MORNING SESSION

James Valentine, JD, MHS (00:15:36):

Good morning. My name is James Valentine, and welcome to the Externally-led Patient-focused Drug Development on Metachromatic Leukodystrophy or MLD. I'm here in the studio with my co-host, Maria Kefalas from The Calliope Joy Foundation and Cure MLD, and we're coming to you live from the Washington D.C. metropolitan area. Actually not too far from where the U.S. Food and Drug Administration's headquarters are located. It's now my pleasure to turn it over to Dean Suhr from the MLD Foundation who'll be providing some opening remarks. Dean, take it away.

Dean Suhr (00:16:12):

Welcome everybody to the Metachromatic Leukodystrophy Externally-led Patient-focused Drug Development Meeting. I'm Dean Suhr. I'm co-founder and president of MLD Foundation, whose mission is we care, facilitating compassion, increasing awareness, influencing research and expanding education for metachromatic leukodystrophy. But I'm most proud to be dad to three girls, including Lindy and Darcy. My two daughters with juvenile MLD. They were diagnosed in 1995 after a six-year diagnostic odyssey. Unfortunately, Darcy passed away shortly after an experimental bone marrow transplant. For Lindy, the textbooks told us that Lindy, who was 14 at the time and was not eligible for therapy, would live to her early 20s. I'm blessed to share that we celebrated her 42nd birthday in Hawaii last month, but Lindy's an outlier. She reminds me that the study of MLD's basic science is still critical. But today, we're focused on the translational science by taking the learning from the patient experience and using that to inform new therapies and clinical care strategies.

(00:17:12):

As you'll learn over the next few hours, MLD is a ravenous terminal disease. Over the past two decades of MLD Foundation's work, we've journeyed around the globe and have personally met hundreds of MLD patients, and sadly, we must report that most lived of much less than a decade after diagnosis and most haven't had any access to therapies. MLD does not just affect the patient, it affects the entire family, the extended family, and frankly society as a whole as we support those families. Those journeys and the MLD community's hopes are being shared today to spotlight our loved one's symptoms, struggles, concerns, and their hopes for the future. You'll meet some of the most generous, loving, and capable people I know. We've seen them step up and do anything and everything for their loved ones. Often, things they didn't know they even had the ability, skills, or energy to do. They've become tireless advocates and caregivers, often providing first tier medical services 24/7 for their loved ones.

(00:18:06):

Over half of the MLD population is laid infantile. So today, you'll mostly hear from parents, but you'll also hear directly from some patients. For presymptomatic MLD, stem cell transplant has historically been the only option. Also, today, you'll hear about how this is changing. We hope our discussion will directly inform the U.S. Food and Drug Administration staff who have joined us. We also hope it informs the dozens of biopharma staff, researchers, and clinicians that are here too. We're really pleased to have other stakeholders in attendance, including representatives from advocacy and professional organizations, medical institutions, agencies, and universities from around the world. We hope and expect this ELPFDD meeting will encourage and inform future research and new therapy development for the people living with MLD who urgently need more life-saving therapies and better patient-focused quality of life improvement options.

(00:18:56):

For the balance of today's meeting, we ask that you listen carefully to the stories and insights into the daily frustrations, disappointments, struggles, and sacrifices that make up the life of patients and parents

whose loved ones have MLD. Thank you to the FDA for giving us permission to hold this meeting and for attending. We're incredibly grateful for this opportunity to share our experiences with you. Thank you also to our generous financial supporters who've enabled us to produce this meeting, to produce next month's scientific meeting, and also the Voice of the MLD Patient Report, Orchard Therapeutics, Takeda Pharmaceuticals, Athena Therapeutics, Homology Medicines, and Passage Bio. And to the many MLD families who've taken the time to be with us today, this meeting is for us, this meeting is about us. Thank you for being here too.

(00:19:40):

We invite you to call or write in during the meeting and ask that you participate in the live polling, so keep your mobile phones handy. We want to hear as many different stories and perspectives as possible. When calling or commenting, please use only your first name. No other identifying information needs to be shared. We will do our best to get to all of your comments, but please note that any comments we don't share live are equally as important because they will be collected and published in the Voice of the MLD Patient Report, a recap and summary of this special day. And if you need to step away to care for your loved one, the meeting's being recorded and will be available on the mldpfdd.org website immediately after we finish. So let's get started. I'm pleased to turn the meeting over to our in studio co-host, James Valentine and Maria Kefalas.

Maria Kefalas, Ph.D (00:20:26):

Thank you, Dean. Now, to provide some welcoming remarks from the FDA, it is my pleasure to introduce Dr. Sairah Thommi, a clinical reviewer in the division of Clinical Evaluation, Pharmacology/Toxicology in the Office of Tissues and Advanced Therapies in the FDA Center for Biologics Evaluation and Research, the part of FDA responsible for regulating cell and gene therapies. Dr. Thommi, take it away.

Sairah Thommi, MD (00:20:55):

Thanks for that introduction. Hi, everyone, I'm Sairah Thommi. I'm a clinical reviewer in the Center for Biologics Evaluation and Research, also known as CBER. I have not spoken at or attended a live patient-focused drug development meeting before. However, I have reviewed previous submissions for rare pediatric disease. And for these files, I have watched previous meetings to gain insight into the patient and caregiver's experience to gain further clarity on the impact of disease and outcomes that would be meaningful to them. It has been extremely beneficial to have both patient and caregiver perspectives when reviewing these files. Although there are many sources that discuss a disease's course, having firsthand stories that can relay the effect of the disease on both the patient and the family is a powerful resource and aids in our understanding of clinically meaningful priorities that we hope to be assessed in future drug development programs.

(00:21:45):

So, I wanted to thank you all for being part of this meeting and sharing your experiences with us. I'd also like to thank Cure MLD, The Calliope Joy Foundation, the MLD Foundation, United Leukodystrophy Foundation, and The Global Leukodystrophy Initiative, and all the staff that were involved in planning this meeting.

(00:22:03):

While FDA plays a critical role in medical product development, we are just one part of the process. These meetings give the FDA and other key stakeholders, including medical product developers, healthcare providers, and federal partners an important opportunity to hear directly from patients, their families, caregivers, and patient advocates about the symptoms that matter most to them, the impact the disease has on patients' daily lives and patients' experiences with currently available treatments.

(00:22:32):

We would like to hear what specific things patients look for in an ideal treatment to manage their condition. This will help inform the focus of new product development and clinical trials. The FDA shares the patient community's commitment to facilitate the drug development of safe and effective medical products for MLD. And when we say medical product development, we mean it in the broadest sense of identifying, developing, and evaluating potential therapies or devices that can help patients manage their condition. FDA protects and promotes public health by evaluating the safety, effectiveness, and quality of new products, but we do not develop medical products or conduct clinical trials. It is however, FDA's responsibility to ensure that the benefits of the product outweigh the risks. Therefore, having this kind of dialogue is extremely valuable for us because hearing what patients care about could help us lead the way in figuring out how to best facilitate medical product development for MLD and to understand how patients view the benefits and risks of therapies and devices for MLD.

(00:23:39):

As part of the agency coordinated effort to support and accelerate the drug developments for rare diseases, CBER has launched the Natural History of Metachromatic Leukodystrophyhy, also known as the HOME Study. The HOME is an exploratory study to evaluate the feasibility of establishing an external control cohort, which could be used to either augment or replace a control arm in a future clinical trial. In addition, HOME uses innovative methods to streamline the conduct of the study, from enrollment to follow up using video visits and the SHAPE platform to assist in data collection. The HOME Study combines innovative methods and the collection of fit for purpose data to support regulatory decision making.

(00:24:21):

Rare disease drug development is a top priority for the agency and one way for this community to help advance treatments for MLD after this meeting is to advocate for companies and academic investigators to donate their placebo arm or natural history data to the Rare Disease Cures Accelerator. The Rare Disease Cures Accelerator data analytics platform has been created through a partnership with FDA and C-PATH.This platform pulls together data for many sources for many rare diseases from organizations and companies around the world. The data provided for this platform is meant to be pulled together and built into a clinical trial simulator that makes it a lot easier for companies to develop successful clinical trials.

(00:25:08):

We look forward to incorporating what we learn today into the agency's thinking and understanding of how patients view the benefits and risks of therapies and devices for MLD. Your input and perspectives really help us and will also help industry and academia to move the drug development process forward and to ensure that new medications meet the needs of people living with MLD. Once again, we're all here today to hear the voice of the patient, so thank you for your participation. We're grateful to each of you for being here and sharing your personal stories, experiences, and perspectives. And now back to the studio.

Maria Kefalas, Ph.D (00:25:45):

Thank you, Dr. Thommi, for sharing the importance of the patient voice to FDA officials. Now, to provide a clinical overview of MLD, which will set a scientific foundation for today's meeting, we will hear from Dr. Laura Adang, an attending physician in the Division of Child Neurology at the Children's Hospital of Philadelphia and principal investigator of the MLD Natural History Study. Dr. Adang.

Laura Adang, MD, PhD (00:26:13):

Hello. Thank you so much for inviting me here to talk about the clinical overview of metachromatic leukodystrophy. My goal today is to provide the context for the family stories that we are to hear later. I

have some conflicts of interest. So I do work with Orchard, Takeda, and Biogen on therapy development for Leukodystrophies as both a research and as a consultant. I have several different forms of NIH funding and several family foundation funds as well.

(00:26:42):

Our objectives today, again, are to talk about the diagnosis of metachromatic leukodystrophy, discuss the clinical course of the disease, address the genotype/phenotype correlation, and talk about the different clinical categories or spectrums of presentation that we see as part of clinical care.

(00:27:03):

MLD is a biochemical disorder. It's a lysosomal storage disorder where affected persons have a deficiency or a decrease in the amount of Arylsulfatase K, which is a lysosomal enzyme. When ARSA's activity is low, we get an accumulation of sulfatides and those sulfatides are associated with a central and a peripheral demyelination. We can easily measure the levels of ARSA activity in both blood as well as dried blood spots. And there's a clear difference between MLD patients, which is shown in the center left and normal controls both adults and newborns, where the activity of ARSA is much lower within the MLD population. And as such, the diagnosis of MLD is relatively straightforward. It's a combination of biochemical testing where we can measure the level of urinary sulfatides as well as a measurement of how active the enzyme is. We can also do sequencing of the ARSA gene. And so the combination of these three factors lead us to a definitive diagnosis of MLD.

(00:28:19):

Classically, MLD has been divided into four and sometimes three different subtypes. There's the late infantile form, which is the most common and associated with an early onset where children begin to manifest symptoms of disease before two and a half years of age. The first symptoms are often difficulty with walking, so we call those early motor symptoms and there is universally a rapid and severe loss of neurologic function in the late infantile cohort.

(00:28:51):

If you look on the far right, there's the adult onset form. You have onset anytime from the age of 16 up until well into adulthood. You tend to have a more cognitive predominant phenotype where personality changes or anxiety depression, those kind of things are the first symptoms oftentimes in the adult onset form, and it tends to have much more chronic changes. So changes happen over years or decades, not weeks to months as we see in the late infantile form.

(00:29:25):

In the middle of these two forms is the juvenile form of MLD. And more recently, we've started to divide it into two different subcategories of early juvenile and late juvenile, with early juvenile patients presenting typically before the age of seven to eight, and they have a presentation much more similar to the late infantiles where there's a rapid onset of motor symptoms and then a relatively rapid decline, whereas the late juvenile patients oftentimes have more cognitive symptoms and have a slower course compared to the late infantiles.

(00:30:03):

When we look at how MLD changes or how well we can predict it, if you look on the left, this is group work from the German Lucranet group, where they compared the age and onset of family members as shown by the red dots linked by the lines for both the late infantile in the juvenile forms of the disease. And here, juvenile is both early juvenile and late juvenile and you can see by the dots that are very closely connected in time as well as that very small box plot for the late infantile population, children with late infantile disease tend to present at a very homogeneous time course, and there's really very little variation in that disease. In the juvenile population, you can see both the representation of the early juveniles who tend to have various similar disease onset timing. And when you include the late

juvenile population, it becomes a much more heterogeneous group and is harder to predict exactly when the disease is going to take effect.

(00:31:10):

When you look at not just when it begins, but how quickly it changes, you can see in the box plot on the right, the first box plot is representing children with late infantile, and you can see very narrow box plots, and these are when the children transition from interdependently ambulatory all the way down to non ambulatory. And so it really is showing that gross motor change across the population. And you can see the late infantile boxes are stacked on top of each other and have a very narrow window. This represents that very rapid change in motor function that we see in late infantile individuals.

(00:31:55):

When we look at motor change across the entire juvenile population, both early juvenile and late juvenile, you can see there's a broad range, and so there's a huge range in time from when children are transitioning from interdependently ambulatory to needing assistance walking to head control, only down to a level six, which is non ambulatory, no head control. And so the change that happens in the late infantile population over the span of months, in the juvenile population is much more heterogeneous. And some of that population is transitioning quickly and some of the population is transitioning more slowly.

(00:32:37):

When you begin to look at how fast it's changing, one of the key metrics in metachromatic leukodystrophy is that rapid change once ambulation is lost. And when you look and compare late juveniles to juvenile population, once ambulation is lost and children can only walk with their hands being held, irrespective of those early phenotypes, they're transitioning-

Laura Adang, MD, PhD (00:33:03):

Irrespective of those early phenotypes, they're transitioning to loss of floor mobility and sitting skills at the same rate. And so that's really something that's important to note, that although the juveniles are beginning later, by the time they're starting to lose ambulation and walking skills, that pace of change is actually very similar to what we see in elite infantile early onset forms.

(00:33:28):

I wanted to show a representative case from the doctor's perspective, because you're going to hear about these experiences from the family's perspective. But from a doctor's perspective, we oftentimes will see a child with MLD many, many times during the early disease course, before we have a clear answer as to what's going on. Children can present with esotropia or strabismus, so ocular defects are very common as the first presenting symptom, and that oftentimes precedes the difficulty with walking. And during a time when you're expecting children to be clumsy and be gaining new skills, the families are noting a mild clumsiness with walking or a new difficulty, but as a clinician, it's really hard to that out because it is a time when new skills are emerging.

(00:34:20):

Oftentimes, families are presenting multiple times to orthopedics, neurology, ophthalmology, their general pediatrician during this time period, searching for answers for these very small things that the families are detecting. Ultimately, MRIs are obtained and oftentimes, that first MRI can be normal or very mildly abnormal. Sometimes, there's no evident demyelination, but rather cranial nerve enhancement referable to the early ocular symptoms we see in many children with late infantile MLD. But on subsequent MRIs, we oftentimes can see that classic diffuse demyelination and children at this point have often unfortunately progressed from just a little difficulty walking to being unable to walk independently. And so we're going to focus a lot on how we can reduce this time from the first

symptoms to when really children have progressed to a point where I'm worried about the ability of therapies to help change their disease course.

(00:35:27):

While we define MLD as being a neurologic disease, it is actually a multi-systemic disease, and you'll hear that from the families later, but it's a progressive neurologic disease and the needs are changing. Children have both a peripheral and essential neuropathy. They can, in a matter of weeks to months, really lose the ability to sit, control their head, and that impacts their functional skills and how they do at home. Extreme irritability is actually classic for the early phases of MLD, particularly in the early onset forms, and this can be from a variety of reasons. Demyelination itself is not to be painful. You can have severe tone abnormalities in GI dysfunction, and in fact, we oftentimes see GI motility issues far before the neurologic expected course and many of our children have failure to thrive and require early G-tube placement in order to maintain nutrition.

(00:36:35):

Tone is a major issue in MLD as well. Many of our children are both spastic and dystonic and require multiple pain medications to help to manage that tone. And as their disease progresses, oftentimes, children have a mixed tone and central hypotonia or head control, which affects feeding and swallowing and breathing also plays in. There are some extra neuronal direct effects of MLD as well. We know that the gallbladder can be involved and this does lead to a risk of carcinoma and there's been some case reports of renal involvement as well. And so the prevalence of the gallbladder and renal I think needs to be sorted out with future perspective studies, but some individuals have actually been known to present with gallbladder abnormalities.

(00:37:25):

So what's the natural history of MLD? I think we've learned a lot about MLD and there are some wonderful large case series in case reports and even longitudinal natural history studies. I think one limitation, from a traditional prospective natural history study, is it's a rare disease and it takes a long time to accumulate that information. And also, with prospective studies, you're, by necessity, locking in the first visitor encounter after the time of diagnosis, but we know that the children begin to have problems or issues well before a diagnosis is made. As the clinical case example illustrates, oftentimes, children are in the medical system for months, sometimes years before a diagnosis of MLD is made. And so prospective natural history studies capture with rigor that time post-diagnosis, but I think that there's important information we can gather from the retrospective history to better understand exactly how MLD is beginning.

(00:38:29):

We have an international cohort of collaborators who have worked with us to better understand the beginnings of MLD, and this is unpublished data from our international cohort. When we look at, on the Y axis, the age at which the onset of MLD to time and suspicion, so how long did it take for us to diagnose MLD compared to the year at which the child began to have symptoms? One would expect that overtime, were going to be getting faster, and that's not really the trend we see. We're getting faster at diagnosing individuals, the late juvenile and adult forms, and maybe somewhat with the early juveniles. With late infantiles, because of the rapid nature of the disease and the lack of existing newborn screening, we're not really getting faster at recognizing children with this form of the disease, which is both the most common and the most rapidly devastating.

(00:39:35):

I'm interested at looking at when the diseases truly begin so I can better time future clinical trial targets and therapeutic interventions. When we look at when children who are gaining sitting or ambulation, you can see that by the time of sitting, the late infantile population is shown by the red line on the

bottom chart. You can see that they're starting to differentiate from the rates of sitting in the non-late infantile cohort, suggesting that maybe as early as sitting, we might be having a differentiation in how milestones are gained. And when you look at all the way to something like a gain of ambulation, you can see that the late infantile cohort is both a sizable percentage of the population is never even gaining independent ambulation. Moreover, when they do gain it, they sometimes are gaining it late too. And so I think as a big international consortium of physicians dedicated to better understanding MLD, it's really important to better understand when we should be targeting intervention.

(00:40:50):

So in conclusion, MLD is relentlessly progressive. This change, this loss of motor function happens very quickly in the late infantile and early juvenile forms and much more variably in the late juvenile and adult forms. There is a delay in diagnosis that is not improving over time and underscores the need for early presymptomatic screening. An MLD as a systemic disorder. It may be caused by demyelination in the central and peripheral nervous systems, but the entire body is affected, and so we need treatments that help to manage the symptoms across the entire body. I want to thank the organizers for inviting me to speak today about the clinical overview of metachromatic leukadystrophy. It's my pleasure and honor to support the MLD community, and I want to go back to the studio now. Thank you.

Maria Kefalas, Ph.D (00:41:47):

Thank you, Laura. I'd now like to welcome our moderator for today's meeting, James Valentine, who has been working with us for with us over the past several months as he's helped us plan this meeting. James has worked the last 14 years as a champion for the patient voice. James previously worked at the FDA where he was a patient liaison, helping to incorporate the patient voice into medical product review. There, he helped to develop and launch the patient-focused drug development initiative. In private practice, James has worked with many patient organizations to ensure their community's voices were heard by decision-makers. Relevant to today's meeting, James has been involved in helping plan and moderating three-fourths of the over 65 externally led PFDD meetings, so we are in really good hands with James.

James Valentine, JD, MHS (00:42:38):

Well, thank you so much, Maria, and it's such a pleasure to be with this MLD community today, and I really look forward to hearing and talking with so many of you. So now that we've heard a clinical overview from a disease expert, we do get to turn to the core of today's meeting, which is to hear from you, the people living with MLD and their family members and direct caregivers. As we've heard, patient-focused drug development is a more systematic way of gathering patient perspectives on their condition and on available treatments. As we heard from FDA's Dr. Tomi, your input can help inform the agency's understanding of MLD to inform drug development and review. While FDA has held many of its own patient-focused drug development meetings, today marks the 66th externally led PFDD. With over 10,000 known rare conditions, this is truly a unique and important opportunity for this community.

(00:43:37):

Today's meeting is interactive, so let me tell you a little bit about what we'll be asking of you and how today's meeting will be organized. First, the meeting itself is structured and will cover two different topical sessions. In our first session, which will be this morning, we'll be exploring the patient and caregiver experience of living with MLD and its impacts on your loved one's daily lives. In our second session, we'll bring everybody back together to explore various approaches to treatment, including participating in clinical trials, and we'll also be asking you for your preferences for future treatments for MLD.

(00:44:13):

So what will these two discussions look like? We'll primarily be using three methods for hearing from you. The first thing is for each of our sessions, we'll be hearing from a panel of patients and caregivers living with MLD, who will help set a foundation for the discussion and were selected to reflect a range of experiences of those living with MLD. Of course, we know that a single panel can't represent the full range of experiences, which is why after those panel discussions, we'll be launching into a facilitated audience discussion with all of you who are here live, all of our patients and caregivers tuned in today. I'll be asking questions and inviting you to state your name and you or your loved one's subtype of MLD and provide a comment. This can be done in one of two ways. We'll be inviting you to dial in by phone as well as submit written comments that we'll be sharing throughout the program.

(00:45:08):

We'll also have a Zoom panel of patients and caregivers who will be contributing to that live discussion as well. We'll also be broadening our discussion through the use of polling questions. We'll ask parents and caregivers and patients only to use their phones to respond, or you can use, alternatively, a web browser, and in fact, we want you to go ahead and get into our polling system now, as once you're in it, you'll be able to stay on this throughout the entire day and when we get to our first set of polling questions in just a few moments, you'll already be able to answer that. So at this point, we'd like to invite you to pull out your phone, open up a browser, you can open up a tab on your web browser on your computer if you're following along there, and go to www.pollev.com/mldpfdd. Again, feel free to go there now, www.pollev.com/mldpfdd, and again, we'll be getting to polling very soon.

(00:46:10):

We'll be using these polling questions to help get a sense of the experiences of our broader audience as well as a way to aid in the discussion. Finally, we'll also have the opportunity for you to provide written comments for 30 days after this meeting. So whether you're attending live today and there's something else you wanted to share that you didn't get to or something comes to mind after the meeting's concluded, whether that's tonight or a few days from now, we invite you to contribute through a written comment. Or if you're watching this on-demand after this meeting and you'd like to share some comments, we invite you to provide those as well. All of this input, both from today and from additional written input will be summarized in what's called a Voice of the Patient Report, which is the summary of today's meeting, which will be provided to the Food and Drug Administration, as well as be made publicly available for researchers and drug developers to access and reference as well.

(00:47:10):

One last thing, I'd like to cover some ground rules before we get into our first set of polling questions. I would like to encourage individuals with MLD and their caregivers to contribute to this dialogue. Again, that's going to be through polling, calling in by phone, submitting written comments. This is limited to patients, family members and other direct caregivers living with MLD. Meanwhile, our other stakeholders from the FDA, drug developers, and clinicians are here to listen only. I'd also like to mention that views expressed today are inherently personal and the discussion may get emotional at times, so respect for one another is paramount. To that end, we do ask that you try to be focused and concise when providing your comments so that way we can hear from as many voices as possible. So without further ado, let's get to it. And we're going to go to our first set of polling questions, which are designed to give us a sense of who we have in our audience from the MLD community today. Again, if you haven't already, please open up a browser on your phone, please open up a new tab in your browser, go to www.pollev.com/mldpfdd. Once you get here, you can just keep this browser open, whether on your phone or your computer, and anytime we get to a new question, it will automatically appear there and you'll be able to answer that question. So our first question for you this morning, again, for our patients and caregivers, we want to know, are you either someone, A, living with MLD or, B, a caregiver of someone with MLD? And while some of these initial questions are pretty straightforward, we'll be giving

a few extra moments here to allow people to respond. We want to make sure everyone has a chance to get into this polling system so that way you'll be able to answer all of the questions throughout today.

(00:49:20):

All right, we'll give you a few more moments here to get your responses into this first question on either are you, A, someone living with MLD or, B, a caregiver, someone with MLD? It's been pretty stable, little fluctuations as results are coming in, but we're seeing the vast majority of our participants are the caregivers of someone with MLD. However, we're seeing a little over 10% of our audience are those living with MLD themselves. So we very much encourage and welcome both individuals with MLD as well as caregivers to contribute by calling in, submitting written comments, and of course, continuing to participate in these polling questions.

(00:50:05):

If we can go to our second polling question here this morning. Here, we would like to know where you or your loved one with MLD, where they currently reside. The options are, A, in the US East, B in the US Midwest or Central, C, in the US West, D, Europe, E, Middle East, F, Asia, G, Canada, H, Mexico, I, South America, J, Africa, or K, some other country or region not represented in these response options in this question here today. Today's meeting is an open public meeting that's open worldwide, so I'm glad to see that we have some participation from outside of the United States. This meeting is for you too, so we encourage you and welcome you to contribute to the dialogue as well. As it stands, it looks like we have a good range of participation from all across the United States as well, and from outside of the US, we have both representation from Europe and Canada, so that's wonderful. And again, encourage no matter where you're located, for you to participate in this discussion today.

(00:51:27):

All right, if we can go to our third polling question. Here, we want to know is your MLD loved one or if you're living with MLD yourself, are you either, A, female, B, male, C, non-binary, or D, other or prefer not to identify? So again, here we want to know the gender of the person living with MLD, whether that's you as someone living with the condition or if you're a caregiver, your loved one with the options, either A, female, B, male, C, non-binary, or D, other or prefer not to identify. While final results are trickling in, it looks like the trend is we're around three quarters of our audience. The individuals living with MLD that are represented are female, and about a quarter of the people with MLD represented today are male and nobody reporting non-binary or other or prefer not to identify.

(00:52:34):

If we can do our fourth polling question. So here, we want to know how old is your MLD loved one? Or if you're living with MLD, how old are you? The options are, A, zero to five years of age, B, six to 10 years of age, C, 11 to 18 years of age, D, 19 to 30 years of age, E, 31 to 50 years of age, F, 51 to 70 years of age, or G, 71 years of age or older. So again, we're going to, here in this question, understand that the current age of those living with MLD that are represented in our audience. We'll give you a few more moments to answer this question.

(00:53:26):

I promise as we move later in the meeting, the polling questions will definitely be more difficult and you'll probably be wishing they were as easy as these types of questions here early this morning, but as it stands, it looks like the groups that are with the most representation this morning are those zero to five years of age and those six to 10 years of age, both slightly under one third of our total participants. We're seeing just a little over 15% of our participants in the 11 to 18 year age range or the 31 to 50 year age range and a little under 10% of those with MLD represented today in that 19 to 30 year age range, nobody represented today living with MLD between 51 to 70 years of age or over 71 years of age.

(00:54:20):

So if we can move to our final question for this morning to get a sense of our audience here. So here, in one moment, we'll get up this fifth polling question where we want to know here what type of MLD do you or your loved one have, and the options are, A, late-infantile, B, juvenile, C, adult, or D, if you're unsure. So again, what type of MLD do you or your loved one have? I think Dean when he was giving his opening remarks, forecasted that we would probably see a large representation from the late-infantile segment of this community, which we do see reflected here with just over half of our overall participants representing those living with late-infantile MLD. We see a little under a third representing the juvenile forms and just over 10% with the adult. And we do see that there's a small proportion of people represented today that are unsure which MLD form they or their loved one have.

(00:55:44):

Really important. We want to hear about all of these types of MLD. We are not focused on any one singular form of MLD today, so whether you're one of the more common types of MLD that's represented or you are in one of the less common, we do want to hear from you and encourage you to have your voices heard. So now we get to move into our first topic for today where we're going to learn from you all what it is really to live with MLD. And so I'd like to pull up our first set of discussion questions. These are questions that we're going to be exploring over the course of this morning. We're going to be wanting to have you weigh in and help us understand of all the symptoms and health effects of MLD, which one to three of those have had the most significant impact on you or your loved one's life? We want to know how does MLD affect your loved one or you on best versus on worst days and we want to hear you describe that variability from day to day that exists.

(00:56:51):

We also want to know how these symptoms have changed over time, whether that's day to day, week to week, month to month, or over the course of years living with MLD. And not only do we want to explore those direct symptoms and health effects, but we want to understand how they impact your daily lives. So are there specific activities that are important to you or your loved one that they can't do it all or as fully as they would like because of their MLD? And finally, recognizing that while there's much you've already experienced living with MLD, that you may also be thinking about what life with M LD looks like in the future, and so we want to hear from you any worries, fears, or concerns that you have for yourself living with MLD or you have for your loved ones living with MLD.

(00:57:37):

And so to kick us off in this discussion and weigh in on these questions, I'd like to welcome a panel of your fellow MLD community members. We have George, Michelle, Matthew, and Lauren, Corrine and Heather who will be sharing their experiences. George, why don't you take it away

George D. (00:57:59):

If you'll indulge me, imagine for a moment it's 15 below zero in North Pole Alaska. It's the perfect temperature for dog mushing competition. You're seven years old and it's February. You've just clenched the championship title with your team. You are the best musher in Alaska. You're a good student, you're a fair hockey player, and you enjoy canoeing, camping, hiking, and all the other outdoor activities. Outgoing and friendly, you're never at a loss to strike up conversation with anyone. Unknown to you now, within eight months of being the state champion dog musher, you'll have spoken your last word, taken your last step and saying your last song. Four years ago, this was the experience of my 11-year-old son, Ronan. Metachromatic leukodystrophy came suddenly and dramatically to our family. One year was all the time it took from the onset of first symptoms to being fully caregiver dependent.

(00:58:53):

At the beginning of his school year, his concentration began to diminish and he started demonstrating some slightly awkward social behaviors, so we treated Ronan for ADHD. By spring of that year, his gate

had changed and he began intermittent toe walking. His fine motor coordination was becoming noticeably impaired. It was apparent that this was not ADHD. Within two months of observing the first physical symptoms, especially his walking challenges, Ronan's speaking and swallowing ability rapidly decreased and we scheduled an MRI. His diagnosis of a degenerative terminal condition was shocking and the knowledge that there were only symptom management therapies available heartbreaking.

(00:59:38):

From the onset of the first symptom, the concentration deficit, to being unable to speak was a period of 12 months. There were only six months between complete vocal capacity to an inability to speak. Physically, he had hiked four miles in June, he was diagnosed in July, and by October, he was fully wheelchair-bound. It was incredible how swiftly MLD removes someone of Ronan's capabilities. My name is George Drinkwater and I'm a grandfather, father, and husband living in the remote tribal community of Chistochina, Alaska. We are an Alaskan native and American-Indian family from the [inaudible 01:00:16] Crow tribes. Ronan has two brothers, a sister, and a niece. Our environment here is beautiful, harsh, and isolated. We live four hours from our hospital, the nearest Costco and Anchorage. Our nearest grocery store is an hour away and we get wind temperatures as low as negative 40.

(01:00:36):

Ronan has thus far traveled about 24,000 miles to receive care and treatment since his diagnosis and going forward, he will need air ambulance medevac for urgent care needs. His present condition is such that now, four years since symptoms began, he has no voluntary motor function. There are no areas of independence in his life. He cannot move, he cannot eat, toilet, or speak. He is also challenged with blindness, neuropathy, and seizures. He requires wheelchairs, lift systems, internal feeding appliances, and supplemental oxygen. One appliance that he would benefit from is a high flow nasal cannula, a therapy he has used multiple times in the hospital and one that his providers would prescribe but is not approved for home use for his condition.

(01:01:27):

Before losing his speech, Brandon was aware that his life was changing and he shared how frustrating and sad he was at losing his abilities. Upon reflection, I think he knew for some time before we did that he was facing a challenge, unlike those around him. He spoke of seeing an old man who comforted him just before he could no longer talk. Whatever spiritual messenger this was, he was given an assurance of peace and we noticed that the anger he felt was replaced by gratitude and an abundance of love. Ronan's spirit and courage remains strong and he is a happy young man with a joyful heart, even in the midst of the boredom he feels.

(01:02:08):

He lives and will pass this life with love, hope, and faith. I want to leave you with a prayer of our late tribal leader and matriarch, Katie John. May God who created our world send his spirit to be in you, may he protect you from evil, may his blessing be upon the land. May the land be good where we walk, may the animals have enough to eat for winter, may the water be good, and may the goodness of God dwell within you. Amen, [foreign language 01:02:43]. Thank you all for listening.

Michelle H. (01:02:47):

I'm Michelle and my six-year-old daughter, Willow, has MLD. She was perfectly developed at three years old, but within a year she lost speech, swallowing continents, and body control. Before the diagnosis, we noticed Willow was always very clumsy. She would stumble when walking or fall off of her stool. In daycare, she occasionally got accident reports where she fell into the bushes or hit her head. Around Christmas 2018, Willow began to lose interest in Legos and had trouble stacking blocks. She passed a developmental evaluation with her PCP. He referred her for physical therapy. After six weeks, there was no progress in her motor skills, but instead, a slight decline. A neurologist referred Willow for an MRI,

which showed a white matter disorder. After blood and urine analysis, we had a positive diagnosis for MLD, a terminal illness for which there was no plan of care.

(01:03:40):

All we could do was keep her as comfortable as possible. Just before her diagnosis on May 28th, 2019, she began experiencing Hypertonia. Specialty equipment became necessary. A 20 degree scoliosis curve developed by 2021. Treatments for loss of muscle control include therapy, AFOs, tendon lengthening, Botox, positioning, and body work. We used CBD, Baclofen, Klonopin, and Keppra to control these symptoms. Insufficient swallowing is the scariest symptom because she could choke. Loss of muscle control compacts this significantly. In order to provide nutrition, Willow had a G-tube placed in a nice and fun population fold three days after her fourth birthday. Even with preventative measures and use of scopolamine patches, we remain on 24-hour alert with a suction machine because of asphyxiation precaution. We also had her gallbladder removed because carcinoma will likely develop in the gallbladder of MLD patients.

(01:04:39):

The most heartbreaking symptom is loss of speech. My gut wrenches when I remember her sweet voice singing her favorite song, You Are My Sunshine. Nothing's worse than being trapped in your own body with no way of communicating. We have speech therapy teaching us how to communicate with Willow through blinking and the use of an Eyegaze device, but it's not without difficulty. Willow started drooling uncontrollably around the same time her speech slowed. Once, kids were playing at our house and when they saw Willow drooling, they chanted, "Don't touch Willow." This would be the first of many heartbreaks on our journey. On my worst days, I've thought about driving off a cliff or been unable to get out of bed because I can't face the tragic horror that is my baby girl dying from a disorder that I can do nothing about.

(01:05:24):

It seems cruel to speak of losing a loved one who's still living, but we grieve for her voice, her songs, her laughter, hugs and kisses, her getting to be a kid. I got psychiatric help during this unimaginable time. Without that and support from friends in the MLD community, I might not be here today. Willow's worst days consist of crying, joint stiffness, and neurological pain. We'll see [inaudible 01:05:48] in Willow's mouth and fasciculations in her arms and legs. When all three symptoms persist, this means she needs a medication increase. Days stuck inside are emotionally and mentally detrimental as well. When isolated, the mind atrophies and breeds despair.

Michelle H. (01:06:02):

When isolated, the mind atrophies and breeds despair. Although Willow cannot speak, I believe she feels loneliness, isolation, embarrassment, abandonment, insecurity, and confusion as to why this is happening to her. All I can do is give her love and attention and communicate with her as much as possible. Our best day is start with a smile or even a grunt or giggle. We look forward to outings and adventure. Willow loves to be outside and see new people and animals. A good day also consists of normal bowel movements, no fevers, clear respiratory airways, good urine output, and no muscle stiffness. Every day is challenging. Other children meet on the playground, have sleepovers, run around at parties, and enjoy their favorite treats. Willow can't do any of those things. She'll never be able to live on her own without 24-hour care. I think she'd like to go to school with other kids, but due to the lingering COVID threat, the best option for her is a homebound teacher.

(01:06:54):

One worry about the future is Willow scoliosis becoming so bad that she'll need reconstructive surgery or getting to a point where surgery is no longer viable. I'm concerned about her respiratory wellness and I fear the need of a trach one day. I worry about what I'll do when willow's too heavy for me to carry. My

ultimate fear is losing her because I don't know that I'll survive that. The frustration of MLD is overwhelming. I wish my child's doctor knew what to say to a family dealing with this diagnosis. I wish that we had more care and support for Willow. I wish that our friends knew that we still want to see them, but it's harder leaving the house. I wish society knew how to talk about children with terminal illnesses. Most of all, I wish that other kids knew how much Willow wants to interact with them and that even though she can't respond, all she wants is to be talked to.

Matthew H. (01:07:49):

My name is Matt and I'm here with my wife, Lauren. We are the parents of our daughter Loie, who lost her battle with metachromatic leukodystrophy, or MLD, on January 27th, 2014 at the age of three and a half, approximately 13 months after she was initially diagnosed. There's a bit of background, always seemed like a normal little girl. She loved being outside, dogs, and irritating her big brother, Owen. It was not until Loie was not reaching her milestones in her first year, rolling over, crawling, and balance issues that we noticed something may be wrong. She was initially diagnosed with cerebral palsy and when the symptoms seemed to be getting worse during her second year, the doctors conducted additional testing. On December 24th, Christmas Eve of 2012, we received the MLD diagnosis and were told to spend as much quality time together with Loie as she would likely not live beyond the age of five. No treatment options were available for her beautiful daughter.

Lauren H. (01:08:59):

There are many different challenges that came along with a terminal illness like MLD, especially since Loie was such a young child. Feeding, breathing issues, pain, discomfort, and the loss of all motor functions combined to create a Category 5 hurricane of a disease. While Matt and I struggled to try and address all of these issues associated with this disease as they change on a regular basis, there were two symptoms that Loie struggled with on a daily basis, GI and discomfort. Shortly after Lowe's diagnosis, her health started to rapidly decline. She lost the ability to walk, talk, sit up, and eat through her mouth. Within just six short weeks of diagnosis, Loie received a G-tube for feeding. In the beginning, Loie seemed to tolerate her feedings well, although we constantly had to monitor weight to ensure that she was getting the nutrition she needed and at a minimum, maintain her weight.

(01:10:02):

Loie went from being a plump little girl to an extremely frail child within weeks. We struggled with motility, gas buildup, and a significant overgrowth of bacteria within her digestive system. After several weeks, Loie was no longer tolerating her feedings. Matt and I tried different formulas to provide the nutrition needed and at the same time, limit the painful gas buildup, bacterial overgrowth, all while minimizing the endless discomfort that she had when eating. Loie would tolerate each formula for a few weeks until she could not. The GI issues would worsen each time. We exhausted all of our options and our team of doctors were also out of loss of how to keep our daughter alive as a result of every formula causing Loie to scream out in pain.

(01:10:56):

All we wanted to do was feed Loie as she constantly struggled with pain and discomfort. In addition to GI issues, a significant portion of this discomfort was due to constant nerve pain. We tried to manage the pain. A cocktail of medications was given to her around the clock to try and address her issues. It was a struggle to find the right combination of medication in order to provide Loie with some semblance of comfort. Experimentation was a necessity. Loie took between seven and 10 different medications every day.

Matthew H. (01:11:35):

When Loie was with us, we did not travel and rarely left the house except for medical appointments. We struggled with balancing the needs of a child with a terminal disease, the needs of a six year old boy, Loie's brother, Owen, and our marriage. These are items for which no prescription can be provided. It should be considered a symptom of the disease. Beyond the pain medications available, Lauren and I would hold Loie 12 to 16 hours a day to help ease the pain and discomfort. Most of the pictures we have of Loie during her last year with us are of Loie sitting on our lap, are lying on her chest. It seemed to calm her. Loie passed away in my arms. We are hopeful that in the near future and because of what has been accomplished so far in so little time, other children will not have to endure what Loie and her family has had to endure. Thank you for your time.

Corrine M. (01:12:43):

This is my story as told by my mom. She will be my voice that was silenced by MLD. My name is Trent and I was born on July 26th, 1990, the third child of my parents, Kent and Corrine. I have an older brother who was my idol and my sister was next. She and I played together when we were young. I loved my family very much. I was born a normal healthy boy and had a normal upbringing and nothing was out of the ordinary. I was smart, funny, and loved many things. I got along with everyone. When I was eight years old in third grade, I had a little tremor in my hand when I was brushing my teeth or eating. I also had trouble stopping my bike when I was riding. I couldn't seem to hit the baseball that year because I always swung too late. My mom, who's a teacher, noticed that I was not putting spaces between my words at school and I'd quit using capital letters, which wasn't a problem before. I saw a pediatric neurologist at age nine. He dismissed my mom's concerns and told her to take me home and exercise me. Well, she put me in more swim lessons, which I had done many times before, but the swim teacher said I just wasn't making progress. After my fourth grade year, my mom took me to another pediatric neurologist who ordered an MRI before a visit. He told my mom and dad while I wasn't in the room that he suspected MLD and we would need blood work and a urine test to confirm. My parents were devastated. There was no information at the doctor's office and they had never heard of this. They were told to go home and look it up on the internet.

(01:14:20):

My parents found a support group called the MLD Foundation. The next step was the many appointments at Doernbecher's Hospital to decide what to do next. At the appointments, my parents were told my only option was a bone marrow transplant, but it would not cure me. It would hopefully slow down or stop the deterioration that MLD causes. They neither encouraged nor discouraged the decision, but it was decided it would have to be at the Mayo Clinic and not here in Portland. After much research by my mom using the OHSU library, very little information on the success of bone marrow transplants was found. The information showed a 30% chance of dying from the transplant and if it took, it would be at least 18 months before there might be any effect shown. In the meantime, the difficult process of the BMT may accelerate the disease process.

(01:15:12):

Three months later, with lots of prayer, my parents finally decided against a bone marrow transplant. It was the hardest decision of their lives. There is no going back on that decision. My parents never told me I was going to die. They didn't want to depress me as I always had a sunny personality. They wanted to protect me. Between age 10 and 15, I lost bladder and bowel control, the ability to walk, talk, eat, and communicate. Each and every one of these losses was devastating by itself. I would say my parents would tell you that the hardest thing to lose was the ability to communicate. Losing all muscle control, I couldn't even communicate with my head or eyes. My parents also decided to put in a feeding tube at age 15 as I was slowly starving. This was the second hardest decision as they didn't want to prolong my disability, but they couldn't get me to swallow.

(01:16:06):

My parents could not handle watching me not being able to eat while they sat and ate dinner with the food falling out of my mouth that they fed me. I'd lost a lot of weight. Once I got a feeding tube, I quickly gained weight and filled out and continued to grow. I was a big guy and grew to six feet, four inches and probably 190 pounds. I also got a baclofen pump during these years as my painful leg spasms couldn't be controlled with medications. It was hard for my parents to see me in pain. I had my first seizure around 15 as well and was put on anti-seizure medications. I had at least two seizures that couldn't be stopped and I ended up in the ER. I also had a pneumonia once, but I rattled it and came back from that.

(01:16:49):

My parents think I was blind by the end of my life. I could still smile and laugh for quite a while, but I lost that ability after several more years. My parents had to add a bedroom to our house since we had no bedrooms on the main level. Ramps were also added to get into the house. We had a stander, a hospital-type lift bed, a rolling shower chair, and portable lift systems added so my parents could care for me. I had foam booties and a foam mattress pad to keep away bed sores, which we had problems with on my heels. I had a neck support brace when I couldn't hold my head up anymore and leg braces to keep my feet from drooping. We had caregivers come to the house so my parents could keep their jobs and work. My parents bought a wheelchair van for my last two years of life and always took me on walks, to church, and any place we could go with my wheelchair.

(01:17:40):

My dad and brother even carried me to the beach several times in my wheelchair. My dad remembered when I could still talk, asking him if I couldn't walk, would he still take me down to the beach? They did all they could so I could have some quality of life, but I was severely disabled for most of the time. Eventually, I developed a respiratory infection and my lungs were collapsing. My mom got home from work and my dad had taken me to the doctor that day. She was on the phone to get hospice started for me and she looked over at me and I wasn't breathing. I'd lost the ability to cough for the last couple of weeks of life and we thought maybe a mucus plug was blocking my airway, but I passed away very quietly without struggling on December 11th, 2019, 19 years after diagnosis. I hope my story helps some other children with MLD to get the help they need before they have to live through what I lived through. My family loves me and they can't wait to see me again in heaven. My parents think I'm the bravest person they know.

Heather K. (01:18:48):

What doesn't kill you makes you stronger. What doesn't kill you makes you stronger. My brother Joel wrote that to me in a letter before our family knew what was coming. He, like myself, has MLD and it is killing us both. We are not stronger for it. My name is Heather and I'm 35 from a town called Bemidji in rural Minnesota. My family first learned we carried MLD in 2002 when my oldest brother, Daniel, started exhibiting symptoms at age 18. He had dropped out of college, lost employment, became emotional, and was taking an unsteady path in life. When he started to decline more, my family had an MRI done and lesions were found on the frontal lobe. Further testing confirmed MLD and four of the six of us siblings tested positive.

(01:19:49):

Daniel, the eldest sibling with MLD, passed away in 2003 from a failed bone marrow transplant. I was 16 years old and he was 27. I think about my brother Joel now who's still living with MLD. He was my best friend. When I was a teenager and not allowed to leave the house, he would convince our mom with his charming personality to let me go on a ride in his truck around the lake. When he became sick and I got older, our roles reversed with me driving him. Watching Joel's health decline has formed a deep and enduring sadness in our family and in me. Joel is currently 42 years old.

(01:20:35):

He first showed symptoms of MLD at age 24 with changes in his behavior. He would forget how to do things he once knew how to do or would have inappropriate behavior in public. He became withdrawn and was not his normal, funny, happy, and witty self. He would get lost when driving and was unable to hold a job after a while. The symptoms that affect him most now are his loss of his communication and his overall ability to take care of himself, such as feeding and bathing and toileting. Joel is a shell of the person he once was. He was kind, funny.

(01:21:19):

For myself, my best days are spent with the people I love. My worst days are when I'm alone and reality invades its way back into my mind. Those days are spent grieving for my family and for myself. I've had dark and fearful moments of not wanting to live. I'm wholly aware of what has happened, what can happen, and what is to come with this disease. I've lost a brother to MLD and I'm watching two more wither away. My physical symptoms include lost sensation at the tips of my fingertips. I know this is due to my nerves slowly dying due to the demyelination. I lose focus quickly and struggle with my concentration. There's not a day that goes by that I don't wake up and think about MLD. I struggle with the knowledge and everyday moments are impacted.

(01:22:22):

If I forget a task or become sidetracked, I automatically think I'm getting sick. Insomnia and depression are constant in my life. I've developed severe anxiety where occasionally, I'll have a panic attack. I have little patience for myself as I try to be perfect in everything I do because in my mind, if I'm perfect, that means I'm not getting sick. In an attempt to circumvent my anxiety, I over-prepare in order to feel in control, but there is no control with a disease like MLD. It affects everything I do in my entire life. If my siblings and I did not have MLD, we would be empowered to live full lives and have the privilege of growing old.

(01:23:14):

Joel would've started his own roofing company and most likely would've been married and had children. He would've been a really great dad. My fear about him getting older is the gradual loss of more of the functions he's still able to do, such as swallowing or walking. My fears for him are also my fears for myself. There is no guarantee in any treatment and gene therapy, which is a beacon of hope for the MLD community, is not available for adults like my two brothers and myself living with MLD. The only treatment, specifically for adults, is no treatment, and to put it plainly, I'm terrified.

(01:24:03):

In closing, I would like us to think about how there's a last time for everything, the last time we see the people we love, the last time we hug them. There was the last time that Joel and I drove around the lake. My optimism for the future is that there will be a last time we hear MLD is incurable and rather, there's hope.

James Valentine, JD, MHS (01:24:35):

Wow. Heather, thank you so much for sharing your and Joel and your family's stories and really to all of our panelists who are so brave to be first to share today. We know it's not easy, but I think what you shared is exactly what we need to hear and have a discussion about today, so thank you. So this brings us to our first opportunity today to broaden the discussion to all of you that are living with MLD and are direct caregivers of people living with MLD in our live audience to hear your voices as part of this dialogue and discussion. And so if you would like to share some of your experiences of the symptoms and health effects of MLD and how they've impacted your life, we'd love to hear from you and invite you

to call in by phone. You can do so by calling it in now or anytime during the session at +1 703-844- 3231. Again, that number is +1 703-844-3231.

(01:25:37):

You can also scroll down on the webpage that you're on today. There's a comment box. You can also submit written comments throughout the program, which we'll be sharing some of those throughout the session as well. But to get us thinking about this topic a little bit more and all of these different impacts of MLD, we're going to go and start with a couple of polling questions. If you were with us already this morning, you'll know that you can pull out your phone, open up web browser, go to a new tab on the web browser on your computer, go to www.pollev.com/mldpfdd. Even if you've just joined us, if you're a person living with MLD or a caregiver, we'd love for you to jump into these polling questions again at www.pollev.com/mldpfdd. Our first question this morning in this session is we want to know which of the following MLD-related health challenges have you or your loved one ever had? And here you can select all that apply. The options are A, mobility and balance, B, cognitive or memory issues, C, feeding, swallowing or constipation issues, D, respiratory issues, E, speech and communication issues, F, tone, muscle cramps, or rigidity, C, pain and irritability, H, incontinence, eye seizures, J vision issues, K, behavioral issues, or L, other direct symptoms and health effects related to MLD that aren't otherwise listed in the responses here, and you can select all that apply.

(01:27:21):

This is our first question today where our audience can pick more than one option. I want to point out the percentages that you're seeing are not a percentage of the people that selected any individual response. It's a percentage of overall responses. So the best way to look at this and interpret this is use those bars as a relative ranking to one another. We'll give you a few more moments here to select all of the different MLD related health challenges. What's striking at first glance is just how many of you and your loved ones have experienced so many of these different health challenges. Some of the most common ones experienced in our audience today are mobility and balance, speech, communication, feeding, swallowing and constipation, tone, muscle cramps, rigidity, pain, irritability, and right behind that is cognitive memory and incontinence.

(01:28:19):

So many highly selected by a large proportion of our audience. Some of those that are perhaps a little bit lower are vision and behavior being reported as well as others, and we really do want to hear about all of these different symptoms and the impacts that they have, so thank you for answering this question. If we can go to our second polling question. Here, we'll notice that the response options are the same; however, unlike before where you selected all that you or your loved one have experienced, here, we want to know what are the most troublesome MLD-related health challenges that you or your loved one have ever had? And so the same response options will apply, but now we just ask that you select up to the top three that are the most troublesome.

(01:29:12):

And as you're making these selections, I want you to be thinking about what has come to mind, what is making you pick amongst the three? Just having seen in the last polling question the large degree of experiences of so many symptoms by so many, what is making some of these stand out as being your or your loved ones top one, two, or three? And I'll ask that you think about and consider calling and in writing in to share which of these you picked and why. So we'll give a few more moments here to get responses in. As it stands, it's looking like speech and communication along with feeding, swallowing, constipation and tones, muscle cramps, rigidity, and then in that same upper tier mobility and balance.

(01:30:07):

Those four groups of health challenges being the ones that are most commonly being reported as a top three, but what also is standing out to me is that almost everything on this list besides vision and other are in somebody's top three, meaning it is their most troublesome health related challenge. So it is not completely uniform in what is most troublesome for this community. And so whether you were one of the people that is selecting incontinence and seizures as being your top challenges or speech and mobility, we want to understand why is this the top health challenge? What has this symptom translated to and what does this look like in your loved one's daily life?

(01:30:51):

So again, we encourage you to call in and write in to help us understand that. And I now would like to welcome our zoom panel, some of your peers from this MLD community who will also be weighing in and helping share perspectives on this. And maybe, Susan, we can start with you. As you were looking at that polling question and so many different MLD related symptoms and health effects, what stood out to you as being maybe the most troublesome one or two of those?

Susan Sullivan (01:31:23):

Hi, my name is Susan. My son Daniel was diagnosed with MLD in 2014 right before he turned three and then passed away in 2018 when he was around seven. When I looked at those symptoms, I think for me, the tone, muscle cramps, rigidity, and pain, and irritability were among the most difficult because we really had almost no way to control those symptoms. They were somewhat managed with clonidine and diazepam and other things, but really, our doctors seemed to be at a loss and we were too.

James Valentine, JD, MHS (01:31:54):

Sure. And with those, were those always the things that were most troublesome, or was it really once other symptoms were a little bit more managed, those were just the things that were left least managed?

Susan Sullivan (01:32:11):

Well, as a lot of other people have talked about, the onset of symptoms is very rapid. And so for Daniel, I would say the last three years of his life, he couldn't move. We had lost hope on communication aside for some blinking. And so for us at that point, it was mostly just trying to make him comfortable and for a long period of time, that was really difficult and almost impossible. So I think it did change as the disease progressed, but for the majority of his life, those were our primary concerns.
James Valentine, JD, MHS (01:32:41):

And for Daniel, you mentioned that his progression was rapid. We heard a little bit about earlier during the clinical overview how rapid that can be. Can you tell us what his progression looked like over the course of how many weeks or months? Would you describe how he was communicating and functioning before and after that progression as well?

Susan Sullivan (01:33:13):

Yeah, around two, he started to have problems with walking, but he wasn't diagnosed about until May. And at that point, he could sit up, he could talk, he could communicate, he could eat, and between May and September, he lost the ability to sit up, to speak, to eat. He had to have a G-tube put in immediately after diagnosis because he was really already losing weight. So it was really quick and really rapid.

James Valentine, JD, MHS (01:33:48):

And were those mobility regressions the first thing that you noticed or was it something else? A different symptom?

Susan Sullivan (01:33:57):

The mobility was the first thing that we noticed and because it took actually about seven to nine months before it became clear that he wasn't making any progress and things were getting worse, we tried using a walker, physical therapy, all of those different things. And really, what we didn't know at the time was that we were just making him do things that were painful for him. There was no hope of things getting better. We just didn't know that.

James Valentine, JD, MHS (01:34:23):

Sure. And one more question for you, Susan. You talked about his loss of communication skills and towards that latter part, it being reduced to blinking. Can you just describe a little bit about what those losses of communication looked like as he progressed? And then describe how did communication work with blinking?

Susan Sullivan (01:34:52):

So as I said, he lost the ability to speak and move, but a little bit after his third birthday. And so for the last four years of his life, first, we tried the Eyegaze technology. We didn't really make a lot of progress with that. We had the blinking, one for yes, two for no, but that was inconsistent and it was really hard to determine exactly whether or not he really was responding to questions. I will say, unlike a lot of the other kids that I know with MLD, Daniel also lost the ability to laugh and smile pretty early on and that was really difficult because we really had no way to tell how he was doing or having him respond. He also lost the ability to see probably two years after diagnosis, and so he was really solely relying upon hearing and we're not even sure if in the last six months of his life he could hear either.

James Valentine, JD, MHS (01:35:52):

Wow. Well, thank you so much Susan for sharing. Tara, I'd like to bring you in on this discussion of all these different symptoms and health effects of MLD. I know it's hard, but to pick the one or two things that's most troublesome, what stands out to you?

Tara Casey (01:36:13):

Yeah, thank you for having us. My name's Tara. We're from Charlotte, North Carolina, and I'm the proud mom of Cece. She's joining us today. She is nine and a half and was diagnosed with MLD at the age of two and a half. I think of all the symptoms, which are many, that you've heard from everybody, I think one of the most that's been most devastating is her ability to communicate. So before she was diagnosed, she was talking, she was laughing, she was silly, she was sassy, bossy, and fun. And shortly after she was diagnosed around three, we had her GT placed and from there, she lost her ability to speak, and about six months later, around three and a half lost her ability to laugh. And then shortly after that, we saw her last smile. So that's been probably the biggest devastation.

James Valentine, JD, MHS (01:37:23):

Can you maybe share a little bit about today? How do you communicate with her? How does she communicate with you? What does that look like?

Tara Casey (01:37:30):

Yeah, it's difficult because we have to guess what she's thinking, how she's feeling, and we have to be her voice. We have to decide whether she likes something or not. I decide that she likes pink, she

probably likes orange, but we try the best we can without her being able to tell us whether she's in pain, what's hurting, is she comfortable, is she not?

James Valentine, JD, MHS (01:38:10):

Right. Yeah, thank you for helping us understand that. I think one other thing that really stood out to me when you were talking was just her great personality that you described. When she was not able to communicate, were you able to still see her personality coming through? How would you describe her overall sense of self and engagement outside of maybe just direct communication?

Tara Casey (01:38:52):

It's really hard. MLD took it from her ability to communicate to us, so we have to rely on monitors to tell us if her heart rate's...

Have to rely on monitors to tell us if her heart rate's up while she must be in pain. So then therefore, we have to give her medicine, but we don't know if that's really what's going on. We rely on machines to breathe for her more comfortably. We rely on so many medications to prevent what we think is happening. We think that she might be uncomfortable so we give her more meds. We think she has a cold, but she can't tell us how she's feeling, so we give her more medications.

James Valentine, JD, MHS (01:39:36):

Right. And Tara, would say that she has better and worse days in terms of some of those things that you're trying to help manage for her, whether the pain, or breathing, or anything else?

Tara Casey (01:39:51):

Yeah. I really feel like it's like a rollercoaster and it changes minute by minute. For example, on Tuesday, she was fine. She sat up for homeschool and was engaged. And by Wednesday, we called our hospice team into the house because she was having trouble breathing and we weren't sure what was going to happen. And now today here, she's resting comfortably. So it's really up and down.

James Valentine, JD, MHS (01:40:24):

Yeah. And is there anything that clues you in or allows you to anticipate maybe more worse days? Or is it really just unpredictable?

Tara Casey (01:40:39):

I'd say it's really unpredictable. It's always something. As you guys heard, MLD impacts every single part of the body. So whether it's constipation, she's constipated, that's causing more seizures. She has allergies. It's going to cause her more respiratory distress. It's always something, I would say. And we do the best we can with what we have. We have a lot of hope, but that doesn't change things. That doesn't change the course of MLD.

James Valentine, JD, MHS (01:41:18):

Right. Wow. Well, thank you so much, Tara, for sharing. I do see that we have a phone caller that I'd like to bring into the conversation on this topic of what it is to live with MLD. We have Veejay from India who has a daughter living with MLD and wants to share some of her experiences. So Veejay, I'd like to welcome you to the program. Are you with us? Hi, Veejay. Are you with us?

Vijay (01:41:53):

Yes, I am here.

James Valentine, JD, MHS (01:41:55):

Wonderful. Well, we'd love to hear a little bit about your daughter's experience, maybe the things that are most troublesome for her.

Vijay (01:42:05):

Okay. Do you want me to explain?

James Valentine, JD, MHS (01:42:08):

Yes. Please share anything that's important to you about her experience living with MLD, any of the symptoms or health effects that have most impacted her?

Vijay (01:42:21):

Yes. Actually, we are trying to do for the trial itself. Right now [inaudible 01:42:33] seeing lot of problems for sitting and walking. She's not at all speaking.

James Valentine, JD, MHS (01:42:40):

Yeah. And how old is she and how long ago did she lose the ability to speak and walk?

Vijay (01:42:53):

So up to the age 3.5 years, she was talking very nice, or she used to sing and dance. So after 3.5 years, the year four onwards, she started losing for walk. Once [inaudible 01:43:11] effect came on the age of five, she lost her walking ability. Then the age of six, one [inaudible 01:43:19] came, and she lost her total speech she lost. Now she completely in the bed for toilet, for walking, everything. We are getting in hand only. [inaudible 01:43:36], especially to her right from wheelchair. And the toilet facility is [inaudible 01:43:45]. The day to day activities since since the age of four getting growing. We have a female child, mentally and everywhere, and always we are getting maybe no affected when I'm seeing very beginning of how she was now. So as a parent, it's very difficult to tolerate.

James Valentine, JD, MHS (01:44:10):

Sure.

Vijay (01:44:11):

Those are words to express.

James Valentine, JD, MHS (01:44:14):

Yeah. Well, thank you so much for weighing in and sharing those most troublesome aspects of your daughter, both the loss of speech and walking. I think two things that we're starting to hear is a little bit of a theme of being some of the things that are some of the top most troublesome aspects of living with MLD, both in the polling and from our discussions today. I'd like to bring Tyler from our Zoom panel into this discussion as well. Again, thinking about all of these different symptoms, what has been really troublesome? What would you like to share on this? Tyler?

Tyler Widman (01:44:56):

Hi everyone. I'm Tyler Whitman. My daughter Libby is four years old, diagnosed with late infantile MLD right before her third birthday last year. And I think I would agree with everyone. Speech was probably

the hardest for everybody. Her ability to communicate was very similar to CC's story. She was a sassy little girl, and so much personality and so smart. And it was a matter of months that she went from being able to just say, "Yes, no," and then completely no communication at all other than her beautiful smile.

James Valentine, JD, MHS (01:45:40):

So one thing that hearing a little bit of some of these similarities has been ways that you're able to try to communicate, or at least I think Tara said, guess what is really going on. In your experience, what does that look like? How do you communicate today?

Tyler Widman (01:46:03):

Sure. It's definitely difficult. We found that her smile is definitely a good way to communicate. At least we feel like she's pretty consistent with being able to tell us yes with a smile. Although she's a happy girl most of the time. So a smile is always on her face. But it can be difficult, especially we want to give her choices and we want her to be a four year old. And it's so hard to be able to do that without her being able to just tell us this or that. So sometimes we'll hold something up and try to have her use her gaze to pick something like do you want the red one or the blue one? And we hope that she's telling us, and I know she's in there and she wants to tell us. But some days are better than others like everybody said. So you use our best guess and hopefully we can keep her happy and communicate the best we can.

James Valentine, JD, MHS (01:47:01):

Can you give us a couple of examples of the types of things, whether it's with the gaze or seeing if she's smiling in response, the kinds of things that you'll be talking about or even some of the choices that you're hoping that she'll be able to participate in?

Tyler Widman (01:47:18):

So the first thing that comes to mind, she loves her mama and papa. And she knows they come over on Thursdays. So when we wake up on Thursdays, we ask her, " Do you know what day it is?" And she gives a big smile and tells us. She communicates in that way, like, "Are mama and papa coming over?" And a big smile tells us, "Yes." She knows. She knows. She knows on Thursdays they come over. And some of the more difficult things, like I said, choosing this or that. Halloween costume this year, how do we know what she wants to be for Halloween? It's so hard. We know what she liked when she was two. But she's four now. Four year olds don't like what two year olds. So we try to give her choices and show her do you want Elsa? Do you want to be a Minnie Mouse which is her favorite? So this year she's going to be Elsa. But we do our best and hopefully we make her happy with it.

James Valentine, JD, MHS (01:48:20):

Sure. And Tyler, do you find that there's some days that she's more communicative and interactive than others? Is there any predictability to that? If there are days where maybe they are more bad days and she's less communicative, how often does she have those types of days versus the ones you were just describing?

Tyler Widman (01:48:43):

Sure. And while I would love to have rose-colored glasses and just remember her happy days, she does have bad days, especially if she's working her butt off in therapy and things like that. She's just so tired and worn out. Or if she's coughing a lot, even that will take it out of her. So it's harder for us to make that communication even to get a smile out of her sometimes. And I feel like she's just so fatigued, she can't even put that effort out there to just a smile, which is, I don't know how many muscles in your face, but not much. So it's so devastating sometimes to not be able to have that communication with her.

James Valentine, JD, MHS (01:49:21):

Right. And you talked about being worn out, whether it's from coughing or from therapy. Can you just tell us what type of therapy are you referring to? And can you also describe, is this coughing just like something that's a chronic thing that she lives with? Or is this when she maybe comes down with a bug?

Tyler Widman (01:49:40):

So therapies, she actually does go to school. We have an incredible elementary school close to us. She has a para that helps her with PT, OT and ST. She has that every week at school. And as far as the coughing and that type of thing, it's really related to her swallowing ability. She can't swallow anything. So I don't know if it's just her or due to the condition, but she tends to have a decent mucus build up. And I would say throughout the day, she's coughing on a good day maybe a handful of times. On a bad day, every two or three minutes and we got to suction and be on top of her. And she definitely needs 24/7 monitoring because of that sole symptom.

James Valentine, JD, MHS (01:50:29):

Right. Well really, Tyler, thank you. Very interesting to hear about the interrelation between swelling and cough and her energy level and impacts on even communication. So thank you so much for sharing that. Just to continue along here, Debbie, as you're again, thinking about that huge list of symptoms that we saw so many select, what is really troublesome from your experience?

Debbe Harris (01:51:03):

Hello everyone, I'm Debbie. We are in the Chicago area. My daughter has MLD and she was diagnosed the week after her seventh birthday and she's now 12 and a half. So that gives her the early juvenile form of MLD we've heard about. And I'm going to join everybody else in saying that communication is definitely the hardest thing to lose. Maybe a slightly different perspective from the parent of a juvenile MLD child is that Annabelle was totally normal in every way until we started seeing symptoms probably three or four months before her diagnosed. So everything, above average in school, played soccer, did all the sports, dance, everything. Everything that all of her, well, she has a twin sister, fraternal twin sister, and all of her friends did. And she's lost everything like everyone else that you described. But the communication, definitely, it's the feeling that she is locked in. And I want to just emphasize one thing that Tyler said. We know she's still in there because we haven't really touched on that, but that fact.

James Valentine, JD, MHS (01:52:26):

Yeah. Well, Debbie, there's a few things I definitely want to talk about here about Annabel's experience. But knowing that you said communication is probably the hardest thing, was that something that you noticed early on? Was there loss of communication abilities or is that just really more today the hardest thing to deal with?

Debbe Harris (01:52:50):

Yes, it definitely changes. Although as we've heard I think from everyone, with Annabel, the disease did progress very quickly. So right at the beginning, it was mainly pain from muscle spasms and things like that. But she lost her ability to talk completely almost exactly a year after she was diagnosed. She lost the ability to walk about six months after. And in the beginning, we had much more ability, she was still mobile then, so she could raise her hand or a leg to respond to questions. And that has decreased to the point where she is only capable of blinks now. She does still smile some. Although just as Tyler said, often we think that the effort of smiling is just too much because fatigue at this point, five and a half years in, fatigue is the number one adversary for us.

James Valentine, JD, MHS (01:53:48):

And when you say fatigue, can you describe what that looks like, feels like? I think people might have different ideas of what fatigue might be. What does that mean for Annabel?

Debbe Harris (01:54:01):

Yes. I think the disease itself and then all of the medications that most of these children are on, both just make them tired. And when she was first diagnosed, I know someone described to me do you ever have one of those dreams where something's chasing you and you're running in quick sand and you can't move and that awful feeling? And that person said, "That's what MLD feels like for everything. Not just trying to move, but trying to think, talk." And so I think everything that she does is fatiguing. And so on the days that she's most fatigued, we definitely feel like she's still in there. We always feel like she hears us and she understands, but we feel like she just doesn't have the energy even to blink.

James Valentine, JD, MHS (01:54:47):

And how often does she have those days? Once a week, once a month? What is if you had to try to somewhat quantify it?

Debbe Harris (01:54:58):

For us, it varies and it goes in waves. And we'll have a period that can go two, three weeks a month, and we think, Oh my goodness, her disease, she's progressing more. Maybe she really can't respond anymore. Or like Tara said, we go through the range of what it could be medically, more medicines? Is something bothering her? Does she have an infection? All of the things that Tara enumerated. And then for us, we'll see Annabel sometimes bounce back a little bit and all of a sudden we'll think she's doing better. She's responding more this week than last week. And her caregivers will see that as well. So it's intermittent, I think, to answer the question,

James Valentine, JD, MHS (01:55:41):

And I think you mentioned that those waves sometimes you're like, oh, this is progressing and it's weeks at a time. Is that something that happens a few times a year? Again, just trying to understand the ebbs and flows here.

Debbe Harris (01:56:00):

Yes, I would say maybe three or four times a year. But consistently over the course of her disease, if you were drawing a graph, it would be a spiky, but always declining sort of. But I just want to emphasize honestly, the communication, I think it's what it embodies for all of us. Because we haven't talked a lot about the fact that we think most of these kids stay mostly cognitively intact. Certainly we know that for Annabelle and her school team corroborates that she is still in general ed classes. She is not in special ed classes. She's in seventh grade and all of her teachers and helpers are convinced that she grasps the content. And so it's the fact that she can't tell us what she's thinking. Not only preferences, but we know that she can understand and think and the inability to express herself in any way, it's torturous.

James Valentine, JD, MHS (01:57:03):

And very interesting to get the educator perspective on that. It sounds like the educators have shared with you their perspective that she is comprehending. Can you give an example of a thing that maybe they've shared as an example of how they know that she's comprehending? Just again, to give us a little bit of context to understand.

Debbe Harris (01:57:31):

Sure. We just had her annual IEP meeting last week and they were talking about the speech people. And also she has a special ed teacher that works with her every day just to modify the content and be sure of her comprehension. And they said she always lets us know what stories, what topics she's interested in and which she doesn't. She clearly has her preferences. But they said she's also a good kid and she'll respond to our questions, comprehension questions even about the one she doesn't like, but she's very clear in expressing her preferences for subject matters.

James Valentine, JD, MHS (01:58:08):

Wow. Well thank you so much Debbie for sharing that. I do see that we have gotten actually quite a few people writing in with comments on this topic of some of the symptoms and health effects that are most troublesome for them and their loved ones. So I want to check in with you, Maria. I know you've been looking through those. What are we seeing?

Maria Kefalas, Ph.D (01:58:28):

Again, we are just hearing in the written comments what our presenters have been sharing what we saw in the original video statements. Stacy from Massachusetts says that, "The most burdensome symptom for Brooks is the inability to communicate. Brooks's brain remains stable since his stem cell transplant in 2018. His brain knows what he wants, but his body can't tell us." We have another comment from Kayla in Alabama. She also talks about her child's loss of speech for a late infantile parent, loss of speech, the loss of fine and gross motor skills being among the biggest challenges. Shanna from Minnesota with an early juvenile child, talks about how her son's breathing was labored and he needed oxygen to survive. He was unable to walk. He had a G-tube because of the inability to eat and enough to stay healthy. Again is talking about feeding issues. All these of these symptoms kept Gavin from living life to the fullest, and we were exhausted with all the care he needed.

(01:59:32):

Lexi from Bloomington, Illinois with the late infant child says, "Communication, frustrating because he still knows what he wants and likes to do it, but cannot express himself." And she also talks about motor function because he cannot function as normal four your old probably, and it's probably harder for us as parents to watch, but I feel like he could still know what he is missing out on and also losing the ability to eat.

James Valentine, JD, MHS (01:59:58):

Sure. Yeah. Well, thank you to everyone who's been writing in. We'll continue to share those quotes from what you're providing throughout the session today. And if we are not able to read out your comment or your full comment, know that we are recording all of these and we'll be including them in that Voice of the Patient summary report.

(02:00:22):

So we've focused on some of the direct symptoms and health effects. I think we're starting to hear pretty loudly and clearly few of those that are most troublesome for this community. I want to broaden the discussion a little bit now to understand what that translates to and means for the daily life of people living with MLD. And so to get us thinking about that topic, we're going to go to another polling question. So go ahead, pull your phone back out with the web browser. Go to that tab maybe that you opened on your computer. Go to www. pollev.com/MLDPFDD. Again, if you just joined us, if you're a person living with MLD or a caregiver, please join these polling questions. Once you have this website open, you'll be able to come here as we bring up different questions throughout the day and answer these questions to share your experiences.

(02:01:22):

So here we want to know what specific activities of daily life that are important to your loved one or to you if you're living with MLD that you or they are not able to do or struggle with as a result of MLD? And select up to the top three of those activities that are important, that are limited. Options are A, breathing independently, B, communication, C, feeding, eating, swallowing, D, sitting, E, sleeping, F, walking or mobility, G, traveling H, social interactions with family and friends, I, attending school and participating in education or J, some other specific activity of daily life that's important to your loved one that they are not able to do or struggle with as a result of MLD. And again, please select up to the top three of those most important activities that are impacted.

(02:02:20):

And similarly to before, I want you to be thinking about what does this look like in daily life? I'm sure as you were making these selections, there's certain aspects of daily life that are informing your selection as it stands. Some of those top specific activities that are important that are limited, being communication, feeding, eating, and swallowing. We haven't heard so much about that, but yet it's a top activity that's impacted. So we want to ensure that we hear a bit more about that. Of course, walking and mobility. But unlike the earlier discussion, we're really trying to understand what that symptom looked like. We want to know how does this limit daily life and what you or your loved one are able to do and participate in daily life? It looks like most people have responded. So I'll just also point out that again here, every single one of these things is in somebody's if not a number of people's top three most important things that are limited because of MLD.

(02:03:27):

So everything from breathing to sitting and sleeping, traveling, social interactions and attending school, as well as some other things we didn't have listed. So I'd like to encourage you, if you're someone that's picked one of these less commonly reported as a top impact, we do want to hear about that and understand that as well. And so if you would like to share your experiences of these impacts, we encourage you to call in. That phone number to call in is 1-703-844- 3231. Again, that's 1-703-844-3231. We'd love to hear and talk with you live about some of these impacts that MLD has on your you or your loved ones daily life.

(02:04:16):

But to start this off, I'd like to come back to our Zoom panel. And Kelsey, we haven't had a chance to speak yet. So as you were thinking about this and how the various symptoms and health effects of MLD actually impact daily life, what really stands out to you as some of those most important things that are impacted?

Kelsey Donnelly (02:04:40):

Hi everybody, I'm Kelsey. My daughter is Teagan. She's actually joining us here snoozing on the couch. We are in Colorado. She was diagnosed with late infantile MLD in 2018, exactly one month before her second birthday. As far as the polling question, I mean, I think any one of us could choose every option. But out of my top three, I'm going to pick one that might not be as commonly chosen. For us, I would say traveling. With Teagan, she started camping at three months old. She's outdoorsy. That that was her life. And after diagnosis, and because of how quickly things progressed for her, it was almost like we froze. We didn't know how to continue giving her that. And that's hard.

James Valentine, JD, MHS (02:05:43):

And is that impact on the ability to travel and do these kinds of outdoor activities, is that really one or a couple of the different symptoms that are making that difficult or is it really the constellation of different things that she's experiencing?

Kelsey Donnelly (02:06:03):

I would say it's a combination. The amount of equipment needed to ensure all of her cares are provided. She requires 24/7 oxygen, suction machine, pulse/OX monitors, CBT treatments and all of the things. So that in itself is quite taxing. Her weakened immune system, that's a really big one. The wrong climate, stepping into the wrong gas station, I mean, those small things can cause pretty detrimental. For a quick example, we took her on a trip in June a couple states away to meet some other MLD families, and she ended up intubated after a nine minute code.

James Valentine, JD, MHS (02:06:55):

Wow. And that was from an infection or illness? Yeah.

Kelsey Donnelly (02:07:01):

Yes. She ended up with aspiration pneumonia and a mucus plug blocked her airway and she was exhausted, so her heart stopped for nine minutes.

James Valentine, JD, MHS (02:07:11):

Oh my goodness. And you also mentioned, I think you were alluding maybe to some seasonality effect or weather impacts. Can you maybe describe what you meant by that and tell us a little bit more about that?

Kelsey Donnelly (02:07:26):

Absolutely. So we live again in the state of Colorado, so we can get all seasons in one day, which proves very, very hard on her body. She can typically detect the rain or snow well before I can. I actually have a barometric pressure gauge downloaded on my cell phone to try to help warn me beforehand because any change in that pressure causes her sinuses to flare up, her muscles to start aching, dystonic episodes, seizure activity, just from a weather change.

James Valentine, JD, MHS (02:08:04):

Wow. Yeah. And some of those changes, I mean, just to give us a sense of the range, whether it's spasticity or seizures or when there are those spikes, can you just describe how much more severe those symptoms are?

Kelsey Donnelly (02:08:23):

Yeah, I mean I would say as we're coming into winter time, my nerves are high, very nervous, because typically what that looks like for Teagan is we'll get hit pretty hard with a blizzard out of nowhere. Her heart rate can spike 170s, 180s, full dystonia, I mean, stiff arms, stiff legs. She doesn't have the ability to fully cry anymore, but she'll tears in her eyes. And no amount of medication can really touch or relieve that. So we're trying the baths with the bath bombs and the massage with the salves, and all of the different things while being mindful, again, going back to medication, being mindful of her respiratory system because that's already weakened. You do too many of those rescue medications and then you run the risk of really suppressing the respiratory and then you've got a whole other problem.

James Valentine, JD, MHS (02:09:19):

Right. Wow. Well, thank you so much, Kelsey, for helping us understand some of these impacts in daily life and what's really driving that. I do see we have a caller, we have Osmahan from Minnesota and she's

calling to share about her daughter, Laura, living with MLD. So Osmahan, I'd like to welcome you to the program. Are you with us?

Osmahan (02:09:43):

I am. Can you hear me?

James Valentine, JD, MHS (02:09:45):

You hear me? We can, yes.

Osmahan (02:09:48):

All right. Thank you for allowing to participate in this discussion. My daughter Laura has MLD. She was diagnosed when she was two. She's now six going on seven. And she has two sisters who are three and 11 year old. One of the things that has been very impactful for us is the amount of muscle spasms that she has affect a lot of different things in her daily living and her ability to connect with that. So similar to what everybody on the panel talked about is that loss of communication has been very impactful. When she has a lot of spasms, she gets very tired and it can cause vomiting, and therefore she's very distressed and we have to help her with suctioning. We never know when it's going to happen. So we have to always be on the ready.

(02:10:45):

She lost ability to talk and ability to see. She still blinks sometimes. The cue we have is if she had one tear coming out of her eye, she's trying to talk. She's sad. And then her hearing is really impacted by the amount of energy she had that day. So if she's really tired and she's very, very tense, she's going to tune out and she's going to be able to communicate with us. And that has impacted her ability to stay with her and connect with her. So on the days where she was very rigid, I cannot hold her and her have her feel that we're with her. It has also impacted her relationship with her sisters because of course at that age it is very hard to be and communicate with your siblings when there's like no cue for how she's feeling and the fact that they know she's there, but there's not much we can do with her. And sometimes her older sister will read her stories, but because there's no response, it's disengaging. And I've seen my daughter's relationship with Laura kind of evolve over time as to what they could do.

Osmahan (02:12:03):

My daughter's relationship with [inaudible 02:12:02] can evolve over time as to what they could do. The way they connect with her right now is helping us with the function machine and helping her with touching different items, but that's really limiting and the experience that they have with more.

James Valentine, JD, MHS (02:12:18):

Wow. Yeah. There's so much in what you just shared that's really, really illuminating. If I can maybe go back to one of the first things that you mentioned, just because we haven't heard so much about the muscle spasms, could tell us how long do those last, do they affect her whole body and how often do they happen? Just to give us a sense of what that actually looks like for a person living with MLD.

Osmahan (02:12:46):

Yeah. Very similarly to everyone, her muscle spasm got worse over time and it was very rapid progression over the course of the first six months of her disease. The way that affects her now is she's not comfortable sitting in the same position all the time. She can not really move, but it can feel that it gets tense in her neck and most likely in her legs. And she's always in that very tense position. Her hip actually dislocated and the way she's being able to manage that thing is to be in that sitting position,

which is what's relaxing her right? Or alleviates the most pain. But because she's in that position, that becomes the thing as to where she can sit, getting her into the car seat, what wheelchair we have to use, how she sit, how she sleeps. And over time it gets worse because the more strain you put on your muscles, the more stiff it gets over time. Where the points where she can always cross her leg anymore and keep them straight, they're always in that crossing leg position and it aggravates your problem unfortunately.

James Valentine, JD, MHS (02:14:10):

And kind of that rigidity or being ... Having limitations in her positioning, what does that translate to in terms of what you all are able to do together? What she's able to do, whether around the house or even outside of the home?

Osmahan (02:14:32):

It means that we had to be very versatile and adapt over time as to how do we move her from one place or another one?

James Valentine, JD, MHS (02:14:43):

Yes.

Osmahan (02:14:44):

And what can she sit when we're in the living room, when we're having dinner, we want her to share the experience of dinner with us. It has meant that ... And we had the opportunity to travel to visit her grandparents over this summer. I did have in the airplane to ask the person sitting right in front of me to not recline their chair. Otherwise they were crushing her legs because there wasn't way for her to have them sitting in the right position. The most distressing piece is the fact that I cannot hold her in my lap anymore.

James Valentine, JD, MHS (02:15:22):

Right. Wow. Well I just want to thank you so much for calling in and I know these are hard things to share, but I really appreciate you sharing your daughter's experiences and really helping us see what that looks like in daily life. It sounds so difficult, so just again, thank you so much for sharing. Again, I see that we have written comments coming in on this topic and so want to make sure that we hear from these many voices. So Maria, what are we seeing in terms of impacts on activities in daily life?

Maria Kefalas, Ph.D (02:16:02):

Oh, just so much. We have Less from Ireland. My son Kyle, lived a short and painful life. Like so many of these beautiful children, he died at age six two years ago. The most difficult symptoms he endured after his rapid decline age two and three were gut pain from digesting and passing his liquid feedings and the muscle spasticity he suffered from. He cried more than any child should, but he met all the worst MLD could throw at him with a cute smile on his face. There is another comment from Karin in West Lynn, Oregon who has a juvenile child. She says, we spent years with Trent not being able to communicate his needs. Not even an eye blink or head turn.

(02:16:44):

The last year he could not laugh or have any involuntary response. We also guessed at all his needs. We didn't know if he was sad, uncomfortable, itchy, pinched, or whatever. Kristen from Iowa talks about at the beginning it was the spasticity. Grayson was in constant pain and uncomfortable through that stage. It was hard to enjoy life when he was constantly hurting and all he wanted was to be home and in his

safe place. Nutrition was a huge challenge with a slow gut motility. Every day was a constant battle to figure out if he was tolerating it, if we could be mixing it up by changing formulas, volume rate, et cetera. And then respiratory was the other next biggest challenge. These kiddos worked so hard to breathe.

James Valentine, JD, MHS (02:17:38):

Wow. Incredible comments that are coming in and these are just a few of those. So we'll continue to bring those into the discussion here. I want to check in with our zoom panel. Is there either a symptom or an impact on daily life that maybe we haven't talked so much about yet, but is something that is important and impactful and understanding? If you could just give me a little wave of a hand if there's something you'd like to share on a topic that we haven't covered so much yet. Or maybe it's something we have talked about but it's a different take or experience with it. Sure. Susan, we'll start with you.

Susan Sullivan (02:18:19):

I wanted to follow up on that point about feeding. That was a major struggle for us for several years after initially diagnosis, we tried to avoid putting Daniel in the hospital, but there was periods where he couldn't even hold down his meds and we had no choice. We had to come into the hospital for an IV for fluids. We also had a really hard time convincing doctors the gallbladder was involved. And so we spent I think three to four days in Hopkins before the GI doctor was actually willing to take out his gallbladder. And it wasn't until the doctors and the nursing staff would see him projectile vomiting that they were convinced there was an issue. It was really difficult to manage that and especially because of the respiration problems that every time he would vomit, we would have to be perpetually concerned that that was going to have lead to an aspiration pneumonia, make sure his airways were clear. So it was a real struggle and it was really painful for him.

James Valentine, JD, MHS (02:19:20):

Yeah. Can you tell us a little bit about that vomiting and is that something that was a kind of a daily struggle? Was this something that there would be periods where maybe there was vomiting and others not?

Susan Sullivan (02:19:34):

Yeah, it would happen for a couple days. He would go through periods where it was off and on and because it wasn't consistent, it was hard to tie it to his gallbladder.

James Valentine, JD, MHS (02:19:45):

I see.

Susan Sullivan (02:19:46):

But also wasn't sure, especially for parents who don't necessarily understand how to use a feeding tube and how to use a feeding pump to understand how slow his feeds were needed to be. There's a lot of motility issues. So just in some cases he just wasn't digesting food quickly enough. There's a lot of things that factored into it, so it's hard to pinpoint the exact cause.

James Valentine, JD, MHS (02:20:09):

Yeah. And just since you mentioned the motility issues, what did that look like? Does that also an ever present symptom or again, or was there more of periods where that was more of an issue than others?

Susan Sullivan (02:20:24):

It just progressively got worse. I think towards when he was around seven, he was only taking maybe 20 mls of food an hour. That was all he could tolerate. And he was on continuous feeds because there was no way to actually give him enough nutrition. So it was just constant. And others have talked about the amount of equipment necessary that you have to move with you if you want to go anywhere. It's essentially a mobile pick you if that's what you need from everything.

James Valentine, JD, MHS (02:20:54):

Right. Yeah. Tyler, well thank you Susan. Tyler, want to bring you in, something to add on this or something different?

Tyler Widman (02:21:01):

I just wanted to kind of add in on our experience with feedings because it's very similar, but towards the beginning of this year, end of last year, we went almost six months of her vomiting almost five days a week.

James Valentine, JD, MHS (02:21:16):

Wow.

Tyler Widman (02:21:17):

Consistently and trying to figure out what was going on and navigating everything. And we went through so many different food changes, tried changing foods and just nothing was working. And amazingly an allergy medicine, [inaudible 02:21:34], once we started giving her that, she's a whole different person, it was a game changer for her. And it was something that isn't normally prescribed. It was something that was like a shot in the dark for ... Luckily we work with Dr. Dang and her team is amazing. Along with our children's hospital in St. Louis. They collaborated and allowed us to try it out and now she's doing excellent just off that one medicine. It was such a life changer for everybody.

James Valentine, JD, MHS (02:22:01):

And when you describe the response being excellent, is that just the ability to keep food down, the amount or type of food that she was able to?

Tyler Widman (02:22:10):

All of it. I mean some days she could not tolerate anything. And medicine, water, we'd give her five mils of water and she'd throw it right back up.

James Valentine, JD, MHS (02:22:23):

Wow. Okay.

Tyler Widman (02:22:25):

And now with this medicine, her vomiting over the past, I would say it's been about six months, has reduced to maybe once a month.

James Valentine, JD, MHS (02:22:34):

Wow. Okay. Yeah. Thank you so much. Tara, I think I saw your hand and then Kelsey will come to you, Tara. So on this kind of topic of it, maybe things we haven't covered as much yet.

Tara Casey (02:22:46):

Yeah, I mean we had similar feeding but also something else, the autonomic dysfunctions. So anything that is controlled by autonomics, so impacts these kids. So that's breathing, high heart rate, vomiting, then it's temperature and stability. So we're constantly putting six blankets and a heating pad on and then all of a sudden we have take it all off because then her temperature went the other way and then it's causes a seizure. So all the autonomic functions disfunction.

James Valentine, JD, MHS (02:23:23):

Sure.

Tara Casey (02:23:23):

And so that goes to the motility issues as well.

James Valentine, JD, MHS (02:23:26):

I see. Sure. Thank you so much. And Kelsey, did you want to add something?

Kelsey Donnelly (02:23:33):

Yeah, I definitely want to touch also on feeding. And then I love what Tara was just saying too. Maybe I can play into both. But what I think about the most with feeding is, and what I like to ask people is go home and tell your two year old that they can't have bites your [inaudible 02:23:51]. They're still fully cognitively aware. And this little girl of mine was the one at Thanksgiving, eat her whole plate and then she'd go find everybody else. They fight, fight, fight. Oh. And that ability went so fast but she still wanted it. She just didn't realize that of each time she would choke.

James Valentine, JD, MHS (02:24:15):

Oh my goodness.

Kelsey Donnelly (02:24:16):

That's incredibly difficult. And then as Tara was describing, just the ability to breathe, something you or I take for granted. Because it's so easy.

James Valentine, JD, MHS (02:24:30):

Right.

Kelsey Donnelly (02:24:31):

24/7 oxygen, her nose bleeds almost every day.

James Valentine, JD, MHS (02:24:37):

Wow.

Kelsey Donnelly (02:24:38):

Heartbreaking.

James Valentine, JD, MHS (02:24:40):

It is. Thank you so much. I do see that we continue to get comments coming in on this. So would like to check back in Maria? What else are we seeing?

Maria Kefalas, Ph.D (02:24:50):

Oh well we have Jennifer from New Jersey. One of the worst stem symptoms that my daughter has is the tone and muscle spasms. Most days the tone is controlled by Baclofen, but there are times that the tone kicks in so badly. she screams in pain, her arm sticks out straight. I can feel her shoulder blades sticking out her back. Her leg gets so tight that she cannot control it to bend it. It is always difficult to figure out what is causing the tone to kick in extra. It could be being cold, being scared, not feeling well. Constipation, when the tone kicks in so bad she screams and becomes unable to communicate. We have Kendra from Phoenix, Arizona with late infantile child. She says, traveling via airplane with our daughter who has late infantile was is so extremely difficult with airline staff. Having to tell them each and every time that her what her illness is and what prevents her from doing what, I'm sorry, screen.

(02:25:52):

Traveling via airplane with our daughter who has late infantile was extremely difficult with airplane staff. Having to tell them each and every time what her illness is and what it prevents her from doing such as using the airplane laboratory and why she can't sit up by herself in her own seat, even though the airline standards say she must. It was terrible to relive and retell that story. It's a hundred percent prevented us from traveling with her via airplane.

(02:26:20):

And let me see, I think I have one more here I wanted to share. All right, this is Lexi from Illinois who's an late infantile child. She says, losing the ability to eat as a family. We like to bond over food, going out to eat, having cookout parties, trying new places, used to bring us a lot of joy. But another thing we are no longer able to do. And Gabby who says she's from the US with a late infantile child, says Gabby is unable to walk, to speak, eat, or to participate in any activities of daily life. She's completely dependent on her parents and caregivers. She's constantly monitored by machines and needs rescue interventions such as pulmonary treatments and oxygen to help her breathe and assistance such as catheterization and suppositories to help her.

James Valentine, JD, MHS (02:27:10):

Yeah. Thank you for Maria and thank you everyone for sharing your experiences. So with the remaining time that we have in this first session today, I do want to make sure that we tackle one more topic. We know that as we've just heard, that there's so much that you and your loved ones are already experienced, have experienced, but we also know that you're thinking about life with MLD in the future and what that looks like. And so we want to explore some of your worries, fears, and concerns for the future. So we're going to go to our last polling question of this morning session. So please open up, pull out your phone, go to that browser, open that tab on the browser on your computer, go to www.pollev.com/MLDPFDD. And here what we want to again ask you about is what are those worries, the things that worry you most about you or your loved one's condition in the future.

(02:28:17):

And here we want you to select up to the top three of those worries that you have. Are those worries? A, related to pain in the future? B, breathing. C, scoliosis and hip dysplasia. D, the eating and feeding issues. E, walking or mobility issues. F, managing care long term. G, needing increased nursing or hospice support. H, decreased communication or responsiveness. I, a progressive loss of abilities that you or your loved one have today. J, dying prematurely. Or K, some other worry that is one of the things that you worry most about for you or your loved ones, MLB. So I'll give you a few moments to think about this. I

promised these questions would get harder as the they went on and I think I'm fulfilling coming through on that promise here. I'm sure. So as it stands while final responses come in, it looks like some of the top most common worries from our audience today are both dying prematurely as well as breathing issues in the future. After that, we're seeing decreased communication, responsiveness or worries about pain in the future, kind of being maybe the second tier. And then after that that we're seeing a lot of the other things kind of together maybe as a third tier. Everything else except for walking and mobility issues, being again a top three worry for the future. So as you were making these selections, we want you to think about what about these different aspects of your you or your loved one's condition makes you worried.

(02:30:13):

Is there a certain degree of either increasing of some of these symptoms or onset of these symptoms? That is kind of what is the specific worry you have. If you'd like to share about your worries, we encourage you to call in and share that with us today. You can do so at +1 703-844-3231. Then you can call in share your ... Certainly still happy to hear your experiences living with MLD to date, but we're broadening this discussion now to hear your worries for the future. And again, you can call in at +1 703-844-3231. So just to check in with our zoom panel here, maybe again with a little wave of a hand who would like to share as you were looking at that polling question, what was one of the biggest worries that you had? Debbie, let's maybe start with you here.

Debbe Harris (02:31:14):

I would say that ours is, we are older parents and when she was diagnosed, we thought we could easily lose her and we could have within a year or two. And we're five and a half years in and now it's shifted a little bit to could she be with us another 20 years? We've already outgrown ... She's outgrown my ability to lift her. My husband can still lift her with a lot of effort. He's thrown out his back multiple times. So we're looking at the world of, we already have a Hoyer in the home, but of modifying the van, of getting some of the track systems that people have. So some of those sort of logistical issues. But as her mother, and I'm kind of going back to an issue I touched on before, I think the thing I worry about most is when she can no longer communicate with us at all.

(02:32:09):

Whether it's due to fatigue or not even being able to control her blinks or be able to smile because I feel like her brain and her cognitive function is going to outlive her body's ability. And to me that is just the worst kind of torture. She will truly have locked in syndrome then and will be there alone, unable to express anything, unable to be heard. And to me, that's just a thought that I can barely contemplate. All of the hardships on us, the care and the inconvenience. We worry about that as older parents and because we would never ever consider sending her to a home or whatever. Just all we can do is love her. And we do that in abundance. We just can't imagine anything else. But when she gets to the point where she feels like she just can't communicate with us at all, that's going to kill me.

James Valentine, JD, MHS (02:33:18):

Yeah. Yeah. Debbie, thank you so much for sharing that. Kelsey, I think you also wanted to weigh in on this.

Kelsey Donnelly (02:33:28):

This is a difficult one and I agree obviously with everything Debbie said and for me for dying prematurely, this is a very recent and raw incident for us, knowing she coded just a couple months ago because she can't ... Because her lungs are failing her. She still has so much will to live and so much fight. But her body does not cooperate.

James Valentine, JD, MHS (02:34:16):

Yes. Wow. Thank you so much Kelsey, for sharing that. So difficult and all of these concerns, both that we heard from you and Debbie, it's things, these are things that are not concerns necessarily for 20 years in the future. It doesn't sound like, but things that you really are worried about every day when that loss could happen. Yeah, absolutely. We do have a phone caller that I'd like to bring into the conversation. We have Kendra from Phoenix who wants to share both maybe some experiences as well as worries for the future with her experience with MLD and her family. So Kendra, I'd like to welcome you to the program. Are you with us?

Kendra R. (02:35:08):

Yes. Can you hear me?

James Valentine, JD, MHS (02:35:10):

Yes, we can.

Kendra R. (02:35:13):

Great. So I have three daughters, two of which have MLD. Our middle daughter, Olivia was the first to be diagnosed and she's currently four years old and enrolled in hospice. And our youngest Kira received gene therapy in Milan and she's living the life of a normal two and a half year old girl right now, our lives are very bittersweet, but I did want to comment on the few things we were talking about. What we're worrisome for us right now with Olivia is her breathing. She easily can choke on her drool, we are having to use a suction machine a lot more. We often wonder if she'll be awake when we walk in her room in the morning or did she choke in the night. So those are real and regular concerns for us. And I know a lot of other parents as well. But I did also want to touch on the fact that how it can change the entire family unit.

(02:36:10):

We can't take Olivia anywhere like via plane. Like Maria mentioned in my comment earlier, and her older sister Ava, it's really hard for her to understand how to interact with her. Kira interacts with her regularly. But that's because Livy been like this since Kira was born really. So it's interesting to see the dynamic and how it can change the relationship with her sisters. And it does make an impact on the family at large as well because my husband and I will have to split up. So if we can take Ava our oldest and Kira our youngest to do fun activities or go places and do things, but one of us will have to stay with Livy because traveling to wherever we're going or thinking about foods and medicines and suction machines would be too difficult to bring with us. So it really does impact every person in their life.

James Valentine, JD, MHS (02:37:09):

No, absolutely. And Kendra, if I can ask you about one of the first things that you were mentioning about breathing and worrying that you might go in and one day she might have stopped breathing, is that related to choking or is that also just related to pulmonary function? Can you maybe share a little kind of context about Olivia and her breathing ability currently?

Kendra R. (02:37:37):

Right now it's more related to choking, but definitely if she gets a cold, there's more of an issue with breathing being a problem. And anything respiratory can just have detrimental effects for these children as you've heard. But right now it's more of choking. So like other parents said, we have to be careful with how we lay her down in bed at night and make sure she's on her side and we had to buy a special bed

that was thousands of dollars to make sure she could be propped up in a way that would keep her safe when she's sleeping in at night and give us a little bit of peace of mind to know that we have that extra measure in place.

James Valentine, JD, MHS (02:38:23):

Sure. Well Kendra, thank you so, so much for calling in and sharing. I see we have another phone caller. We have Pam from Maryland that wants to share some other symptoms that are being experienced and also some worries for the future. So Pam, I would like to welcome you to the program. Are you with us?

Pam (02:38:46):

Hi, thank you for having me. I am calling in regards to our son. He's a 26 year old that was diagnosed with MLD at the age of 17, but basically presented with symptoms from age 12 on. A lot of his symptoms are more cognitive in nature, which typically happens with the adult onset, more of a schizophrenia type look. And that was actually what he was diagnosed with originally. We have a lot of problems finding caregivers for ancillary staff I guess to help us because at first we were still working, my husband had to take basically an early retirement to help manage his care. And so a lot of our fear for the future is if he outlived us because we're aging and a lot of our friends that are in these situations are also aging out. What happens to them that they've outlived their pediatric diagnoses and caregivers and physicians.

(02:39:57):

Now, just the struggle of trying to find caregivers in the medical world that will help us is hard. He has a lot more social issues, trusting people that he shouldn't necessarily trust, financial problems, things of that sort. But then also mixed in there with the falling and seizures and I see isolation of not having friends anymore, people not coming around anymore, him not being able to have organizations or groups that typically adults his age would have as far as peer support, job support, things like that. And a lot of the struggles that go with that.

James Valentine, JD, MHS (02:40:48):

Right. Pam, you mentioned these are some really important experiences that are ... Sound like it's maybe a little unique to the adult onset part of this community. You know you said that essentially the schizophrenic kind of experience, both kind of cognitive but also and related to that, I think the example you gave was being very trusting and being open to being taken advantage of. Are there other ways cognitively or in terms of maybe personality or behaviors that he's been affected by this aspect of MLD?

Kendra R. (02:41:39):

Yeah, there are a lot of impulse control issues, safety on social media, the internet, things like that are problematic. When he was much more mobile, we had issues with him wandering. He got in a car and Uber with somebody and decided to go 45 minutes away to a bar.

James Valentine, JD, MHS (02:42:01):

Oh wow.

Kendra R. (02:42:01):

Just things that you don't think about until you're in the middle of it and how are you going to manage it? Medic alert bracelets on them because a lot of times these adults present neurotypically, they have a denial of what their disease process is and they feel like they are normal and they can somewhat present normal until you get into a 15 or 20 minute conversation with them and then you realize, oh, something's a little bit off.

James Valentine, JD, MHS (02:42:27):

Yes.

Kendra R. (02:42:28):

So it's a big safety concern.

James Valentine, JD, MHS (02:42:31):

Yeah, absolutely. And how long has he been having some of these cognitive types of issues? Has it gotten progressively worse or since it's kind of onset, has it been relatively staple?

Kendra R. (02:42:52):

Typically he does well and then he's got a plateau for a while and then something happens usually in illness. He got pneumonia, he got COVID, something will trigger and we see a decline and then he will ramp back up, but never quite makes it back to that baseline. So his plateau level changes and you'll see a trajectory of symptoms get extremely bad and then he kind of stabilizes and he's at a new plateau level. So it does change quite a bit. But like I said, we've been dealing with symptoms we think for about 14 years when he started at age 12. But I would say in the last three years it's been the most noticeable.

James Valentine, JD, MHS (02:43:40):

Okay. Wow. Well Pam, thank you so, so much for calling in and sharing your son's experiences and your family's experiences and worries. I want to in this morning, give final word to some of the number of written comments that we have coming in again to try to hear some additional voices on this topic of worries for the future. So Maria, what are we seeing?

Maria Kefalas, Ph.D (02:44:07):

Yeah, so Jennifer from New Jersey writes and she's a juvenile child, early juvenile child. This disease affects the whole family, not just the child who has it. It is devastating for parents to watch their child slip away. It is confusing and life changing for siblings and extended family. Your whole life and whole being is now this disease. You learn to live each day as it comes because you don't know what the disease will bring from day to day. Meg who actually lives in Texas and is married to an adult onset patient says my husband is only 29 years old now, has a whole life of being cognitively impaired ahead of him and has to spend most of his days alone and confused at home. I must work and I will probably always have to work long hours because he cannot and he can't go out on his own because he gets lost, an entire life of being stuck at home alone and confused is not a good prospect.

Maria Kefalas, Ph.D (02:45:03):

... home alone and confused is not a good prospect. And Debbie from Florida, who has another adult MLD child says, "My daughter was a competitive dancer, varsity athlete, award-winning artist and high achieving student who graduated with honors from high school. At age 16 with plans of becoming a surgeon, we saw social awkwardness and difficulty remembering or discerning truth versus something she thought about. Now, she cannot draw a smiley face, retain what she reads, follow steps, like getting dressed or remember things from one moment to the next. She cannot live independently and we grieve what she has lost and worry about the future progression." So these are amazing comments from a range of patients' families.

James Valentine, JD, MHS (02:45:46):

Yes, they are. So at this point, we're at the end of our first session and opportunity to hear from all of you today. We've heard so, so much about what it is to live with MLD. It's been an incredible morning discussion. But at this point, what we're going to do is we're going to take a 30-minute break. So we'll be resuming at 1:00 PM Eastern Time. And this afternoon, we're going to ask you all to rejoin us and build on this morning discussion where we want to now explore the range of different treatments and other management strategies that this community employs to try to make living life with MLD, a little bit easier. And importantly, get your perspectives on what would be an ideal future treatment for MLD. So again, thank you so much for all of your participation to our Zoom panel, to anyone everyone that called in and wrote in, and we look forward to hearing from you this afternoon. Again, we'll take a 30 minute break and resume at 1:00 PM Eastern.

Maria Kefalas, Ph.D (02:46:49):

Thank you.

AFTERNOON SESSION

James Valentine, JD, MHS (03:15:23):

Good afternoon and welcome back to the Externally-Led Patient-Focused Drug Development meeting on MLD. I'm James Valentine, your moderator, and I'm here with Maria Kefalas from the Calliope Joy Foundation Foundation and Cure MLD, who's my co-host this afternoon. We want to just welcome everybody back after such a engaging morning, learning so much about what it is to live with MLD day in and day out for you and your loved ones. And now this afternoon, build on that by understanding your experiences with current treatments and clinical trials, your perspective on future treatments. But before we get into that, we're going to get a overview of the current treatment landscape. And so I'll turn it over to Maria to introduce our afternoon speaker.

Maria Kefalas, Ph.D (03:16:09):

Thanks, James. Now to provide an overview of the treatment landscape, it's my pleasure to introduce Dr. Adeline Vanderver, an attending physician in the division of neurology, the Program Director of the Leukodystrophy Center, and Jacob A. Kamens Endowed Chair in Neurologic Disorders and Translational Neurotherapeutics at Children's Hospital of Philadelphia. Dr. Vanderver, take it away, please.

Adeline Vanderver, MD (03:16:38):

Thank you so much, James and Maria, for that kind introduction. It's my pleasure to share with you some of our experience with an understanding of MLD. At this point, I am Adeline Vanderver from the Children's Hospital of Philadelphia. Going to talk to you today about treatment challenges in MLD. So I'm happy to disclose conflicts of interest. I have interactions, in kind material support, and clinical trials, and grant support from a number of different pharmaceutical partners, but take no personal compensation. And we are also fortunate enough to receive grant funding from the NIH through the NINDS and NCAS for the grant numbers below.

(03:17:18):

Today, I am happy to discuss some understanding that our community has about treatment and its challenges in MLD. I'll talk briefly about current treatment and the overall landscape of clinical trials ongoing in MLD. And I'll also discuss what we understand as treatment challenges for the community, including limitations in access, delays in diagnosis, and the unmet need for symptomatic and later-onset population of therapeutic options. MLD is a disorder that's been known for quite some time at this point. And so there have been a number of different therapeutic efforts in this disorder, which is otherwise devastating and progressive. And one of the first things that was tried was bone marrow and stem cell transplantations. The results of these efforts that were-

Adeline Vanderver, MD (03:18:03):

The results of these efforts that were tried across both late infantile, early juvenile and adult patients are highly variable. Most reports of this are single case reports that limit our ability to really understand the significance of the findings. Then across a small number of larger groups of patients numbering in the several dozen at most, there are very variable results with overall some understanding that the earlier treatment is started, the better prognosis is. There is some indication, however, especially in more recently tried approaches where some of the transplant methodologies has been optimized, that transplanted patients may have better longer term survival as well as better longer term survival without progression to a GMFC-MLD of 5 or 6. There have also been a number of recently more robust clinical trials including gene therapy approaches through the Orchard program OTL-200. Libmeldy and several different enzyme replacement efforts, including some ongoing replacement efforts at this time through intrathecal delivery.

(03:19:32):

The gene therapy with ex vivo transplant and gene therapy have been tried in lay infantile and early juvenile and the data is not yet known for later onset patients, and that is available only outside the U.S. except for a compassionate use protocol and really is only in presymptomatic or very, very early symptomatic individuals. There are some efforts around intrathecal or enzyme replacement to recruit more symptomatic patients, but those efforts have only encompassed late infantile MLB patients. You can see overall that the therapeutic option in particular in symptomatic patients or later onset patients remain very limited even in the context of clinical trials. Right now, the only approved therapy that is available outside of the United States is Libmeldy through the efforts of Orchard Therapeutics and the Fondazione Telethon and Ospedale San Raffaele in Italy, and that is a gene therapy using autologous CD 34 plus cells encoding the RSA gene and ex vivo gene therapy approach. That has standard market authorization by the EMA since December 2020 and in the U.S. is available as an expanded access program. It has limited indications and currently is recommended only for late infant and.

(03:21:05):

Early juvenile patients without clinical manifestations of the disease or early juvenile with very early clinical manifestations for the disease, but who are still able to walk independently and don't have overt cognitive decline. You can see here from the recent paper of Fumagalli et al., at all in Lancet that the time the proportion event-free survival in the Figures B and C of patients who have survival and do not get to a GMF CMLD of 6 or 6 is improved in patients who receive Libmeldy versus patients who do not according to the available natural history data, and that in C remains true in the early juvenile patients, even for mildly symptomatic patients, but to a lesser degree. Importantly, one of the significant challenges to MLD treatment is the delay in diagnosis and that most patients remain too symptomatic for treatment at the time of diagnosis, so there's overall an unmet need for presymptomatic diagnosis. Newborn screening is currently in pilot form with likely under diagnosis of atypical later onset forms, particularly in the adults.

(03:22:33):

There's also an unmet need for disease modifying treatment options for those with symptomatic disease. There's really no options for later onset disease presentations currently with an unmet need for therapy development across the spectrum of disease and importantly, the need to understand the natural history in later onset cases. In conclusion, HST is a standard clinical option is limited to patients with transplant matches with a large bias in access and limited to patients who are asymptomatic or minimally symptomatic. There's a significant limitation of this therapy with highly variable efficacy such that in most cases it's undertaken with significant concern about the potential efficacy even in very early onset or presymptomatic cases. There is an ex vivo gene therapy approach, but it's limited to late infantile and early juvenile patients who are asymptomatic or minimally symptomatic and that the acts of that is therefore also limited by frequently late diagnosis and geographic disparity in access.

(03:23:41):

The goals for the community are earlier diagnosis and intervention equity of access and defining meaningful improvement in symptomatic patients through improved understanding the natural history of the disease. I'd like to thank the many people who support our research at the Children's Hospital of Philadelphia, including the families affected by MLD, our research team and our collaborators at the University Children's Hospital in Tübingen, the University of Pittsburgh Medical Center, our collaborators as well in Italy, Copenhagen, at Stanford Children's Health, Massachusetts General Hospital, McGill University Health Center, Children's National Hospital, Baylor College of Medicine, CHOA in Atlanta, Kennedy Krieger, Murdoch Children's Research Institute, University of Iowa, Stead Family Children's Hospital, Phoenix Children's Hospital, and the University of Utah, all of who contributed patients to our

ongoing natural history data and through the GLIA at the Children's Hospital of Philadelphia. Thank you very much. Maria and James, back to you and to the studio.

James Valentine, JD, MHS (03:24:50):

Thank you, Dr. Vanderver, for that fantastic overview of the treatment landscape and MLD. Now we get to move to our second session of the day where we're, again, going to be asking all of you that are living with MLD or the caregivers of those living with MLD to weigh in and help us learn about your experiences, in this case, on current and future approaches to treatment. If we can pull up our discussion questions for this afternoon, you will see that there's a range of things that we're going to ask for you to weigh in on. We're going to ask that you share what you're currently doing to manage you or your loved one's MLD symptoms. When we talk about this, and we'll use treatments as shorthand, we're really casting a broad net. Of course, we do want to hear about the different medications and drug treatments as well as clinical trial drugs that have experienced and have access to, but we're looking more broadly beyond that to include things for mobility assistance devices, different types of therapy like OT, PT, speech therapy.

(03:25:56):

But even broader than that, we're looking to more holistic approaches, perhaps dietary modifications, more alternative types of treatments, even adaptations that had to be made maybe to the home environment or outside to allow you and your loved one, again, to live life with MLD a little bit easier. Thinking about that broad range of different management or treatment strategies, we're going to ask that you weigh in and tell us how well those different treatments help with the most significant symptoms and health effects of MLD. Everything you taught us so much about this morning, we now want to get your assessment of how well the treatments that you have are helping with those things. We want to hear about the most significant downsides, so knowing that treatments whether or not they're working, they may come with downsides.

(03:26:53):

We want to know what those are and how they affect daily life. Finally, towards the end of our session, we'll look towards the future and understanding that we all want a complete cure for MLD, but thinking about a product that might come down the pipeline that might help with short of that cure, we want to know what would that ideally look like for you, or maybe a little differently, what factors would be important in deciding whether or not you would use a new treatment if it became available? Now to get us kicked off on this topic, this Session 2 topic on current future treatments it's my pleasure to welcome a panel of your peers. We have Kendra, Sonal, Victoria, Gary, Amy, and Giovanni who will be sharing their experiences with treatments. I'll go ahead and ask Kendra to get us started.

Kendra R. (03:27:44):

In July 2020, my entire family was fighting like mad to raise $500,000 in a month's time to move to Italy during the height of the pandemic to save the life of our five-month-old baby girl, Keira, who like one of her older sisters was diagnosed with a devastating terminal illness known as Metachromatic leukodystrophy, or MLD. My name is Kendra. As I sit here today, Keira's four-year-old sister, Olivia or Livvy as we call her, who is now enrolled in hospice, is beside me unable to talk, walk, eat on her own or hold her head up. Because she was already symptomatic in 2020, it was too late for her to get the treatment that was offered to Keira. Livvy's only option in the entire world was a clinical trial aimed at stalling the disease's progression, not curing it. My husband, Dave, and I, were in the midst of Olivia's weekly trips from Phoenix, Iowa for the clinical trial when we got the news about Keira.

(03:28:32):

Unfortunately, our doctors in Arizona knew of no other options available aside from the same clinical trial she was in, and the doctors in the clinical trial urged us to enroll our newborn daughter. Thankfully, I heard there was an experimental gene therapy treatment only available in Milan, Italy. Not only would it require us to move our entire family to Italy for five months while Keira completes the treatment, but we would also have to transfer Livvy's clinical trial treatments to a European site. We had one month to raise enough money to make this move a reality and get Keira the treatment she needed before symptoms began. These seemingly insurmountable odds, however, did not deter us. We would literally do anything for our children. One month later on August 15, 2020, we boarded the plane to Milan for that treatment. It was an extremely emotional difficult time for all of us to see Keira endure chemo treatments, lose her hair, not be able to eat, and yet, maintain her smile through it all while Livvy was getting worse with each passing day was heart wrenching. To this day, our lives are very bittersweet. We see Livy only get worse while Keira is now living the life of a happy, healthy, normal two-and-a-half year old girl. She does things that Livy never got the chance to do. Unfortunately, after we returned from Italy, Livy needed to exit the clinical trial due to complications with the internal port. After the port was removed, she was the happiest we had seen her in a really long time, but by then she'd already lost the ability to walk, talk, and eat on her own. As she worsened, her treatment plan had to change what initially started as only Baclofen for spasticity and CBD lotions for muscle pains has now turned into eight medications on a daily basis, and two additional medications is needed. Livvy now receives Baclofen three times a day for spasticity; Gabapentin three times a day for neuropathy; levetiracetam two times a day to keep seizures at bay; Sulfatrim once a day to keep UTIs away; Clonidine and melatonin to help her have a painless rest each night; THC twice a day for pain and anxiety and glycopyyrolate three times a day for drooling. For the moments when she's screaming in pain and because she can no longer speak to tell us what's causing it, we have to use day Diazepam as needed, which is also on deck for seizures. When that doesn't do the trick, we have to use morphine. She also receives physical therapy once a week, music therapy once a month, and due to staffing issues, she hasn't been able to receive OT and SLP therapies once a week as usual. This has rendered her augmentative communication device almost useless. Her hospice nurse also visits us every two weeks for checkups, and they now deliver all of her medications to our home. For Keira, however, she doesn't need anything, no meds, no therapies. She's running, she's jumping, climbing, spinning, saying her ABCs and 1, 2, 3s. She's actually advanced in communication and is currently attending preschool. The gene therapy she received in Italy transformed her life and ours. Being able to see her not just survive but thrive brings us to tears. This is what Livvy could have had if this disease was caught earlier. Now, our lives are spent at home.

(03:31:32):

We can't risk Livy getting COVID for free or shorten her time with us even more. Family vacations have come to a halt aside from our annual checkups for Keira in Italy, but that doesn't include Livvy because the trip would be too hard on her. We can't even go to a restaurant as a family anymore. Dave and I are often forced to divide and conquer. One of us can take our oldest daughter, Ava, along with Keira to do activities, but one of us always has to stay with Livvy whose life revolves around her sisters. She's sad when they're away and she lights up upon the return. Every morning, Ava and Keira, run into our room to get Dave and I, and then we all go get Livvy. Yet, every single time we do that, I wonder if she's still going to be breathing when we open that door. We live in a constant state of fearing that fateful day. When I think of an ideal treatment for MLD, gene therapy would absolutely be it, hands down. As a parent, I would gladly give up five months of my life to endure a treatment that would provide a normal life for my child.

Sonal P. (03:32:31):

One minute and 15 seconds a multitude of events can occur in this short interval that are beautiful, devastating, or even both at the same time for Radha, my six-year-old daughter with late infantile MLD. This one minute and 15 seconds has been truly life saving. For over two years, Radha has been involved

in enzyme replacement trial involving the infusion of just five milliliters of enzyme therapy over one minute and 15 seconds. This treatment has given her an opportunity for life and living that I thought she had once lost. My name is Sonal and I'm a pediatric gastroenterologist. The moment Radha was diagnosed with MLD, I instantly knew the medical complications that would eventually unravel as the disease progressed. Radha was not a candidate for gene therapy or bone marrow transplant. Enzyme replacement therapy seemed to be the only option; however, at the time, the only ongoing trial was close to enrollment.

(03:33:21):

For the next year-and-a-half, we watched as the sparkle in Radha's eyes faded. Then as if a shot of darkness had been lifted, a modified ERT trial was open, giving us a whisper of hope that we could keep rather stable. My husband, Bibob and I initially had simple expectations regarding outcomes when Radha was first enrolled. Her disease was advanced by that point and she had lost nearly all gross and fine motor skills. She was non-verbal and required internal nutrition for sustenance. Our hopes were that enzyme replacement would prevent her disease from progressing and would minimize discomfort and suffering. After all, these are and always will be our goals for Radha's care. Little did we know that our expectations would be far exceeded. At the very start of the trial, we almost immediately noticed an increase in Radha's vocalization. She began queuing us with her voice, whereas previously, she'd become completely silent. This has allowed her to interact more with her environment and the people around her. Her sleep patterns have improved, requiring less administration of melatonin, and she is much more comfortable while awake.

(03:34:25):

Over time, she has regained gross and motor fine motor skills, something we never could have imagined. She reaches and holds objects, activates toys with her hands, kicks her legs gently in the water and independently pushes down on tricycle pedals she gives hugs. Her reflexes, which previously were lost have returned in all four extremities. Additionally, Radha has had significant improvements in cognition. Her school teachers and therapists send messages regularly that she has reached her therapy goals and that more advanced goals need to be formulated. She asks to take a nap, to read books, sing songs, for diaper changes with a visual gaze language device. She answers comprehension questions with an 80% accuracy. She was hospitalized three times in two months prior to initiating enzyme replacement therapy. Since trial enrollment, Radha has been hospitalized only once in over two years. Lastly, and most importantly, this treatment has allowed Radha to reveal her true personality to us. She is brilliant, tenacious, sassy, patient, and forgiving. She'll repeatedly knock objects off a table intentionally just to watch you pick them up. She will laugh when you sneeze or trip over yourself.

(03:35:34):

She both loves and is annoyed by her younger brother. She senses when someone is frustrated, and what I love most is that she complains when she's not being given attention. We've been fortunate that Radha has had no side effects from the enzyme infusions to date. We spend our Friday mornings at the trial clinic site for two-and-a-half hours, then carry on with the rest of our day. I could not imagine a smoother process which has had such an immense impact. Regarding future drug development. I feel that research emphasis should be placed on management and treatment of those who are currently symptomatic in order to decrease morbidity and mortality. Improvements in oral intake, head control, gut motility and hypertonicity can help alleviate suffering and further decompensation. Improvements in these and other similar issues should be the primary endpoints of future clinical trials involving symptomatic patients as opposed to the achievement of gross motor milestones, which is less realistic and has a less significant clinical impact. Patient and patient and family reported data and videos should be used to assess whether there have been improvements since starting an experimental therapy. Patients may respond to treatments differently, but this does not mean that each response is not significant and beneficial. I know there's a little likelihood that my daughter will ever walk. She likely will

not be able to eat by mouth. She will not be the same child she was prior to her diagnosis of MLD, still Radha's life has value and significance Through the help of enzyme replacement, she is able to interact with the world and the world can interact with her, which has led to a substantial improvement in the quality of her life. Could there be a more worthy reason to pursue further drug development? As a physician, I know when treatments are futile. I've seen firsthand the implications of prolonging life when the quality is poor. This treatment is not futile. It has given Radha an opportunity to experience and enjoy life to the best of her ability. Thank you.

Victoria R. (03:37:29):

Hello, everyone. My name is Victoria and I'm the mother to six beautiful children. My youngest daughter, Adeline, who is six-years-old and my youngest son Oliver, both have MLD, Adeline flourished as an infinite toddler. She developed normally until 15 months old, hitting all of her milestones on time, if not before. She was walking, talking, and so incredibly smart. Then one day, our entire world turned upside down. Adeline started falling and having trouble walking. I made it my mission to figure out what was going on with our sweet girl. This started our nine-month odyssey of numerous specialist appointments, misdiagnosis, MRIs, and countless hours of physical therapy all during which she continued to lose more and more of the milestone she previously had mastered. We received her MLD diagnosis the day after her second birthday. Within a month, she had lost her remaining milestones. Adeline had no treatment options available since she was too far progressed. We have watched as MLD has stolen more and more from her. She now suffers from chronic respiratory failure, seizures, is non-ambulatory, can no longer speak and is completely dependent upon us for everything. Oliver, however, has a much different path.

(03:38:43):

Oliver was tested within two weeks of birth and since Oliver was presymptomatic, he was eligible for gene therapy. Oliver, unlike our daughter, Adeline, had a chance at life. Unfortunately, the only place we could receive this life changing treatment was in Milan, Italy, thousands of miles from home. It meant a six-month relocation for Oliver and myself away from family, which would mean missing out on precious time and memories, especially of those which involved Adeline, who is already living up borrowed time. We also knew that the treatment would be difficult. The thought of chemotherapy, months in isolation in a hospital and knowing Oliver would be immuno-compromised was scary, but we had to do it. We had to give all over this opportunity despite the risks. We did not want to see him suffer like his sister. To potentially be able to live his life not trapped inside his own body, free of seizures, and to be able to breathe without machines and constant respiratory therapies, gene therapy could be his miracle and we could not pass it up.

(03:39:43):

On June 25, 2021, Oliver received Libmeldy, also known as OTL-200, the life-saving gene therapy, which has been approved in the European Union, UK, Iceland, Liechtenstein and Norway. We are now one year out from gene therapy and just recently celebrated Oliver's one year birthday. Oliver is followed by neurology, BMT, his team in Milan physical and occupational therapists. He undergoes testing every six months with at least one yearly visit to Milan to assess how Oliver's body is responding to the OTL-200. I can tell you without a doubt that gene therapy has helped Oliver. While the therapy did not result in an absolute outcome, he is thriving and growing each day, and we are hopeful for his future. Oliver does have some delays but has not regressed. Oliver turns two on October 20th, the day before this meeting. He is now the same age as my daughter was when she could no longer stand or walk.

(03:40:41):

While Oliver has weakness in his legs and tightness in his left ankle, his latest neuro connectivity test revealed that it was stable when compared to the one performed when he was six-months-old. This means that during the time that Oliver should have been regressing and showing nerve damage, he was

not. Instead, at the age of two, Oliver is getting stronger, has started to stand up and has now started taking steps on his own completely unassisted. Oliver does have a speech delay, which can very much be attributed to spending so much time in a hospital setting and also hearing two languages constantly during his formative months for language learning; however, he is gaining new words daily and starting to speak in two or three-word sentences. He also has a bit of a hearing deficit and oral aversions, which we believe to be due to side effects associated with the chemotherapy he received.

(03:41:33):

He is trying new foods and eating more each day. In comparison, Adeline could no longer speak, could no longer swallow without the risk of aspiration and was G-tube dependent for her food at his age. We have no regrets about Oliver receiving the Libmeldy gene therapy to give Oliver the gift of time to give him the opportunities never afforded to Adeline, there was never any question. While it may not be a cure, it changed Oliver's quality of life and is giving him a chance his own body would not have allowed. As a parent, I can tell you how completely soul crushing it is to witness your child's body turn against them and watch their daily struggles to do things we take for granted each day. I would give anything to help my child and I would be willing to try any treatment that it would improve the quality of life and slow down this awful disease. To be able to give my child more time to experience a life they deserve is everything.

Gary H. (03:42:32):

Hello, my name is Gary. This is my daughter Celia Grace. Celia Grace was the first child to receive gene therapy in the United States. She was diagnosed in March of 2020 at the age of three-years-old. It is really amazing how we found out she had MLD. She started complaining of her belly hurting. We thought it was gas or constipation. One Saturday night she started vomiting. The next morning she was laid over in the floor holding her stomach complaining of severe pain. She was taken to the local emergency department where they did a CT scan that appeared to have fluid and gallstones in her gallbladder. She was transferred to Children's Hospital of Alabama in Birmingham where they did surgery the next morning. The surgeon come out and advised us that there was a large mass inside her gallbladder and that it was going to be sent to pathology for further testing.

(03:43:48):

The report come back from pathology within a couple of weeks and it come back of a neoplasm inside the mass that was associated with a disease called metachromatic leukodystrophy. We were in disbelief. My wife and I cried. We did what most parents would do. We Googled metachromatic leukodystrophy. We were devastated because we thought we were going to lose our daughter at such a young age. We went for further testing for genetics. Two weeks later, we got the horrible news. The testing confirmed that she did test positive for metachromatic leukodystrophy, but as it turns out, we discovered disease early on. There was a treatment available called gene therapy. This is a incredibly rare for the disease to be found this early with a non-symptomatic child.

(03:45:04):

Most families find out about the disease after an older sibling has tested positive for MLD and had symptoms. All the MLD families before us had to travel to Milan, Italy for a clinical trial, but in October of 2020, Dr. Nath contacted us. Our neurologist contacted us and said, "What if I told you your daughter was going to make history books?" The neurologist just told us that Celia Grace was going to be the first child in the United States to receive gene therapy for MLD. We packed our bags and traveled almost a thousand miles to get the treatment in Minnesota at the Masonic Children's Hospital. After her cells went to Italy to be repaired, Celia Grace underwent four days of chemotherapy. Most of her side effects was from the chemotherapy such as hair loss, fatigue, sores in her mouth.

(03:46:20):

After the infusion of her new cells, we stayed in the hospital for about a month. She was uncomfortable for a while after the high dose of chemotherapy, but she started recovering after a couple of weeks. While we were nervous wrecks throughout the treatment, we were also amazed to see our little girl bounce back so quickly to herself. Our story is different from other stories you will probably hear. Most kids do not have the time before it's too late for them to qualify for gene therapy. We were lucky to catch this early on. Celia Grace has not had no symptoms of the horrible disease and hopefully, never will. After her checkup in January, her enzyme levels were even on the higher end of the normal scale. We are now one year out from Celia Grace's gene therapy and she is doing great. It took a few months for her to get back to her normal self, but since then, she is a normal, happy five-year-old child thanks to gene therapy.

Amy P. (03:47:55):

My husband Brad and I had never heard of metachromatic leukodystrophy before our daughter, Livianna and son Giovanni were diagnosed in December 2010. Giovanni was just 11-months-old and his three-year-old sister's symptomatic diagnosis led to him being tested and diagnosed. Just three weeks later, we were in Milan, Italy where Giovanni was the second child in the world to undergo gene therapy for MLD in February 2011. At the time of diagnosis, we already had witnessed Livianna, our once vibrant, hilarious, beautiful daughter regressing in abilities at a startling pace. Our child who started walking at 11-months-old, suddenly struggled to walk across the room, scooting on the ground instead. Her early and impressive vocabulary was dwindling rapidly and nights, became restless and filled with tears rather than a toddler or sleeping peacefully in bed.

(03:48:52):

We are often asked, "How did you decide to go to Italy with so much unknown and the potential risks?" We knew painfully the risk of doing nothing. The potential of seeing our son gradually lose every learned milestone, losing the sound of his voice and knowing that we, my husband and I, and our two older children would not only lose Livianna, but also Giovanni. Of course, as a former researcher, I thoroughly read the medical literature. I sought to understand all I could about gene therapy and asked questions of our local physician and the doctors in Milan. What I learned reinforced our decision that the only certainty would be the outcome of not treating Giovanni, which is certain death.

(03:49:38):

The potential gene therapy risk includes sterility, leukemia, HIV infection, during conditioning were all less terrifying and absolute than the risk of untreated late infantile MLD. After returning home from Milan in June 2011, Giovanni was a normal one- year-old outside of his hair growing back and his implanted port. We never had a single physical or medical complication or difficulty during or following his gene therapy. He has never had motor skill deficits or delays. At 12-years-old, Giovanni has never shown any symptoms of MLD. The difficulty of our experience with Giovanni's gene therapy was the practical, logistical, and psychological. It was relocating our family to Milan, Italy for six months, missed work, financial burden and stress, cultural and language barriers, stress, fear of the unknown, which will never go away, and the follow-up visits where you relive it all over again.

Giovanni P. (03:50:41):

This is Giovanni. I'm 12-years-old. It is strange to hear when my mom talks about MLD because I just feel like a normal 12-year-old kid. I was a baby when I went through gene therapy. I've looked at photos, heard stories, and feel like I remember that time and visits back-

Giovanni P. (03:51:02):

...that time and visits back [inaudible 03:51:05]. It may just be because we talk about it a lot and that becomes my memories. I like to play games online with my friends, hang out at their houses, play with my cats, and sometimes play games with my siblings. We like to go watch the sunset and go camping with my dad too. My mom says I am a natural leader, so I guess she is right. I always organize my friends and schedule our calls or online meetings, name our teams, create logos, and make sure that everyone is following the rules. I like to draw and I am pretty good at it, but don't do it all the time.

(03:52:03):

I don't like to see people unkind or hurting other people's feelings. Life is too short for that. I remember my sister Liviana. There were stories and pictures too. I had gene therapy and she couldn't because she had already had MLD. We had lots of pictures of her and her old stuffed animals. We talk about her all the time. My parents told me that Liviana said I was her best friend. I think it is sad that my best friend isn't here anymore. It is hard to understand why she could not have had gene therapy too and be here like a normal kid too. She would be starting high school this year and that would've been so cool. Gene therapy changed my life because well, I am here. Without gene therapy, my parents would only have photos and memories of me just like my sister, and that makes me sad to think about.

(03:53:22):

I think I am going to do some amazing things in my life and the world would've missed Giovanni Price if it wasn't for gene therapy. For me, there isn't a gray area with MLD and gene therapy. We lost my sister at five years old and here I am thriving and enjoying my 12th year of life. My hope for a future is to have an impact on the world. Through my experience with MLD and gene therapy. I plan to be a leader who will have the capacity to do everything I set my mind to do.

James Valentine, JD, MHS (03:54:13):

Wow. Thank you so much, Giovanni, and Amy, and all of our panelists for sharing your treatment experiences, your journeys with MLD. It's so important to hear that and hear both what has helped and as well as understand the things that have not. Now we're at the point in our meeting. It's our second opportunity to now open it up to all of you, those living with MLD, and the caregivers and family members of people living with MLD, to hear your experiences on current and future treatments. If you'd like to share your experiences, we'd invite you to call in and write in. You can call in at 1-703-844-3231. Again, that's 1-703-844-3231 to share some of your current and past treatment experiences. But to get us started on this topic and thinking about this and understand the experiences of our audience, we're going to first start with a few polling questions.

(03:55:18):

So, for all of our patients and caregivers, this is your opportunity to pull that phone back out, open that browser. You can do it on a new tab on your computer as you're following along there. Go to www. PolleEV.com/MLDPFDD. Again, PolleEV.com/MLDPFDD. Please just keep this open throughout the afternoon and as we go to different questions, they will automatically appear there for you to give your answers to. So, our first question for this afternoon is we want to know what types of medications have you or your loved one used either currently or previously to treat the symptoms associated with MLD. And you can select here all that apply. This question is focused more on the medications and medical treatments themselves. We'll have another question that's focused on other types of treatment and management strategies.

(03:56:13):

So, the options here are A, medications for pain, B, antispasmodics or drugs to relieve muscle spasms, C, drugs for gut motility, D, drugs to help with sleep, E, anti-anxiety medication, F, anti-seizure medication, G, drugs to help with respiratory or breathing issues, H, dietary supplements or nutritional supplements, I, cannabidiol or C B D products, or J, other medications that aren't listed here that you or your loved one

either are currently using or have used in the past. And again, you can select all that apply. Since this is the first question we're seeing this afternoon where our audience can pick more than one option, I'll just point out again that these percentages that you're seeing are not the percentage of people who are picking any one answer. It's the percentage of total responses. So, any of these types of questions, you can think of the bars as kind of relative rankings to one another.

(03:57:20):

So as it stands, it looks like some of the most common treatment medications that are being used or have been used by our audience include medications for pain, for muscle spasms, as well as dietary and nutritional supplements. However, we're also seeing quite a great deal of experience with drugs for gut motility, for seizures, sleep, and anxiety. And really all of these... None of these are really on the low end. We're seeing that this community is using a wide range of these different drug treatments to try to address these different symptoms of MLD, including some other things, which of course we want to hear about. Things that maybe we didn't list, maybe they're not as commonly used. Of course, we would like to hear those experiences as well.

(03:58:08):

If we go to our second polling question. So now, going beyond just medications and thinking about other types of therapies and supports, which of those have you or your loved one used, again, either currently or previously to help manage these symptoms of MLD? And again, you can select all that apply. The options are A, physical therapy, B, occupational therapy, C, leg and hand braces, D, wheelchairs, canes, or walkers, E, a urinary catheter, F, speech therapy, G, aqua therapy, H, naturopathic therapies, I, assisted communication devices or other communication methods, J, feeding supports, K, respiratory supports, or L, some other type of therapy or support that you or your loved one has used to help manage the symptoms of MLD that maybe is not otherwise listed here in this question. And again, you can select all that apply here.

(03:59:16):

So, while final responses are trickling in, it looks like some of the most commonly used non-medication therapies and supports include physical therapy, occupational therapy, leg and hand braces, and wheelchair, canes, or walkers. After that, it looks like maybe a second tier would include feeding supports and speech therapy, maybe also assisted communication devices and methods. But once again, we're seeing each of these things is being utilized heavily by this community with one of the maybe less common things being urinary catheters. And we're seeing quite a few other things being listed as well. So again, we'd love to hear about these range of different treatment and support approaches that you use to help manage symptoms of MLD.

(04:00:05):

One more question for you here as we think about these different... This kind of treatment regimen. So, if we can go to our third polling question. Here, we want to know, thinking about all of these things, the medications, therapies, supports, how well does this in totality, this treatment regimen, treat the most significant symptoms of you or your loved ones' MLD? The options are A, not at all, B, very little, C, somewhat, or D, to a great extent. And as you're thinking about this question and selecting your answer, I want you to think about why it is that you're making this selection. What therapies have you been able to access and try, how has that...? Where you have seen a treatment help, what has that looked like and what has that meant for your life? And if things have not been that useful, which things come to mind and how did you notice or what was your way of assessing whether or not the product worked, where the approach worked?

(04:01:12):

These are the kinds of things we would love to have you call in or write in and share those treatment experiences about. As it stands, it looks like roughly half the audience is saying that treatments have helped somewhat. We're seeing just below that, around 40% saying that they've helped very little, just around 10% say that they've helped not at all, and about 5% saying that they've helped to a great extent. So, quite a range with somewhat and very little certainly representing the majority of experiences. But we recognize that these are kind of your subjective classifications. So, we want to hear the explanations behind these selections. That will be so important to help us understand how well current treatments are treating the most significant symptoms of MLD.

(04:02:04):

So with that, I want to thank you for doing these polling questions. Keep those webpages open. We'll be coming to polling a little later in the program. While people continue to call in and write in, I'd like to welcome another Zoom panel that we have joining us this afternoon, some of your peers who will be sharing their experiences and participating in this discussion as well. So, I'd like to start the discussion with those things that have been most useful. Thinking through those lists of those different, both medication treatments as well as other types of treatment approaches, what maybe has been the most useful? How have you noticed that? And maybe Cache, we can start with you on this question. What stands out in your mind as fitting that bill.

Cache Christensen (04:02:53):

For my daughter, she's 10 years old and she's starting to... She's showing symptoms and still recovering from her bone marrow transplant. So, we've been mainly focusing on physical and occupational therapy. And with these two treatments, we're noticing small but noticeable improvements over the past several months. She's been doing it since about April of this year. We're still working on a lot of the basic functional activities that we originally set goals on, but there is some improvement.

James Valentine, JD, MHS (04:03:31):

Sure. So, a couple of follow-up questions for you Cache. One, could you tell us a little bit about your daughter in terms of did she have infantile-onset form, juvenile-onset? And then, more specifically, when you were talking about some of those goals that you've been setting and kind of tracking and monitoring as a way to gauge whether there's been any improvements or maybe even stabilization. Can you tell us about what some of those were and how did you come up with them?

Cache Christensen (04:04:00):

Absolutely, James. So, Leah was diagnosed just over a year ago with MLD. At the time, functionally, when you looked at her you couldn't tell there was anything going on. She happened to fall off a trampoline. That's how we found out through a CAT scan for her concussion. When she received her bone marrow transplant in November, still pretty functional, but we did see that decline in function throughout her bone marrow transplant. Independence went down significantly, dressing herself, putting on shoes and socks, writing, just all of these basic things she was no longer able to do on her own.

James Valentine, JD, MHS (04:04:47):

Right.

Cache Christensen (04:04:48):

And so, that's what we've been focusing on in occupational therapy and physical therapy is doing those things. She went from being able to ride a bicycle to needing assistance to ride on a tricycle in physical therapy.

James Valentine, JD, MHS (04:05:05):

And just over time have there been any gains? Has it really just been an attempt to keep things stable and work on maintaining?

Cache Christensen (04:05:18):

Yes, definitely. There have been some improvements. Of course, it's not a constant line going up, but it's been down and up and down and up with a gradual increase over time. But she's been able to improve on her writing. She's still not to able to do things independently, but she's getting faster at putting on her clothes with coaching, riding a tricycle with coaching. She's being able to focus more on that.

James Valentine, JD, MHS (04:05:49):

And then, how does she feel when... Does she notice that she's experiencing some of these incremental improvements? Has she said anything, expressed, have you noticed anything in terms of how she feels about that?

Cache Christensen (04:06:08):

Oh yes, definitely. So, initially, she does get very frustrated because she remembers being able to do these things. She remembers what it was like to have it so easy. And now when we do these, even as she gets better, she still expresses frustration. But when she does achieve these things where she levels up to another level, she does get excited. She recognizes it and that encourages her to try harder.

James Valentine, JD, MHS (04:06:41):

Wonderful. Well gosh, thank you so much for sharing that. I'd like to bring Debbie into this conversation as well. Thinking about things that maybe have been most helpful of that menu of different treatment approaches, what stands out to you, Debbie?

Debbie Sweet (04:06:56):

Hi, I'm Debbie. I am located in Florida and I have a daughter who is currently 22. And even though she wasn't diagnosed until about a year ago, we believe the onset was around age 15 or 16. So, it puts her on the border of a late juvenile or adult-onset. Before her diagnosis, we'd actually tried several things. We had tried ADHD meds, antidepressants and bipolar meds, anti-seizure medications. When it seemed like she was kind of zoning out, they thought it might be absence seizures. But really since she's had her diagnosis, there is nothing. None of those medications worked, number one, and there really aren't any treatments. She's not in need of physical therapy, occupational therapy, speech therapy. She mostly needs monitoring of kind of her activities. She's not independent. She will never be able to live independently, we don't believe. So, just making sure that she's safe and making sure that she can get through activities like toileting, bathing, dressing, anything that requires a sequencing of tasks is a challenge.

(04:08:05):

Also, when we're in public with her, we have to make sure that she doesn't wander off. We've actually just added a GPS tracker. I wish they made them small enough to solder onto a medic alert bracelet, to be honest, because when they have some of these behavioral symptoms, they would be likely to take it off or somehow remove it. So, that's really what we're doing. It's really more a management of activities. The only thing we found that really helps, and maybe this gets to the point that Cache was making about his daughter remembering she used to be able to do things. My daughter used to be a competitive

dancer, so we found that music and dance, participating in those activities actually brings her a lot of joy and happiness and remembering what she used to enjoy of that.

James Valentine, JD, MHS (04:08:56):

Sure. Thank you so much, Debbie. One thing that you commented on that kind of stands out that I want to follow up on is you talked about the monitoring and how that's really important with all kinds of different activities in daily life, including some really fundamental ones like self-care and toileting. And so, maybe can you describe what you meant by monitoring and what kinds of safety issues do you think that has helped avoid or prevented for her?

Debbie Sweet (04:09:33):

Sure. So, let me give showering as an example. She's capable of physically showering herself, but we need to make sure the water doesn't get too hot and burn her. We need to make sure. We have to go through body part by body part to tell her to wash it because the sequencing just wouldn't happen automatically. She's able to do it all. She understands what we're saying. She can repeat it back, she can do the activities, but it has to be managed. It's like, " Left elbow, left upper arm.", things like that.

James Valentine, JD, MHS (04:10:03):

Right. And with the temperature, is that just something that she does not have the self-awareness of what the temperature is or when she's experiencing a temperature that's maybe not safe for her, or can you describe that a little bit, Debbie?

Debbie Sweet (04:10:24):

Sure. There are a couple of things there. So, one is that she's recently been talking about how the shower water hurts her. And so, we checked and it seemed a little warm but it could just be also nerve endings too.

James Valentine, JD, MHS (04:10:38):

Right.

Debbie Sweet (04:10:39):

And then secondarily, something could be hurting her and she wouldn't necessarily tell us. She doesn't offer information because that requires initiating. So for example, if we ask her if she's hungry, "Yes. I'm starving", but she'll never tell you an offer that she's hungry.

James Valentine, JD, MHS (04:10:57):

Right.

Debbie Sweet (04:10:58):

So, it's things like that.

James Valentine, JD, MHS (04:11:00):

That's very helpful, Debbie. I do see that we have a phone caller. We have Les from Ireland, who wants to share some of the treatment experiences of his two children. So, Les, I'd like to welcome you to the program. Are you with us?

Les (04:11:17):

Hi James and Maria. Can you hear me?

James Valentine, JD, MHS (04:11:19):

We can. Welcome.

Les (04:11:20):

I'm calling all the way from Ireland here and I'd like to, first of all, thank you for the opportunity to speak. I think the MLD community is a global thing and the effects of the disease. My boys over here in Ireland are the very same as all of what I've heard from almost all of the speakers there today. It's sort of heartbreaking and heartwarming to hear so many people speak about things that are so familiar to me in our life here.

James Valentine, JD, MHS (04:11:55):

That's great.

Les (04:11:55):

But I'd like to just briefly, if I could, tell it. Our family stories is I have two boys. We had two boys, Cathal and Ciarán. They're both late infantile. In 2017, after about 18 months of testing and watching Cathal decline, he has received his diagnosis of MLD and like so many other stories, too symptomatic to treat and a terminal diagnosis. But because of that, obviously, we tested our younger son, Ciarán, who was 11 months at the time. And the next day we received Ciarán's diagnosis. And both our boys had a terminal illness. But with that diagnosis came the kicker, the opportunity, the lifeline that we were offered...

James Valentine, JD, MHS (04:12:52):

Yes.

Les (04:12:52):

...was that we had an opportunity to possibly be enrolled in the gene therapy trial in Milan, should we be able to travel and should he be eligible. And so, then for the following day, like some of the other speakers, we upped sticks and we moved for six months to Milan, Italy. Ciarán, luckily, was eligible for the trial and he received that at age one. I think he would be classified as a late infantile but maybe early symptomatic patient. He was showing some nerve conduction slowness and as he was treated then and just after his first birthday, he was a little slow to start walking, but the treatment got a hold and it arrested the progress of the disease in Ciarán's body and he has been fine ever since. He's thriving.

(04:13:48):

I mean, at the moment, unlike his older brother, Cathal, he passed away two years ago. He was age six and he experienced all of the symptoms and the difficulties that were described in detail this morning. And sadly, he passed away. And so, my experience, I suppose is of both sides of the coin in terms of treatment and non-treatment. And in my mind it's black and white, it's life or death. Ciarán is six now. He's the age that Cathal died. At the age of three, Cathal is completely paralyzed on that low-level plateau and right at the end. But Ciarán has grown to meet all the milestones. He has some nerve damage. He walks slowly, he kind of drags his feet a little. He wears splints on his lower legs.

James Valentine, JD, MHS (04:14:50):

Sure.

Les (04:14:50):

But other than that, he's an absolutely fine, healthy, and thriving six-year-old boy. He's in his second year of primary school and doing really well. I've been involved in attempts to forward the cause of gene therapy here in Europe, here in the UK and the Netherlands, and spoken at different forums like this one, so impressive as this one, but I've told me story and contributed to the assessment process of the gene therapy in those countries. And...

James Valentine, JD, MHS (04:15:27):

Sure.

Les (04:15:28):

Happily, one by one, following the EMA approval, which of the individual countries are agreeing that the treatment does what it's supposed to do and then agreeing to allow access for their kids to receive it.

James Valentine, JD, MHS (04:15:43):

Right.

Les (04:15:44):

And finally, I've just in terms of the points that you put up at the beginning of the discussion...

James Valentine, JD, MHS (04:15:52):

Yes.

Les (04:15:53):

I'd like to speak about what I'd like to see in the future.

James Valentine, JD, MHS (04:15:56):

Sure.

Les (04:15:57):

In my logical mind as an engineer, the way I see it and my experience in life is gene therapy is the only solution to this disease. And that has to be coupled with the rollout and implementation of newborn screening for MLD. And that's the end game in my mind, to be able to identify at birth...

James Valentine, JD, MHS (04:16:27):

Right.

Les (04:16:27):

... and immediately treat with gene therapy. We'll leave the problems of MLD behind for the majority and should be the vision of the future.

James Valentine, JD, MHS (04:16:38):

Yes. Well, Les, this has been incredibly helpful. I really appreciate you sharing both and Cathal's and Ciarán's experiences and so glad to hear Ciarán's story and getting that early intervention with gene therapy and what that's really meant for him and your family. So, really appreciate you doing this and

being a part of this and calling in from across the pond to be a part of this discussion today. This is really... Couldn't agree more. This is a global community and your participation means a lot. I do see we have another phone caller I'd like to bring into the discussion, Cassie from Alabama who wants to share her daughter's treatment experiences. So, Cassie, we'd like to welcome you into the program. Are you with us?

Cassie (04:17:33):

Yes, sir. I'm here.

James Valentine, JD, MHS (04:17:34):

Hi, welcome.

Cassie (04:17:36):

Thank you for allowing me to call in.

James Valentine, JD, MHS (04:17:39):

Yes.

Cassie (04:17:41):

I know that y'all have already probably seen the video that Gary and Celia Grace did earlier. Because I'm Cassie Hamlet, of course, the mother of Celia Grace Hamlet, the first child treated for MLD in the United States.

James Valentine, JD, MHS (04:17:55):

Yes.

Cassie (04:17:56):

And I just wanted to, since I'm not able to be off with Gary today, to be able to watch all of the things that are going on today. So, that's why I took a moment to call in...

James Valentine, JD, MHS (04:18:07):

Great.

Cassie (04:18:07):

...to just say that how thankful we were to be able to get this gene therapy for our daughter. Of course, our situation is way different than most have experienced, but we were just thankful to be chosen to be the first ones. And of course, we didn't experience some of the things of the stories that I've been hearing today and that I've already heard. And of course, we've made some very close friends in our MLD community.

James Valentine, JD, MHS (04:18:43):

Yes.

Cassie (04:18:44):

And so, we know what can happen if this doesn't take place. So, I just think it's important to get this approved in the United States because, truthfully, a lot of fundraising was done for us. We were planning

to go to Milan, Italy. And even though all the fundraising was done around our community for us, sadly, we probably wouldn't have had enough money to go.

James Valentine, JD, MHS (04:19:16):

Right.

Cassie (04:19:16):

And I mean, we would have done everything we could do to have gotten there to get her the treatment but it could have took longer. And anyone that has a child with MLD knows that you don't have time.

James Valentine, JD, MHS (04:19:30):

Yes.

Cassie (04:19:30):

There's no time. You can't waste it. Thankfully that Celia Grace didn't have any symptoms and from the time that we found out she had it was to treatment with 18 months. And even though that we didn't... It was just a long waiting game for us to get it done. And I was away from my family. Even though it was in Minnesota, we were thankful that it was closer to home. But I did well while me and her were away. But when I got home, back to normal, that's when everything kind of hit me that I wasn't doing well because it's kind of like everything really hit me when we got back home. So, I really think that if we would've been in Italy that far away from home, because I would've been there, just me and Celia Grace, because Gary couldn't have went with me and stayed the whole time. You hear families that move. Ours probably wouldn't have been able to do that, so.

James Valentine, JD, MHS (04:20:36):

Well, that's really important to hear, that the trade-offs that come, of course in Celia Grace's experience, with gene therapy being a really positive one. But it is really important to know that there are these trade offs that come with therapies. And in this case, the difference between Minnesota and Milan being one that might have actually been really significant for you and your family. So, thank you so much for calling in and sharing about that, Cassie, and to your family for participating today.

(04:21:15):

I do want to take a moment to broaden the conversation. Of course, we're very happy to continue hearing about things that have been helpful, but we know that there's also treatment experiences with things that maybe haven't been as helpful. Or maybe, as we were just talking with Cassie, even when things have been helpful, maybe they come with some downside or trade-off, whether that's side effects or the burden of undergoing or keeping up with the treatment regimen. And so, to get us thinking about this expanded discussion around current treatments, we're going to go to a polling question.

(04:21:50):

So, please pull out those phones, go to the tab in your web browser, go to www.pollEV.com/MLDPFDD, and we're going to ask you here to weigh in on maybe what are some of the biggest downsides of existing treatments. So specifically, we are asking you what are those biggest drawbacks to your current approaches to treatment? And you can select up to three here. So, the options are A, not very effective at treating the target symptom or symptoms, B, it treats some, but not all of the symptoms, C, the high cost or copay or that the treatment is not covered by insurance, D, the limited availability or accessibility of the treatment, E, the side effects of the treatment, F, the route of administration of the treatment, for example, whether it's something that's oral or administered some other way, G, it requires too much

effort and/or time commitment to keep up with the treatment, or H, some other big thing that you view as a biggest drawback of a current treatment approach that's not otherwise listed here in this question.

(04:23:04):

And again, you can please select up to three of the things that you view as the biggest drawbacks for your treatments for MLD or your loved ones' treatments for MLD. So, we'll give a few more moments here to get responses in. It looks like some of the top biggest drawbacks being reported by our audience today include that the treatments that exist have limited availability or accessibility, followed by that they're not very effective at treating the target symptom or symptoms, or that there's high cost or copay and not covered by insurance. After that, maybe in the next tier, we see that drawbacks include that they treat some but not all symptoms or that they come with side effects. Some other biggest drawbacks that are reported a little less but still are in some number of people's top three biggest drawbacks include that route of admin-

James Valentine, JD, MHS (04:24:03):

Some number of people's top three biggest drawbacks include that route of administration and that it requires too much effort and or time commitment, as well as some other things that we didn't have listed. So as you're thinking about these and you made these selections, we'd like to hear from you and invite you to call in or write in. You can scroll down on the webpage you're on and see that comment box. You can submit those comments and we'll be sharing some of those. But to get us kicked off here and thinking about this topic, I want to come back to our Zoom panel and this time start with you, Amy, as you're thinking about all of these treatment approaches, is there either something that maybe hasn't been as helpful or maybe something that has been helpful, but there's some important trade offs or downsides to share about that as well?

Amy (04:24:52):

Hi, my name is Amy. I live in Maryland with my three children. They are seven, eight, and nine. The seven year old and the nine year old both have MLD and they were diagnosed at the ages of three and five with early juvenile MLD. One of my sons has had a traditional bone marrow transplant, the oldest son and my youngest son went to Milan and had gene therapy. So I kind of have had both experiences very close together. They were transplanted almost within two months of each other. What can I say about the therapies themselves and what the aspects that are hard about them or are beneficial? I would say with traditional bone marrow transplant, Cache had mentioned this yesterday, there's no certainty given to you about the outcome. There's no, 'He'll walk better again' or 'He will function more normally again.' They just can't tell you anything like that. And that actually goes for the gene therapy as well. They're both just two huge unknowns.

James Valentine, JD, MHS (04:26:28):

Yeah, I mean, that makes a lot of sense how that would be difficult to make those treatment decisions with that degree of uncertainty about what the outcomes will be. Can you maybe speak a little bit, Amy, to what your children's experiences have been thus far? What is it that you're kind of looking for and observing in terms of wanting to know or see a potential either improvement or stability? And what are your own little metrics for what you think would be those key things to see something moving on and then have you seen anything so far?

Amy (04:27:15):

For me personally, newborn screening I wish had occurred, obviously we all do, but it nine months to get him a diagnosis. This is my oldest son, the one who had traditional bone marrow transplant, during that

nine months, the disease kept progressing in his limbs. So I would say newborn screening is probably the biggest thing that I wish could have.

James Valentine, JD, MHS (04:27:50):

Sure. And I presume that given the presentations we've heard from our key opinion leaders, our scientific experts today, that there's the evidence and expectation that earlier treatment would lead to better prognosis overall that could have led to our earlier treatment with both of these two therapies that you mentioned. Just, again any observations thus far, now that you've been through both of these treatments, any trade offs that you've had to experience or take on and do you view them as worth it in order to had these treatments?

Amy (04:28:39):

110% worth it for both of my children. As hard as bone marrow transplant was compared to the gene therapy, 110% worth it. Both of my boys, the seven year old who was three when he had his gene therapy, he has absolutely no symptoms of MLD to this day. And then my other son who's nine and was five when he was diagnosed, he still has some progression in his limbs, but it was there before and we're not seeing that increase in the four years since transplant. So I am speaking from a perspective that is, both treatments I can speak highly of because my results were good with both treatments.

James Valentine, JD, MHS (04:29:35):

Well, thank you so much, Amy, for all of those insights. Patricia, we haven't had a chance to hear from you yet, so I want bring you in on this topic of maybe treatment experience where you haven't been able to notice or maybe you can tell that something hasn't worked or again, maybe whether or not something has worked. What have those downsides been and how would you evaluate that against the potential benefits of the treatment?

Pat Lang (04:30:02):

Yeah, my name is Pat Lang and I'm the mom of Madigan Lang who just passed away in May. She was diagnosed with late infantile and she exceeded all expectations and lived until she was 25. I am from Minnesota now, but I came here because no one else could identify it. And it was a young doctor who did her residency in Minnesota. And when I was being a mom and upset because I couldn't get answers, she came to the rescue. She wasn't even our doctor, and she heard me and she came to the rescue and had seen it. We came here for bone marrow transplant. The first one didn't work, but we were fortunate that she had another donor that we could go do it, another one. But that second transplant, they had never done that yet, so they had to go back and look at her and had to make patient-centered decisions about how much more chemo could she have, how much radiation, all those kinds of things. So they kind of had to come up with a recipe to do the second bone marrow transplant.

(04:31:24):

She became wheelchair bound probably at five and later she was on a trach vent feeding tube shunt, had to have spinal fusion. But I almost hate to say those things just because we had a quality of life that even though she was totally dependent, we didn't let any of those things stop us. She couldn't feed herself, she couldn't do any of those things but there wasn't a concert that we didn't go to or there wasn't things, we just kept doing. And I truly believe that those positive things that we did and the wonderful support team of doctors that went over and above and the different things, the different drugs and therapies that we tried are the reason that she lived to 25.

James Valentine, JD, MHS (04:32:17):

So Pat, I'm really glad to hear about that quality of life. I'm kind of trying to maybe picture it and understand it a little bit better. Hearing just how much support and lack of independence that she had on her own. I don't know, maybe if this is really the right way to ask it, but if there were some things that were more severe or there was more loss or regression, is there something that would've made it so those types of great quality of life activities wouldn't have been possible?

Pat Lang (04:32:55):

Probably, but I'm pretty independent. I'm single mom. I worked full time and when I had nursing and people were shocked that we did some of the things we did, we were on a pontoon boat on one of the 10,000 lakes here, and a doctor came by and he goes, 'What?' And my daughter, he looked at her face and saw her giggling and said, 'Nevermind.'

James Valentine, JD, MHS (04:33:22):

Were there any adaptations or adjustments you had to make these kind of activities work?

Pat Lang (04:33:29):

Oh, yeah.

James Valentine, JD, MHS (04:33:30):

Can you give maybe an example or two of that?

Pat Lang (04:33:32):

Yeah. So I'm lucky that she was very little. So at 25, she weighed about 40, 43 pounds. And so because of that, I could handle, I could move her and do. We had to move her every hour because she was so tiny and we worried about wounds, we had that. But we had the adapted van and we had a wheelchair. We had a wagon with all of our extra supplies. And it was amazing when people saw us and saw her little face with the vent and everything, how they said, 'Let us pull the wagon for you.' 'Let us do this', 'let us do that.' We had to add a ramp. We had to put systems because you couldn't sleep because of all the machines she was on. So we had speakers and things set up so that I could hear everything. When we had nurses, they were there to do all those things but I had to learn to do those things and I had to work and the financial devastation was unbelievable.

James Valentine, JD, MHS (04:34:40):

Sure. Well, thank you so much, Pat. This has been really helpful to hear particularly how you all were able to do these things. Obviously it looked a little different than how others would do it, but it was still possible. I do have a couple of phone callers I want to get to, but Cache, I see that you want to add something here, so ask if you can briefly comment.

Cache Christensen (04:35:06):

I just want to circle back to the drawbacks of treatment and just cover three really quick. I'm Cache from Logan, Utah. One of the drawbacks is when you get a diagnosis for MLD, it's usually not just for one kid, it's for two or more. And I have two children that have it, Leah, who's 10, and then Hazel who's three. They both had different treatment options. Leah opted for the traditional bone marrow transplant because of her progression. Hazel was asymptomatic, so she was able to go to Italy and have the gene therapy, which was a great opportunity. However, both of these treatments, they have a major life disruption. Here we are, almost a year out from bone marrow transplant for Leah, and we haven't

worked consistently for almost a year. My wife and I haven't been able to work consistently because they got treatment roughly the same time. My wife went to Italy, I stayed here and moved to Salt Lake City to be with my other daughter. She was being treated. That's a huge thing.

(04:36:18):

Also, the time that it takes to actually have the treatments start to be effective. Bone marrow transplant, it was several months after the transplant before Leah was able to make enough of the enzyme to be able to start fighting back the MLD. And with gene therapy, it's even longer. And when you have MLD, which is a rapidly progressing disease every minute, every day, every week counts. It's the difference between being able to continue to walk and being in a wheelchair.

(04:36:56):

And another one that not many people talk about is where we are approaching a time in science where children are surviving this, they're living normal lives. Both of these treatments require chemotherapy and/or radiation. And one of the side effects is that is the possibility of sterilization and that's a very likely possibility for every child. And it's amazing to be able to say that I'm going to survive this and be able to continue on with my life, but later on in life, when they get to that point, that can be a heartbreaking effect of these treatments.

James Valentine, JD, MHS (04:37:41):

No, absolutely. I appreciate you sharing all three of those things, Cache, so much. I do want to bring a couple of phone callers into the discussion. We have Linda from Minnesota who wants to talk about some of her son's treatment experiences. So Linda, I'd like to welcome you to the program. Are you with us?

Linda (04:38:02):

I am here. Thank you.

James Valentine, JD, MHS (04:38:04):

Yes, so we'd love to hear about your son's experiences.

Linda (04:38:09):

Our now 29 year old son, Evan was transplanted at, what was the implants at the time, almost 10 years ago, 2013. And he has a terrific quality of life physically. There's almost a thing he can't do. He can drive a golf ball, he can play goalie, he can skate out, he fishes, he can really physically do just about everything cognitively significantly impaired. And I just wanted to maybe piggyback off what Debbie was saying with her daughter about the amount of almost hand over hand directions needed to get things accomplished. Whether it's showering, whether it's going to the garage and getting a hammer, whether it's getting dressed appropriately for the weather. But truly, I think the hard thing for some of us with olders, he was diagnosed at 15... No, he was diagnosed, I'm sorry, he was diagnosed at 19 and transplanted at age 20. And the hard thing for me, and I think for a lot of us with olders is I was going to hang up. It's like, listen, you got a kid who's out there fishing with his dad right now, your story isn't as heartbreaking. Sorry.

James Valentine, JD, MHS (04:39:47):

No, Linda, I-

Linda (04:39:51):

It's just that I can't compare with the other stories yet it's our story and we live in that story and really want to [inaudible 04:40:02]-

James Valentine, JD, MHS (04:40:00):

And every story matters Linda.

Linda (04:40:04):

Of course, but in this tight MLD world, we're well aware of many stories and we don't want to fight to be heard because we know how devastating it is at other levels. But at the same time, we also don't want our children forgotten. And I'm not saying that that's what's happening, but our needs are less. But he's vulnerable. We have to keep an eye on him 24/7. We are... like Debbie was saying, the idea of some sort of geo tracking.

(04:40:47):

And a child that looks, Oh gosh, some of these kids are just gorgeous. They look normal. And because of that normalcy there's a vulnerability that goes along with it that makes the world kind of an unsafe place for them. And so our needs are different and we pray and we work towards treatments for all and just hoping that there's something in the mix that can make life... I'm one of those that click none of the therapies help. We did the PT, we did the OT, we did the speech therapy, we've done meds. There really isn't anything. This is just where we're at. And so to live it, to accept it but to still advocate I think is where I'm at.

James Valentine, JD, MHS (04:41:38):

And I appreciate you doing it, Linda, and speaking up and being a part of this meeting today. I really want people like Evan's voices and experiences to be heard. Could you maybe tell us what would be your treatment goal for Evan? What would make a difference in his life? Can you maybe give some words to that?

Linda (04:42:03):

Well, I think a lot of us with olders, we deal with the isolation for our children, just as probably all families do. Your life has changed. But when they're 20 something, there's a realization of what was and what isn't anymore. And just last night, he said, as we're visiting with his cousin who's soon to be married, 'I need a girlfriend' or something like that. And to have a matter of fact conversation with them, not to fall apart while you're driving, recognizing that that probably, maybe isn't going to happen. But yet to always remain positive and optimistic. But just knowing how isolated they are and how much more isolated they are becoming as opposed to things opening up for them because they do have a quality of life. They are out there in the community. So I guess that socialization piece, I think is the heartbreaking thing for us with olders that have... because of fabulous treatment and follow up care, have a quality of life. So you're never away from it, I guess is the hard part.

James Valentine, JD, MHS (04:43:23):

Well, I really, really appreciate this, Linda. Again, thank you so much for giving voice to Evan. I do have another phone caller, Mary from Kansas City, also the parent of a child, a daughter with adult MLD that wants to share some of their treatment experiences. So I would love to bring Mary into this conversation as well. So Mary, I'd like to welcome you to the program. Are you with us?

Mary (04:43:49):

Hi. Thank you very much. I have to ditto everything Linda said. It's hard when you're the parent of an adult and you know what, how difficult it is for all families of children with MLD. Chris was diagnosed at the age of 33, but actually her onset they feel was age 18. So for 15 years she was given mental health diagnosis and that's what we went with. When it was discovered through an MRI that she had possibly MLD, then she did have a bone marrow transplant, and that was eight and a half years ago. We're grateful for the transplant because it did stop the progression. Some of the physical things that she had, she no longer has. Her hand no longer tremors, her mouth no longer moves.

(04:44:48):

The first two years were very, very difficult because of having no enzyme and that enzyme building back up. So it's almost like a regression. However, after the first couple years, then things started getting better. And we really attribute that to the fact that her donor had a high enzyme level, and was a strong match.

(04:45:18):

It still was a difficult time, but cognitively is where Chris continues to have issues. We do know that she receives the information, but she can't really get it out on her own. And so much of what she used to be able to do, she can no longer do. She's a mother. She has a son who's actually 20 now. And one of the things that is difficult is that he was 11 when his mother had a transplant. So he doesn't really remember his mom, what she was like before she was sick. He just remembers her now not being able to do things that other moms do.

(04:46:08):

So I think for us, the social, there is no social. She does work eight hours a week through a job program. So she does work eight hours a week, which is good, that is her social life as well too. But I keep thinking the enzyme replacement therapy that's out there, that's not available for adults, is there something that could help bridge that gap and a different type of therapy, a way that they could be diagnosed sooner than going through 15 years of mental health issues on medications that she doesn't even need. She does take Adderall now, which does help her focus. She also takes 10 milligrams of Prozac, which keeps her mood stabilized. She's 100% self care except for things like she can't wash her hair, but she doesn't think that, 'Oh, I didn't take a shower yesterday. Should I take a shower today?' I mean, she has to be told, or we use a list of things to do if she... I think probably the biggest difficulty we face, if she were to go to cook herself an egg and she walks away, then that is out of sight, so-

James Valentine, JD, MHS (04:47:34):

Yeah, that's really helpful to-
Mary (04:47:39):

... egg burns [inaudible 04:47:40].

James Valentine, JD, MHS (04:47:40):

Yeah. Well Mary-

Mary (04:47:42):

It is very difficult the first two years after transplant, but for us it was successful so far. In the back of our minds we do worry, is it going to continue to be successful? Will she ever regress? Is there enough information out there to let us know that?

James Valentine, JD, MHS (04:48:03):

Yeah and that's another recurring theme, the information and knowing what outcomes will look like, longer term. But really I want to thank you for sharing Chris's experiences and helping understand both, where maybe she has been helped by bone marrow transplant, but also what her ongoing needs are. With the time we have left, I want to make sure that we cover a very important question that we have for you. But before we do that, I do know that there's been a lot of written comments that have been coming in both on treatments that have been helpful as well as maybe some treatment experiences with downsides. So Maria, I want to check in with you. What are we hearing from the written comments?

Maria Kefalas, Ph.D (04:48:47):

Okay, James. So we have Stacy from Massachusetts who says, My child had a bone marrow transplant using umbilical cord stem cells that saved his brain. However, he continues to lose function with his peripheral nerves. Because of the peripheral nerve disease, brooks has a lot of pain and stiffness in his extremities.

(04:49:08):

Jennifer from New Jersey, who has an early juvenile child who is treated with gene therapy says, my daughter ultimately received gene therapy, but she was mildly symptomatic. While waiting for gene therapy and during treatment, there was also some decline. She now requires adaptive equipment, daily medications and therapies. Despite this, we are beyond grateful that this disease has stopped progressing and that our daughter is still with us. Most importantly, our daughter is grateful to be alive and is happy.

(04:49:38):

And then from Melanie in Canada, she writes that my daughter Noel had has LI-MLD. She just turned eight years old in September. She was currently a participant in the Embolden Enzyme Replacement Therapy Clinical Trial here in Canada. We feel that her medications manage her symptoms somewhat, but wish that her quality of life was better and that she was less drowsy. Drowsiness is a big trade off that she experiences to control her pain and seizures. Our hopes for the future include reversing the damage to nerves and demyelination. Our kids are so resilient, so strong and courageous, and have endured the unimaginable. And we don't want research and drug development to forget about the kids that are living with significant ongoing neurodegeneration. We still have hope that they can live lives with significant improvement to their quality of life.

(04:50:35):

On the issues of treatment, failures and downsides, Francois from Texas, who has an early juvenile child who was treated with a transplant says bladder and bowel issues. My child, has been in pull-ups since transplant. He has accidents with bowels maybe four times a month and has wet beds five to seven nights a month. He lacks executive function and it's difficult as he needs help with everything as he forgets what steps are next like a toddler, which we've heard many people describe.

(04:51:13):

Jennifer again from New Jersey, who has a child who was treated with gene therapy says there are very unpredictable tone issues. Loss of speech is devastating. The nerve damage also causes her to feel lost in space. She's taking Baclofen for tone, Gabapentin for nerve pain, Sinemet for tremors, Cremalax for bowel issues, Bactrim as part of her transplant, Zyprexia settles her at night. She has a G-tube as she cannot swallow fast enough to take the volume of medication by mouth. She's in OT, PT and speech therapies, several times a week. We try to incorporate exercise to keep her from getting stiff. Our whole life is modified at this point.

(04:51:56):

Meg in Dallas talks about her adult onset husband who was transplanted. She says we would make the decision to do the transplant again because there was no other treatment option available, but it's very dangerous and Michael now has graft versus host disease for the rest of his life.

(04:52:14):

Shannon from Minnesota, who has an early juvenile child who was treated and has passed away from a BMT, says we were very optimistic about the stem cell transplant and the actual treatment was successful for my son, but he ultimately died of graft versus host disease. Although the BMT treatment was successful with ARSA, he was far too progressed in the peripheral nerves to be successful. We knew all the risks, but we just wanted to save our son. We did look into gene therapy in Milan, but Gavin was too far progressed for that option.

(04:52:46):

Jennifer from Alabama another early juvenile patient who was treated with a transplant says Emma has passed and I don't know what I could have done differently. If we didn't seek a bone marrow transplant, we would be left wondering if that path would've helped her. She went into septic shock that caused a lot of damage and felt like it made her MLD progress rapidly. Cause of death was ultimately heart failure.

(04:53:11):

Ngeidtre from Cameroon says it's not easy for me with two children suffering from this disease in my house, under my roof with a monthly income of just $250 a month. So I think that we have a, really I think, expansive review of some of the symptoms, upsides and downsides of these treatment options.

James Valentine, JD, MHS (04:53:33):

Yeah. Thank you for covering so many of those. We been getting so many comments coming in and it's, I think really nicely complimenting some of the things that we're hearing and giving us some additional experiences that we haven't heard yet on the phones or with our Zoom panel.

(04:53:53):

So I do want to move us to our final question of the day, which is thinking about what it is that's important for you all, that you would like to see, short of a cure for MLD from a next future therapy or therapies. So we're going to go to a polling question to help us get some of your input on this and to get us thinking about it. And again, you can access this final polling question of the day by going to PollEV.com/MLDPFDD. So here we want to know, short of a complete cure, what would you look for in your ideal therapy for MLD? And you can select up to three answers here. The options are A, increased communication, engagement and responsiveness. B, improved or retained voluntary movement. C, increased ability to walk or mobility. D, reduced spasticity and tone. E, reduced pain. F, improved ability to breathe independently. G, improved eating, swallowing and motility. H, slowing or stopping the disease progression, overall. I, longer lifespan, or J, something else that represents something you would look for in an ideal therapy for MLD that's short of a complete cure.

(04:55:17):

So as you're making these selections, as we have throughout the day today, I want you to be thinking about what is driving your choice here. Can you help us understand, with whatever you picked, why you picked that. As responses continue to trickle in here, it's already looking like a couple of things are rising to the top as some of this community's top preferences for what represents an ideal future treatment that's short of a cure. Certainly it looks like the top one is slowing or stopping the disease progression. After that the next would be an increased communication, engagement and responsiveness. We've heard so much today about the impacts on communication and ability to interact with caregivers and family members. So I think that makes a lot of sense based off of the burdens we've heard about. And then beyond that, everything else has been selected as a top three for some number of people, we see

longer lifespan, increased ability to walk and mobility, improved and retained voluntary movement and reduced pain, all amongst some of the slightly more commonly selected options. But really again, every single thing here is a top three treatment goal for our participants today, again, short of that complete cure. So to get us started on this topic, I'd like to check in with our Zoom panel here. I'd like to ask each of you to weigh in on.

James Valentine, JD, MHS (04:57:03):

Here, I'd like to ask each of you to weigh in on this, so maybe we can start with you, Pat, thinking about what would represent a meaningful new treatment short of a cure for MLD. What would that look for for you?

Pat Lang (04:57:18):

I had a hard time with that one because I wanted to check them all. And limitation of three was very, very difficult. I know that my daughter was cognitively there, but she lost the ability to talk, but she communicated with her eyes to our questions. So we quickly learned how to do that. And I think one of the big things that we also need to do that wasn't listed there is to, with all these treatments and our children are living longer or with late treatments and children are living to adults, we need to get the adult primary care positions up to speed in what these diseases are and what the treatments have been and what these families face. And so family engagement, family participation, and education of doctors that didn't see this disease as a pediatric disease or for adult onset. We just need to make sure that everybody is aware so that we can do the best we can to accomplish all of those things that were on that polling question.

James Valentine, JD, MHS (04:58:29):

Absolutely. Thank you, Pat. Cache, how about you on thinking about what might represent an important or even ideal next treatment that's short of a cure, what stands out to you?

Cache Christensen (04:58:43):

Ideally, I'd like to see a treatment that would be able to deliver the enzyme more rapidly. I mean, even with our BMT for our oldest, it took over two months to get the diagnosis, to find a donor. Had there been something that she could be doing in the medium or in the interim while we were waiting for all that to come through, that could have saved some of her functioning. Also, MLD is a rare disease, which means that we tend to not get as much attention as other diseases that might be more prevalent throughout the world, but we do have similar outcomes to these more prevalent diseases. So I would love to see more collaboration through research with these other diseases, the organizations that are working on them so that we might benefit from their research as well.

James Valentine, JD, MHS (04:59:42):

Thank you, Cache, so much for that. Debbie, how about you? I know really hard to pick amongst the list. What did you pick and why?

Debbie (04:59:52):

So I definitely picked stopping or slowing the progression of disease. I find it frustrating that the late juvenile and adult onset patients or people who have already started showing symptoms don't even have the option to try the gene therapy or the enzyme replacement therapy or potentially even the emerging options. I feel like that part of the population, the MLD population, really doesn't have any choices other than the transplant option. And given that, I know we're not the only ones that have seen that if there's physical or emotional stress, there's a decline and then they can plateau. But if there's

physical or emotional stress, there's a decline. So a transplant is really a physically and emotionally stressful procedure and it's just not something that we can take the risk of. My daughter has a daughter of her own. We can't put her through a transplant and potentially have her daughter lose her mom.

James Valentine, JD, MHS (05:00:51):

Yeah. Very well said, Debbie. Thank you. And Amy, of course, when I also ask you the same question, what would you pick as a top priority for an ideal next future treatment?

Amy (05:01:05):

I'm the same as Debbie. I would say something that slows the progression and then inevitably increases lifespan. So short of a cure would be knowing that, at least knowing that the progression can be stopped and lifespan increased is what I pick.

James Valentine, JD, MHS (05:01:28):

Sure. And Amy, what would that look like? Do you have any particular symptoms or health effects in mind or is this really just a global slowing or stopping?

Amy (05:01:43):

Well, speaking just from personal experience and also from other stories that I've heard, the demyelination of the nerves in the peripherals is what we've experienced the most of and it leads and is leading to his inability to do things that he used to be able to do.

James Valentine, JD, MHS (05:02:11):

Absolutely. Well, I just want to thank our Zoom panel. You all have contributed so much throughout this discussion today. So wanted while I'm going to go to some phone callers here, just wanted to make sure that we recognized you for all of your contributions. I'd now to go to Kelsey who's calling in from Colorado and wants to share some thoughts about treatments with her daughter with late infantile. So Kelsey, I'd like to welcome you to the program. Are you with us?

Kelsey Donnelly (05:02:46):

Yes, I sure am.

James Valentine, JD, MHS (05:02:48):

Hi, welcome.

Kelsey Donnelly (05:02:50):

Hi. So I kind of want to touch on the last two. As you all know, I have Tegan, late infantile. She did not qualify for any of the clinical trials or treatments. So essentially she is sustained with medications and with that there are side effects. So when you look at it as a big picture, there's days where it's okay, we're controlling her seizures or her dystonic episodes. But now we are on a scary edge of suppressing her respiratory system and which already struggles daily being that she needs 24/7 oxygen support. So to piggyback that with this most recent poll question, I would love to see things that slow down and stop the progression. But that really falls on having that newborn screening available for kids to qualify and get this treatment before any type of symptom arises, as any management medication that's available will without fail affect a different part of their body.

James Valentine, JD, MHS (05:04:08):

Sure. And Kelsey, you mentioned some of the side effects and how that interplays with kind of breathing and pulmonary function. I would also assume, but don't want to, that any next future treatments you would want to avoid those types of side effects and interactions that kind of counter some of exactly what you're trying to manage day to day anyways.

Kelsey Donnelly (05:04:41):

Yes. Yeah, exactly. I mean, trying to find ways scientifically. I've heard from these families on the panel with the chemotherapy, I mean, that's so incredibly hard on their bodies trying to find different ways to attack MLD without essentially destroying other pieces of their body, their functions.

James Valentine, JD, MHS (05:05:16):

Right. Yeah. Well Kelsey, thank you so much for sharing that and weighing in on both of these important questions, both downsides and trade offs of existing treatments, but also really appreciate you adding and sharing some of your treatment goals. I want to bring one more caller into the discussion here. We have Jennifer from New Jersey who wants to talk about her daughter Jana and some of her treatment experiences and would love for her to also reflect on this question of what would represent an ideal future treatment. So Jennifer, I'd like to welcome you to the program. Are you with us?

Jennifer (05:05:56):

Yes, I am. How are you today?

James Valentine, JD, MHS (05:05:58):

I am well thank you. Thank you for being on with us.

Jennifer (05:06:02):

No problem. Thank you for having me. And thank you for having this call. I think it's so important for families to hear each other. Yes. My daughter, Jana has early juvenile. We are eight months post-gene therapy. She received it through compassionate care use in Minnesota and every day we feel blessed. We feel blessed that we had an early diagnosis. We feel blessed that she was able to receive this and while she was mildly symptomatic at the time of diagnosis, so some of the other callers who have had asymptomatic children, their children don't have any symptoms right now, my daughter does. But the most important thing is she's happy and she started back to school last week. Therapies are progressing along. We're seeing some small improvements, but if I had to do it all over again, I would 150% do gene therapy again. I've definitely seen the benefits of it.

James Valentine, JD, MHS (05:07:17):

And can you maybe mention, just because you said it, and I'm really interested, because I think this does feed into this topic of what represents meaningful therapy. You mentioned that there have been some small improvements. Can you just comment on what you've seen so far with Jana?

Jennifer (05:07:35):

Yeah, post-transplant my daughter was really not a safe eater, so she could only drink really thick liquids. She had some difficulty swallowing. So it was really just soft foods and very thick things. We've gone through food therapy so she can now eat anything that she wants. She's able to swallow liquids, she still swallows slowly, but she can enjoy eating now. We still have a G-tube for supplemental nutrition and just because she takes a large volume of medications every day, that's just too much by mouth. We're going through serial casting right now. We're hopeful that she will be able to, she'll always need a wheelchair,

but hopefully she'll be able to stand on her own or do some small steps for transfers. So, we've definitely seen some improvements there.

James Valentine, JD, MHS (05:08:30):

Yeah, that's so helpful. Jennifer, thank you so, so much for calling in and sharing your and Jana's treatment experiences and reflecting on some of these things that have been meaningful and helpful to her and therefore your family as well. I do want to check in with Maria because I know we've been getting so many good comments throughout the day today. What are we seeing on this topic of what people are looking for from future treatments?

Maria Kefalas, Ph.D (05:08:58):

Yes. So Jamie from Washington, who has an adult MLD loved one says, I want treatment for symptoms to keep our standard of living. Stacy from Massachusetts says, we need a treatment that can improve or prevent disease progression in the peripheral nerves. Again, something we've been hearing a lot about. Yvonne from Georgia with an early juvenile child says, we need peripheral nerve treatments. Carey, an early infantile mom from New Hampshire says any treatment where odds are greater or equivalent to natural progression of the disease. Again, speaking about the fear of losing a loved one. Tom from California asks, when and how can we get gene therapy to be approved for symptomatic children? Crystal from Illinois asks, every child should have the right to try gene therapy. Genetic testing at birth should be mandatory across the globe. My daughter lived for eight years as a healthy girl until she started having difficulty in school and then led to difficulty walking.

(05:10:01):

We are watching our daughter slowly die. Our daughter is upset. Amelia does not understand why her legs used to work and now they do not. This is cruel and inhumane to watch our daughter go through this with no available medication. Our family and friends are devastated. And finally, George from Alaska, he says, with a juvenile onset child, "As a parent and primary caregiver, I just want to mention risk. Our experience is that all symptom reduction therapies, OT, PT, AFOs, et cetera, or medications that don't reduce the myelin degenerative processes may slow symptoms for a while, but they don't improve underlying disease processes. They give some comfort to the patient for a time, but they don't provide hope. Where therapeutic methods that arrest or reverse that degenerative process exist, hope exists. As a caregiver of a patient with advanced MLD, our risk tolerance is extremely high. We would just like to share that our family would take big risks to treat the myelin erosion if there are solutions considered or developed for trial or implementation in the future in advanced cases." So thank you. Yeah, some amazing insights from our families.

James Valentine, JD, MHS (05:11:18):

Yes, incredible insights which have just been consistently coming in all day. And while we're at the point of the agenda where we now have to wrap up getting your input, at least for today, it's just been so incredible to hear from all of you. And as your meeting moderator, we've been having these conversations together, I just really want to commend this community for stepping up today. We've heard some really devastating experiences across all of the MLD types and to hear just about these losses that are unpredictable and your loved ones becoming trapped in their own bodies and just having no relief from that over time if you haven't been able to access certain treatments, to really be so brave as you were to pull back this curtain and make it so real for all of us. This is exactly what we needed to hear to help the regulators at the FDA to help those trying to develop drugs and gene therapies and other approaches at all points in the pipeline.

(05:12:51):

Everything that was shared today is exactly what we need to help advance those therapies in a meaningful way for all of you. So I heard your needs and I feel confident that decision makers have heard your needs as well. So again, just thank you so, so much.

(05:13:08):

At this point it's my pleasure to hand the meeting over to my friend and colleague Larry Bauer, who has the impossible task of trying to give some summary remarks. So much has been covered today and Larry is going to talk about some of the key themes and things that he heard throughout the day. While it is a nearly impossible task, Larry is a great person to do this. Larry spent 17 years at the NIH where he was a clinical research nurse and worked with pediatric populations and rare disease populations. He then went to FDA where he co-founded the Rare Diseases Program within the Center for Drugs and worked there for 10 years as a regulatory scientist and now in private practice has been a real partner and an integral part of planning this PFDD meeting. So without further ado, I'd like to hand it over to Larry to share those summary thoughts.

Larry Bauer, RN, MA (05:14:09):

Thank you so much, James. It's been an incredible day hearing everyone's stories. And like you said, I will try to give a very high level summary of the day and what we heard today. I will not be able to get into a lot of detail, but please trust that those details will be captured in the Voice of the Patient Report that will be written after this meeting and will become publicly available. So this morning our meeting was started out by Dean Suhr, who's the co-founder and President of the MLD Foundation. His talk was followed with the presentation from Dr. Sairah Thommi from the FDA's Office of Tissues in Advanced Therapies in CBER. Dr. Thommi shared that PFDD meetings provide insight into the FDA to learn from the experts, the caregivers and people living with MLD, and it helps facilitate treatment development, design clinical trials, and review new drugs for MLD. She also discussed that rare disease drug development is a priority for the FDA.

(05:15:11):

This was followed by a clinical overview, which was presented by Dr. Laura Adang from the Children's Hospital of Philadelphia. She shared with us that MLD's a neurological disease causing demyelination in the CNS and affects multiple body systems. They're four types. The late infantile is diagnosed before age two and a half. There's early juvenile, late juvenile and an adult onset. The late infantile has early motor symptoms and tends to progress rapidly and there's more of a variable progression in the late juvenile and adult. There are rapid changes once ambulation is lost and it's a relentlessly progressive disease and unfortunately diagnosis is often delayed.

(05:15:59):

We heard then from a panel of people, of people impacted by MLD. The first person we heard from was George, who's the dad of 11 year old Ronan. Ronan was once very active and progressed swiftly and went from first symptoms to fully caregiver dependence in just a year. They live in Alaska, which causes additional challenges. And currently Ronan has no voluntary motor function and he's completely dependent, is blind and has neuropathy and seizures. He shared that Ronan was sad as he saw his abilities begin to fade.

(05:16:33):

Next we heard from Michelle, who's the mom of six year old Willow. She also lost her abilities within just a year. She said poor swallowing is the scariest symptom due to choking, but loss of speech has been the most heartbreaking because Willow used to love to sing. She experiences neuro pain and they think she experiences loneliness and insecurity. She's missed out on all the activities of a healthy developing child.

(05:16:59):

Next we heard from Matthew and Lauren who are parents of Lowie, who passed away from MLD at the age of three and a half years, which was just 13 months after diagnosis. She developed feeding issues, breathing issues, pain and discomfort, and lost all motor function. Her stomach and GI issues became severe and she had strong reactions to tube feedings. They said that holding her in their arms for hours was the main way that they could help calm and comfort her.

(05:17:29):

Corrine shared the story of her son Trent, who passed from MLD at age 19. His symptoms started at age eight. They decided against a bone marrow transplant. And then between the ages of 10 and 15, he lost bladder and bowel control, the ability to walk, talk, eat, and communicate. He eventually lost the ability to even laugh or smile, and Trent eventually developed a respiratory infection which led to his death.

(05:17:56):

And then the final panelist this morning was Heather, who's 35. Heather herself has adult onset MLD and four of her six siblings in her family have had MLD, and her brother Daniel died at age 27. Her brother Joel is 42 and has progressed to losing his ability to communicate and take care of himself. And she says he's just a shell of himself. Heather herself is losing focus and struggles with concentration, and experiences, depression and anxiety as the disease progresses. She says MLD affects everything she does in her entire life. So all morning we heard that MLD rapidly robs people of mobility, speech, the ability to care for themselves. Symptoms can include pain, spasticity, and dystonia, gallbladder abnormalities, depression, anxiety, and many families have multiple affected family members, which just complicates this scene all the more. And we also heard that MLD is slow to be diagnosed and has some relentless progression from onset, which is a great concern for the future.

(05:19:02):

After our lunch break, we heard a treatment overview from Dr. Adeline Vanderver from the Children's Hospital of Philadelphia. She's talked about the MLD treatment landscape including human stem cell transplant, which has had variable results, gene therapy and enzyme replacement therapy. The gene therapy is approved in the European Medicines Agency and expanded access only in the United States, but that there's a real need for disease modifying therapies and we also need treatment options across the spectrum of disease. So at every stage, even after people are symptomatic.

(05:19:37):

Our panel in the afternoon, we heard from Kendra, who's mom Te Kira and Olivia. Olivia is four years old and is currently enrolled in hospice. Kira had received gene therapy in Italy. Olivia gets PT, music therapy and uses Baclofen for spasticity, sulfatrim, clonidine, and melatonin. Kira is advancing in her skills and attending preschool and it's been extremely frustrating to have such different outcomes for their two daughters.

(05:20:08):

Sonal is mom to six year old Radha. Radha gets enzyme replacement therapy in a clinical trial and she can now cue with her voice. Her sleep's improved. Motor skills have improved and cognition is improved. And although she'll likely never walk or feed herself, the changes seen have been life-changing.

(05:20:27):

Victoria is mom to Adeline, age six, and Oliver, age two. Adeline has chronic respiratory failure and is completely dependent on care. Oliver was eligible for gene therapy, which he had in Italy. And after one year post-gene therapy, he's getting stronger and has started to stand up. He has some delays, but he has not regressed.

(05:20:48):

Gary is dad to five year old Celia Grace. She was found to have a mass in her gallbladder associated with MLD. But in 2020, Celia Grace became the first MLD patient to get gene therapy in the United States. Most of the side effects she experienced, hair loss, fatigue, and some sores in her mouth were from the chemotherapy associated with the gene therapy. And he says she's now a normal five-year-old.

(05:21:13):

And finally we heard from Amy, who's mom to Giovanni and Liviana with late juvenile MLD. Liviana by age three regressed quickly and was not eligible for gene therapy. And sadly, Liviana passed away from MLD at age five and a half. Giovanni was the second person to receive gene therapy in Italy in 2011. And now at age 12, Giovanni has never shown any symptoms of MLD and he gave an excellent presentation on behalf of himself.

(05:21:42):

So we've heard about the tremendous unmet medical need in the MLD community. Each of the major symptoms including impaired mobility, cognitive decline, seizures, pain, GI issues, and especially communication issues can have incredible quality of life impacts. And the treatments are mostly palliative, including things like PT, OT, speech therapy, orthotics, and there are currently no FDA approved treatments for MLD. But treatments are being developed and currently have variable results, and gene therapy is in experimental stages. And once again with gene therapy, the results have been varied. So now to close the meeting, I'd like to turn it over back to Maria in the studios. Thank you.

Maria Kefalas, Ph.D (05:22:27):

Thank you for that summary, Larry. There was so much to cover and that was a thorough overview. Today has been a powerful day. Thank you to the FDA for allowing us to hold this meeting. We appreciate FDA staff carving time out of their busy schedules to listen. Many thanks to our FDA liaisons, Shannon Sparklin and Karen Jackler for helping us plan this meeting. Thank you to Dr. Sairah Thommi for your overview on the significance of patient focused drug development meetings to the staff at the FDA. And thank you to Dr. Laura Adang for the MLD Clinical Overview and to Dr. Adeline Vanderver for her review of treatments. I'd also like to acknowledge the members of our organizing committee, Erica Barnes, Dean and Teryn Suhr and Bob Rouner. And a special thanks to Cure MLD's Melanie Rumble. And our team couldn't have done this without the expert support and moderation from James Valentine and Larry Bower, as well as the production team here at Dudley Digital Works.

(05:23:32):

Most importantly, I must thank the MLD families who have shown incredible vulnerability and courage in sharing their stories together today. To recount the most traumatic thing that has ever happened to you and do it repeatedly is a gift to the scientists, doctors, researchers, and FDA reviewers.

(05:23:51):

10 years ago when my daughter Cal was diagnosed, I had no idea how I would survive watching my daughter lose everything. She could no longer sit up on that 4th of July weekend at the beach. The final word she uttered was daddy in August of 2012. She took her last steps in the atrium at the Children's Hospital of Philadelphia when she saw one of the therapy dogs that same summer. I cannot remember her first steps and first words as clearly as the moments when she lost those things. I would've cut off my arm for my daughter to hug and kiss me one more time before she died. As I sank into a suicidal despair, the only thing that got me out of bed was holding onto the idea that the children who came after Cal would not suffer as she did.

(05:24:43):

We lost Cal earlier this year in March. Over her 10 years living with MLD, she had over 1,720 confirmed provider contacts. Please take a moment to ponder what that number says about the emotional,

physical, and financial toll of caring for a child with MLD. And yet, the MLD community continues to have hope. Our families have taught me that miracles do not happen because we wish for them or pray for them, or even because we deserve them. They must be earned through sacrifice and hard work. And I believe our families have suffered and sacrificed enough. We have earned our miracle. This meeting today is dedicated to my beautiful Cal and all the others we have lost.

(05:25:32):

In the coming months, we'll compile all of the information you heard today in the Voice Of The Patient Report, which will be publicly available on the organizing committee member's websites. Today's program will be available for on-demand viewing right after we conclude on mldpfdd.org. And in the coming weeks on each of our organizing committee member's websites. The comment form will be open for 30 days after the PFDD. So please consider submitting additional comments so they can be incorporated into the Voice of the Patient Report.

(05:26:08):

We also hope that everyone here today will attend our follow up scientific meeting on November 18th from 11:00 AM to 1:00 PM Eastern Standard Time. The meeting is called, Integration of the Patient Perspective into Therapy Development for MLD. MLD clinical experts will take a deep dive into issues identified by families in today's meeting. We want to understand how to design better clinical trials for MLD. You can pre-register for free at mldpfdd.org. Our heartfelt thanks for everyone who attended today and to my fellow MLD families, please know that your voices are tremendously important and the impact of your participation today cannot be overstated. Thank you for being here.