadline, there are already harmful effects that are playing out and may negatively impact the future of rare pediatric disease drug development.

The uncertainty about the future of rare pediatric drug development increases with each passing day, and millions of children and families in the U.S. cannot afford any lapse in this program. Children's lives are dependent on it—it's that simple.

LGMD News: **As you might have heard, we are holding *LGMD Day on the Hill* September 18, 2024. What can the LGMD community do to support the renewal of the PRV if they are unable to attend this event in person?**

Dr. Hoelzer: The LGMD community in the U.S. can take action by sending a NORD ACTION ALERT[2] to their elected officials. All advocates need to do is to click on the ACTION ALERT,[3] and enter the home address and zip code; the system uses this information to pull up the contact details for their elected officials, and an automated message will populate asking their elected officials to

cosponsor the "Creating Hope Reauthorization Act of 2024," which would reauthorize the Rare Pediatric Disease Priority Review Voucher program for at least five more years.

Advocates can add their contact information and personalize the message to their senators and representatives by sharing their experience with rare diseases and expressing how reauthorizing the PRV program would impact their everyday life. The emails can be sent to the elected officials directly through this system.

In addition, NORD encourages individuals to contact their lawmakers to set up individual meetings at their offices in the state to explain how vital this program is for rare disease families.

LGMD News: **What are some of the other ways the U.S. LGMD community can get involved to collaborate with NORD's patient advocacy efforts?**

Dr. Hoelzer: Here are some ways the LGMD community can get involved to help ensure Congress reauthorizes the RPD PRV program by September 30:

1. **Be a State Advocate — Currently, we are looking specifically for advocates in CO, MA, PA, and WI:** Right now, we are seeking advocates in Colorado, Massachusetts, Pennsylvania, and Wisconsin to help support our efforts in these states. If you live in one of these states and you or your child have benefitted from this program or your child is currently faced with a rare disease and you are willing to share your story, we would love to hear from you. Please reach out to us at: **Policy@RareDiseases.org** or visit **RareDiseases.org/contact**.

2. **Join the NORD PRD PRV Sign-On Letter:** Currently, NORD has nearly 200 patient advocacy organizations that have signed on to our RPD PRV letter of support. We welcome your patient advocacy organization to join this letter. If you are interested in joining this letter, you can reach us at: **Policy@RareDiseases.org**.

3. **Learn more by watching the webinar:** NORD recently hosted a webinar on our RPD PRV reauthorization efforts to help advocates understand the issue and included highlights of the program's success on rare pediatric drug development. The webinar can be found at: **RareDiseases.org**.

4. **Contact Us:** Please feel free to reach out to NORD as a resource for rare disease advocacy. You can do so by contacting us at: **Policy@RareDiseases.org**. ▪

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Written By **Peter B. Kang**, MD, FAAN, FAAP
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Vice Chair of Research, Neurology Department, University of Minnesota Medical School

Our Goal:

Genetic Diagnosis for All LGMD Patients

Thanks to stunning advances in genetic technologies and widespread adoption of genetic testing, we can now find genetic diagnoses for many more patients with limb-girdle muscular dystrophy (LGMD) than we have been able to in the past.

More than 30 different genes are now linked to LGMD. Yet, a significant number of individuals who are diagnosed with LGMD continue to be faced with completely negative genetic test results or genetic test results that only provide a partial explanation.

The laboratory of Dr. Peter Kang at the University of Minnesota has been studying genetic puzzles in LGMD for over a decade. They have published research articles on specific subtypes such as LGMD R9/2i (*FKRP*), LGMD R5/2C (*SGCG*), and LGMD R27 (*JAG2*), as well as addressing genetic questions in larger groups of LGMD patients representing a broad array of associated genes.

When the laboratory enrolls an individual with an unresolved genetic diagnosis into their study, they collect clinical information, prior genetic test results, and DNA samples from blood or saliva, and undertake a comprehensive analysis that is summarized in the flowchart (Figure 1). Sometimes a diagnosis becomes apparent after a review and re-analysis of genetic information that was previously generated, especially with increasingly sophisticated online tools to help analyze genetic changes, as well as more rigorous criteria to distinguish (a) pathogenic variants (disease-causing DNA changes, otherwise known as mutations) from (b) variants of unknown significance (VUS, DNA changes that are currently indeterminate) from (c) benign variants (DNA changes that are not predicted to cause disease). In other cases, further DNA analysis is needed.

Over the years, the laboratory has adopted numerous genetic technologies, including traditional Sanger sequencing (which looks at a single gene), as well as newer approaches such as whole exome sequencing (WES—which looks at the most active parts of genes in a person's DNA) and whole genome sequencing (WGS—which also looks at regions of DNA that are in between the most active parts of genes and those that are entirely outside of genes).

Recently, the laboratory has adopted a more advanced form of WGS, known as nanopore sequencing. Nanopores are microscopic electrical current detectors and thus can read current changes as each nucleotide of DNA passes through the central pore. Nanopore sequencing generates data from much longer strands of DNA than prior technologies. Data generated in this manner is referred to as "long read whole genome sequencing" (LR-WGS). The complexity and quantity of data generated by LR-WGS is voluminous, typically exceeding a terabyte (TB) when stored on a computer. There are several steps in analyzing nanopore LR-WGS data. The raw data in the form of electrical signals need to be converted into a stream of DNA-sequence reads. The individual DNA-sequence reads must then be connected to each other, eventually forming sequences of entire chromosomes. After that, the sequences are compared to those that are expected to be seen in a healthy individual. This final comparison will yield information about whether there are genetic changes that might be disease-causing. Each of these steps requires large amounts of computational power. The process of diagnosis is summarized in Figure 1.

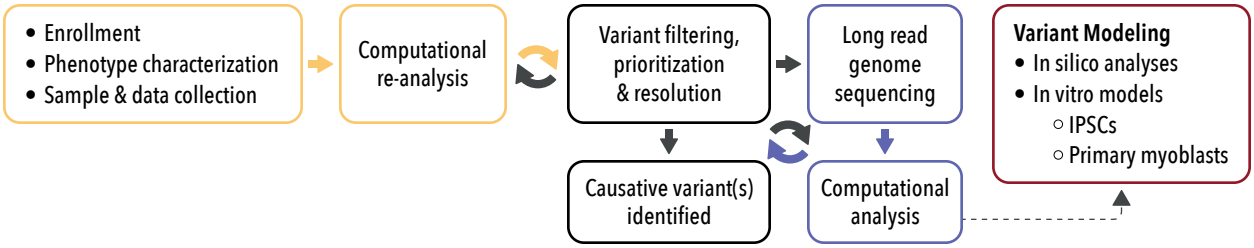

Figure 1: Flowchart showing steps in the workflow for research-based analysis of genetically unresolved cases of LGMD

Nanopore LR-WGS has sequencing capabilities that are now comparable to those of the more traditional short read form (SR-WGS). An advantage presented by nanopore LR-WGS is that it can more reliably detect larger-scale changes in the DNA, which are known as structural variants (SVs). These SVs can be large chunks of DNA that are missing or duplicated or flipped around so that they are reversed in the chromosome. This capability of nanopore LR-WGS for muscular dystrophy diagnosis was demonstrated in a research article published in 2022, and the laboratory has sequenced additional individuals since then.

Dr. Kang's laboratory continues to enroll and study families with unresolved genetic diagnostic questions into their study. The research involves cutting-edge genetic technologies that are not widely available in clinical settings. The enrollment process may be completed remotely for those who are not available for in-person enrollment at the University of Minnesota. ▪

For more information, Dr. Kang's laboratory may be contacted at **Neurogenetics@umn.edu**.

fortify

Thank You

to the participants and clinical sites in FORTIFY, our Phase 3 study. We appreciate the entire LGMD2I/R9 community for all you do on behalf of LGMD drug development.

ML BioSolutions

Stars indicate approximate location of participating Fortify study sites. For a list of trial sites please visit clinicaltrials.gov.

MLbiosolutions.com

Written By Joshua Thayer

An Exploration of Natural History Studies of Rare Diseases and the LGMD Community Perspective

When someone says you are "one in a million," do you feel special? How about "five in a million," or "ten in a million?" Since you are reading this article, the chances are that you, or perhaps a loved one, friend, colleague or patient, are indeed quite special. Worldwide, each LGMD subtype impacts between less than one and just over eight people out of a million (with regional variations).[1] Unfortunately, special or not, having a rare disease makes diagnosis, proper medical care, and the development of therapies challenging. This article focuses on one step to overcome these obstacles: "natural history studies," which can lead to improved care for patients and facilitate therapy development.

An Overview of Natural History Studies

The goal of a natural history study is to analyze the natural progression of a disease absent any treatment in people who are receiving the current standard of care from their physicians.[2] The clinicians conducting the study record and analyze functional abilities and biological samples of persons with a disease, often repeatedly over time. They also review participants' historical medical data, including age at symptom onset and diagnosis. As suggested by the name, these studies are observational only and do not involve drug testing.

The biological measurements may include the concentration or absence of proteins in the blood or muscle, and fat intrusion in muscle. Functional measurements, referred to as "clinical outcome assessments," or "COAs" (and sometimes as "clinician-reported outcomes," or "ClinROs") may include strength of the heart, lungs, and skeletal muscles, as well as the ability to conduct simulated activities of daily living. Also, participants will respond to surveys, such as quality of life questionnaires, which are referred to as "patient-reported outcome measures," or "PROMS." Doctors do love their acronyms!

One example of a multicenter, international study of LGMD patients is the International Clinical Outcome Study for Dysferlinopathy, or COS.[3] The first phase, COS1, enrolled 209 participants, of whom 174 completed at least six visits over a 3-year period at 17 sites worldwide.[4] The second phase, COS2, has enrolled 200 participants at 16 sites worldwide.[5]

Please see Table 1 for a representative list of natural history studies for LGMDs.

Table 1: List of Representative Natural History Studies*

Name of Study	ClinicalTrials.gov ID and Status	Lead Site and Number of Additional Sites by Country	Clinical Outcomes and Biomarkers by LGMD Subtypes
Defining Clinical Endpoints in LGMD (GRASP-01-001)	**NCT03981289 Active, not recruiting**	**Virginia Commonwealth University Richmond, VA** 8 additional sites in the U.S. and 2 in the UK	**LGMD R1/2A, R2/2B, R3/2D, R4/2E, R5/2C, R6/2F, R12/2L, and D1/1D**
Jain Clinical Outcome Study of Dysferlinopathy (COS1 and COS2)	**NCT01676077 Active, not recruiting**	**University of Newcastle Upon Tyne, Newcastle, UK** 6 sites in the U.S., 3 sites in Spain, and 1 each in Chile, Denmark, France, Italy, Japan, and South Korea	**LGMD R2/2B**
Trial Readiness and Endpoint Assessment in LGMD R1 (GRASP-01-003)	**NCT05618080 Active, recruiting**	**Virginia Commonwealth University Richmond, VA** 9 additional sites in the U.S., 1 in the Netherlands and 1 in the UK	**LGMD R1/2A**
Biomarker Development in LGMD2i (MLB-01-001)	**NCT04202627 Completed**	**Virginia Commonwealth University Richmond, VA** 9 additional sites in the U.S. and 1 in Denmark	**LGMD R9/2i**
Prospective, Longitudinal Study of the Natural History and Functional Status of Patients with LGMD2i	**NCT03842878 Active, not recruiting**	**Copenhagen Neuromuscular Center at the National Hospital, Rigshospitalet Copenhagen, Denmark** 1 site in France and 1 site in the UK	**LGMD R9/2i**
JOURNEY: A Global, Multicenter, Longitudinal Study of the Natural History of Subjects with LGMD	**NCT04475926 Active, recruiting**	**No lead site specified** 11 sites in the U.S, 3 in Belgium, 1 in Brazil, 1 in Canada, 2 in Germany, 3 in Italy, 1 in Spain, 1 in Sweden, 1 in Turkey, 2 in the UK	**LGMD R1/2A, R2/2B, R3/2D, R4/2E, and R5/2C**

Not a complete list; for more information we recommend you contact your neuromuscular specialist or the advocacy group representing your subtype.

Right: The very first participant in the GRASP 3 study, **Brooklyn Garza**, about to receive an MRI evaluation. MRIs are often used in LGMD natural history studies.

Uses of Natural History Study Data

Source of Clinical Endpoints and Surrogate Endpoints

As described in the last two issues of *LGMD News*, natural history studies are often used to collect and test biomarkers that serve as surrogate endpoints for Accelerated Approval and also to validate clinical outcome assessments for use as clinical endpoints to support full drug approval. For example, the North Star Assessment of Limb Girdle Type Muscular Dystrophies, or NSAD, was developed and validated as a clinical endpoint for LGMD R2/2B therapies in the COS1 and later for use more broadly across LGMDs in a number of other studies.[6]

Improved Healthcare

Natural history studies can help improve patient healthcare by improving understanding of the impacts of diseases on patients. In a study conducted in France on patients with LGMD R5/2C and LGMD R3/2D, results showed that while both diseases caused impaired respiratory function and cardiomyopathy, respiratory failure caused loss of life more often than heart failure. That study has led to recommendations on increased monitoring and testing.[7]

Gateway to Meaningful Research

Some diseases are so rare that they are not covered thoroughly in medical literature and therefore are not easily researched. Together with genetic testing programs and patient registries, natural history studies are putting rare diseases on the map. By understanding age of onset, primary symptoms, biomarkers, and disease progression, clinicians can launch broader research programs, pursue more ambitious natural history studies, and design protocols for drug trials.

Establishing Correlations

To support full FDA approval of a drug, clinical trial results must show that the drug will prolong life, improve function, or improve the way a patient feels. It is not enough to know that the absence of a protein in muscle is due to mutations in a gene, or that muscle is replaced by fat over time in patients who lack the protein. Unless clinicians can link the lack of a protein or change in muscle to the onset and progression of disease symptoms, the FDA will not accept those biomarkers as endpoints for the approval of a drug. Natural history studies help to make those connections.

For example, COS1 showed a correlation between infiltration of fat in muscle of LGMD R2/2B patients and a decline in their functional abilities by comparing MRI results with changes in NSAD scores.[8] The study also showed a correlation between clinician-observed functional measurements and patient-reported outcomes. The responses to the questionnaire "Activity Limitations for Patients with Upper or Lower Limb Impairments," or ACTIVLIM, closely tracked loss of function shown in

Unless clinicians can link the lack of a protein or change in muscle to the onset and progression of disease symptoms, the FDA will not accept those biomarkers as endpoints for the approval of a drug.

NSAD. Such correlations further prove the reliability of all applicable measurements. Also, having a variety of assessments to choose from helps maintain study budgets, as some, such as MRI, are more costly to administer and interpret than others.

LGMD natural history studies have also shown that symptom onset at a younger age is associated with more rapid decline[9] and that the steepest functional decline occurs during the first several years after symptom onset.[10] Knowing these connections helps drug sponsors recruit trial participants whose progression rate will most clearly establish efficacy during a relatively short period of time, and also helps them compare patients with similar progression rates.

Another link that LGMD natural history studies seek to establish are so-called "phenotype-genotype" correlations, meaning whether certain gene mutations within the same subtype cause milder or more severe symptoms. So far, establishing such correlations broadly has been elusive — they seem to apply to certain subtypes but not others. For example, it has been found through natural history studies of LGMD R9/2i that people with two copies of the common FKRP L276I mutation tend to have slower progression than people with one copy of a different mutation. In contrast, in LGMD R2/2B, most dysferlin mutations appear to impact symptoms similarly.

E Pluribis Unum and Helping Rare within Rare

While we often speak with one voice, LGMD is a collection of many separate genetic disorders. So far, we have focused mostly on natural history studies that track and analyze patients with the same LGMD subtype. But studies can also focus on similarities among different LGMD subtypes. For example, the study "Defining Clinical Endpoints in LGMD (GRASP-01-001)" is being conducted at multiple sites throughout the world by the GRASP LGMD consortium. Led by Dr. Nicholas Johnson at Virginia Commonwealth University, the study tracks, both individually and collectively, the subtypes that have the highest prevalence in the U.S. or are nearest clinical development: LGMD R1/2A, LGMD R2/2B, LGMD R12/2L, LGMD R3/2D, LGMD R4/2E, LGMD R5/2C and LGMD R9/2i.[11] The study's goal is "to evaluate the utility of a set of outcome measures on a wide range of LGMD phenotypes and ability levels to determine if it would be possible to use similar outcomes between individuals with different phenotypes." Validating LGMD-wide clinical endpoints could streamline drug trial designs for all of us. For more information about the GRASP LGMD consortium and its studies, please see Page 17.

Some LGMD subtypes are so rare that they have not yet been included in any natural history study. Fortunately, Dr. Johnson has started to include patients with very rare subtypes as part of a basket protocol in the GRASP study. The data collected on such individuals can be used broadly in the study to support the establishment of LGMD-wide clinical endpoints. But it can also be used to benefit each participant individually as an external control specific to them in future drug trials.

Left: Dr. Nicholas Johnson, Director of the GRASP site at VCU, with **Sammy Brazzo**, a participant in a natural history study.

Use as External Controls

The gold standard for clinical trial design is to have one group of participants receive the study drug and another, the "control group," receive an inactive substance, or placebo. Neither the participants nor those involved in evaluating outcome measures know who is in which group during the trial. Such trials are referred to as "double-blinded, placebo controlled" studies and are intended to eliminate bias from the study personnel as well as the participants.

However, the use of placebo control groups is challenging in LGMD trials. Recruiting enough trial participants from small patient populations is daunting, especially when such participants must have similar ages of onset and rates of progression whether receiving the drug or the placebo. Also, the progressive nature of LGMDs and the duration of trials means that enrollees in the control group can experience continued decline in function over the course of the trial. For gene therapy trials, members of the control group (who are often eligible for the drug in a subsequent extension arm) may also become exposed to the virus used for delivery of the transgene, precluding their being treated.

Fortunately, data collected from natural history studies can help address these issues. In drug trials with a placebo control, the historical data of all participants could be used to ensure that the placebo control group would be a good match with the group receiving the drug. Alternatively, use of an "external" or "historical" control group could replace the placebo control within the study entirely. The external control group would typically be individuals selected from the natural history study who are matched in age, progression, and other parameters to the trial participants. This approach minimizes recruitment challenges since a control group doesn't need to be recruited, and also avoids the ethical issues of control group enrollees continuing to progress and potentially developing immunity to the viral vector. Of course, for these uses of natural history data, the same outcome measures used in the drug trial must also have been evaluated in the natural history study in a consistent manner.

Joshua Thayer is the General Counsel of the Jain Foundation. Before that, Josh worked in private practice representing organizations involved in drug development, including biotech and pharma companies, as well as universities, hospitals, and academic research institutions. He lives with dysferlinopathy (LGMD R2/2B).

Concluding Thoughts

More than in any other industry, the consumers of rare disease drugs are active participants in the research and development of the commercial products.

We present our journeys at medical schools, hospitals, research labs, companies, and regulators, all in an effort to spread the word to stakeholders. We donate samples of blood, muscles, skin cells, etc. for study after study. We agree to take experimental, unproven drugs in clinical trials despite the potential risks. And, as noted in this article, we participate in natural history studies that often require a long-term commitment, numerous exhausting visits to distant locations, and various struggles with travel as disabled people.

What I hear from my fellow rare disease patients and their families is that they are happy to do all of this, so long as our academic, industry, and regulatory partners treat us as valued collaborators and put the fruits of our labor to good use. I call on our partners to use the lab samples and clinical assessment data we donate as extensively as possible, and I urge my fellow patients to join in that call. ■

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For additional program information and a list of approved centers, please visit: **TheSpeakFoundation.com/grant-programs**.

Muscular Dystrophy UK
at the RHS Chelsea Flower Show

In May 2024, Muscular Dystrophy UK displayed a Show Garden at the internationally renowned Royal Horticultural Society (RHS) Chelsea Flower Show in London. With more than 160,000 people visiting the show over five days, and many more watching television coverage, taking part in this hugely popular, annual garden design competition enabled Muscular Dystrophy UK to engage with people who may have never heard of muscular dystrophy, give the community a voice, and raise awareness. This opportunity also encouraged future support of Muscular Dystrophy UK — the leading charity for more than 110,000 people in the UK living with one of more than 60 muscle-wasting and weakening conditions, including all forms of LGMD.

Below: London-based designer Ula Maria

Above: Martin Hywood's story inspired Ula to create an accessible, sanctuary-like environment for LGMD patients and their familes.

Forest Bathing Garden

Funded by Project Giving Back, a grant-giving organization, the garden was designed by London-based designer Ula Maria and inspired by the Japanese practice of *Shinrin-yoku*, which translates as "forest bathing"— a modern practice with ancient roots. This therapeutic activity involves spending time in the forest absorbing your surroundings with intention and reconnecting to nature using all of the five senses.

Ula's design was influenced by the personal experiences and stories she had heard from the Muscular Dystrophy UK community, particularly a man named Martin Hywood. Martin, now 50, was diagnosed with limb-girdle muscular dystrophy while in his 20s. He shared with Ula how scared and isolated he felt after his diagnosis, and how the only place he felt at peace was being immersed in nature. On hearing Martin's story, Ula wanted to create an accessible outdoor space providing a safe, sanctuary-like environment to support patients and their families during their most challenging times, including their initial diagnosis and into the future.

After having been viewed by the judges and visited by many thousands of members of the public, the forest bathing garden exhibit received two of the Flower Show's most prestigious awards — a Gold medal and Best Show Garden.

The Garden featured a flint wall with a pattern reminiscent of muscle cells, 50 birch trees to create an immersive birch grove atmosphere, and reclaimed smooth clay paving stones to ensure accessibility for wheelchair users. After the show, the entire garden was transported to Scotland, where it will be replanted at The Prince and Princess of Wales Hospice in Glasgow, continuing to offer a tranquil and healing space for patients and families to benefit from for years to come. ■

Written by Mandi Hirsch
Muscular Dystrophy UK

Photography by Rebekah Kennington

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

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- Information on the clinical trial can be found on clinicaltrials.gov.

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