Vol 5 / Issue 1

LGMD News

Uniting the Limb-Girdle Muscular Dystrophy Community

A Plea for Change

Bringing Care to Those Who Live with LGMD

BECOMING ONE VOICE FOR CHANGE
LGMD Day on the Hill 2024

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CURE HSPB8
When Muscles Fail: The Story Behind Cure HSPB8

DRUG DISCOVERY, DEVELOPMENT, AND COMMERCIALIZATION
Meet the Primary Players

ML BIO SOLUTIONS
Q&A with Douglas Sproule, MD, MSc

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 (aged 18 to 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, scan the QR code or go to https://clinicaltrials.gov/study/NCT05230459

AskBio™

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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.

Contents

Departments

Vol. 4 / Issue 4 Corrections

- In the last issue, the Ask the Expert column incorrectly stated that there are "current clinical programs in gene transfer therapy for LGMD R1/2A." The programs are in the preclinical stage (being tested in animals).
- In the previous article on Natural History Studies, the LGMD subtypes listed for the JOURNEY study included LGMD R2/2B in the subtype listing—it should include LGMD R1/2A instead of R2/2B.

Feature Articles

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We Need Champions Who Care About the Real Needs of Our Community

We are pleased to announce that this issue is dedicated to our community who are facing the growing caregiving crisis in the United States. The stories in this issue highlight some of the lived experiences of those with LGMDs. As we face this crisis, we want to find champions of this cause around our country and the world. We cannot continue to live in a situation where families are without the at-home care they desperately need.

The 2025 International LGMD Conference will highlight many sessions that focus on improving the quality of our lives. Be sure to register, purchase your tickets, and book your hotel room soon, as our Orlando conference features a family-friendly format in 2025, which will allow more time to enjoy connecting with others in addition to our incredible lineup of sessions. For more information, visit **InternationalLGMDConference.com**. ▪

Kat Bryant Knudson

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

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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**

John Vissing, MD, DMSci

University of Copenhagen, Denmark

Meet the Expert

John Vissing, MD, DMSci is Professor of Neurology at the University of Copenhagen, Denmark, and the Director of the Copenhagen Neuromuscular Center at the National Hospital, Rigshospitalet, in Copenhagen, Denmark, since 1998. His research focuses on hereditary muscle diseases and myasthenia gravis. He has authored more than 500 scientific papers on neuromuscular diseases. He has had a longstanding clinical and research interest in LGMD. Studies have involved natural history studies, discovering new types of LGMD, characterization of muscle involvement by MRI, exercise training studies, including defining exercise injury markers, development of outcome measures in LGMD to be used for follow-up and therapies, and currently ribitol and gene therapy trials in LGMD R9.

Q

I am 27 years old and diagnosed with LGMD R5/2C since the age of 7. I have been using various supplements, including L-carnitine, L-arginine, Q10, and EAA, and feel I have noticed benefits. Why do many doctors consider these supplements ineffective, despite some reporting positive experiences?

A

With no disease-specific therapies available for a disease, it is a normal reaction to look for alternatives. The market for such "alternatives" is huge, even for otherwise healthy people who want to improve health and appearance. The internet is booming with such products, and you can find information about almost all products telling you that they are efficacious. This billion-dollar market is completely deregulated and exempt from normal quality control and approval from authorities, meaning you do not know what you are buying. The bottom line is that such supplements rarely help, and in some cases, may even cause harmful side effects. It's recommended to adopt a balanced diet, as it is for healthy people. But there is no evidence that supplements, including those mentioned in the question, provide any benefit.

Q

Thank you for your past research into whether some truncating variants in titin can lead to both cardiomyopathy and skeletal muscle disease (e.g., in your 2024 publication, "Skeletal Muscle Involvement in Patients with Truncations of Titin and Familial Dilated Cardiomyopathy"). Do you think heart health problems are a risk factor for people with LGMD R10 titin-related muscle disease?

A

People with titin-related muscle disease are potentially at risk of heart involvement and should always be screened for this. The trouble with titin is that it is one of the biggest proteins in the human body, and it is spliced differently in different tissues. This means that variable forms of the protein are expressed in different tissues and mutations may affect these forms in different ways. Depending on the mutation, only versions of titin expressed in skeletal muscle may be affected, or versions in both cardiac and skeletal muscle. We still don't know exactly which forms result in heart involvement, but it frequently happens with truncated forms of the protein such as those studied in the paper you refer to, so cardiac screening is important for all patients with titinopathy.

Q

What would be the advantage of having a muscle biopsy done if a muscle MRI is normal?

A

With the advent of improved genetic techniques, a muscle biopsy is rarely needed for diagnosis of a suspected hereditary muscle disease. If genetic testing is unavailable, or if a non-genetic cause is suspected, a muscle biopsy can be used to show characteristic findings in the microscope, including presence or absence of proteins and sugars on the muscle cell surface, which can help with diagnosis. Proteins from the biopsy can also be analyzed biochemically. For research purposes, a muscle biopsy can be very important, to show changes in the affected protein when disease-specific therapy, such as gene therapy, is given.

Q

Is it normal to be in pain? I am curious whether there are new developments to combat pain associated with LGMDs. A lot of medication has been tried, also physical/physiotherapy; however, the pain is sometimes unbearable. In the Netherlands, they have not yet found any means to help me with this. What are your thoughts as far as treatment for pain?

A

Pain is more frequent in people with muscular dystrophy, including LGMD, compared to the general population. There might be several reasons for this. First, weakness may result in overextension of joints when used, such as overextension of the knee when in the stand phase of walking when the quadriceps muscle is very weak as in LGMD. Muscles may also be susceptible to more pain because of the altered tissue composition and secondary inflammatory changes in muscle. Other causes can be attributed less to the use of the muscle and, instead, to anxiety or depression — all factors that decrease the threshold for pain sensation. Obviously, the above causes can to some extent be counteracted by addressing overextension by using splints, being more active, or addressing psychological problems. Analgesic medical treatment follows the same principles as in the general population. There are no special drugs for pain specific to people with neuromuscular diseases.

Q

My son is 22 years old, and we are wondering if gene therapy is going to be available for LGMD R1/2A in the near future.

A

There is still no gene therapy available for persons with LGMD R1. Preclinical studies have been carried out in animals and in human cells of individuals with LGMD R1 using CRISPR-Cas9 technology, showing promising results. Phase I gene therapy trials in people with LGMD R1 are planned in the U.S. and France, but the exact timing of when the trials will start is unknown, as are the clinical and laboratory criteria people must meet to participate. To stay informed about future developments, you can join a patient registry for your subtype and check **ClinicalTrials.gov**.

Pain is more frequent in people with muscular dystrophy, including LGMD, compared to the general population.

Have a Question for Our Experts?

Send Questions To:
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ClinicalTrials.gov

Featured Resource

John Vissing's Clinical Trial:
ClinicalTrials.gov/study/NCT05180188

Question

The good thing about skeletal muscle is that mature cells don't divide, unlike many of our other cells in the body (for instance, blood, intestine, and skin cells). Most gene therapies provide the missing gene as an episome in the nucleus of the cell, i.e., in an extra piece of DNA in the nucleus that is not incorporated into the chromosomes.

Q

Muscle cells are gradually replaced by new ones derived from satellite cells. Does this mean that, after gene therapy, the new cells that replace the old ones won't be corrected? Would there be a need for re-injection after a certain time?

A

It is valid to ask whether gene therapies can have a sustained effect throughout life. The good thing about skeletal muscle is that mature cells don't divide, unlike many of our other cells in the body (for instance, blood, intestine, and skin cells). Most gene therapies provide the missing gene as an episome in the nucleus of the cell, i.e., in an extra piece of DNA in the nucleus that is not incorporated into the chromosomes. We don't know if these episomes can be retained indefinitely—gene therapy for muscular dystrophies is so new that we don't know what recipients' long-term experience will be. Also, some gene therapies do not transduce the stem cells on the surface of the muscle (the satellite cells), and as the satellite cells divide to join the muscle fiber, this may "dilute" the corrective gene. In general, concern about dilution of gene therapy is more pertinent to growing children than adults. So, retreatment might be necessary in some patients. The trouble with this is that once treated, the person is immunized against the AAV virus used to deliver the gene. In such cases, a different transport particle (another virus type or different way of packaging the gene, such as a lipid vesicle) would have to be used. Retreatment hasn't been implemented yet for any gene therapy.

Q

I have LGMD R9/2i, and I am wondering about any progress in clinical trials and drug development for my subtype. What phase are these in now? Are any drugs proving to be effective and what are the side effects?

A

There are quite a few interesting developments ongoing for LGMD R9. One treatment option under study is gene therapy, in which a correct copy of the FKRP gene is delivered using a viral vector. Two such studies are ongoing in phase 1 (first human trials), one in the U.S. and one in Europe. The one in Europe is now fully enrolled, while the American one is still enrolling. Side effects have so far been acceptable and mostly related to the immunosuppression needed in the first months after dosing, and a temporary liver reaction to the high viral load. Efficacy is still not known, as such early-stage experiments are mainly aimed at proving safety and finding the correct dose. Larger studies will likely begin in 2025. Another clinical trial studies the use of ribitol, to improve glycosylation in spite of FKRP mutations. A derivative of ribitol is the sugar that FKRP sticks on to alpha-dystroglycan, so the study patients are taking ribitol orally in relatively large amounts. This is now under investigation in a large phase 3 study, which is fully enrolled. The study is double-blinded, meaning some patients are taking a placebo, so study results are not yet known, and it will be more than a year before we will know anything. Importantly, all these disease-specific treatments are not a cure. They will, if fully

effective, halt disease progression, but not produce new muscle tissue to replace lost muscle. The treatment goal is, therefore, primarily stabilization of the condition.

Q

I have LGMD R12/2L and have experienced a steady decrease in leg and ankle muscle function over several years. I can still walk with a cane or by "furniture surfing" in the house, but ankle weakness means that I have to concentrate on placement of almost every step. It has been suggested that I get an AFO (ankle foot orthosis) for ankle stability, but I'm wondering if relying on a device will speed up the loss of muscle function. A related question is how much exercise is too much? Is it better to do moderate weight training for whatever muscle I have left, or should I just rely on day-to-day activities to keep muscles active and preserve them as long as possible?

A

Exercise is important for maintaining muscle, and immobility will speed up muscle wasting in muscular dystrophies. A recent study showed that even high-intensity exercise produced little muscle damage in individuals with LGMD R12. However, safety is the highest priority, and if muscle weakness limits mobility or poses a safety issue, then one should consider assistive devices, such as AFOs. In principle, people with muscle diseases can exercise at an intensity appropriate to their muscle strength; in practical terms that means working at a lower absolute intensity. Warnings that exercise intensity may be too high include an elevated CK level and increased muscle pain the day following exercise. It is also important to be on the lookout for rhabdomyolysis and to maintain adequate hydration during and after exercise. It would be best if all patients consult their neurologist and/or physical therapist about recommended exercise levels prior to starting an exercise program. Both strength and endurance training are beneficial and can likely be combined. If you choose just one, go for endurance training as it seems to have the most benefit.

Q

What is the status of your clinical trial, "Moderate Intensity Training in Patients with Truncating Genetic Variants in TTN"?

A

The study is complete and has recently been published (Flensted IF, Stemmerik MG, Skriver SV, Axelsen KH, Christensen AH, Lundby C, Bundgaard H, Vissing J, Vissing CR. Exercise training improves cardiovascular fitness in dilated cardiomyopathy caused by truncating titin variants. Heart 2024 Sep 24:heartjnl-2024-323995. doi: 10.1136/heartjnl-2024-323995.). Exercise was found to improve fitness and was associated with increased blood volume and oxygen-carrying capacity, and improved function of the heart's left ventricle (the chamber that pumps blood out to the body). ▪

A recent study showed that even high-intensity exercise produced little muscle damage in individuals with LGMD R12. However, safety is the highest priority, and if muscle weakness limits mobility or poses a safety issue, then one should consider assistive devices, such as AFOs. In principle, people with muscle diseases can exercise at an intensity appropriate to their muscle strength; in practical terms that means working at a lower absolute intensity.

Written By Todd King with Ania Kordala, PhD

When Muscles Fail:

The Story Behind Cure HSPB8

Right: Todd King, 1988, A.P. All-State; North All-Star; Academic Team Offensive Lineman

I grew up playing sports—I was always very strong. Even after college I remained athletically inclined—I could still run a 5:20 mile and bench 225 lbs into my early thirties. So, after being strong my whole life, it was especially jarring to be diagnosed with a mysterious myopathy in my late thirties.

For those of you with an adult-onset disorder, tell me if this sounds familiar…

I grew up playing sports—I was always very strong. Even after college I remained athletically inclined—I could still run a 5:20 mile and bench 225 lbs into my early thirties. So, after being strong my whole life, it was especially jarring to be diagnosed with a mysterious myopathy in my late thirties.

I shouldn't have been surprised, as my uncle and others in the extended family had some unknown muscle-wasting condition. But I figured that since I was athletic, I must have been spared. I figured wrong.

So, I reached out to dozens of academic researchers, doctors, and genetic counselors, trying to find *someone* who would work with me to figure out what this condition was. After *seven years* of searching, in 2015, I finally found a researcher, Dr. Virginia Kimonis of UC Irvine, who agreed to work with me. A little more than a year later, we found the mutation in the HSPB8 gene that was causing my symptoms. What a momentous event for our family! I simply can't overstate how much that discovery meant to us.

Since then, I've continued working with the Kimonis Lab and other researchers to study the condition and look for a treatment. In the meantime, my health has declined substantially. The list of maladies is lengthy and includes constant hip pain, leg muscle weakness, and decreased breathing capacity, among other issues that many of you also live with. As you would expect, this has caused a dramatic drop-off in quality of life for me and my family. Over time, I've become increasingly reliant on family, especially my wife, to serve as caregivers. This disease has impacted all of us.

Cure HSPB8—A Patient Advocacy Organization

In late 2023, I was considering starting a patient advocacy group (PAG) but needed someone with a scientific background to take the lead. That's when a mutual contact introduced me to Dr. Ania Kordala, a brilliant, driven Ph.D. in Physiology, Anatomy, and Genetics at Oxford University. Dr. Kordala has an

> **The mission of Cure HSPB8 is to improve the lives of people with HSPB8 Myopathy and their families. Our ultimate vision is a life free from HSPB8 Myopathy and all its burdens.**
>
> **—Todd King**

interest in grassroots movements in rare disease research and patient advocacy. We soon began working together, with Dr. Kordala agreeing to jointly found Cure HSPB8, which is the only patient advocacy organization for HSPB8 Myopathy. Cure HSPB8 is a charitable project of Social and Environmental Entrepreneurs, a 501(c)(3) organization, and a professional fiscal sponsor.

A brief aside—if you're not familiar with how Fiscal Sponsorship works in the United States, it's worth investigating if you are considering a patient advocacy organization of your own; we think it's ideal for a small grassroots initiative that doesn't have the capacity to set up a 501(c)(3) charity itself, in addition to providing other benefits.

Mission

The mission of Cure HSPB8 is to improve the lives of people with HSPB8 Myopathy and their families. Our ultimate vision is a life free from HSPB8 Myopathy and all its burdens.

Our work is grounded in research and development. We're dedicated to finding a treatment—and ultimately a cure for HSPB8 Myopathy. As part of our research toolkit, we're developing iPSCs (induced pluripotent stem cells) from patients and healthy controls, along with a mouse model (mice with the same disease-causing genetic trait). We've also launched a Global Patient Registry in collaboration with Coordination of Rare Diseases at Sanford (CoRDS), available in English and Japanese, to gather data that is essential to

Above: Dr. Ania Kordala and Todd King at 2024 MDA Clinical & Scientific Conference, Orlando, FL.

advance research. To support treatment development, we're establishing reliable methods to measure autophagic flux from blood, aiming for a biomarker of treatment response. Moreover, we advocate for the inclusion of HSPB8 in myopathy genetic panels to ensure more widespread testing.

Cure HSPB8 also hosts research meetings, bringing together world-class HSPB8 experts. In addition, we connect with patients and their families, building a supportive community that understands living with HSPB8 Myopathy.

Think You Might Have HSPB8 Myopathy?

If you think you or a loved one might have this condition, genetic testing is the only way to receive confirmation. You can request specific sequencing of the HSPB8 gene or undergo Whole Exome Sequencing (WES) to help diagnose the condition. For more information on genetic testing options and resources, please visit **CureHSPB8.org**.

Already Diagnosed with HSPB8 Myopathy?

We encourage you to register in our Global Patient Registry. Also, be sure to connect with us via **CureHSPB8.org**! Every patient contributes valuable insights that move us one step closer to finding a treatment.

Stay up to date with the latest developments and ways to get involved by signing up for our mailing list on our website or by following us on social media: Facebook, LinkedIn, and X. Together, we can bring hope and support to all those affected by HSPB8 Myopathy. ▪

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Ania@CureHSPB8.org
CureHSPB8.org
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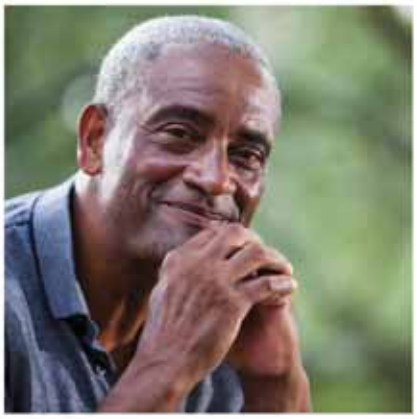
We welcome individuals with LGMD2A/R1 to join our journey

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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SAREPTA THERAPEUTICS

Birth of a Research Consortium

Above (L to R): Nicholas Johnson, MD, MSci, FAAN, Chris Weihl, MD, PhD, Jeffrey M. Statland, MD, Erin DeSpain, and Matthew Wicklund, MD

As a community of persons living with LGMD and researchers invested in ameliorating the burden of LGMD, we have come a very long way over the past 25 years.

In Spring 2018, Nicholas Johnson, then at the University of Utah, invited Chris Weihl (Washington University, St. Louis), Jeff Statland (University of Kansas), Erin DeSpain (University of Utah), and myself (University of Colorado) to Deer Valley, Utah, for a grant writing retreat. The intent was to apply for, and be awarded, a Rare Disease Clinical Research Network (RDCRN) grant from the National Institutes of Health (NIH) to establish a research consortium for limb-girdle muscular dystrophies. We spent four solid days from April 8-11, 2018, writing and writing and writing (actually, Nick, Jeff, and Chris did nearly all the writing, as grant writing is not my forté). Although the submitted grant was not awarded funding in 2018, those four days were not wasted. On the drive back from Deer Valley, Chris Weihl spent 30-40 minutes deep in thought until he blurted out his idea for the name of a new group: 'Genetic Resolution and Assessments Solving Phenotypes in LGMD,' with the catchy acronym of GRASP-LGMD. And thus, a research consortium was born. We were five institutions spread across the United States from west to east: University of California at Irvine, University of Utah, University of Colorado, Kansas University, and Washington University in St. Louis.

It is noteworthy that we were not the first LGMD research consortium. In the 1990s, a research consortium involving the University of Iowa, The Ohio State University, Washington University in St. Louis, Vanderbilt University, University of Pennsylvania, and University of Rochester evaluated 370 persons with limb-girdle weakness. They published the first description of a large cohort of persons in the United States living with LGMD.[1] At that time, only nine LGMD genes were known, diagnosis was by muscle biopsy in 162 patients, and in only 83 patients was a genetic diagnosis possible.

As a community of persons living with LGMD and researchers invested in ameliorating the burden of LGMD, we have come a very long way over the past 25 years. We certainly understand the LGMDs much better, and various therapeutics (gene replacement, small molecules, substrate augmentation, and others) are currently being investigated at the stage of human trials, with some treatments showing promise for approval for specific types in the near future. With more than 18 clinical research sites now spread across four continents, the GRASP-LGMD research consortium continues to assess phenotypes, resolve genetic uncertainty, understand disease mechanisms, and strive for disease-impactful interventions and therapeutics.

Please also make sure that if you have a genetic diagnosis, you join the patient registry for your type, as together we work toward future cures. ■

Reference

1. Moore SA, et. al. Limb-Girdle Muscular Dystrophy in the United States. *J Neuropathol Exp Neurol*, 2006; 65:995-1003.

Written by Matthew Wicklund, MD
Professor of Neurology and Vice Chair for Research, UT Health San Antonio in Texas

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ClinicalTrials.gov

UPDATED: JANUARY 1, 2025

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)

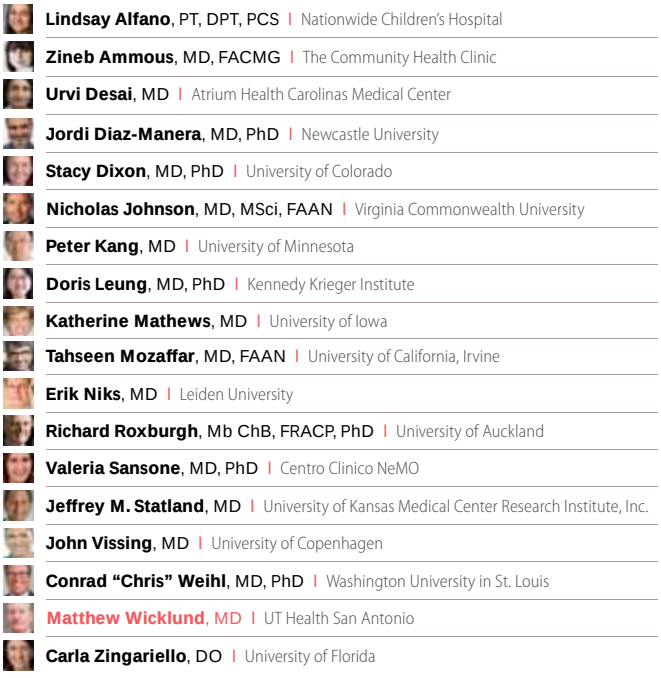
Exclusion Criteria

- 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

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

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

GRASP-LGMD Consortium Members



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- **Zineb Ammous**, MD, FACMG | The Community Health Clinic
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- **Matthew Wicklund**, MD | UT Health San Antonio
- **Carla Zingariello**, DO | University of Florida

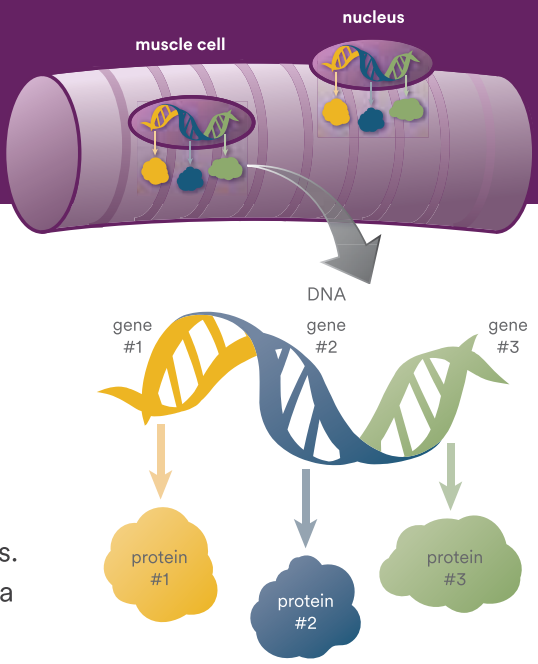
Spotlight:
Dr. Matthew Wicklund
UT Health San Antonio

Dr. Matthew Wicklund is Professor of Neurology and Vice Chair for Research at UT Health San Antonio in Texas. He completed his undergraduate and medical degrees in Colorado, his internship at Dartmouth, his neurology residency in the United States Air Force, and his neuromuscular fellowship at The Ohio State University. His major research interest involves genetic muscle diseases. Dr. Wicklund is author or co-author of more than 140 published articles, chapters and abstracts, and lectures at national meetings. He has been involved in clinical care and research involving patients with neuromuscular disorders, with an emphasis on genetic and acquired muscle disorders. He is currently the primary investigator or site investigator on clinical trials related to the limb girdle, facioscapulohumeral, myotonic, and Duchenne muscular dystrophies. Dr. Wicklund is director of the Muscular Dystrophy Care Center and has extensive experience providing multidisciplinary care to neuromuscular patients.

What is the goal of gene therapy?

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

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



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

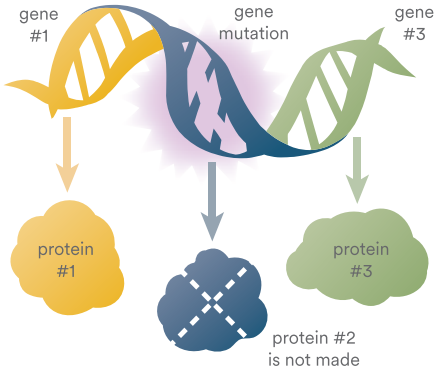
"DNA at Work"

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

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

Genetic Disease

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

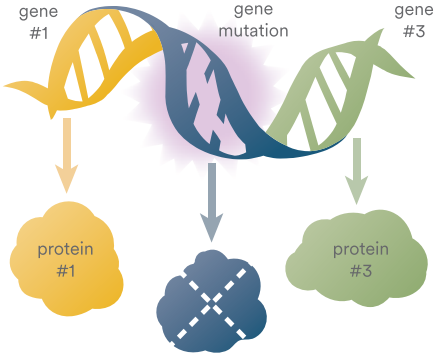


So, how does gene therapy aim to slow or stop progression of a disease?

After Gene Therapy

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

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



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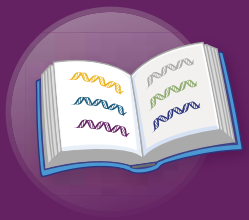
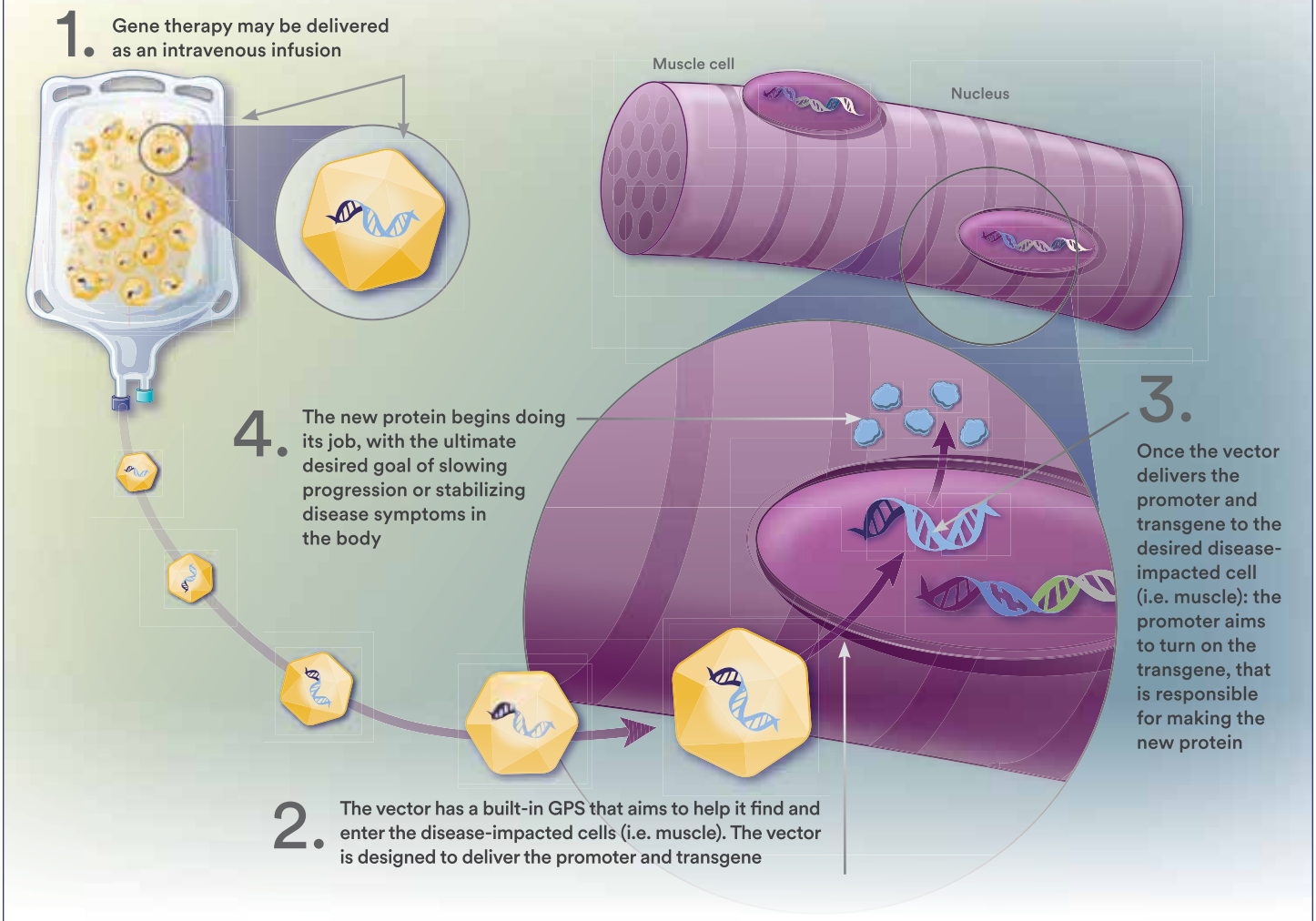
How does gene therapy work?

SAREPTA THERAPEUTICS



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

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



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

In 2023, Sarepta published a four-part educational series on the science of gene therapy. To access the series, including quizzes to test your knowledge, scan the QR code

Written By Kathryn Bryant Knudson, Bliss Welch, Anne Brastow, Rania Maali, and Victoria Nedza

Bringing Care to those who live with LGMD

This issue focuses on the current crisis of at-home care in the United States LGMD community. Those of us living with neuromuscular conditions requiring assistance with activities of daily living (ADLs) are in a precarious position.

Skyrocketing costs over the last two years have created an untenable scenario in which care at home has become unaffordable for most. The lack of caregivers and certified nursing assistants (CNAs) has only exacerbated the issue. Additionally, many service providers now require a minimum of 4 hours daily for a CNA to provide at-home care. The average cost of 4 hours of care is now $120 per day or $3,720 a month. In many cases, parents and spouses end up in the caregiver role because CNA or caregiving services are not affordable. Team Joseph, an advocacy organization for Duchenne Muscular Dystrophy, recently published a paper on this very topic as well. It is a huge, systemic crisis in the neuromuscular disease community. To see the overall trend for costs of care, visit **Nationaldisabilityinstitute.org/wp-content/uploads/2020/10/extra-costs-living-with-disability-brief.pdf**.

When advocating about the long-term needs of the LGMD community, we must be clear in explaining that many young people begin to need assistance with ADLs, such as bathing, dressing, feeding, and toileting starting in their twenties, and that this need continues into later life. This reality is not being discussed, as there is a widespread assumption that assistance with ADLs is only needed by elderly people. We must emphasize our overwhelming need now so that our voices can be heard, and needed changes can be effected. Of course, these needs are shared by those with other forms of disability too, so advocating for our community benefits others as well.

What has been done to address these problems? Medicaid waiver programs (or home and community-based waivers) in the United States allow individuals with disabilities and chronic conditions to receive care in their homes and communities rather than being placed in long-term care facilities, hospitals, or intermediate care facilities. Unfortunately, many states have a lack of waivers available, and each state has different policies.

> *We need champions who care about the real needs of our population. Moving forward, the Speak Foundation will survey the LGMD community to assess our needs and our desires for advocacy.*

Some state programs are less restrictive, allowing an individual with a disability to work for a certain number of hours and still qualify for services through what is called a buy-in program. The buy-in program makes caregiving services available to those who work and make over the Medicaid limit. We share a story in this issue from an individual who successfully advocated for the state of Tennessee to pass legislation for disabled workers. However, many states do not allow people with disabilities to have income beyond a certain amount and still qualify for home care. Essentially, this creates a scenario in which families are living in poverty to obtain or maintain at-home care.

Medicare, on the other hand, does not currently cover any long-term at-home caregiving services to help someone with ADLs. Consider the difficult scenario that so many in our LGMD community find themselves in, where they are required to either pay $120.00 a day for care at home or rely on family members to act as caregivers. This problem is, by far, one of the most challenging in our community, as a majority of individuals living with LGMD will be using the Medicare system for healthcare. Unless this problem is solved, the vast majority of individuals in our community will face a financial and caregiving crisis.

We have such a complicated system in the United States that it is very hard to even problem-solve. Many countries have adopted more generous programs to assist individuals with disabilities. At the same time, we have a huge disparate need in more developing countries where social programs are nonexistent.

We need champions who care about the real needs of our population. Moving forward, the Speak Foundation will survey the LGMD community to assess our needs and our desires for advocacy. We cannot allow the voice of the patient to be ignored or the issues we are facing to be overshadowed.

Where is the voice of the patient being shared through the lived experiences of disabled individuals? In this issue, you will hear from those living with LGMDs who are struggling in a dysfunctional system that fails to provide care to those who most desperately need it — care that would allow us to live full and rewarding lives. Please listen to our voices in this issue, and join us in becoming a champion for our cause.

Concerns of the LGMD Community: Assistance with ADLs

INTERNATIONAL READERS: **If you have your own story of barriers surrounding caregiving in your country that you'd like to share, send a brief email to: *Jessica@TheSpeakFoundation.com* highlighting your challenges. We hope to share more stories in the future.**

Bliss Welch

I was diagnosed with LGMD R2/2B (Dysferlinopathy) at the age of 18. The diagnosis came with more questions than answers because there was so much unknown about the dysferlin gene at the time.

As a scared teenager, I can clearly remember my biggest fear was becoming so weak that I wouldn't be able to take care of myself. Determined to control my future, I vowed to do everything within my power to remain as independent as possible for as long as possible. And over the course of the last two and a half decades, I have done just that. Staying ahead of my deteriorating muscles has required a lot of forethought, tons of gadgets and equipment, thinking outside of the box, trial and error, technology, and so many "new normals" with each stage of weakness. But inevitably the time came when all of that was no longer enough.

The realization that I was going to soon need assistance from a caregiver began around 2019. Transfers from my wheelchair to my bed, bath lift, and toilet were becoming significantly harder, more time consuming, and hazardous to my safety. The declining dexterity in my hands and arms was also affecting my ability to cook, dress, type, and write.

My doctor and I extensively discussed my physical decline, my need for a caregiver, and my ability to continue working. He did not know what supports and services were available, so I was referred to a NeuroRecovery specialist at a local rehabilitation hospital. After my clinical assessment, the specialist said that with my diagnosis and poor strength, I should have no problem being approved for Social Security Disability Insurance (SSDI). He was unsure how to receive coverage for a caregiver, so I was referred to a caseworker on staff at the rehabilitation hospital. While the caseworker was very nice, she was only able to tell me that private insurance would not cover a caregiver, but long-term disability insurance or Medicaid would cover a caregiver. I was already aware of this, as I had done my research.

I didn't want to stop working; my ability to work wasn't the issue. The issue was my ability to independently perform the ADLs needed to get ready for work. I needed a program that would pay for a caregiver. So even if I went on SSDI and stopped working, I would still need a caregiver, and SSDI doesn't cover the expense of a caregiver. This Catch-22 situation is sadly the case for many people living with disabilities.

I wasn't getting any stronger or any closer to a solution. Instead, I was being told, "There's just not a box you fit in." But the problem isn't me or my need for a caregiver, the problem is a broken, outdated system. Living with LGMD is challenging enough; accessing vital health services and supports shouldn't be equally challenging.

Bliss with State Senator Bo Watson

> *Living with LGMD is challenging enough; accessing vital health services and supports shouldn't be equally challenging.*

Bliss with State Representative Greg Vital

I have private insurance through my employer, but as I've pointed out, private insurance doesn't cover a caregiver. Medicaid covers long-term supports and services that are home and community based. This means Medicaid would cover the expense of a caregiver; however, I wouldn't qualify for Medicaid because, in Tennessee, your annual income must be below $19,392, and you can have no more than $2,000 in assets.

Luckily, in 46 states, there is another pathway to Medicaid coverage if you have a disability but don't meet the income and asset limits. If you are working, the program allows you to "buy in" to the Medicaid coverage. Essentially, you would pay a premium, and Medicaid would become your secondary health insurance. You would then have access to the unique supports and services, such as a caregiver, only provided through Medicaid coverage.

Unfortunately for me, my home state Tennessee is one of only four states that does not offer a "buy in" option for Medicaid coverage. For the past four years, I have been a small part of the advocacy efforts to change that. There have been many trips to Nashville for meetings with my state representatives to share my story and bring to light the need for a Medicaid buy-in program. This year, the "TennCare for Working Individuals with Disabilities Act" was drafted. The bill passed unanimously in the Tennessee House of Representatives and in the Senate.

Tennessee will be establishing their Medicaid buy-in program (TennCare for Working Individuals with Disabilities) over the next several months. If all goes according to plan, the program should be up and running by mid-year 2025. Look what advocacy for our needs can accomplish!

With monetary support from my family, I have been paying out of pocket for a full-time caregiver since 2021. Being able to buy into Medicaid coverage next year will lift a huge financial burden from my family. While I am grateful for Tennessee's new program, there are still vast improvements needed across the country concerning supports and services for individuals with disabilities. Now is the time to continue to advocate together as a community for these changes, so that those living with the prospect of increasing care needs can look to the future with a greater sense of assurance than fear.

Anne Brastow

I am a 63-year-old woman diagnosed with LGMD R1/2A. I've had symptoms since I was a toddler but was not formally diagnosed until adulthood. I've been using outside caregivers for about 25 years.

For 10 years before that, my husband had gradually been helping me as things became more physically difficult. It started with keeping me steady by holding my hand while walking. After a while, it evolved into helping me to get my nylons on for work or helping me to get up from a chair. Bit by bit, the help he provided increased. Then one day he needed emergency eye surgery. That's when I started using outside caregivers.

Bringing someone into our home was hard, but because it was an urgent situation, I didn't have time to dwell on it. I needed help repositioning at night, showering, and caring for our dog. Those first few caregivers struggled with a language barrier, sometimes canceled at the last minute, and weren't particularly fond of dogs! Quickly, I came to realize that it was important to know my needs and to communicate them well to my caregivers. Thankfully, the result of that experience is that I ended up with one caregiver who stayed with me for 22 years! She was an angel. She recently retired, and I feel like I've lost my right arm!

In 2020, my husband had another issue requiring surgery. I established a relationship with a new caregiving company to cover for the few days of his recovery. Unfortunately, he had complications and spent three weeks in the hospital and another four weeks in recovery. The company was great, and the 24/7 caregivers did a fantastic job. My sister-in-law was also able to help for a week. Even with that help, the cost was astronomical. We spent about $15,000 to care for me during that period.

At this point, I need help with all my ADLs, including getting out of bed, bathing, dressing, food prep, and getting back into bed. However, for a good part of the day, I am independent. I like to take dog training classes with my dogs and go to local parks where my husband and I can walk them. I seem to have a lot of medical appointments lately, so I need transportation and some assistance with those as well.

Outside of personal care, I also need to maintain my living environment. We have housekeepers to clean and help with laundry and dishes. There is yard maintenance, as well as maintenance of things like the furnace, appliances, and our accessible van. I've found it much easier to hire people to take care of these things, as those we hire are then consistent and reliable. The upkeep of the house is, of course, another expense, but only a fraction of what caregivers cost.

My current dilemma is that I need more caregiving help. I only have one person for 4 hours, 2 days per week, as the agency has been unable to fill another day of care since the last person left in early September.

> ***For the future, I'd like to see a feasible path where I can continue to be a part of the community and obtain affordable care at home. We need to be talking about this as a community and share ideas about how to address the gaps in our needed supports.***

My situation spotlights the frustration and difficulty present when what I need and what I am able to access are not in sync! In my area, the hourly charge for in-home care is $50-55 with a 4-6-hour minimum shift. Each caregiver arrives with little to no experience with Hoyer lifts or dressing assistance. "No shows" and last-minute cancelations are ordinary at this point, so we have grown accustomed to the constant changing of plans. The $200+/day to get me up, showered, dressed, and maybe the dishes taken care of is only a small part of my day. In order to live an independent life, I need more help!

My husband and I have completed our will and retirement planning. We are aware that we are approaching an age where things can go wrong, and life can drastically change at a moment's notice. I would like to see more support for the LGMD community as we progress in age and weakness. I don't have children or family members who are able to step in and help if my husband becomes incapacitated. Access to care is always on my mind, and it's what I worry about at 2:00 a.m. when I can't sleep! What will I do if he suddenly can't care for me? At this point, I fear my next step might have to be a nursing facility.

For the future, I'd like to see a feasible path where I can continue to be a part of the community and obtain affordable care at home. We need to be talking about this as a community and share ideas about how to address the gaps in our needed supports. Presently, I have more questions than answers. We've always saved for "retirement," but do we really know what that looks like and how it will all happen? With caregivers costing $200/shift, our savings will not last very long. Do I really need 24/7 care? How can I get care at the times I need without 24/7 care? Are there viable alternatives to nursing facilities, and, if so, what are they? As a community, we need answers to these questions. ■

Rania Maali

For those living with limb-girdle muscular dystrophy, the need for a caregiver is something most of us will face at some point in time, and some of us already deal with every day.

Whether it's a family member, friend, or a professional, having someone to help with basic tasks like getting out of bed, bathing, and preparing meals is a part of our lives. Without that help, many of us simply wouldn't be able to get by.

Our caregivers are often our parents. As a 38-year-old female living with LGMD R4/2E, I rely on my mom as my primary caregiver. She has been helping me with everything from getting out of bed to bathing to getting dressed for almost two decades. My dad helps too, driving me to and from work and helping me run errands. But here's the most difficult part: my parents are getting older. My mom is in her seventies, and the physical demands of caring for me are starting to take a toll on her body and health. It's hard to watch because I can see how much energy and stamina it requires of her. I know I'm not alone in this. Many of us in the U.S. LGMD community rely on aging parents for our care, and the reality is — it's not sustainable. The fear of what happens when our parents or family members can't take care of us anymore is something

> *The current system doesn't provide enough help, and it's time we start advocating for real change.*

that looms over us. When that day comes, who will step in? How will I get out of bed or feed myself? Will I be able to keep my job or continue living in my home? These are questions that keep us up at night. That's why we need to talk more about the help caregivers need. They're often working 24/7, giving up their own lives, and not getting much in return. In many cases in the U.S., family caregivers don't get paid, don't get breaks, and rarely get the support they need.

Being a caregiver for those living with LGMD, especially those with complex physical needs that require 100% total care, as I do, is a tough, isolating, and demanding job. So, what can we do? For starters, we need more programs that offer affordable, trained caregivers who can come in and help when our family members can't. It's not easy to think about relying on someone else outside of our family, but the truth is we're going to need that help as our parents age or become unable to continue caregiving. Having access to reliable, in-home care or personal assistants who understand LGMD is essential for our future. We also need to push for more respite care programs. Our caregivers need and deserve breaks. The emotional and physical toll of caregiving is huge, and without time to recharge, burnout is inevitable. Respite care gives our caregivers the chance to step away, even just for a little while, to take care of their own health and well-being.

Financial support for caregivers is another big issue. Many family members end up cutting back on their own work or even leaving their jobs to take care of us. That means a loss of income, which only adds to the stress. Programs that provide caregiver stipends or tax breaks could make a world of difference in helping families manage both the financial and emotional load. Check with your state's Medicaid waiver program to see if family caregivers are eligible to be paid.

And let's not forget about technology and adaptive equipment. The more access we have to things like patient lifts, power chairs, and home modifications, the less physical strain it puts on our caregivers. Having the right equipment can give us a little more independence and allow our caregivers to focus on the things that really need their attention. At the end of the day, caregiving in the LGMD community is a team effort. It's not just about us — it's also about the people who support us.

The current system doesn't provide enough help, and it's time we start advocating for real change. LGMD patients and their families deserve better. Our caregivers deserve better, and so do we. If we push for more support, more programs, and more resources, we can look forward to a future where we can thrive together. Our caregivers give so much — it's time we make sure they get the support they need, too.

Victoria Nedza

As my disease progressed beyond my ability to manage ADLs on my own, it was prudent for my parents and brother to move in with me.

This has been a blessing in disguise as their help has extended beyond me and has been the support system I needed to raise my son. It has also been the helping hand that pulls me through the harsh realities of this disease. I'd be lying, however, if I didn't admit that this transition has also brought with it challenges that we as a family could not have predicted or prepared for.

On the surface, it appears as if we all work seamlessly together, like a well-oiled machine. My brother takes care of errands, the yard work, the trash, and maintains the pool. My father, "Mr. Fix-It," MacGyvers his way through various home repairs. My mother is a godsend; she cleans, does laundry, and cooks fresh meals multiple times a week. She is the matriarch, the rock, the voice of reason, and the protector all wrapped up in one. She runs at the drop of a hat to rescue me from sticky situations, whether it is to depress the button on my seatbelt, brush the back of my hair because I lack the range of motion to do so, or to give me an extra hand to hold onto if I feel like I'm about to fall. Lately, she also carries my portable commode into public restrooms without complaint, graciously enduring the barrage of stares from onlookers.

Put together, these responsibilities are difficult to cope with. Enter "caregiver burnout"—an overwhelming feeling of physical, emotional, and mental exhaustion. There is a distinct heaviness that can

> ***Finding ways to alleviate caregiver burnout is an important step toward giving us the peace of mind we need, by ensuring that those of us with LGMD will have the care we need without jeopardizing the well-being of those who care for us.***

build from constantly feeling responsible for another's well-being, particularly when this disease makes accomplishing the smallest of tasks feel like a huge feat. There are times when my caregivers and I all feel helpless, when our anger is amplified by the shared situation, and when our boundaries melt rather than stand as protective dividers. However, we are quick to apologize and are learning that we all have to take responsibility for our own mindsets and be intentional about not letting our imperfections stand in the way of our care for each other.

Caregiving is a full-time job, addressing everything from my morning routine up to the moment I fall asleep at night. In the constant chaos of our crazy little life, a day of respite—a day to reflect and recharge—would greatly help us. It would allow an opportunity for each one of us to take time for ourselves, remind ourselves of what matters to us as a family, and then regroup, stronger and more energized. In my moments of solitude, I often think about the future and how to ease the transition to hiring in-home care services while not jeopardizing my career goals, living arrangements, and financial security. I am grateful for my family fulfilling the caregiver role; without them, I would have been a single mother needing help to take care of a newborn and herself, while trying to maintain a job, a home, and a shred of sanity.

This raises the question, how do we remedy the issue of healthcare affordability and accessibility as they pertain to in-home caregiving in the United States? Solutions should include more societal support and government assistance regardless of income. Ideally, family members who are providing care for loved ones should be compensated regardless of Medicaid eligibility status. I'd also like to see a multidisciplinary care team, which would include physicians and social workers, who could help navigate the red tape in this deeply exhausting and frustrating unbalanced system of care. At times, this may require physicians to step outside of their specialty role to help advocate for the best care needed for their patients.

The topic of how LGMD affects our psyche and how we perceive ourselves is seldom discussed in our community. Many of my insecurities stem from worrying about what others close to me in my environment think and how they feel. And it is ingrained in me as a nurturer to make sure that those close to me are doing well. My greatest hope is that my parents, brother, and child never feel that I'm a burden to them. I want my son's heart to be filled with an abundance of love and joy, not drowned with the obligation of taking care of his mother. I do not want my family to feel the weight of this disease like I do. Faced with this set of circumstances, I will choose to continue remembering this adage: though the mind doesn't have the power to heal a disease, it has the power to push through obstacles and find peace with difficult situations. Finding ways to alleviate caregiver burnout is an important step toward giving us the peace of mind we need, by ensuring that those of us with LGMD will have the care we need without jeopardizing the well-being of those who care for us.

Q&A

With Douglas Sproule, MD, MSc, Chief Medical Officer at ML Bio Solutions, a BridgeBio company

Interviewed by Kelly Brazzo, M.S., Co-Founder and CEO, CureLGMD2i Foundation

Q **Tell me a little bit about yourself?**

A

Absolutely! I am the Chief Medical Officer of ML Bio Solutions (ML Bio), a BridgeBio company, responsible for the clinical program in FKRP. I am a trained child neurologist and neuromuscular specialist and devoted my early career to the care and management of children with neuromuscular diseases. This was a time before the development of therapies, beyond steroids for Duchenne Muscular Dystrophy, and every day I watched the frustration, hopelessness and loss the families I served experienced. I moved into industry in 2013, and it has been an immense privilege to have been able to contribute, in a small but meaningful way, to the radical change that is occurring in neuromuscular medicine with the development of an ever-expanding list of effective therapies. My work at ML Bio is a natural extension of the personal mission I embarked upon almost two decades ago to improve the lives of patients and families impacted by neuromuscular disease.

Q **Tell us about ML Bio and what you're working on right now?**

A

ML Bio Solutions was founded by the McColl and Lockwood families after a family member was diagnosed with limb-girdle muscular dystrophy type 2I/R9 (LGMD2I/R9), a rare genetic disorder caused by variants in the fukutin-related protein (FKRP) gene. There are no approved therapies for LGMD2I/R9 so these families established the McColl-Lockwood Laboratory for Muscular Dystrophy Research and the therapeutic approach we're developing at ML Bio came out of the work led by Dr Qi Long Lu, MD, PhD, at this lab. In 2018 we became part of the BridgeBio family with the goal of developing our investigational product, BBP-418 (ribitol), as a potential treatment for pediatric and adult patients with LGMD2I/R9. Since then, our BBP-418 clinical development program has completed a natural history study, two Phase 1 studies and we have ongoing studies including a Phase 2 study, and a Phase 3 study. FORTIFY, our Phase 3 study, is designed to evaluate the safety and efficacy of long-term administration of BBP-418 in people living with LGMD2I/R9.

Q **What gets you excited to get up and go to work each day at ML Bio?**

A

The development of a drug is complicated and frustrating! Every day presents new challenges and problems to solve. It is never boring. I love the opportunity to work with the amazing physician partners who run our clinical studies and engage our community partners as we live our mission to remain patient centric. What gets me excited is the potential impact that our therapy, if approved, could have on people affected by LGMD 2I/R9. We're also incredibly excited about the innovative and novel biomarker we've developed which measures the important molecular driver of LGMD2I/R9 glycosylated alpha-dystroglycan (αDG) in muscle biopsy tissue. It's an exciting time for the LGMD2I/R9 community and what an obligation and a privilege to be able to work on such an important program.

Q **Can you tell us how BBP-418 (ribitol) is designed to work?**

A

To set the stage, I'll start with the genetic driver of LGMD2I/R9. As I mentioned, LGMD2I/R9 is caused by a mutation in the FKRP gene which codes for the FKRP enzyme. This enzyme is involved in glycosylation (adding glycans) of α-DG. In a muscle in which the FKRP enzyme is working well, the FKRP enzyme uses upstream molecules, called substrates, to glycosylate α-DG. These substrates are used by the FKRP enzyme to perform the glycosylation process. During glycosylation, glycan chains attach to the backbone of the α-DG protein. Glycosylation is critical for the normal function of α-DG. Once glycosylated, α-DG stabilizes muscle cells by acting as a "shock absorber" for muscle fibers during contractions.

In individuals with LGMD2I/R9, the FKRP enzyme works a little bit, but it doesn't work well enough and, as a result, people with LGMD2I/R9 have reduced levels of glycosylation of α-DG. Without enough glycosylation, α-DG is not able to anchor to the muscle cell, limiting its role as a "shock absorber" and making the muscle fragile and prone to damage — even with everyday movement.

Our oral investigational product, BBP-418, is expected to add more of the substrate molecules upstream of the mutated FKRP enzyme to potentially help it work better and take advantage of residual enzyme activity. This additional substrate may support the glycosylation of more α-DG allowing it to better stabilize muscle cells and act as a "shock absorber" for muscle fibers. By increasing the shock absorbing mechanism in muscle cells, we hope muscles may be less prone to damage.

Q **How can you determine, in people who are taking BBP-418, whether they have increased levels of glycosylated α-DG?**

A

ML Bio has developed a way to measure the protein levels of glycosylated αDG in biopsy muscle tissue, an important biomarker for the study. In our FORTIFY Phase 3 study we ask that each study participant complete four biopsies during the study. These biopsies are taken at baseline (before participants start taking BBP-418), at 3-months, 12-months and at the end of the study (36-months). Using our new method, we can measure the levels of glycosylated αDG in the tissue from each biopsy. It's critical that each FORTIFY participant complete the biopsy assessments at these specific points of the study in order that these data can inform us accurately as to whether those on the investigational drug have increased levels of glycosylated αDG compared to the placebo group (those who are not on BBP-418).

Q **We recently learned that the FORTIFY study is fully enrolled. What does this mean for the community?**

A

This is fantastic news for the LGMD community as this means we are one step closer to having the key data we need from this study to submit to regulatory authorities and support potential approval of this product for LGMD2I/R9. The FORTIFY study enrolled more quickly than anticipated and exceeded the target number of study participants and we are grateful to the community and the study investigators for their interest and enthusiasm in our study. We could not have done this without the community!

Next, we plan to conduct an interim analysis which will look at data from the first 12 months of FORTIFY. Since the study enrolled more quickly than anticipated we will potentially have more data to look at during the interim analysis. These results are expected in 2025.

Q **What happens during the interim analysis?**

A

The interim analysis will evaluate the biomarker we were discussing earlier, and we believe this biomarker (glycosylated αDG) can function as a reasonably likely surrogate endpoint in LGDM2I/R9. Reasonably likely surrogate endpoints are supported by strong scientific rationale, but are not yet validated. Reasonably likely surrogate endpoints can be used to support FDA's Accelerated Approval program, which is intended to provide patients living with serious diseases or conditions more rapid access to promising therapies.

Q **What can patients and patient advocates do to advance LGMD drug development?**

A

There are many ways that people living with LGMD2I/R9 and advocates can support advancement of LGMD drug development. We encourage involvement in advocacy with the CureLGMD2i Foundation and other organizations like yours because as you know firsthand, advocacy groups are pushing forward important initiatives such as building community, helping to develop standards of care, supporting genetic testing, and encouraging natural history and registry involvement and all these things are critical to helping the LGMD community and advancing drug development.

Our company originated from a family focused on helping a loved one and we continue to always strive to establish and build enduring, supportive relationships with the LGMD community and actively seek to include the perspective of patients, families, and advocates in the drug development process by listening and learning from them — knowing that every minute counts for patients and families affected by this devastating condition.

A collaboration between CureLGMD2i Foundation and ML Bio Solutions, Inc.

Written By Melina Garza

Becoming One Voice for Change: LGMD Day on the Hill 2024

On September 18, 2024, I joined 18 other families and individuals impacted by limb-girdle muscular dystrophy (LGMD) in Washington, D.C., to make our voices heard.

Our group consisted of patients and caregivers with LGMD R1/2A, R2/2B, R3/2D, R5/2C, R9/2i, R10/2J, and 1D/DNAJB6. Kathryn and James Knudson, Kelly Brazzo, Rachel and Josh DeConti and family, Joe Dion, Michell Clayton and family, Carol and Tim Abraham, Chris and Joy Carroll, Victoria Nedza, Kemi Robertson and family, Faran and Justin Day and family, Doug and Heather Wright and family, James Garner, Jennifer Levy, Kelly McCormick, John Faver, Amy Koran, Heath Gunter and myself—Melina Garza—joined together. Constituents of 12 states had the opportunity to address their elected officials with one shared goal: to advocate for legislative actions that could support those affected by this progressive disease and to remind lawmakers that we—the patients and caregivers—are central to shaping solutions.

The Training: Learning the Legislative Process

The evening before, Thorn Run Partners equipped us with essential training, offering insights into the structure of Congressional Offices, the roles of staff, and a deeper understanding of the regulatory process for treatments for ultrarare diseases. We learned about the FDA's role and the Accelerated Approval Pathway, which can expedite treatments through surrogate endpoints. However, the FDA often underutilizes these tools, creating an urgency for us to advocate for more modern regulatory approaches.

Presenting Critical Legislative Priorities

Equipped with an understanding of our mission, we set out the next day with a clear agenda. Our primary focus was on three key legislative bills that directly impact the LGMD community:

1. BENEFIT Act (H.R. 1092)
   This bill aims to ensure that patient experience data is included in the FDA's review process. We emphasized that patients, the ones directly experiencing the risks and challenges, must have their perspectives put front and center in regulatory decisions.

Melina Garza (mom of Brooklyn Garza, age 17, LGMD R1/2A) and Kathryn Bryant Knudson

2 Creating Hope Reauthorization Act (H.R. 7384)

The Rare Pediatric Priority Review Voucher (PRV) Program incentivizes the development of treatments for rare pediatric diseases, with half of rare disease patients being children. Time was critical, as this program was set to expire on September 30, and we passionately voiced its importance to representatives. To our joy, we received word that the vote to reauthorize had passed that very day!

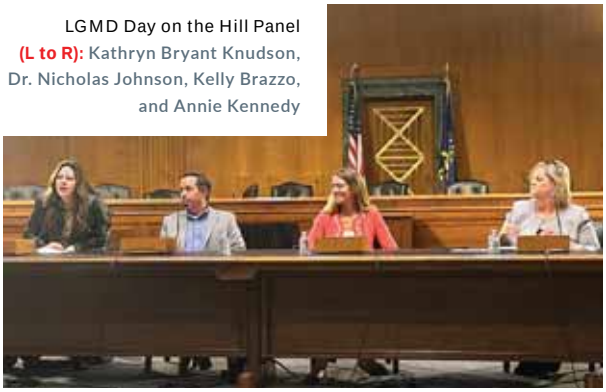
3 The Protecting Health Care for All Patients Act (H.R. 485)

This bill challenges the use of Quality-Adjusted Life Years (QALYs) in determining treatment value—a metric that almost inevitably undervalues the lives of those with disabilities. Extending this policy across federal programs would prevent discriminatory valuation and expand access to vital health care for individuals with conditions like LGMD.

(Far Left): Melina Garza and LGMD Awareness Foundation's Carol Abraham; **(Left):** Dr. Nicholas Johnson and Melina Garza

We also highlighted the importance of access to reliable home care. **H.R. 8110** touches on the issue but does not go far enough. Many LGMD patients face a difficult choice between employment or Medicaid access to personal care attendants, with income limits often standing in the way of essential support.

LGMD Day on the Hill Panel
(L to R): Kathryn Bryant Knudson, Dr. Nicholas Johnson, Kelly Brazzo, and Annie Kennedy



A Sense of Purpose and Community

At midday, we attended a Senate briefing where advocate, mom, and founder of CureLGMD2i Kelly Brazzo, leading neurologist Dr. Nicholas Johnson, founder and CEO of The Speak Foundation Kathryn Bryant Knudson, and rare disease expert Annie Kennedy of the EveryLife Foundation shed light on LGMD's drug development challenges and opportunities. Hearing these passionate voices affirmed our mission. By day's end, I felt a renewed sense of purpose, camaraderie, and determination that our efforts could indeed create lasting change.

Being part of this experience underscored that every voice matters and that, together, we can make a difference. Please consider joining us at future LGMD Days on the Hill. This is just the beginning—together, we are stronger. ▪

Participant's Feedback

I successfully advocated for the community in an official capacity, and I am proud that 2J was one of the many subtypes in attendance that day. A win for one is a win for all of us, and we all just moved one more step (or ramp!) closer to meaningful outcomes and real hope for treatments in the near future. As I reflected on the experience, I felt like the LGMD community as a whole would be proud of us.

John Faver
Patient living with LGMD R10/2J

Elizabeth and I began our journey this past June following our middle son Henry's 2i diagnosis. The strength and unity we see in the LGMD community are both inspiring and encouraging to us. It was a privilege to advocate alongside patients and caregivers for the entire LGMD community across the country. The senators and representatives we met with were receptive and engaged in constructive discussions. I pray each day that the time and energy spent on Capitol Hill will lead to meaningful advancements in care and treatment for our LGMD community.

Heath Gunther
Father of Henry Gunther, LGMD R9/2i

We were so grateful for the opportunity to share my story on Capitol Hill, along with our group of incredible Pennsylvania constituents! To get the chance to be vulnerable and put a face to this disease, in front of the very people who have the ability to pass these legislations and gain the attention of the FDA, is an experience that we will never forget!

Christopher Carroll
Patient living with LGMD R3/2D

Having 3 children with LGMD, we jumped at the chance to advocate for them and the community on Capitol Hill. The work is just beginning, but we know we had a positive impact on the staffers, and we will continue to push for a cure. Our kids left with a different perspective on their place in all of this, and I think we have at least two rare disease lobbyists in the making.

Heather Wright
Mom of Walker, Reagan and Rex, LGMD R1/2A

LGMD Day on the Hill is a program that gives individuals and families living in the United States the opportunity to advocate in person with congressional representatives in Washington, D.C. You can also be a delegate in the 2025 LGMD Day on the Hill event. Our selection process occurs via an online application. Please see our upcoming 2025 Spring issue of *LGMD News* for more information.

Empowering the LGMD Community

Introducing the LGMD Advocacy Bundles (LAB) Project

This unique project is focused on bringing LGMD awareness to clinicians, patients, family members, and caregivers. The LGMD Advocacy Bundles project bridges the gap between clinicians and patients through advocacy support while supplying helpful tools and resources.

Together We Are Stronger!

Visit lgmd-info.org to learn more and get invoved.

LGMD AWARENESS FOUNDATION

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Download these FREE resources:

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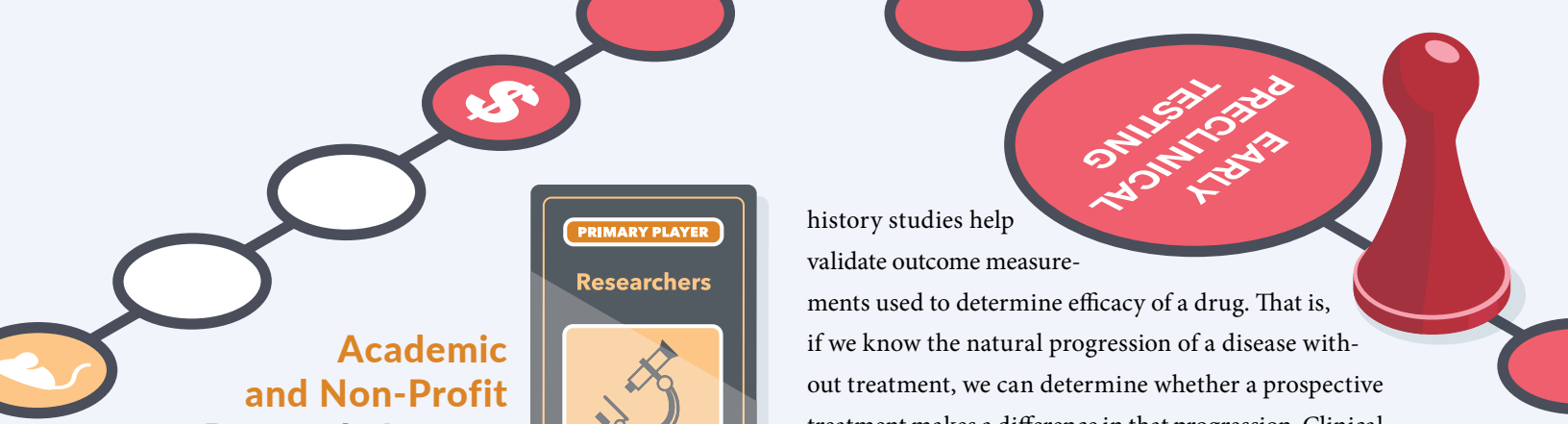
- Desk Reference Card

Written By Joshua Thayer

Drug Discovery, Development, and Commercialization

Meet the Primary Players

If your life is touched by LGMD, you may encounter a myriad of references to individuals and organizations involved in drug discovery, development, and commercialization, often without explanation of their roles. This article aims to help you navigate scientific presentations, press releases, and journal articles by explaining what each of the primary players does.



Academic and Non-Profit Research Centers

Universities and Hospitals

Universities, teaching hospitals, and similar academic research institutions play several roles in drug development, as illustrated.

Laboratory staff at these institutions conduct early disease-related research, including identification of disease pathways and the search for compounds that alter those pathways. For example, the primary pathway for most LGMDs is the absence of a specific protein in muscle cells due to mutations in the gene for that protein. Once that pathway is known, researchers may seek ways to either restore the protein to the muscle or mimic its muscle-saving functions with drugs.

As part of their educational mission, staff members also write articles summarizing their research. These articles quite literally teach the world about rare diseases. Please note, however, that the media and patient communities often misinterpret such articles by overlooking the early, exploratory nature of academic research. The articles usually describe preclinical studies; any 'miracle' cures predicted may take years to come to fruition, if at all.

In the United States, academia is one of the largest sources of innovation and intellectual property, or IP. Research center personnel often generate patentable inventions as a result of their research, which they must assign to their institutions as part of their employment arrangements. The institutions then protect the inventions by filing patent applications. In other countries, the relationship between academia and commercial patents may be less direct.

Of particular importance to patient communities, hospital clinics both in the U.S. and elsewhere serve as sites for natural history studies and clinical trials. As discussed in detail in the last issue of this magazine, natural history studies help validate outcome measurements used to determine efficacy of a drug. That is, if we know the natural progression of a disease without treatment, we can determine whether a prospective treatment makes a difference in that progression. Clinical trials happen late in the drug development process, after efficacy and safety have been tested with *in vitro* assays (cell cultures in a lab) and animal models (animals specifically bred to have the equivalent of the human disease being studied).

However, academic research centers do not fund or manage large-scale development or commercialization of drugs, and running a for-profit business is not part of their academic mission or consistent with their tax-exempt status. Therefore, as noted below, academic institutions reach out to industry partners to take over those activities.

Principal Investigators (PIs) and Postdoctoral Fellows (Post-Docs)

The primary players in laboratories and clinics are research doctors and physicians referred to as Principal Investigators, abbreviated as PIs, and junior researchers, including Post-Doctoral Fellows and graduate students, abbreviated as Post-Docs.

The term PI can have two meanings: first, the head of a research laboratory in charge of discovery and preclinical research; second, a physician in charge of conducting clinical trials. The first role requires either a Ph.D. or M.D., while the second requires an M.D. Doctors with both degrees often fulfill both roles.

The junior lab members may also have, or be working towards, PhDs. They do much of the "grunt work," such as conducting and monitoring experiments, writing research grant applications, dosing animals in the middle of the night, and drafting manuscripts.

Institutional Review Boards (IRBs)

An IRB is a group of specialists that reviews and approves clinical research studies, including research

protocols and patient informed consent forms (ICFs). IRB approval is required to initiate clinical research to ensure that trials adequately protect patient safety and follow ethical guidelines.

Technology Transfer Offices (TTOs)

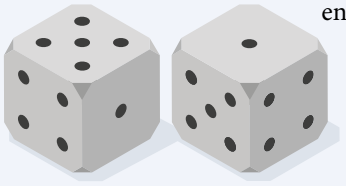
Each academic research institution has a group of professionals responsible for monitoring the development of intellectual property in the laboratories and for licensing technologies to industry for further development and commercialization. These licensing offices are often referred to as the technology transfer office, tech transfer office, or TTO.

Industry Players Take the Baton from Researcher Centers

At a certain point, non-profit research centers turn to for-profit companies that have an interest in further advancing a program and have access to necessary personnel and financing. To accomplish this technology transfer, the TTO and the company negotiate a license agreement for exclusive commercial rights to the intellectual property covering the applicable therapy.

Small Biotechnology (Biotech)/ Pharmaceutical (Pharma) Company

The initial industry partner is usually a small, privately-held company. One reason for this is that federal law favors small businesses as licensees of government-funded inventions. These start-up or early-stage companies may be virtual (without its own office or labs) and founder-funded or have raised tens of millions of dollars with dozens of employees, but they are usually not the final entity to obtain regulatory approval and commercialize the drug, at least not without outside help.



Big Biotech/Pharma

The initial licensee will typically partner with a larger, more established company for the final stages of development and commercialization. To obtain rights to the target program, the "Big Pharma" company might acquire rights to the technology through a collaboration agreement or purchase the small biotech outright. The reason for this paradigm lies in the financial burden and the specific expertise and infrastructure required to bring a drug through the final phase of regulatory approval and commercialization. Companies that take over the programs tend to be publicly-traded, giving them access to funding through public markets.

Scientific Advisory Board (SAB)

An SAB is a group of specialists who advise a company, foundation, or other entity on scientific aspects of its projects. Membership consists of scientists and physicians with a professional focus relevant to the organization's field of drug development.

Patient Advisory Board (PAB)

The PAB is a group of outside patients and patient advocates who serve as the voice of the patient communities within a company.

Contract Research Organization (CRO)

A CRO is a company that conducts research or facilitates clinical trials on behalf of drug development companies and research institutions on a fee-for-service basis. CROs assign all rights to data and intellectual property they generate to their customers. That can be an advantage over sponsored research at a university lab where IP ownership is retained by the university.

Contract Manufacturing Organization (CMO)

A CMO is a company that specializes in manufacturing clinical trial or commercial-grade drug supplies for drug companies. CMOs have specialized processes and facilities that are proprietary and difficult or expensive to replicate.

Who Pays for All of This?

The funds for early research at university and hospital research centers are sometimes provided internally at the institution but, most often, through grants by government agencies, such as the NIH, or under research agreements with non-profit entities, such as patient advocacy groups. Later research to expand existing technologies at such institutions is often funded by drug development companies to advance their programs. Such funding is typically project-specific, entailing predetermined activities in a written research plan in accordance with a budget.

Once programs are licensed to for-profit companies, two primary groups of private investors take over most funding: first, individuals who are sometimes called "angel investors" for their willingness to assume risks of loss when a company's future is most uncertain; and second, partnerships of individuals, retirement plans, and other institutions, which are called venture capital funds. Such financings are usually in the form of an ownership interest in the company, referred to as equity. The equity sold in these financings must generally be held by the investors until the company is acquired or becomes publicly traded. These investments are less project-specific (compared to those at university or hospital research centers), as the company may own several therapeutic programs.

As a therapy advances through development, the company might be acquired by a well-funded, publicly-traded pharmaceutical company, or it might go public itself through an initial public offering, or IPO.

Finally, companies at all stages of development continue to apply for government grants and advocacy group funding. They also often partner with other companies willing to share the ongoing financial burden in exchange for a share of the revenue if the drug is approved. For example, a company might grant commercial rights within a specified territory to another company in exchange for that company making a cash payment, assuming all further development costs in its territory, and then paying royalties on its sales.

Government Agencies

U.S. Food and Drug Administration (FDA)

In the United States, the FDA regulates research involving human subjects as well as the sale of drugs. You might hear references to "CBER" (pronounced *SEE-ber*) and "CDER" (pronounced *SEE-der*). The former, the Center for Biologics Evaluation and Research, regulates most biological products, including blood, vaccines, allergenics, tissues, and cellular and gene therapies.

The latter, the Center for Drug Evaluation and Research, regulates small chemical compound drugs, including both prescription and over-the-counter drugs. Additionally, CDER regulates certain "small" biologics outside of CBER's jurisdiction, such as monoclonal antibodies.

National Institutes of Health (NIH)

The NIH is the major U.S. agency that funds biomedical research. The NIH conducts its own internal research and also provides research funding to university and hospital laboratories as well as to drug companies.

The U.S. Patent and Trademark Office (USPTO)

In the United States, the office that reviews patent applications and issues patents is called the U.S. Patent and Trademark Office. You will generally hear it referred to as the USPTO, PTO, or patent office.

And Let's Not Forget Patients and Their Advocates!

Patient Advocacy Groups

Groups founded by people affected by LGMDs play significant roles in supporting disease research and organizing and educating their communities about clinical trials and access to available therapies. These groups generally focus on disease-specific treatments or cures. Some advocacy groups are primarily funding vehicles while others have scientific and administrative staff and participate in analyzing research results to determine the promise of further research or drug development. Such groups also assist in transitioning drug candidates from laboratories to clinics through early-stage investments as well as by locating, organizing, and educating patients needed for clinical trials. Their efforts may include patient outreach on social media, creation and maintenance of patient registries, funding and review of genetic screening programs, design and funding of natural history studies, and patient educational gatherings. Because the number of patients with rare diseases is limited, and information on their natural histories is often lacking, drug companies recognize the importance of advocacy organizations. With ultra-rare diseases like LGMD, where the number of patients is so small, it is vital that these organizations work internationally.

Patients, Patient Families, and Caregivers

As the people who live with the rare diseases that academia, advocacy groups, and industry seek to research, diagnose, treat, and cure, you and I are at the heart of every activity summarized in this article. Without our participation, the rare diseases we live with are likely to remain overlooked. Through patient advocacy and participation in clinical trials, we keep researchers and companies focused on the disease and enable the development of new therapies.

And, more and more, we also contribute our substantive expertise. Within our ranks are research doctors, physicians, statisticians, physical therapists and, might I add, lawyers, advancing the rights of patients and their advocacy organizations. Our participation as subject matter experts should increase when possible—not only do we live with these diseases every day, but many of us have backgrounds that allow us to take an active role in drug development. ▪

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).

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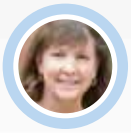
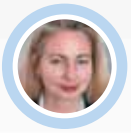


Dr. Joanne Donovan
Edgewise Therapeutics



Dr. Sharon Hesterlee
Muscular Dystrophy Association

Dr. Peter Kang
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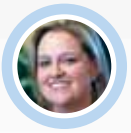

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