Vol 4 / Issue 3

LGMD News

Uniting the Limb-Girdle Muscular Dystrophy Community

ESTABLISHING THE EFFICACY OF NEW DRUGS

An Exploration of "Clinical Trial Endpoints" and the LGMD Community Perspective

ML BIO SOLUTIONS

Compliance in Clinical Trials: Why Following the Study Protocol is Vital

SAREPTA THERAPEUTICS

The Importance of the Muscle Biopsy in Advancing Research & Development

Home Sweet Home!

Integrating Accessibility Into Your Home

fortify

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

About Fortify

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

About the Therapy

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

Who Can Participate

You may be eligible to participate in Fortify if you:

- Have a genetically confirmed diagnosis of LGMD2I/R9
- Are 12 to 60 years of age in the USA, UK, and Australia (18 to 60 years of age in Europe)
- Have not used ribose or systemic corticosteroids prescribed for the treatment of LGMD or other investigational therapies for the treatment of LGMD within 90 days of screening

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

Fortify Locations:

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

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

Scan to learn more

ML Bio Solutions

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Thank you for your support!

The Speak Foundation

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

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

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Looking Ahead:

Announcing the 2025 International LGMD Conference Dates

Planning for the future can feel exhausting at times. In this issue, we share some ways of addressing common home accessibility challenges.

Living with a progressive condition brings with it many challenges. Changes in functioning frequently necessitate problem solving, adaptation, and modification. Planning for the future can feel exhausting at times. In this issue, we share some ways of addressing common home accessibility challenges. From kitchens to bathrooms, we highlight some of the ways people living with LGMDs have created a more suitable living space for their needs. We hope that you will find this a valuable resource should you need to build or remodel in the future.

As a follow up to the article on Accelerated Approval in our Spring issue, we present the second portion of a 4-part series on drug development from Josh Thayer, General Counsel of the Jain Foundation, who lives with LGMD (dysferlinopathy or LGMD R2/2B). Have you ever wondered why certain measures are used to test our abilities in a trial and how they are selected? This article provides a helpful explanation on clinical trial endpoints.

Thank you to the Virginia Commonwealth University (VCU) team, led by Dr. Nicholas Johnson, for sharing more about the excellent care those living with LGMDs receive at their clinic. Science is rapidly moving forward there and we are excited to present their various projects to you. You can also check out the brief interview spotlight with Dr. Johnson (Page 8) to learn more about how he got into the field of medicine and came to specialize in neuromuscular diseases.

Lastly, we are thrilled to announce the dates and location for the next International LGMD Conference! The conference will be held on July 18–21, 2025 in Orlando, Florida. Registration opens in August 2024. Learn more about this important event for our community by visiting **InternationalLGMDConference.com**. ▪

Kat Bryant Knudson

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

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ContactUs@TheSpeakFoundation.com

TheSpeakFoundation.com
InternationalLGMDConference.com

Our Mission

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

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

International Consortium of LGMD Organizations

United States

The Speak Foundation
Uniting the entire LGMD community
TheSpeakFoundation.com

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

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

CamronsCure
Funding research for LGMD R19/2S
CamronsCure.com

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

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

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

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

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

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

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

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

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

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

Argentina

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

Australia

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

France

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

Italy

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

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

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

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

Japan

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

Netherlands

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

South Korea

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

Spain

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

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

Carla D. Zingariello, DO

Assistant Professor Pediatrics
Director, Pediatric Neurology Residency Program
Director, Pediatric Neurology Clerkship
University of Florida College of Medicine

Meet the Expert

Carla D. Zingariello, DO completed her pediatric neurology residency at Vanderbilt, followed by a neuromuscular fellowship at the University of Pennsylvania. She is board-certified in pediatric neurology and neuromuscular medicine. She joined the child neurology faculty at the University of Florida in 2018, where she actively participates in a multidisciplinary MDA clinic, following patients with a variety of neuromuscular disorders, including limb-girdle muscular dystrophy (LGMD). Dr. Zingariello is actively involved in muscular dystrophy research, in particular LGMD. Since 2022, she has served as Co-Principal Investigator on a CDC-sponsored muscular dystrophy surveillance study (MD STARnet), collecting data on all forms of muscular dystrophy, including LGMD. She currently serves as Principal Investigator for two LGMD clinical trials. She additionally serves as PI for the GRASP consortium for LGMD. She has also been an educational contributor for LGMD for The France Foundation.

Q

Why, despite undergoing multiple genetic tests over the past 15 years, am I still unable to ascertain the specific type of LGMD I have, while other individuals are diagnosed promptly with detailed subtype information? I am 58 years old, and things are starting to get really difficult for me.

A

Diagnosis of LGMD has evolved significantly over the past 20 years. Twenty years ago, only 16 genes had been identified, and ten years ago this increased to 31 genes with widespread use of next-generation sequencing panels (Nigro et al., *Acta Myologica*, 2014). With the new classification system, there are more than 30 accepted genetic subtypes of LGMD (Straub et al., *Neuromuscular Disorders*, 2018). Nonetheless, many individuals with a clinical history consistent with a diagnosis of LGMD remain undiagnosed despite genetic testing including with whole-exome sequencing. However, as sequencing technology continues to advance, new LGMD genes continue to be discovered, and researchers are making progress in determining which mutations are disease-causing.

Q

My daughter is eight years old with LGMD R5/2C. Would you recommend a steroid for her? Are there any natural history studies for her to participate in?

A

There have been published case reports on the use of corticosteroids in patients with sarcoglycanopathies. In some cases, an initial increase in strength or stabilization of symptoms was reported. An open-label study of once weekly prednisone in 19 adults with various LGMD subtypes (one participant had SGCG mutations) showed reduction in serum CK at 24 weeks (Zelikovich et al., *Journal of Neuromuscular Diseases*, 2022).

According to **Clinicaltrials.gov** (accessed 5/16/24), there are currently four studies for LGMD R5/2C. Of the two that are actively recruiting, one is a natural history study with 30 U.S. sites recruiting patients of various LGMD subtypes including patients with LGMD R5/2C who are four years or older. The other actively recruiting study is an observational study for patients with LGMD including LGMD R5/2C ages 6-50 years, based at one site in Richmond, VA.

Q

Are there any studies on the effects of the new weight loss injections (Ozempic, Zepbound, Mounjoro, etc.) on people with muscular dystrophy? I have heard they can cause some muscle loss.

A

Semaglutide (*Ozempic, Wegovy*) is a glucagon-like peptide 1 (GLP-1) receptor agonist, and tirzepatide (*Zepbound, Mounjoro*) is a glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 dual agonist. Both GIP and GLP-1 are incretin hormones that stimulate insulin secretion. A meta-analysis of 18 randomized controlled trials on semaglutide showed a significant decrease in fat-free mass (i.e., muscle mass) (Ida et al., *Current Diabetes Review*, 2021). Tirzepatide has also been shown to result in muscle loss. Given concerns for muscle loss, these incretin medications are not currently recommended for patients with muscular dystrophy.

Q

What are the most promising biomarkers for potential use in drug development for LGMDs?

A

Beyond Creatine Kinase (CK), there are a number of biomarkers being explored in LGMD. Muscle proteins in muscle biopsies can be used to diagnose and potentially to monitor treatment response in LGMD. The serum (blood) creatine/creatinine ratio has been found to be elevated in individuals with LGMD R1/2A and LGMD R2/2B (Spitali et al., *Journal of Cellular and Molecular Medicine*, 2018). Elevated myofibrillar structural protein myomesin-3 (MYOM3) fragments have been observed in serum from individuals with LGMD R3/2D compared to controls (Rouillon et al., *Human Molecular Genetics*, 2015). Four myofibrillar proteins (sTnl, MYL3, FABP3, and CKM) were found to be significantly elevated in individuals with LGMD R2/2B compared to controls (Burch et al., *Journal of Neuromuscular Disease*, 2015). MicroRNAs (miRNAs), which regulate silencing of target genes post-transcriptionally, are also being evaluated as non-invasive biomarkers. Various studies on a variety of LGMD subtypes (including R1/2A, R2/2B, and the sarcoglycanopathies) have identified some miRNAs which were increased in LGMD patients and others which were reduced in LGMD patients. Muscle MRI is also being used to monitor fatty infiltration of muscle in LGMD (Diaz-Manera et al., *Acta Myologica*, 2015).

Q

How long until treatments for LGMD R1/2A become available? I am 65 years old. If a treatment does become available, will it be of help for older patients like me?

A

There are currently three actively recruiting natural history studies for LGMD R1/2A. The aim is for the information gathered to aid in development of drug or gene therapy clinical trials. So far preclinical studies of potential drugs have been conducted in mouse models of R1/2A, but human trials of therapies specifically targeted to this subtype haven't yet occurred.

There are currently three actively recruiting natural history studies for LGMD R1/2A. The aim is for the information gathered to aid in development of drug or gene therapy clinical trials. So far preclinical studies of potential drugs have been conducted in mouse models of R1/2A, but human trials of therapies specifically targeted to this subtype haven't yet occurred.

Question

CK is an enzyme often elevated in people with LGMD due to it chronically leaking out of damaged muscle. The elevated CK itself is not dangerous to kidneys or liver.

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ClinicalTrials.gov

Featured Resources

Givinostat:
www.accessdata.fda.gov/drugsatfda_docs/label/2024/217865Orig1s000lbl.pdf

Vamorolone:
www.accessdata.fda.gov/drugsatfda_docs/label/2023/215239s000lbl.pdf

Q

What are the effects of chronically high CK on my kidneys, liver, and other systems? My liver enzymes (AST, ALT) are always high, and my creatinine is always low with a high BUN/creatinine ratio. Admittedly, I am 25 lb overweight, but I eat healthy, don't smoke, and only drink alcohol socially. Is liver or renal disease/failure a potential complication of LGMD R9/2i?

A

CK is an enzyme often elevated in people with LGMD due to it chronically leaking out of damaged muscle. The elevated CK itself is not dangerous to kidneys or liver. Transaminases (ALT, AST, LDH) are found in skeletal muscle as well as the liver (Weibrecht et al., *Journal of Medical Toxicology*, 2010). These enzymes are elevated in up to 90% of patients with muscular dystrophy (Dreyfus et al., *Annals of the NY Academy of Sciences*, 1958). Usually elevated transaminases are of no concern, but there are situations such as a rise of these values from their usual range and other clues such as elevated bilirubin and/or GGT levels that could indicate the presence of new liver disease in a patient with muscular dystrophy. Creatinine is released into the bloodstream from muscle; the amount of creatinine released depends on the amount of muscle tissue. Thus, patients with muscular dystrophy often have low creatinine. This will cause the BUN/creatinine ratio to be elevated despite normal total BUN and kidney function. Liver and/or renal failure is not known to be an associated complication of LGMD R9/2i, but may occur in medically complex individuals for other reasons. If a physician suspects a liver or kidney problem in a person with LGMD, alternative biomarkers would likely also have to be evaluated.

Q

What is your opinion on the use of recently developed medications for DMD like givinostat and Agamree in LGMD patients?

A

Givinostat is a histone deacetylase (HDAC) inhibitor that was recently FDA approved for the treatment of Duchenne muscular dystrophy (DMD). Approval was based on a Phase 3 clinical trial of givinostat in boys with DMD aged six years or older and able to complete motor tests including 4-stair climb (Mercuri et al., *Lancet Neurology*, 2024). A pre-clinical study showed that deacetylase inhibitors increased the size of myofibers in alpha-sarcoglycan-deficient mice (Minetti et al., *Nature Medicine*, 2006). Vamorolone (Agamree) is a recently FDA-approved dissociative corticosteroid for treatment of DMD. A pre-clinical trial of vamorolone versus prednisolone in dysferlindeficient mice (LGMD R2/2B model) showed that vamorolone stabilized the muscle cell membrane and improved repair of injured myofibers (Sreetama et al., *Molecular Therapy*, 2018).

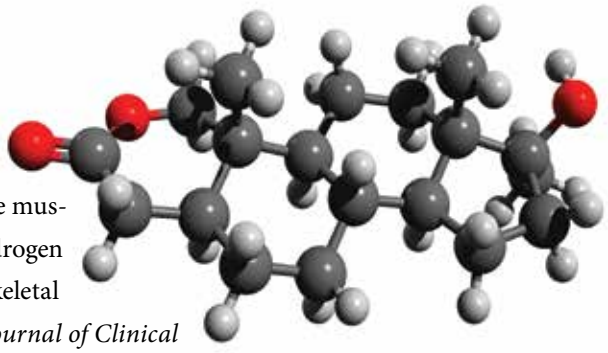
As the mechanisms of action of these medications are not specific to DMD, patients should watch for clinical trials of these treatments for other types of muscular dystrophy. We cannot recommend off label prescribing

of this or any other medication due to the potentially higher risk of unanticipated side effects and less predictability in therapeutic response. Patients should discuss any additional questions with their health care providers.

Q

Why are there virtually no studies on the potentially beneficial effects of androgenic steroids (e.g., oxandrolone), of which there are molecules with a powerful anabolic effect? These steroids have been used for decades by a very large number of sports enthusiasts across the world.

A



Anabolic androgenic steroids directly increase muscle mass by inducing androgen receptor expression in skeletal muscle (Basaria et al., *Journal of Clinical Endocrinology and Metabolism*, 2001). Fenichel et al. found no significant differences in muscle strength between boys with DMD who received oxandrolone compared to placebo (*Neurology*, 2001). Oxandrolone is no longer available on the market for any indication, as it was withdrawn by the FDA in 2023. Additionally, a number of adverse effects are known to be associated with anabolic steroids. ■

Have a Question for Our Experts?

Send Questions To:
ContactUs@TheSpeakFoundation.com

Fighting for a Cure:

An Interview with Dr. Nicholas Johnson

Nicholas Johnson, MD, MSCI, FAAN
Professor and Vice Chair of Research
Director, Center for Inherited Muscle Research (CIMR)
Virginia Commonwealth University

Kathryn Bryant Knudson, editor in chief of *LGMD News* magazine, recently toured the laboratories and facilities at Virginia Commonwealth University (VCU) where she met some of the incredible researchers working under the leadership of Dr. Nicholas Johnson. The Speak Foundation is supportive of the work being done at VCU, as the institution has a rich legacy in treating neuromuscular diseases.

Kathryn recently interviewed Dr. Johnson, Director of the Center for Inherited Muscle Research (CIMR) located at VCU, who also leads the GRASP-LGMD Consortium. In the Q&A below, learn more about why Dr. Johnson has chosen to focus on LGMDs and how the LGMD community can better support his research.

Q

Where did you grow up and what led you into the medical field?

A

I grew up in Phoenix, Arizona, and went to medical school at the University of Arizona. I knew in high school that I wanted to be a physician. More importantly, when I rotated as a first-year medical student in a Muscular Dystrophy Association (MDA) clinic, I knew I wanted to be a neuromuscular physician. I spent my Tuesday afternoons for the rest of that year with Dr. Lawrence Stern who provided the foundations of my training in the muscular dystrophies. I was really fortunate to complete my residency and fellowship at the University of Rochester, where Dr. Berch Griggs, Richard Moxley, Charles Thornton, and Chad Heatwole taught me how to develop into a neuromuscular physician with a focus on developing new therapies.

Q

What influenced your interest in LGMDs rather than other diseases?

A

I suppose I have always been a fan of the underdog. There is so much possibility in the LGMDs in terms of a high impact treatment changing the course of the disease. In many cases, the missing gene is small enough to fit into what we now use for gene replacement therapy. These are slowly progressive conditions that primarily affect the muscle, giving us a wide time period to act and a tissue that is able to regenerate. I was attracted to these aspects and of course to the wonderful patient community.

Q

What do you think is the most promising potential treatment that is possibly being overlooked for LGMD?

A

Exercise. Done in collaboration with a knowledgeable, local physical therapist, there is a lot of opportunity to maintain function as much as possible with a good exercise and rehabilitation regimen. We hear a lot of stories about individuals who lost some function during the COVID-19 pandemic because they weren't moving around enough. It is a good idea and something many can do right now. Even with effective gene replacement therapy, exercise will be twice as important to help regenerate strength and function if and when the gene and protein are restored.

Q

What resources are available to patients at your clinic?

A

We have a full multidisciplinary clinic that has physical therapy, occupational therapy, speech therapy, respiratory therapy, social work, a dietician, and a genetic counselor. That can make for a full day, but we try to address any issue that may arise during the clinic visit. In addition, we will often have a research study that may be available to you.

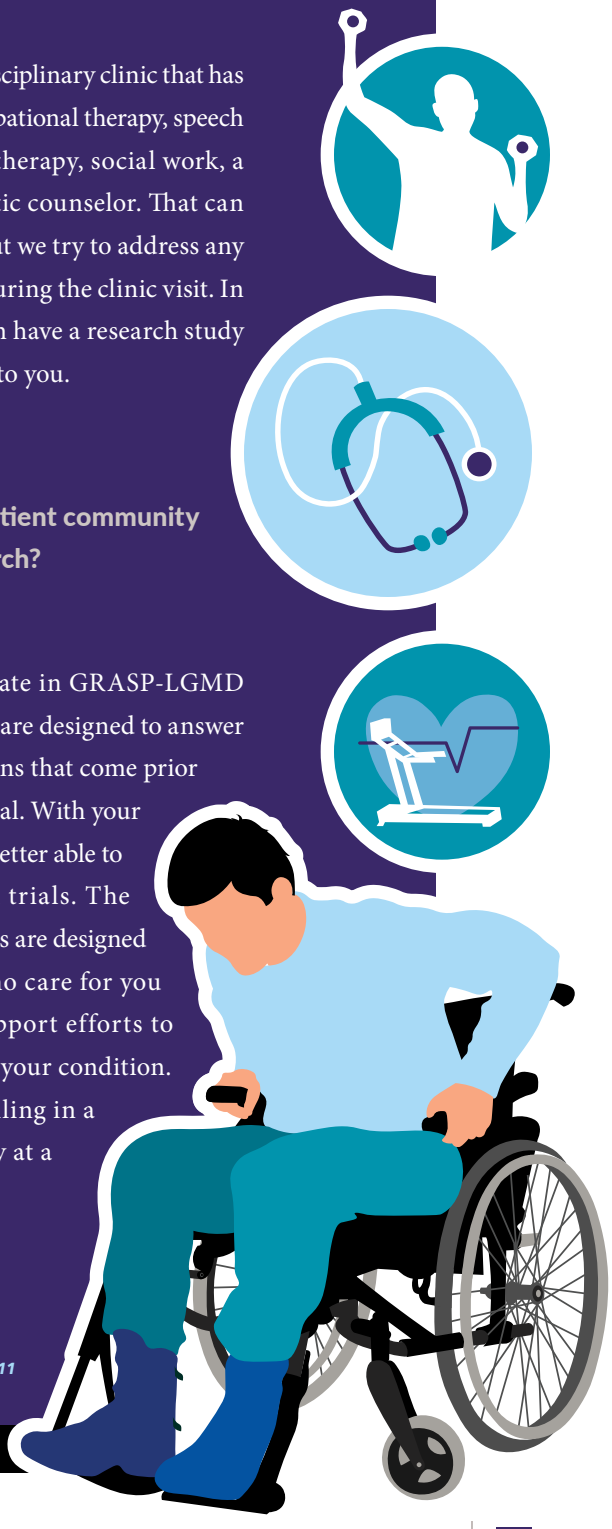
Q

How can we as a patient community support your research?

A

Continue to participate in GRASP-LGMD studies. These studies are designed to answer the important questions that come prior to a drug treatment trial. With your participation, we are better able to design good clinical trials. The GRASP-LGMD studies are designed by the physicians who care for you and who want to support efforts to develop therapies for your condition. Please consider enrolling in a GRASP-LGMD study at a center near you. ▪

For study locations, see Page 11



For more information on GRASP-LGMD Natural History Studies, see Page 13.

CIMR is Committed to Moving Treatments Forward for LGMD

The Center is designed so that the patient experience is closely linked to scientific investigation and development of new treatment approaches. Due to the rarity of muscular dystrophies, patients must be active participants at all stages of research in order to develop therapies.

The Center for Inherited Muscle Research (CIMR) at Virginia Commonwealth University's (VCU) Children's Hospital of Richmond has a longstanding commitment to accelerating the development of new therapies for the LGMDs. The Center's mission is to develop new therapies and make them accessible throughout the world. CIMR has a collaborative team of clinical and research experts who are united in their quest to pursue new frontiers in diagnosing and treating genetic disorders of muscle.

Dr. Nicholas Johnson serves as the Center Director. Over the past year, CIMR has grown to include nine full-time faculty members dedicated to muscular dystrophies. The Center is designed so that the patient experience is closely linked to scientific investigation and development of new treatment approaches. Due to the rarity of muscular dystrophies, patients must be active participants at all stages of research in order to develop therapies. The CIMR multidisciplinary team is composed of more than 50 research and clinical care specialists. Its collaborative approach means that patients benefit from the integration of cutting-edge care with on-site research capabilities.

CIMR serves as the coordinating center for the GRASP-LGMD consortium (Genetic Resolution and Assessments Solving Phenotypes in LGMD). The coordination includes taking information from individuals with LGMD around the world and trying to match them closely with sites that we support. As you, or others, living with LGMD write to us, we also consider your experience in clinical research and how to improve our studies.

A central theme of our consortium is to reduce the barriers to drug development. We primarily accomplish this through our trial readiness studies (also referred to as natural history studies), where we ask those with LGMDs to visit a GRASP-LGMD site and perform tests to see how the disease is progressing over several years. We then take that information and share it with our partners to help design clinical trials. In fact, these efforts led to two of the very first disease-modifying trials in LGMD R9/2i. The first patients in both of these studies were enrolled here at our center.

We hope that expanding trial readiness efforts across all LGMDs will encourage drug development. While many participants in these studies have met the investigator, coordinator, and therapist, they may not realize there is a larger team of people supporting the study. At CIMR, we have network coordinators, regulatory and fiscal specialists, and data managers all helping to ensure this study goes smoothly and collects high-quality data.

The GRASP-LGMD network currently has three ongoing natural history studies for multiple LGMD subtypes and Becker muscular dystrophy, respectively (Page 13; note: GRASP-01-001 is not listed, as it is no longer recruiting). All three studies evaluate the natural progression of these conditions in order to validate a series of physical therapy exercises, also known as functional assessments, as a standard biomarker of the rate of progression among the populations being studied. Each study has individual secondary and tertiary objectives specific to the populations, with the same goal of identifying other biomarkers

that can standardize a measure of change within the population.

Our GRASP-01-001 study, for a variety of LGMD subtypes, successfully enrolled 140 participants, and we look forward to sharing the data later this year. For GRASP-01-002, the Becker natural history study, we have reached 50% of our enrollment goal and look forward to meeting our enrollment goals by the end of summer. Finally, GRASP-01-003, an LGMD R1/2A-specific study, has just begun enrollment and enrolled the first 10 of an anticipated 100 participants. The network hopes to have additional natural history studies open for enrollment later this year.

The CIMR's goal is to collaboratively develop cures for muscular dystrophies and other genetic myopathies and to train future scientists in a team-based bench-to-bedside approach. We have several preclinical scientists dedicated to understanding the mechanisms of the LGMDs and how to treat them. Dr. Melissa Hale has worked to understand the differences in protein expression between those affected by LGMDs and those who carry one bad gene (but not both). This information is helpful in understanding how much gene replacement is "good enough" for successful treatments.

More importantly, Dr. Hale, Dr. Christopher Heier, and Dr. Alyson Fiorillo have developed an AAV-based gene replacement for LGMD R7/2G that showed promise in a mouse model. This team is currently hard at work on two more LGMD gene transfer therapies. These three therapies are either in proof-of-concept testing or ready to move forward with toxicology assessments. Most importantly, the Center is designed to use our trial readiness data efficiently and bring these therapies back into the clinic.

While all LGMDs currently remain without approved therapies, recent advances in genetic medicine are driving new understanding of how to effectively alter the genetic mutation that causes them—and potentially reduce the severity and slow the trajectory of disease progression in some patients. The Center for Inherited Muscle Research is positioned to leverage this momentum, putting the full force of its collaborative research and clinical team to work to fast-track discoveries in the lab and their real-life applications in the clinic.

To learn more about LGMD research, clinical trials, or our multidisciplinary care, please contact Ruby Langeslay at **804-828-8481** or **Ruby.Langeslay@vcuhealth.org**. ▪

Written by Erin Ohrenberger DeSpain, MPA
Director, Business Operations, VCU Health

Above: The Center for Inherited Muscle Research at Virginia Commonwealth Universty's Children's Hospital of Richmond

Connect with Us

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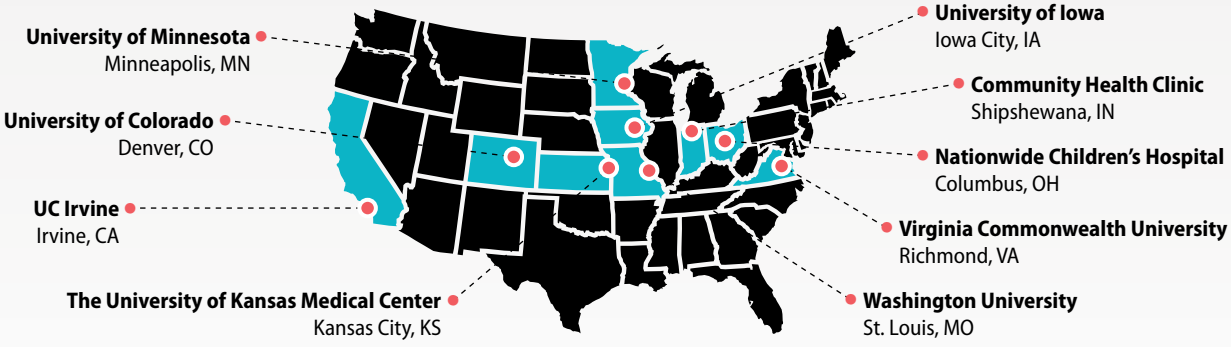
Active GRASP-LGMD Natural History Studies



The Community Health Clinic: Compassionate, Comprehensive, and Coordinated Medical Genetics Care in Northern Indiana

As a medical home for patients and families with complex genetic conditions, our team of health professionals works hard to help patients and their families get needed medical care for the best possible health outcomes.

The Community Health Clinic (CHC) is a 501(c)(3) non-profit healthcare facility located in Shipshewana, Indiana, that provides specialized genetics care consistent with Amish and Mennonite (Plain) values. The CHC provides clinical genetic services to all individuals, regardless of religion, race, or age. Over the past 11 years, the CHC has grown into a successful rural genetics clinic and a thriving clinical research center.

The CHC currently serves 1,500-2,000 individuals per year with special healthcare needs related to genetic conditions. As a medical home for patients and families with complex genetic conditions, our team of health professionals works hard to help patients and their families get needed medical care for the best possible health outcomes.

The world's highest concentration of individuals with LGMD R1/2A (calpainopathy) hail from Indiana's Adams and Jay Counties, where at least 150 affected people live within a 20-mile radius and more than one in 400 babies are born with the disease. The CHC is a medical home for these patients, providing them with affordable genetic testing, counseling, and medical care. Based on this extensive clinical experience and the trust on which it is founded, the CHC recently became a site for the GRASP study.

Rapid advances in genetic therapy for Duchenne muscular dystrophy and LGMD R4/2E have set the stage for LGMD R1/2A, but therapeutic development has outpaced clinical trial preparedness. Calpainopathy is the most common form of LGMD, accounting for 30% of LGMD worldwide, but there are currently no approved therapies to alter the natural course of the disease.

Calpainopathy should be amenable to several emerging therapeutic approaches, including gene replacement, gene editing, and myostatin inhibition. Therapeutic development depends critically on rigorous natural history data as the basis for the design of clinical trials. It is vital to identify the health outcomes that are most meaningful to patients and their relationship to measurable biomarkers. These form the indispensable foundation for enabling high-quality and successful clinical trials. At the CHC, we're honored to participate in this process and inspired by the opportunity to support clinical trials that bring new hope to the families we serve. ■

Written by Zineb Ammous, MD, FACMG
Clinical and Biochemical Geneticist
Medical Director, The Community Health Clinic

Our Mission

Our Mission is to provide excellent and affordable medical care consistent with the needs of the Amish, Mennonite, and other rural northern Indiana communities, with a focus on individuals and families with special healthcare needs. We embrace, incorporate, and promote participation in research to advance medical knowledge and improve care.

UPDATED: JULY 1, 2024

Active GRASP-LGMD Natural History Studies

Recruiting:

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

Inclusion Criteria

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

Exclusion Criteria

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

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

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

Recruiting:

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

Inclusion Criteria

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

Exclusion Criteria

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

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- **Nicholas Johnson**, MD, MSci, FAAN | Virginia Commonwealth University
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- **Doris Leung**, MD, PhD | Kennedy Krieger Institute
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- **Richard Roxburgh**, Mb ChB, FRACP, PhD | University of Auckland
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- **John Vissing**, MD | University of Copenhagen
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- **Carla Zingariello**, DO | University of Florida

Spotlight:

Dr. Zineb Ammous

The Community Health Clinic

Dr. Zineb Ammous completed medical training at Cornell University (Doctor of Medicine, 2009), University of Miami (Medical Genetics, 2013), and University of Michigan (Medical Biochemical Genetics, 2024). In 2012, she co-founded, and serves as medical director for, The Community Health Clinic (CHC), a rural, non-profit clinic providing medical care to genetically and socially vulnerable populations of Northern Indiana and surrounding states, with a focus on the needs of agrarian Amish and Mennonite communities. Dr. Ammous is a member of Indiana's Perinatal Genetics and Genomics Committee and NBS subcommittee. She is also an Adjunct Clinical Assistant Professor of Medical and Molecular Genetics at Indiana University School of Medicine with active research interests in gene discovery, disease outcomes and biomarkers, and precision therapies for neuromuscular disorders and inborn errors of metabolism.

Compliance in Clinical Trials:

Why Following the Study Protocol is Vital

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

Investigational products, which can be drugs, devices, vaccines, or even diagnostic tools, undergo rigorous testing in clinical trials before they can be widely available to the public. Each stage of developing an investigational product (also known as a clinical trial phase) is designed to learn more about the safety and efficacy of the investigational product by collecting more data. Efficacy means how well a particular drug product, device or diagnostic tools produces the expected results under carefully controlled scientific testing conditions.

For these data in clinical trials to capture an accurate picture of the investigational drug's safety and efficacy, one crucial factor often goes unrecognized: participant compliance. In clinical trials, compliance refers to how well participants follow the instructions in the study protocol. Being compliant means following the study protocol meticulously, from taking and tracking the use of the investigational product as directed, to attending all scheduled site visits on time and completing assessments according to the protocol. This seemingly simple act has a profound impact on researchers and regulatory authorities' ability to understand an investigational product.

ML Bio Solutions

Compliance Impacts Data Collection

When the protocol is followed, data are collected for each participant in the same way and at the same or similar timepoint in the study, resulting in consistent data collection. Consistent data collection allows researchers to more accurately assess study data and draw more precise conclusions about an investigational product's safety and efficacy.

Incomplete or missing data can impact researchers' understanding of an investigational product by making the resulting data unreliable. Imagine a trial where some participants miss blood tests, inconsistently take an investigational product, or do not document their compliance as instructed. These actions result in inconsistent, unreliable data, ultimately making it difficult for researchers to determine the true effects of an investigational product.

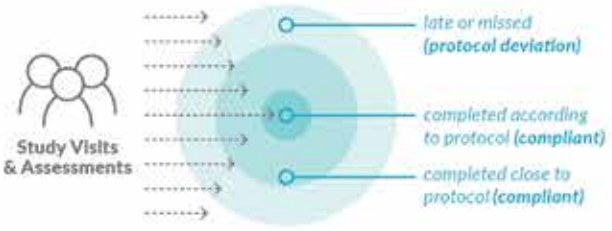
The Power of Precise Data

Compliance with a study protocol is vital to understanding an investigational product. Researchers rely on data collected throughout the clinical trial to inform them about the investigational product. Data collected through assessments help to paint a picture of how the product is distributed in the body and how participants are responding to an investigational product.

Compliance with these assessments ensures researchers gather accurate and timely information. When a participant does not comply with a study protocol or study assessments, this may not only impact the health of participants in the study but also may prevent the development of potentially efficacious investigational products.

What Are Protocol Deviations?

Regulatory authorities, such as the United States Food and Drug Administration (FDA), set strict guidelines for clinical trials. Any deviation from the protocol, including missed assessments or assessments not done on time, may give regulatory authorities reason to question or doubt the integrity of the data of an entire clinical study. If a study participant misses assessments, these missing data points may result in an entire study participant being excluded from the final analysis, reducing the overall strength and reliability of the study. In severe cases, the FDA may even refuse to consider the clinical trial data altogether, leading to wasted time, resources, and potentially delaying the development of a crucial new medication, treatment, device or tool.



A Collective Effort

A clinical trial is a collective effort to advance medical research, that impacts the entire patient community. By following the protocol and participating fully in all assessments, study data can be more accurately collected and assessed, and participants' wellbeing can be accurately monitored. This ultimately contributes to the development of safer and more effective treatments. By adhering to the protocol, participants play a vital role in advancing medical science and paving the way for new therapies.

Written By Vovanti Jones, MD
and Carol Abraham

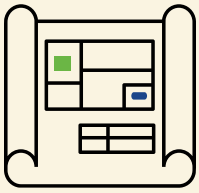
Home Sweet Home!

Integrating Accessibility Into Your Home

SureHands® Ceiling Lift *Courtesy of SureHands® Lift & Care Systems*

For most people, home is a sanctuary. It is a place where we want to be surrounded by the comforts, people, and things we cherish most. Home is the place where we should feel the safest. For people with limb-girdle muscular dystrophy, though, home can become a place of obstacles and stress as our physical abilities change. Stairs become the daunting, sometimes impossible, Everest of a home. For wheelchair users, narrow doorways and spaces create barriers to optimal maneuverability.

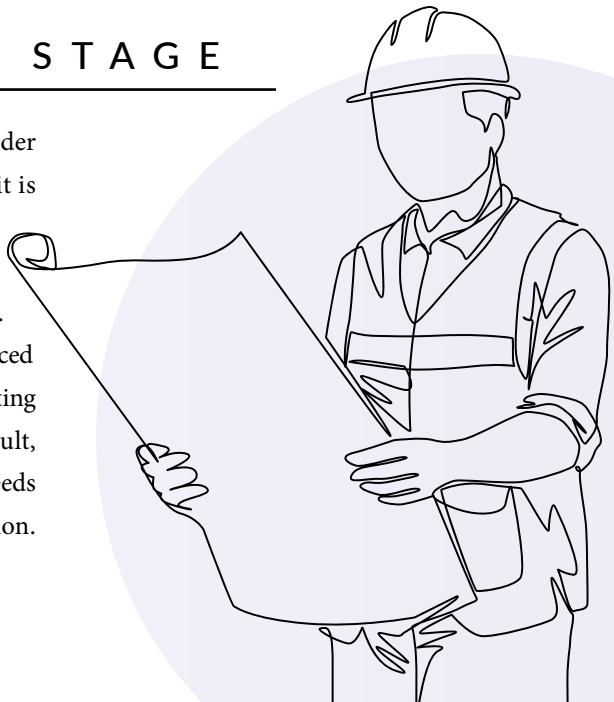
In this article, we explore a wide array of features including structural changes, technology, and appliances that can improve home accessibility and therefore quality of life for those with LGMDs. We want to equip you with information that lays out the "ideal" in terms of accessibility, so that you can reference aspects that may work for your particular budget, physical needs, and space. We have also provided some funding resources on Page 21.



THE PLANNING STAGE

"ALTHOUGH IT MAY BE DIFFICULT, IT IS ALSO WISE TO PLAN FOR POTENTIAL FUTURE NEEDS THAT MAY ARISE FROM A PROGRESSIVE CONDITION."

If you are in a position to be able to consider remodeling or even new construction, it is very important to collaborate with your builder or contractor to make sure that they understand your accessibility needs. We recommend using a contractor experienced in creating accessible spaces and incorporating universal design. Although it may be difficult, it is also wise to plan for potential future needs that may arise from a progressive condition.



UNIVERSAL DESIGN

Universal design is a concept in which the environment is designed to be usable by people of all abilities, without requiring additional adaptation or specialized design. In an ideal world, all properties would be built with this in mind!

PHYSICAL SPACE

Universal design ensures that physical spaces are designed to accommodate wheelchair users as well as ambulatory individuals. This includes features such as:

- At least one ramped exterior entrance with a gentle slope and handrails instead of stairs (see ADA guidelines in the U.S. or other applicable guidelines for your country)
- 36-inch-wide (90 cm wide) doorways can easily accommodate wider power wheelchairs. This also makes it easier to bring appliances and furniture into the space.
- 48-inch-wide (120 cm wide) hallways make it easier to have wheelchair turnaround space.
- 48-inch-wide unobstructed turnaround space in rooms such as the kitchen, bathroom, and living room
- Smooth, slip-resistant flooring is recommended. Luxury vinyl plank (LVP) flooring or hardwood are durable surfaces that work well. Caution should be used when considering floating vinyl flooring. Be sure to use a qualified installer!
- Low-pile Berber carpeting with firm padding is something to consider as thick-pile carpet can be difficult to ambulate or maneuver a wheelchair on. High-pile carpet does not wear well with wheelchair use over time and can become matted.
- Transitions and door thresholds between different types of flooring should be smooth to prevent tripping hazards.

Jessica Evans' (LGMD R1/2A) bathroom remodel

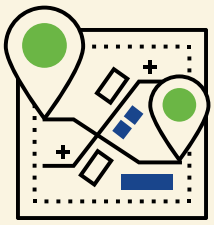
ACCESSING THE ENVIRONMENT

Universal design considers comfort, safety, and independence. These are some features to consider which may improve independence, especially for wheelchair users.

- An automatic exterior power door opener can be controlled by a remote or voice control for added independence.
- Traditional doorknobs and faucets can be replaced with lever-style handles that may be easier to operate.
- Wi-Fi-enabled smart technology can control lights, thermostats, fans, door locks, etc.
- Light switches lowered to a height of 36 inches (90 cm) and electrical outlets raised to a height of 24 inches (60 cm) are more easily accessed from a wheelchair.
- Additional electrical outlets in the bedroom to accommodate plugging in medical equipment (e.g., ventilator, humidifier, electric bed, scooter/wheelchair charger, etc.) which may be needed now or in the future.

Wi-Fi-enabled technology

Lever-style handle



ACCESSIBLE HOME TOUR

Come take a tour with us as we walk through some specific design features of an accessible home.

ENTRYWAYS

For a person with mobility difficulties, the entryway can present an immediate challenge. Not all homes have a low threshold entry, so modifications are often necessary for people who use wheelchairs, scooters, walkers, or rollators. For those who walk but find climbing steps difficult, an extra shallow step with a grab rail can make a big difference.

Above: Silver Spring 12' Side-Entry Straight Modular Ramp with 4' Platform
©DiscountRamps.com

Karen Haley-Wingate's (LGMD R1/2A) exterior entryway ramp with custom high bench seating

Jessica Evans' EZ-Access Vertical Platform Lift

Ramps

- For new homes, consider pouring a concrete threshold ramp at the exterior entryway or purchasing rubber or metal threshold ramps. (**DiscountRamps.com** offers many options.)
- For houses that already have steps, ramps can be built over the steps. These ramps can be built out of wood or purchased as aluminum modular units that are installed. Remember to leave a flat landing at the door entry.

Wheelchair Platform Lifts

- These lifts are designed to vertically raise a wheelchair user up several stairs to a porch or platform. Depending on the type of lift, the user can operate the lift either remotely or with buttons inside the lift.
- These lifts can take up less space than a ramp, especially if there are a lot of steps. They typically lift to around 50 inches (1.25 meters) in height.
- They can be used both inside and outside the home.

Stair Lifts

- Stair lifts are designed for the user to sit in a chair that moves on an electric rail system to bring the person up and down the stairs. Some individuals may require a second mobility device on the other level of the home when using a stair lift.

LIVING ROOM

The living room is generally the most used area of the home. For wheelchair users, an open floor plan allows the room to be configured for open pathways throughout the home. It also allows for better access to furniture like couches for transfers. However, for some ambulatory individuals, this open layout may not be helpful if they are used to using the walls or furniture to help with stability. Meeting individual needs is key to successful home design.

KITCHEN

A kitchen that is accessible for a wheelchair user requires many design elements that are not typical in a standard kitchen. If you are able to make significant changes to your home, careful planning can improve accessibility without overspending.

Appliance Accessibility

- Drawer-style dishwashers are good alternatives to traditional dishwasher designs and allow the user to roll right up to the rack without needing to bend or reach down to retrieve dishes.
- Countertop stovetops can give much-needed knee room to cook meals from a seated position if a roll-under area with accessible controls is created.
- Swing door wall ovens have doors that swing to the side instead of down to allow for easy access to food. A convenient option is to add a retractable shelf beneath the oven to pull hot food onto while it is cooling. This makes it possible to get hot food out of the oven safely.
- Drawer microwaves are installed below the countertop and have a push-button open and close. Users lower the food into the microwave, making the food easier to reach.
- Refrigerator placement is also important to allow the doors to be opened from a wheelchair. For those with limited reach, a counter-depth refrigerator can be used.

ELEVATE AWARENESS

with the LGMD Awareness Day Toolkit!

Join LGMD Awareness Foundation in our mission to elevate global awareness for limb-girdle muscular dystrophy. As we celebrate a decade of progress, we are sharing a toolkit designed to empower and engage our community in advocacy like never before.

Social Media Graphics, Virtual Backgrounds, Media Kits, Merchandise, and more!

Scan here to access the LGMD Awareness Day Toolkit, or enter our VIDEO CHALLENGE or COLORING CONTEST! →

LGMD AWARENESS FOUNDATION

lgmd-info.org/toolkit

Thank you to our sponsors:

ML BioSolutions

SAREPTA THERAPEUTICS

Left: An experienced carpenter was able to retrofit inexpensive cabinets to create this customized look.

A kitchen island can be designed with a pull-under workspace on the end.

Stove Fans/Vents

- Stove fan/vent wall or counter electrical switches are a great options, as standard vents above the stove are difficult to reach for wheelchair user. These fans can be wired to your electrical system for wall switch operation.

Amy Buren's (LGMD R1/2A) ceiling lift with track system is permanently installed on the ceiling.

Sinks

- Sinks can be placed on the island or along the wall.
- Roll-under sinks for wheelchair users allow better seated positioning at the sink. The sink can also have drains that sit farther back or to the side to allow for a garbage disposal.
- Shallow/low-depth sinks are great for those with limited reach.
- Bar sinks are narrower sinks that can be placed next to the stovetop if you have difficulty carrying water from the sink to the stove.

Vovanti Jones' (LGMD R2/2B) kitchen has a bar sink beside the roll-under cook top and a drawer microwave.

Counters

- Careful consideration needs to be given to who will be using the counters most. If your powerchair has a seat elevation feature which allows you to adjust to counter height, this has the advantage of allowing able-bodied people to share the counter height with you while they are standing. Lowering some of the counter heights allows people of differing abilities to use the kitchen together. Be sure the bottom of the counter (and any roll-under area) is higher than your chair/mobility device's armrests while at its lowest position setting.

Islands

- A kitchen island can be designed with a roll-under workspace. This is convenient as it allows more counter space to prepare food while seated and offers additional counter-height space to dine.

Cabinets

- Pull-out drawers in the cabinets can allow easy access to the full depth of the cabinets for those who can't reach that far back. Cabinet pull handles are more accessible than knobs.

BEDROOM

Getting into and out of bed can become a major difficulty for those with LGMDs. If space allows, a ceiling lift may be able to be installed to help assist with transfers. There are several different types of ceiling lift systems available.

- Ceiling lifts with track systems are permanently installed on the ceiling. The individual can be lifted and transferred using a sling. In some circumstances, the tracks can be modified to go where needed (e.g., from the bedroom to the bathroom).
- Temporary ceiling lifts may be an option for people living in apartments or where there is insufficient support structure in their ceiling. An independent base reaches from the floor and may touch the ceiling for support. However, these can only be used for transferring in or out of one location.
- SureHands Ceiling Lift or Prism Independent Body Lifter systems are easier for many to independently operate, as they do not require the use of a sling. The body support grips your upper body as a result of pressure on the hook-shaped leg supports. They do require the user to have good head and neck control, moderate upper body strength, and good torso control. These lifts can also be modified to go where you need them (e.g., in-and-out bed transfer, bed to bathroom).

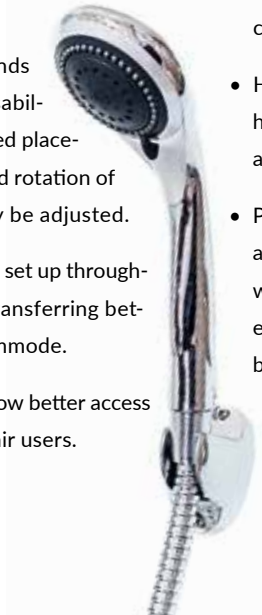
Right: Amy Buren's zero threshold roll-in shower

Above: Tara Boone's (LGMD R9/2i) Stiltz Trio home elevator

BATHROOM

It is essential for health and dignity to be able to bathe or shower in safety and comfort. This may take some thought and planning for people with mobility challenges due to LGMDs.

- Zero threshold roll-in showers are great for wheelchair users. Be sure the shower is large enough for a shower bench and a caregiver, if needed. Many European bathrooms feature a "wet room" like this as standard.
- Wall-mounted shower benches allow for better stability versus free-standing shower chairs. Some of the wall-mounted benches fold up to allow non-disabled users access to the shower. It is essential that the shower bench is set at a height that allows a wheelchair user to transfer or an ambulatory disabled person to stand easily.
- Built-in shower benches can be made of tile at a height that works best for you. The disadvantage for people with LGMDs is, as your needs change, you may need to make major alterations. If these are not possible, a removeable bench or rolling shower commode chair can enable a person to continue to use their bathroom safely.
- Handheld shower heads/wands are helpful for users with disabilities, as they allow for targeted placement of water. The height and rotation of the shower head can usually be adjusted.
- Ceiling lifts can sometimes be set up throughout the bathroom to allow transferring between the tub, shower, or commode.
- Roll-under bathroom sinks allow better access to the sink area for wheelchair users.



- Grab bars in the right place make the user much safer in the shower and beside the commode. Asking a contractor to block at least a 1-foot area in the wall to provide extra reinforcement for the bars will allow a grab bar to be installed in the future, even if you do not require one now.
- Bath/shower lift systems like the Pro Bath Chair Lift may be be installed to safely transfer the user into a bathtub or shower. This chair lift can lower the user to the ground, which can help with stability while bathing oneself.
- ADA-height toilets make using the toilet much easier for patients with LGMDs, where a first symptom is often difficulty in rising to standing. For a wheelchair user, there needs to be ample space for maneuvering a wheelchair to the toilet in order to transfer. If a raised toilet is not an option due to space or cost, toilet risers or portable frames (e.g., Mowbray Toilet Seat and Frame) can be less expensive options.

OTHER AREAS AROUND THE HOME

- Having access to a first-floor bedroom and full bathroom is an important part of planning for the future. You might also consider a first-floor laundry room with a side-by-side front-loading washer and dryer.
- To give wheelchair users maximum independence, storage areas should ideally be easily reachable from a seated position. You could consider installing pull-out cabinet shelves as well as having at least one lowered clothes-hanging rod in the closet.
- Home elevators can be installed in multi-level homes. Make sure that it is large enough to fit a power wheelchair and a caregiver.
- Patio sliding doors can be difficult to traverse in a wheelchair due to the raised threshold. One way to solve this is to place threshold ramps on each side of the threshold. The ramps should be at least a ½ inch taller than the threshold to reduce the risk that the power wheelchair wheels will bend the threshold. ■

Jessica Evans' ProBath Chair Lift

Karen Cole's (LGMD R9/2i) swimming pool has a ramped entry with support rails.

Accessibility Funding Resources

- Centers for Independent Living
- Home Equity Line of Credit
- Life Insurance Loan
- Long-Term Care Insurance
- Medicaid Home and Community-Based Services Waiver Program
- Medicare Advantage Plans
- Mortgage Refinancing
- Non-profit Organizations
- Retirement Savings
- Unsecured Personal Loan
- Vocational Rehabilitation Program

Additional Programs and Grants:
LGMD-Info.org/knowledge-base/navigating-lgmd/for-patients/lgmd-grant-opportunities

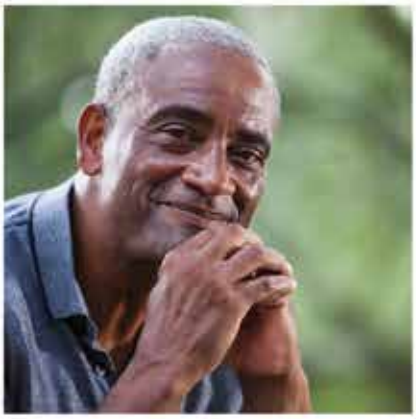
For the UK, contact the local authority to inquire about being assessed for a Home Improvement Grant. Advice about adaptations and grants can also be found at:
MuscularDystrophyUK.org

Disclaimer: The information in this article may not be applicable in every country. We invite those living outside of the U.S. to share your suggestions in The Speak Foundation's online community on Facebook.

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.

Sponsored by SAREPTA THERAPEUTICS

SAREPTA THERAPEUTICS

The importance of the muscle biopsy in advancing research & development

What is a muscle biopsy and how are they performed?

A skeletal muscle biopsy is a medical procedure. Typical biopsy areas include the bicep (upper arm muscle), deltoid (shoulder muscle), tibialis anterior (front lower leg muscle), or quadricep (thigh muscle). Tissue from a muscle biopsy may be analyzed for overall tissue appearance, the presence or absence of key proteins, or changes in the tissue to help diagnose muscle disorders, understand disease impact, and/or assess the effect of an investigational treatment in a clinical trial.

Open biopsies are a type of biopsy where a cut is made in the skin to remove a small piece of muscle. Other types of biopsies exist, such as needle biopsies.

For most biopsies, including open biopsies, local anesthesia is typically administered to numb the biopsy area. In some cases, general anesthesia may be required. After a biopsy, pain medication may also be offered as needed. If a biopsy is a part of a clinical trial or natural history study, there is typically no cost to participants.

Why might muscle biopsies be needed?

To accelerate clinical development.
In some investigational drug trials, laboratory data obtained from analyzing biopsies may be an important assessment to support the evaluation of a surrogate endpoint for drugs pursuing an accelerated approval pathway. A surrogate endpoint is a marker, such as biopsy data, that is believed to predict clinical benefit. Using a surrogate endpoint such as biopsy data may support accelerated approval while researchers continue to collect data on the functional outcomes of the therapy, which may take additional time.

Outside of treatment trials, biopsy data may also be collected in non-interventional studies, such as natural history studies, to gain a deeper understanding of a disease. These data are especially important in growing the body of knowledge for rare diseases such as the limb-girdle muscular dystrophies (LGMDs) and provide critical insights for researchers and regulators.

For diagnostic purposes.
A muscle biopsy can help diagnose conditions that involve the musculoskeletal system. While it is no longer the primary method to definitively diagnose an LGMD subtype, it can aid in the Variant of Uncertain Significance (VUS) reclassification process

What's a VUS?

For a Genetics 101, check out the January 2024 issue (pg. 10-11) of the *LGMD News Magazine*. Scan to access or visit The Speak Foundation's website

Although muscle biopsy was a commonly used diagnostic method in the past, genetic testing such as next-generation sequencing (NGS) is considered a minimally invasive way to help diagnose many genetic conditions, including LGMDs. A saliva or blood sample is often all that is required for genetic testing.

To learn more about genetic testing, visit **limbgirdle.com/genetic-testing**

SAREPTA THERAPEUTICS

Written By Joshua Thayer

Establishing the Efficacy of New Drugs

An Exploration of "Clinical Trial Endpoints" and the LGMD Community Perspective

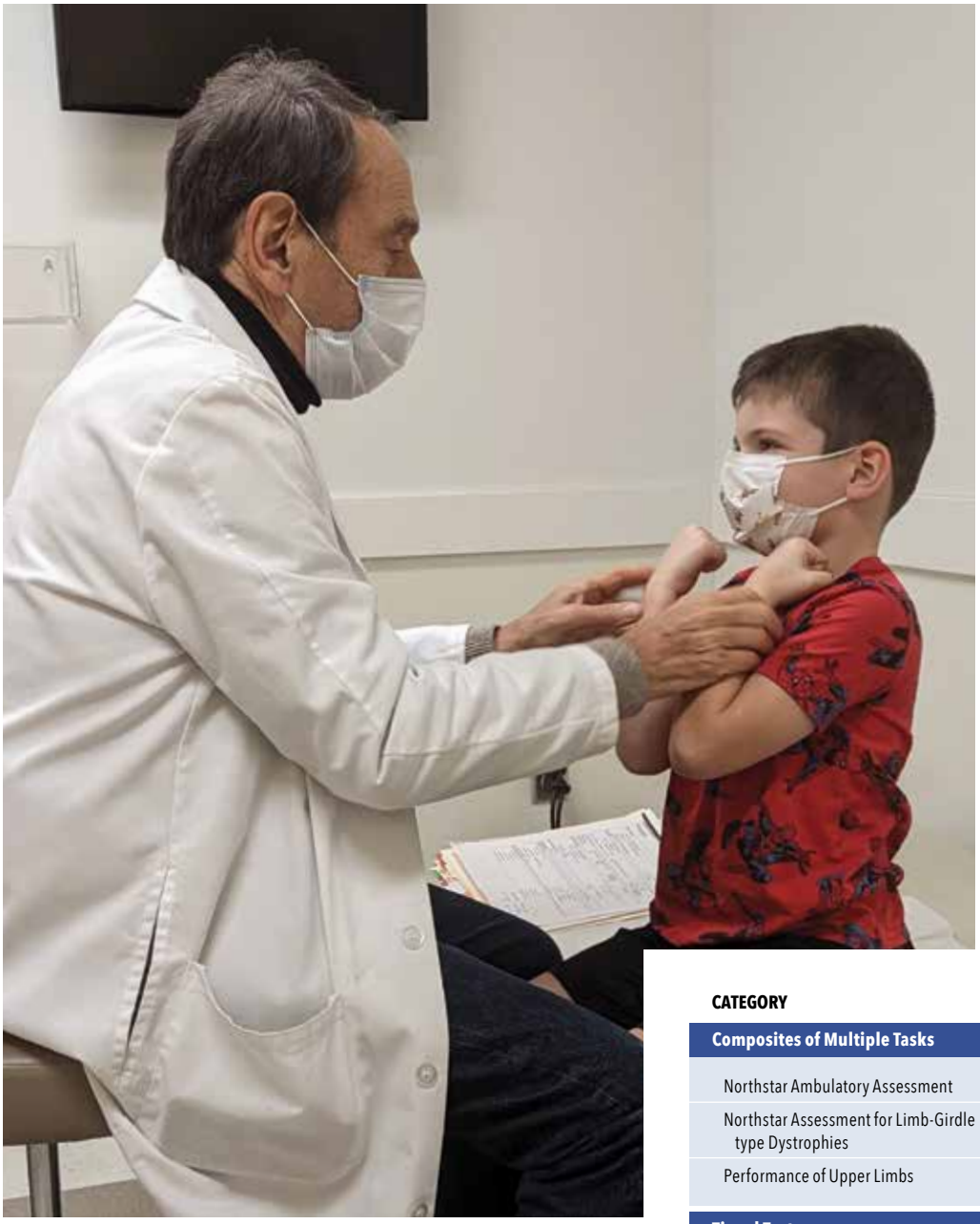
If you or a family member has ever participated in an LGMD natural history study, you're likely familiar with the numerous tests the zealous physical therapists marshal you through. While enthusiastically cajoling you to "push harder," "squeeze tighter," and "exhale, exhale, exhale," they diligently measure and time your efforts. *"But… to what end?"* you might have asked yourself. Well, one goal of those studies is the subject of this article: to help clinicians design and validate so-called "clinical endpoints"— specific functional measurements used in clinical trials to test the efficacy of a new drug.

Brief Overview of the Drug Approval Process in the U.S.

To be approved for sale in the U.S., a drug must be shown to be safe and effective in clinical trials. If the drug treats a serious disease which currently has no available therapy, such as a limb-girdle muscular dystrophy, the U.S. Food and Drug Administration (FDA) may grant either traditional approval or Accelerated Approval. Accelerated Approval, discussed in the previous *LGMD News* issue, is an approval granted to a drug based on surrogate endpoints which the FDA deems reasonably likely to imply an eventual clinical benefit over time. For example, tumor reduction in cancer patients and the expression of a missing protein in muscular dystrophy patients have both served as surrogate endpoints for Accelerated Approval. While Accelerated Approval provides early access to treatments, the FDA requires confirmatory studies to confirm actual clinical benefit.

What is a Clinical Endpoint?

A clinical endpoint is an outcome measurement used in a clinical trial to test whether the drug is providing its intended benefit. Measurements chosen as endpoints might include the ability or amount of time to perform physical activities, or the patient-reported perception of well-being. Most trials include multiple clinical endpoints, with one designated as a "primary clinical endpoint" and others as "secondary or tertiary clinical endpoints." The primary endpoint is chosen as the most important measurement for designing the parameters of the trial and evaluating the drug's efficacy. For rare disease drug trials, however, the FDA may take a "totality of the evidence" approach, with less distinction made between primary and secondary endpoints.



Left: Dr. Jerry Mendell performs strength testing on Jacob DeConti, who lives with LGMD R3/2D, as part of the JOURNEY Natural History Study

Examples of Clinical Endpoints — Alphabet Soup

Clinical endpoints for muscular dystrophy trials fall into different categories, including (1) composites of multiple tasks, which assess ability to perform a range of physical activities; (2) timed tests, which measure how long it takes to perform a task; (3) distance tests, which measure how far a patient can walk or run within a specified time; and (4) patient-reported outcome measures, which are self-assessments covering physical limitations as well as quality of life. Table 1 gives some examples of endpoints and their abbreviations.

CATEGORY	ABBREVIATION *(Pronounciation)*
Composites of Multiple Tasks	
Northstar Ambulatory Assessment	NSAA
Northstar Assessment for Limb-Girdle type Dystrophies	NSAD *(n-sad)*
Performance of Upper Limbs	PUL *(pull)*
Timed Tests	
10 and 100-Meter Walk Tests	10 MWT, 100 MWT
Time To Rise	TTR
Timed Up and Go	TUG *(tug)*
Distance Tests	
Six-Minute Walk Test	6MWT
Patient-Reported Outcome Measures	
Measurement of Activity Limitations	ACTIVLIM *(active limb)*
Quality of Life Questionnaire for Slowly Progressive Neuromuscular Disease	QoL-NMD

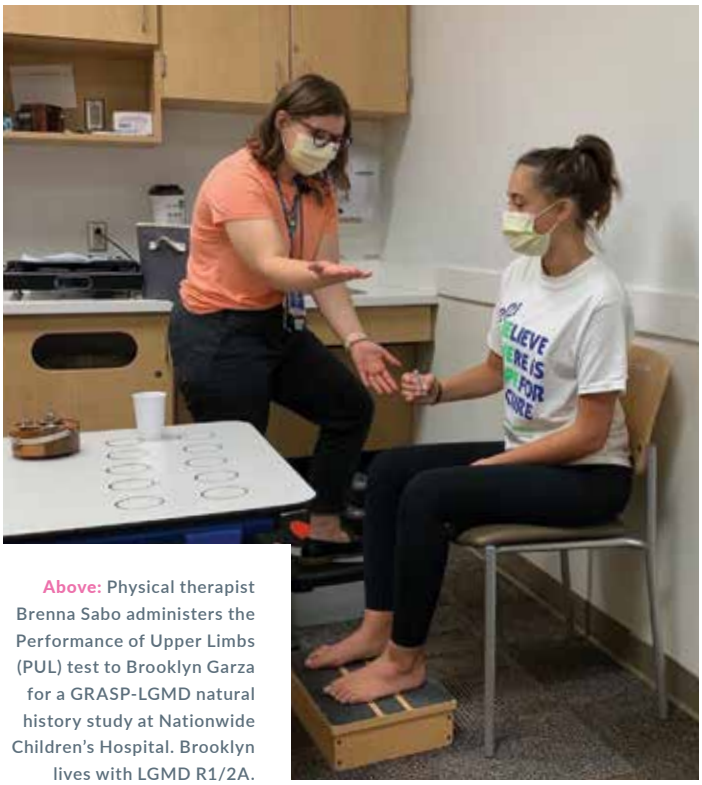
Table 1: **Some Clinical Endpoints Used in Muscular Dystrophy Clinical Trials**

Sources of Clinical Endpoints and Validation for Use in Clinical Trials

There are various sources of clinical endpoints used in trials for muscular dystrophy drugs. One of the first for DMD was the Six-Minute Walk Test, or 6MWT,[1] which was adapted from a 12-minute run test developed by the U.S. Air Force to measure the physical fitness of its members. Other endpoints, such as the 10MWT and 100MWT, were similarly repurposed. The NSAA, by contrast, was developed specifically for DMD.[2] More recently, the NSAD, a modification to the NSAA which is also applicable to non-ambulatory patients and includes additional measurements, was designed for dysferlinopathy (LGMD R2/2B)[3] and later validated for other LGMDs.[4]

Before a measurement may be used as a primary clinical endpoint in a therapeutic trial, it must be validated repeatedly in the applicable patient population. "Validated" in this context does not have a universal meaning but requires evidence that the endpoint is relevant to the disease and consistently reliable through repeat testing in multiple groups of patients at varying stages of progression. While the FDA does not officially approve or reject the validation of an endpoint, they expect to see at least one peer-reviewed publication of the validation studies in a medical journal. If a clinical endpoint is used beyond the scope of its validation (e.g., measurements validated only in pediatric subjects being used in a trial of adults), the sponsor risks FDA pushback. Additionally, even if the FDA grants approval that covers the broader use, payors (typically government programs or insurance companies) may hesitate to reimburse the treatment of patients outside the scope of validation.

As noted earlier, natural history studies play a key role in the design, refinement, and validation of clinical endpoints. The NSAD, for example, was validated in natural history studies, first for dysferlinopathy (LGMD R2/2B) and then for LGMDs generally.[5] Other endpoints have been validated through progression analyses of clinical trial placebo control groups.



Above: Physical therapist Brenna Sabo administers the Performance of Upper Limbs (PUL) test to Brooklyn Garza for a GRASP-LGMD natural history study at Nationwide Children's Hospital. Brooklyn lives with LGMD R1/2A.

Left: Sammy Brazzo, who lives with LGMD R9/2i, takes a Pulmonary Function Test (PFT) at the Iowa Wellstone LGMD R9/2i Natural History Study. The PFT is often used as an outcome measure for diseases with respiratory involvement.

Clinical Endpoint Case Studies

Sarepta's gene therapy drug for DMD, Elevidys, received Accelerated Approval in 2023. For the confirmatory trial called "EMBARK," Sarepta designated the NSAA as the primary endpoint, but it was not met. Fortunately, several secondary endpoints showed significant improvement, including the one-year change in Time To Rise and the 10 MWT. Based on those results, Sarepta applied for unconditional approval of Elevidys, and an expanded label for ambulatory patients beyond the Accelerated Approval labeling.[6] And on June 20, 2024, the FDA agreed, granting traditional approval for all ambulatory patients four years and older, and also Accelerated Approval for non-ambulatory patients.

ML Bio Solutions (ML Bio) is developing BBP-418, or Ribitol, for the treatment of LGMD R9/2i, and has designated several endpoints for its clinical trials. At 21 months after dosing in an open-label Phase 2 trial, data showed stabilization in the NSAD, 10MWT, and 100MWT.[7] Significantly, the Phase 2 trial also met its surrogate endpoints of increasing the ratio of glycosylated alpha-Dystroglycan (αDG) to total αDG and reducing CPK levels.[8]

The company is currently sponsoring a double-blind, placebo-controlled Phase 3 trial, named "FORTIFY." The trial's primary clinical endpoint is the change from baseline in the NSAD at 36 months, and its secondary clinical endpoints are changes from baseline in the 10MWT, PUL2.0, and pulmonary function, all at 36 months.

The company's ultimate goal, of course, is to receive traditional approval, but it does not want to wait three years to treat the patient community. Therefore, given the correlation observed so far between functional improvements and increased glycosylation of αDG, the company is seeking Accelerated Approval in parallel with traditional approval. That is, the company is asking the FDA to accept the changes in glycosylated αDG levels as a surrogate endpoint reasonably likely to lead to meaningful clinical benefits over time pending the outcome of the FORTIFY trial after 36 months, when it will be clear which clinical endpoints, if any, have been met.[9]

A Look Beyond Primary Endpoints: Totality of Evidence

The recent FDA approval of Sarepta's application to remove Accelerated Approval conditions on Elevidys and to expand its label to cover all patients four or more years old confirms the FDA's willingness to look beyond primary endpoints and the specific progression profiles of clinical trial participants. Such flexibility in determining the efficacy of a drug following clinical trials, referred to as a "totality of the evidence" approach, could be a boon for LGMD patients, and favor the approval of ML Bio's BBP-418 based on secondary endpoints even if the NSAD is not met. In fact, even before its Elevidys decision, the FDA had indicated a willingness to use the totality of the evidence approach, albeit not in connection with any specific trial or product.[10]

The Argument for Additional Clinical Endpoints

In recent years, LGMD patients have expressed concern that able-bodied physicians, drug developers, and regulators assume we are waiting for a miracle cure before participating in clinical trials, which is not the case. At multiple meetings and presentations, including the LGMD Listening Session on October 20, 2020, the LGMD Patient-Focused Drug Development (PFDD) meeting on September 23, 2022, the International LGMD Patient Conference on October 27, 2023, and the LGMD Scientific Workshop on February 8, 2024, patients have consistently described modest treatment outcomes as meaningful. Examples have included the improved ability to dress, bathe, brush hair, make transfers, and generally engage in activities of daily living, either independently or with less assistance. Even a stabilization of our current condition would be a valuable result. We lead meaningful lives, but fear an uncertain tomorrow.

Consequently, we would like to see the development, validation, and use of clinical endpoints that are better able to capture such nuanced benefits. Can you imagine being a non-ambulatory person and knowing that the NSAA, and all the distance and timed tests, exclude you completely? While other endpoints, such as the NSAD and PUL2.0, include non-ambulatory participants, their ability to capture subtle improvements in highly progressed patients has not yet been established. They have also been criticized as not being sensitive enough because their scoring system is limited to a range of three functional groups (0, 1, or 2). Even trial participants who experience what they consider noteworthy improvements could find themselves "stuck" as a 0 or a 1 in the NSAA or NSAD.

And yet, the quest to develop the perfect set of clinical endpoints is daunting. So far, improvements have been elusive, and not for a lack of effort. An attempt to increase the range of the NSAD from three points to four was unsuccessful. Despite great efforts, the clinicians who conducted the research found that the high variation in progression among patients made precise placement into more than three groupings impractical.

What is to be done? The answer differs by stakeholder. Academic researchers who invent therapies and drug sponsors who invest in their development can be quick to blame imprecise clinical endpoints for a trial's failure to show benefit. And so, the six-minute walk test, and the NSAA, both initially lauded as promising breakthrough measurements, have become a sort of scapegoat for failed clinical trials. But is that fair? Could the problem actually be in the early-generation therapies themselves? Clinicians who design and validate the endpoints used in current trials will point to the need for more robust therapies, coupled with Accelerated Approval and longer trial durations. Could they both be right?

The good news is that we do have Accelerated Approval to provide the time needed for a trial to meet its clinical endpoints, and we are also seeing a trend of FDA willingness to look beyond primary clinical endpoints, and instead look at all available efficacy data, including secondary endpoints, data from wearable technologies, and control data from natural history studies.

Stay tuned! The value of natural history studies will be the focus of the next article in this series for the upcoming edition of *LGMD News*. ■

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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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