James Valentine, JD, MHS (00:13:55):

Good morning. My name is James Valentine, and welcome to the MLD Scientific Workshop, a direct follow up to the externally-led patient-focused drug development meeting on MLD where today we'll be beginning to integrate the patient perspectives in the therapeutic development in MLD. I'm here in the studio with my co-host Maria Kefalas, the co-founder of both Cure MLD and the Calliope Joy Foundation. We're coming to you live from the Washington DC metropolitan area, actually not too far from where the US Food and Drug Administration's headquarters are located. It's my pleasure to introduce Maria to provide us with some opening remarks. Maria?

Maria Kefalas, Ph.D (00:14:34):

Thanks, James. Welcome to the MLD Scientific Workshop. Today we'll be discussing more about integrating the patient perspective into therapy development for metachromatic leukodystrophy or MLD. My name is Maria Kefalas and I'm the co-founder of both Cure MLD and the Calliope Joy Foundation. I'm honored to be here today to help facilitate this very important discussion.

(00:14:59):

On October 21st, the MLD community hosted an externally-led patient-focused drug development meeting. There, patient families testified in front of the FDA, clinicians, researchers, industry, and advocacy organizations, both to help us understand the lived experiences of MLD and the needs for treatments. We are grateful for the participants from the MLD EL-PFDD for starting this important conversation, providing the patient voice to help inform clinical trial design and therapeutic development.

(00:15:32):

All along we had wanted to host this adjunct scientific meeting today to give MLD clinical and research experts an opportunity to reflect on what was heard during the PFDD as well as identify important subject areas to expand upon. Today you will hear the results of those reflections.

(00:15:51):

To start the program, Larry Bauer will give a short recap of what we learned from the MLD EL-PFDD. Then James Valentine will provide a general framework for integrating the patient voice in drug development. Following James will, we will hear from our expert clinicians. Dr. Laura Adang will provide a landscape analysis of tools to evaluate what's important to MLD patients and a discussion with top MLD experts will follow. The final part of the meeting will be used to discuss opportunities to conduct clinical trials in later onset forms of MLD.

(00:16:25):

I'd like to thank our amazing clinician panelists for being a part of this discussion. Dr. Laura Adang, Adeline Vanderver, Barbara Burton, Samuel Groeschel, Marc Patterson, and Paul Orchard.

(00:16:38):

To everyone watching online today, thank you. Please submit written questions for discussion through the form located just below the livestream player. We may have an opportunity during the discussion sessions to offer your questions, so please fill out the form below the player, submit and be a part of today's conversation.

(00:16:59):

So with that, I'll hand it over to Larry Bauer, a regulatory expert and former NIH researcher and former FDA rare disease regulatory scientist who's going to provide a recap from the October 21st MLD EL-PFDD. Larry, take it away.

Larry Bauer, RN, MA (00:17:17):

Thank you so much, Maria. It's a pleasure to be with you all this morning. As Maria said, I will be giving an overview of the meeting that was recently held. I'll go over the agenda just so to familiarize everyone with how the day looked. Then I'll move in to talk about some of the top symptoms and health effects that we heard from the caregivers and patients. Also, I'll talk about the top unmet medical needs that were identified, additional symptoms that were identified, and then a little bit about the subtype differences with people living with MLD and just a brief section on some current treatment approaches.

(00:17:56):

So as Maria said, the externally-led patient-focused drug development meeting took place virtually on October 21st, very recently, from 10:00 AM to 3:00 PM. The meeting was opened by Dean Suhr, who's the co-founder and president of the MLD Foundation. Then we heard some FDA welcoming remarks from Dr. Sairah Tommi. Dr. Tommi works in the Center for Biologics Evaluation and Research at the FDA in the Office of Tissues and Advanced Therapies where gene therapies are actually approved. Next we heard a clinical overview from Dr. Laura Adang, who you will hear from shortly.

(00:18:37):

And then we moved into the portion of the meeting where we heard directly and had conversations with patients and caregivers. It started with listening to five prerecorded panelist statements. We did some live polling with the audience. Then we had a moderated audience discussion with some Zoom discussion starters as well as people calling in and writing in with comments. Then in the afternoon we shifted gears a little bit. The morning was focused on health effects and daily impacts of MLD. In the afternoon we shifted gears to perspectives on current and future MLD treatments. The afternoon session was opened by a talk from Dr. Adeline Vandever who you'll also hear from later today. Once again, it was the same format with recorded panelists, polling discussion and Zoom discussion starters. I provided a meeting summary and then we had closing remarks from Maria Kefalas, who you just met.

(00:19:38):

So I'm going to use a lot of direct quotes from the meeting. I think the way that we will remember most from the meeting is to hear again some of the direct things that patients and caregivers stated. So one of the overarching topics that we heard again and again was the problem of regression. There were reports of children going from being asymptomatic to needing complete care within as short as one year of time.

(00:20:09):

We heard from Michelle, whose mom to six year old Willow. She states, "She was perfectly developed at three years old, but within a year she lost speech, swallowing, continents and body control."

(00:20:21):

George who participated from Alaska, he's a dad to 11 year old Ronan. Ronan used to play hockey. He was previously the state champion dog musher. And he states, "Within two months of the observing of the first physical symptoms, especially as walking challenges, Ronan's speaking and swallowing ability rapidly decreased."

(00:20:42):

We also heard from Matt and Lauren, who are parents to Loie. Loie sadly died from MLD complications at the young age of three and a half. And shortly after Lowe's diagnosis, they said her health started to rapidly decline. She lost her ability to walk, talk, sit up and eat through her mouth. And within just six weeks of diagnosis, Loie received a G-tube for feeding.

(00:21:08):

One of the other key symptoms that we heard about that impacts people's lives, family's lives is the loss of communication skills. Over and over again we heard the challenges of not being able to communicate with your child, especially around medical issues.

(00:21:24):

We heard from Corrine whose mom to Trent. Trent died from MLD at age 19. Between the ages of 10 and 15, he lost bladder and bowel control, the ability to walk, to talk, eat, and communicate. He could still smile and laugh for quite a while, but he lost that ability after several more years.

(00:21:44):

We heard from Heather who shared the story of her brother Joel, who has adult onset. Joel's currently 42. He became withdrawn and was not his normal, funny and happy self. The symptoms that affect him the most now are his loss of communication and overall ability to take care of himself, such as feeding, bathing, and toileting.

(00:22:05):

We heard from Michelle who stated that, "Willow's loss of communication was the most heartbreaking part of MLD. We have speech therapy teaching us how to communicate with Willow through blinking and an eye gaze device, but it's not without difficulty. We heard that sometimes they don't work well."

(00:22:22):

Susan stated, "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 to have him respond." Another significant symptom was muscle cramps and rigidity. Susan is the mom to Daniel who was diagnosed with MLD before he turned three and then passed away in 2018 when he was around seven years old. "The hypotonia, muscle cramps, rigidity and pain and irritability were among the most difficult because they really had almost no way to control these symptoms. The last three years of his life, he could not move."

(00:23:01):

Debbie whose mom to Annabel and has early juvenile MLD and states, "At the beginning, it was mainly pain from muscle spasms and things like that. She lost the ability to walk about six months after. And in the beginning she had much more ability. She was still mobile. She could raise her hand or leg to respond to questions. And that has decreased to the point where she's only capable of blinks now"

(00:23:27):

Osmahan has a daughter Laura with late infantile MLD and her muscle spasms got so worse over time and it was very rapid progression. She's not comfortable sitting in the same position all the time. She cannot really move. She's tense in her neck and most likely in her legs. She's always in that very tense position. And her hip actually dislocated.

(00:23:50):

Les, who called in from Ireland, is dad to Kyle who died at age 6. "The most difficult symptom he endured after his rapid decline at age 2 and 3 was the muscle spasticity he suffered from. He cried more than any child should."

(00:24:06):

Another big issue was swallowing, feeding and GI issues. Willow's story, "She had insufficient swallowing. It's the scariest symptom because she could choke. She had loss of muscle control, which impacts this significantly. And in order to provide nutrition, Willow had a G-tube placed and a Nissan fundocopulation fold three days after her 4th birthday. And even with preventative measures and use of Scopolamine patches, we remain on 24-hour alert with a suction machine because of asphyxiation precautions."

(00:24:42):

And then Loie, who passed away, "Loie went from being a plump little girl to an extremely frail little girl within weeks. She 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. We tried different formulas to provide the nutrition needed and at the same time limit the painful gas buildup, the bacterial overgrowth, while minimizing the endless discomfort she had when eating. She wouldn't tolerate formula. The GI issues would worsen each time and they exhausted all of their options and their team of doctors were at a loss of how to keep our daughter alive as a result of every formula causing Loie to scream out in pain."

(00:25:27):

Loss of ambulation and ability for self care was a huge impact. Once again, Ronan from Alaska, "His present condition is such that now four years since symptoms began, he has no voluntary motion, no areas of independence in his life. He cannot move, eat, toilet or speak, challenged with blindness, seizures and neuropathy. He requires wheelchairs, lift systems, feedings and oxygen."

(00:25:53):

And Joel, the young man with adult onset, "The symptoms that affect him the most now are his loss of communication and overall ability to take care of himself with feeding, bathing, and toileting. He's just a shell of the person he was and a good day for him now is when he has family with him, eats a full meal and he is taken care of properly."

(00:26:15):

Also a neurologic problems, seizures and cognitive impairment. Heather was one of our adult onset patients who spoke for herself, she said she struggles to acknowledge how everyday moments are impacted. "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 and at times have panic attacks."

(00:26:39):

Trent had his first seizure around 15 and was put on anti-seizure meds. He had at least two seizures that couldn't be stopped and ended up in the ER. And his parents think he was blind by the end of his life. And Loie had a significant portion of discomfort due to the constant nerve pain she experienced.

(00:26:59):

Additional symptoms identified during the meeting where ocular defects, peripheral and essential neuropathy, irritability, failure to thrive in the younger children, gallbladder issues including carcinoma of the gallbladder, renal involvement, and respiratory issues.

(00:27:18):

Just to refresh us about the subtype differences, there are four types, late infantile, early juvenile, late juvenile, and adult. The first two are classified as early onset and the last two is later onset. In the late infantile, the onsets before two and a half years of age with early motor symptoms and rapid progression. The early juveniles is onset between 2.5 to 8. There's some variability in this rapid onset of motor symptoms and rapid progression in a rapid decline. The late juvenile kids have an onset between 8 and 16 years of age. There's variable progression, more cognitive decline, and maybe a little bit slower course. And in the adult onset, it's 16 years and older. You first see personality changes and depression has a variable progression and changes can happen over years and decades.

(00:28:16):

Just briefly about treatment approaches. Hematopoietic stem cell transplant, it's not a standard of care for any MLD patients. A few older patients in the meeting shared that they had some benefits. One of the problems is you have to have a match for the transplant. Patients and caregivers describe the high morbidity and mortality of this treatment. There are issues with graft-versus-host development.

Transplantation related mortalities, approximately 23%, which is very high. And due to that high percentage, the risks versus the benefits are really something to struggle with. And caregivers often choose to avoid stem-cell transplant because of this potential for death. And almost no young patients ever received this type of treatment.

(00:29:10):

There's also gene therapy. There are ongoing clinical trials for gene therapy and it's approved in Europe. It's limited to late infantile and early juvenile patients who are asymptomatic or minimally symptomatic. Access is limited by region.

(00:29:27):

One of the things we heard several times during the meeting is families that have more than one child with MLD where one was treated with gene therapy, one was untreated, they saw a dramatic differences in the kids that received gene therapy. There's also enzyme replacement therapy with ongoing clinical trials and considerations for the possibility of intrathecal administration.

(00:29:51):

Some of the other treatment approaches we heard were medications for symptoms like for seizure, anti-spasmodics, psych meds, sleep meds. Many people use PT, OT, speech therapy, special ed classes, assistive devices and G-tubes for feeding.

(00:30:10):

So the challenges for MLD treatment, there are delays in the diagnosis. And then when people are finally diagnosed, they're too symptomatic to be available for treatment, eligible for treatment. So we have an unmet need for pre-symptomatic diagnosis and treatment. Newborn screening is in a pilot form, which would be such a game changer to identify these kids early. There's an unmet need for disease modifying treatment options for those who are already symptomatic. And there are no options for safe and effective treatments in the US yet. So there's an unmet need for therapy development across the spectrum of disease.

(00:30:48):

So future goals, we'd like to see earlier diagnosis and an intervention, equality of access for people with all four subtypes, and defining meaningful improvement in symptomatic patients.

(00:31:02):

So I thank you very much. And now I'm going to turn it over back to the studio and to my colleague James Valentine. James is a former FDA official and James has been a champion of the patient voice for the past 15 years. James?

James Valentine, JD, MHS (00:31:18):

Thank you so much, Larry. And thank you for that wonderful recap of the externally-led patient-focused drug development meeting. The whole premise of today is to build on and translate that input from this MLD patient community and turn that into action. And so that's what my presentation now will be, is a bit of a grounding and understanding some of the ways, certainly not all of the ways that we can integrate the patient voice into drug development.

(00:31:48):

So patient-focused drug development, we're actually celebrating the 10th year of this program, which launched in 2012, which was really an important recognition that patients who live with the disease have a direct stake in the outcome of FDA's decisions and are in a unique position to contribute to the understanding of their disease. And we'll talk a little bit about the ways that that happened, but it's just an important moment in time to note that while patient engagement as part of drug development and

regulatory review processes certainly existed prior to 2012, this has really been something that's been more systematic over the course of the last 10 years and creates this great opportunity for us again to really anchor our clinical trial planning and drug development around what is most important to patients.

(00:32:42):

So I'm going to talk about a few ways that patient input can be important, and we're going to start with the end and we'll work our way earlier in drug development. And I'd like to start with the FDA approval decision. So when improving a new drug, something that maybe we all know is that FDA has to make a determination that the benefits of the drug outweigh the risks. This is a scientific determination to evaluate what those benefits are, what those risks are, based off of the data and the robustness of the findings, how much certainty there is around those benefits and risks.

(00:33:16):

And while that is a scientific determination, it's important to note though that there is an inherently subjective value judgment that comes into play when deciding whether the benefits of a drug outweigh the risk. There's no quantitative formula that you can plug clinical trial data into to find that out. And in fact, this is going to be variable from one condition to the next whatever the specific population that a drug is being developed for and what is meaningful to them and what risk they would be willing to tolerate.

(00:33:49):

So this leads us to the question of where does FDA calibrate its values on how much risk a patient population should tolerate, and risk, both in terms of safety risk as well as risk in terms of uncertainty of treatment benefit which-

PART 1 OF 4 ENDS [00:34:04]

James Valentine, JD, MHS (00:34:03):

... as risk in terms of uncertainty of treatment benefit, which we'll talk a little bit about more later. And that is from the patients. And so back when patient focused drug development was initiated in 2012, there was this idea that, conceptually, what types of information can patients share with us that will help us understand and inform those benefit risk decisions? And this was what we refer to sometimes as the therapeutic or clinical context, which is important context that informs decision making about any products in development for a particular condition. And this context gets broken down into two major areas of patient experience. The first, the burdens of the disease and the impacts on patients daily lives, helping us understand the seriousness and life threatening nature of what patients live with on a day to day basis, as well as then second, patient's perspectives on the adequacy of available therapies, which helps us define the degree of unmet medical need they have in terms of treating those most significant burdens of the disease.

(00:35:12):

And so by understanding these two things, which is exactly what the externally led PFDD meeting and MLD explored, this helps us the types of benefits that would be matter most to patients. And so as you can see here, this is FDA's structured benefit risk framework, which is a framework that FDA reviewers actually complete as part of their evaluation of new drugs and biologics at the time that they're considering potential market approval. And you can see that while the third, fourth, and fifth rose in this benefit risk and risk management, those are going to apply to the specific information provided around the product, the information generated from clinical trials. The first two rows, the analysis of the condition and the unmet medical need, those directly align to the type of input that we got at the

externally led PFDD meeting. And so the information that Larry just shared can help us think through and inform benefit risk decisions in MLD.

(00:36:17):

But it isn't only about that final approval decision. It also can help inform how we actually go about conducting clinical trials and doing clinical research. One major area where patient input is so valuable is in helping select and develop clinical outcome assessments. Clinical outcome assessments, or COAs, are measures of how patients feel or function. They can be measured in different ways, either through performance tests, they can be evaluated through clinician reports, observers like caregiver reports, and of course, directly reported by patients. Clinical outcome assessments are not the only kind of things that we use as endpoints in clinical trials. We can also include things like measures of survival or surrogate biomarkers, but the COAs, again, are those direct measures of how patients feel and function. And these are important because these are used in adequate, well uncontrolled studies that are necessary to support drug approvals. So, COA selection and development, what ways, where does the patient voice really patient voice really fit into that?

(00:37:26):

There's a few key questions, again, this is not comprehensive, that patient input helps inform. It helps us know what are those right concepts of interest to measure? Are we measuring those things that actually matter to patients? What opportunities are there to measure those important concepts of interest in patients' daily lives? This is really important because we might have different options or approaches we can take to actually measure these different disease concepts. Maybe if there's a lot of day to day variability in something we need to... We can't just measure it periodically because we don't know if we're going to be catching a patient on a good day or a bad day for that given symptom. And finally, and importantly, when we actually get the results from clinical trials on these clinical outcome assessments, how do we know what is considered a clinically meaningful change?

(00:38:20):

One final area beyond just helping select and develop outcome measures, there's other aspects of trial design where patient input is really critical. It's important to note that the quality of clinical evidence that FDA needs to be able to conclude that there's substantial evidence of effectiveness, this is what FDA is evaluating, that quality of clinical evidence. And it's informed not only by the robustness of the trial results, but also trial design and statistical considerations. Substantial evidence must be based on at least one adequate and well-controlled clinical trial, but it's up to FDA to determine whether a particular clinical trial design represents something that is adequate and well controlled, such that it can meet the substantial evidence requirement. So traditionally, FDA views randomized double blind, concurrently controlled trials as providing the greatest amount of certainty, therefore maybe having the greatest chance of meeting that substantial evidence requirement. However, it's important to note that FDA also recognizes that in certain disease settings, that different trial designs may be appropriate. And in their own guidance and regulations, they call out certain scenarios, certain contexts where these different trial designs may be appropriate. And those include situations when diseases are serious or life threatening, also in situations where there's an unmet medical need, and finally in situations when a disease is rare. And so in MLD, we check all three of those boxes easily. And so we should be considering, and as part of our discussion today, thinking about some of these alternative types of trial designs. So, FDA recognizes that in these settings, a somewhat greater risk of false positive conclusions, meaning that there's less certainty about a drug's effectiveness, can still support that conclusion of substantial evidence of effectiveness.

(00:40:26):

And so some examples from FDA guidance of trial designs that can be considered, again, in these serious conditions with unmet needs and in rare diseases include things like use of a single arm trial with an

external or natural history control, use of unvalidated reasonably likely surrogate and intermediate clinical endpoints that can support accelerated approval, as well as somewhat higher P values than the traditional P of 0.05 if pre-specified and justified in terms of powering. All of this is grounded in FDA regulation and guidance. And I list here just a couple of resources where you can find more information on what I've shared today. But for now, what we'd like to do is get into the discussion and start to hear some of those reflections. And so at this point, I'd like to turn it over to Dr. Laura Adang who's going to launch us into our first topic for today, which is really to begin to set a patient-centered research landscape and assess some of the opportunities that we have to actually conduct trials that reflect what is important to patients. So, Dr. Adang, take it away.

Laura Adang, MD, PhD (00:41:49):

Yeah, thank you so much, James and Maria, for having me today. It is my pleasure to talk to you about the tools we have to evaluate what's important to families affected by MLD. I do have some conflicts of interest. I am both a research collaborator and a consultant for Orchard, Takeda, and Biogen. I have several NIH grants and several foundation supported research endeavors. So, our objectives today are talk about what's actually important to patients, what tools do we have to address what's important to patients, and where are the gaps in our understanding and therapies that are available?

(00:42:34):

When we look at what was mentioned by the families during our PFDD meeting, we can see a blend of words reflecting both the challenges that face every single family affected by MLD, but also hope for the future, that the next generation of children affected by MLD don't have to suffer in the same way as we develop treatments that are effective at controlling what's important to families. We all understand that the selection of appropriate endpoints is critical for any clinical trial. And for many rare diseases, well characterize efficacy endpoints are appropriate for the disease are not available. But for MLD, we have a very strong published evidence for the burden of disease, and this is further supported by the testimonies provided by families that really aligned very nicely with what had been published before. As the FDA's guidance emphasizes, it is critical to understand the aspects of disease that are meaningful to the patient and their families that we can assess to evaluate a drug's effectiveness.

(00:43:39):

When we group the patterns of what the family has talked about during the PFDD, we can see some really clear patterns emerging that, again, aligned very tightly with what has been published before and what we understand from an academic or scientific perspective. We know that motor symptoms are really a predominant early feature in early MLD, which is the most common subtype of this rare disease. This is reflected in all of our natural history studies and exactly what we heard from families as well. One parent described this rapid predictable course as physically, he hiked four miles in June, he was diagnosed in July, and by October, he was fully wheel chair bound. It is incredible how swiftly MLD removes someone's capabilities. We do have tools in MLD to identify this change and reflect these clinically meaningful, parent meaningful, patient meaningful outcome measures. A tool such as the GMC MLD has been validated to longitudinally assess neurologic function of gross motor skills, both retrospectively and prospectively.

(00:44:54):

We also know communication is a critical part of all forms of MLD, although in the early onset forms, oftentimes it's superseded or preceded by the movement difficulties. In the later onset form of MLD, however, communication disturbance is actually a very early and strong feature. One family described it as the symptoms that affect him most now or his loss of communication. He's a shell of the person he once was. He was kind and funny. Another family described that shortly after she was diagnosed around three, she lost her ability to speak, and about six months later, at three and a half, lost her ability to

laugh. As you can see, we have a very strong communication burden in this disease as well. When we look outside the central nervous system and the effects, families are reporting complications such as pain, tone management, feeding nutrition, and seizures is also being incredibly important to their day to day lives.

(00:45:59):

And we know that feeding dysfunction is an early and severe consequence of both the early and late onset forms of disease. One family reported that they wonder if their daughter will be awake when they walk in the room in the morning, or did she choke in the night? Another parent described their experience in Thanksgiving, which is coming up just next week. The mother wrote, "This little girl of mine was at Thanksgiving and she would eat her whole plate, and then she would go to find everyone. Oh, that ability went so fast, but she still wanted. She just didn't realize that each time, she would choke." And so I think it's important to recognize what we classically describe as the early features of MLD, the mobility and communication issues, but there are many other features of disease that the families find critically important in a disease like MLD.

(00:46:56):

As was touched on briefly before, we have various ways we can divide the different subtypes of MLD. An endpoint selection is really critical for a clinical trial, as well as defining clinically coherent subtypes. We understand both the range and the clinical course and the disease manifestations associated with the disease and its subtypes, and this is because of extensive published retrospective and prospective natural history data. We really have a deep understanding of this disease sub course, and the differences among the patient subtypes are well defined. And whether we define it by early versus late MLD or the three to four categories of late infantile, early juvenile, late juvenile, and adult, really, the clinical course is predictable. The progression in early MLD has very early motor symptoms and is rapidly progressive over weeks to months versus the more chronic course of late MLD, which involves more behavioral and communication challenges.

(00:48:02):

The stereotyped progression of early MLD particularly was repeated throughout the recent PFDD. One parent described that their child, around two, started having problems walking, but he wasn't diagnosed until May. And at that point, he could sit up, he could talk, he could communicate, he could eat, but between May and September, he lost the ability to sit, to speak and to eat. And so you can see that even when the diagnosis is delayed, the child progresses incredibly quickly through the stages of MLD. And I think that this is something that we should capitalize on as we're designing clinical trials, that we understand the disease course and the features that both we can measure, and importantly, are important to families.

(00:48:51):

When we start to look at the information we have about MLD, this is born out of the natural history studies. Natural history studies can be divided into retrospective or prospective cross-sectional or longitudinal. And as per the FDA's on guidance, when concurrent controls are impractical or ethical, clinical trials for rare diseases can rely on historical control data, but it's critical that we have a rigorously conducted retrospective natural history study that can provide systematically and comprehensively capturing the data that's important, using uniform medical language and methodologies relevant to any potential interventional clinical trial. This will help us, as a community, to ensure that historical controls are comparable to any treatment groups. Retrospective studies are by definition limited by the existing medical records, and so they can only capture elements that are available in those records. And so as such, it is imperative that we have well defined standard operating procedures, including protocols to ensure the rigor of retrospectively collected data.

(00:49:57):

These natural history studies should include patients that are across a wide spectrum of disease severity phenotypes rather than focusing on justice specific subtype. Retrospective studies are actually particularly well suited to this because they allow for a less biased inclusion of patients across geographic and socioeconomic barriers. Participation in a retrospective natural history study is not limited by the ability to travel or by biases in time to diagnosis. As such, we can use standardized collection methods and medical terminology to enhance the value and usefulness of our retrospective natural history study data in rare diseases such as MLD. The challenge in MLD is highlighted by this figure, which is unpublished data from GLIA Clinical Trial Network. What this is showing is comparison between disease onset to time to diagnosis, and the challenge of how long it takes to get to diagnosis, and why this is critical in a rapidly progressive disorder such as the early onset MLD. In MLD, and again, especially the early MLD, you have rapid neurologic change within months of diagnosis, and therefore any delay in diagnosis is by necessity missing that presymptomatic and minimally symptomatic population for any prospective natural history studies.

(00:51:35):

And so the cohort in a prospective natural history study of early MLD would, by definition, be further along in the clinical disease trajectory compared to a child who would've been eligible for a minimally symptomatic targeting clinical trial or therapeutic outcome. And I think that that's a fundamental problem with rare diseases, is our time to diagnosis. But in the early onset form of MLD, it is particularly critical because how fast things are changing. It means the information we're capturing a year or two years after presentation is really a very different child than who would've been eligible for intervention.

(00:52:19):

I think we have some clear gaps in our MLD therapies. We need equity of therapeutic opportunities. There is controversy among the use of hematopoietic stem cell. And furthermore, there's an inequity in the match availability that we know that all racial and ethnic groups do not have equal access to hematopoietic stem cells, and there's a fundamental lack of clarity on the transplant advocacy, particularly in that early infantile population or the early onset population. We also need therapeutic options for patients with symptomatic disease. We have excellent validated outcome measures for the neurologic outcomes in MLD, but we haven't validated the outcomes for pain tone, feeding issues and behavior issues that many families are saying are really the key symptoms after the motoring communication issues.

(00:53:18):

And so we need to validate and design trials that are targeting these symptoms for the symptomatic population as well. We also need more timely diagnosis. I think that this is a huge barrier in our MLD community, but with the advent of newborn screening pilot programs, which have been launched in Europe and several states in the United States, we can be hopeful that the next generation of families affected by MLD, we can get to therapies in time. I'd also like to emphasize the fact that therapy development to date has targeted the earlier onset form of disease and we need to have options for later onset of disease. And so our gaps are equity, targeting symptomatic disease and targeting the late onset disease.

(00:54:10):

So, we have many challenges for MLD design. And our current expectation of a cure really should be revised to the important expectations of disease modification, and the role of the community in defining what is a meaningful outcome for MLD is essential. One of the requirements for drug marketing approval is substantial evidence that the drug will have its claim effect, and this requirement is the same whether we have a common or a rare disease. And as such, we need substantial evidence that is based on the results of an adequate and well controlled investigation. And in the case of a rare disease like MLD, that may necessitate the use of a non concurrent historical control, but we should do our best as a

community to design a trial that permits a valid comparison between the historical data and any prospective interventions. And we will use the FDA guidelines and use them to lead our historic control design that can assess the serious fatal disease of MLD because there is an unmet medical need.

(00:55:16):

There is a well-documented, highly predictable disease course that can be objectively measured and verified, and there is an expected drug effect that is a large self-evident and temporally associated with the intervention, particularly in early onset MLD. In closing, I would like to think the family is affected by MLD, both those that participated in the PFDD last month, but also those that have participated in our international retrospective natural history study, as well as our international collaborators from major academic institutions around the world. I want to thank everyone for your time in listening, and I would like to go back to the studio. Thank you.

James Valentine, JD, MHS (00:56:03):

Thank you so much, Dr. Adang, for that wonderful presentation, really to start us off and kick us off as we collectively reflect on everything we heard from last month's externally led patient focused drug development meeting on MLD, and now look to expand and broaden that discussion with a number of MLD clinical experts. So, if we can pull up a slide here that shows the audience who we have gathered today, who we'll be hearing from throughout the course of our program. In addition to Dr. Adang who we just heard from, we're joined by Dr. Adeline Vanderver, Dr. Barbara Burton, Dr. Paul Orchard, and we will be joined shortly also by Dr. Marc Patterson and Dr. Samuel Groeschel. So, at this point, welcome everybody. I hope you found Dr. Adang's presentation illuminating as I did. But what we really want to do now is to broaden and get some of your own reflections on what we heard at the PFDD meeting.

(00:57:06):

And one place I'd like to start is, because we did have a lot of discussion by patients and caregivers at the PFDD meeting, really about the dearth of adequate treatments, when thinking about planning studies, we need to, of course, consider and should consider what background therapies are relevant. And one therapy that was discussed and Larry summarized was around stem cell transplant. And so my question to you is, could you describe for us where stem cell transplant fits into therapy options? And I'm going to ask each of you to reflect on this, but perhaps we can start with Dr. Vanderver.

Adeline Vanderver, MD (00:57:46):

Yeah, I think that the limitation in understanding that bone marrow transplant, standard bone marrow transplant is really related to significant of evidence. So, there are very few larger groups of patients that have been published. And the few that have, including some by Dr. Orchard's group, which that I'm sure he will speak about, as well as Samuel Groeschel's group, really have demonstrated very limited efficacy, and significantly very, very limited to no efficacy in our late infantile population. And so I think while the verdict is still open about which patients in the later onset groups might benefit and we don't fully understand how to triage those patients to understand which ones might be likely to benefit from that kind of approach in the late infantile patients and in the early onset patients, we really have very limited evidence, to the point that I have not personally recommended somebody with late infantile MLD undergo standard bone marrow transplant in more than a decade.

James Valentine, JD, MHS (00:58:49):

And Dr. Vanderver, given that you don't recommend bone marrow transplant to those patients, can you tell us what do you recommend?

Adeline Vanderver, MD (00:59:00):

I mean, right now, unless patients are eligible for a clinical trial, I recommend symptomatic support for those families, which is heartbreaking because as Dr. Adang pointed out, many of our patients right now are really accrued to us and are diagnosed too late for the kind of interventions that might be currently amenable for clinical trials and for patients who have the means to travel to a European site to get a current [inaudible 00:59:30] gene therapy approach, but many patients just don't have any options at all.

James Valentine, JD, MHS (00:59:33):

Sure. Dr. Burton would like to get you to reflect on this as well, again, the question being, what would you describe as where stem cell transplant fits into therapy options for patients across the spectrum of MLS?

Barbara Burton, MD (00:59:50):

Sure, I'm happy to comment on that. And I agree with Adeline, that there are really very few patients for whom this is a reasonable option. I think we've seen enough data from Paul's group and others on the symptomatic late infantile patients that this is really not an appropriate choice for them. The only late infantile patients where I have discussed this, and I will say I had one who went to transplant before there were clinical trials ongoing, would be the presymptomatic patient. And of course, we have very few of those. Those would all be younger siblings and families where a child has been clinically diagnosed. And I think there's very limited evidence of efficacy in those patients, but it may be that there is some modification of the disease course in a presymptomatic patient, but certainly the one patient that I took care of still had very significant disease progression.

(01:00:56):

So, I think there are situations, I would say this is also true of the early diagnosed, early juvenile patient. If you make a rapid diagnosis and the patient, patient still has a high level of function, it is something we do consider. But I agree with the others, that since we have had clinical trial opportunities, we have very few patients making that choice. And some of the families I have cared for who have made that choice... for example, I have a family who had three diagnosed patients with early juvenile MLD, all diagnosed simultaneously after the first one presented, and all three went to transplant, one died and the other two have had severe disease progression and basically have end stage disease currently. They then had a new baby who also has early juvenile MLD and they do not want to go to transplant, understandably so, even though that child is presymptomatic.

(01:02:01):

And just to underscore the equity issues we've heard about, they also don't have the financial means to travel to Europe for gene therapy. They could not even go to Minnesota from Chicago to try to get gene therapy under compassionate use. So, for that family, it is devastating. And I think we heard over and over again in the patient testimony of the just incredible distress of watching a child deteriorate neurologically, slip away from the family, lose the ability to communicate, feeling that there's nothing they can do and nothing their doctors can do to stop that process. So, the unmet need is huge. I mean, how much greater could it be? There is no greater unmet need, and the urgency of getting therapy for these patients is really tremendous.

James Valentine, JD, MHS (01:03:06):

Absolutely. Thank you so much Dr. Burton, and thank you for raising some of those really important inputs we got at the ELPFGE meeting, one certainly being the inequities. And I think I'll definitely want to circle back to that a little bit later and explore that as a topic, but also summarizing the difficulty of the decision of whether or not to try or seek out stem cell transplant that the patients described so

eloquently at the PF DD meeting. Dr. Orchard, your data has now been referenced a couple times by your fellow panelists here. Would love to get your reflection on where you see stem cell transplant fitting into a therapeutic options for MLD.

Paul Orchard, MD (01:03:57):

Yeah, yeah, I appreciate the opportunity to weigh in here. Yeah, we've had experience with transplant for MLD probably going back 35 years. I think there's maybe three considerations we should discuss here. One is, in terms of the toxicity of transplant, especially if we're talking about this and in the context of gene therapy, but the mortality rate of the transplant procedure itself is somewhere between 10 and 20%, and that varies a bit based on the patient's situation and availability of well-matched donors. So, it's obviously improved over decades, but it still is a procedure that's associated with a lot of morbidity and mortality, which is, if compared to the gene therapy, it's probably an order of magnitude more than what we would expect with gene therapy. In terms of efficacy, I mean it may be the best thing that we have available to us now, but it's clearly inadequate. And as people discussed, it may modify the course of the disease, but it's not curative, certainly.

(01:05:19):

And unfortunately, we've seen a number of patients in the last six to nine months that we've turned away from transplant cause I just can't recommend transplant for symptomatic patients. Some have gone on to other institutions where they may have gotten transplanted, but I really can't, in good conscience recommend that patients proceed with transplant in that sort of situation because we've got data from decades worth of experience that these patients tend to progress and deteriorate and their function is very poor. So, we've stopped doing that in most of these patients.

(01:06:05):

And the other piece would be the feasibility of a comparative trial, and I just don't think that makes sense in any way, shape, or form, frankly. I mean, we've got adequate history in terms of what the outcomes are with transplant. From an efficacy standpoint. It's poor. None of us are happy with that as an option. And I think, I don't know that you can, in good conscience, randomize patients for instance. I just don't think that's a viable option for these families. I mean, patients have come here to see us, hoping potentially to be able to get gene therapy. And when we can't offer that, then they say, "Well, we're not going to go to transplant because we know what that looks like and we don't want do that." So, randomized trial is just not going to be feasible in my view. So, that would be my two cents in regards to these issues.

James Valentine, JD, MHS (01:07:12):

Really, really appreciate your two, three, four, all of your cents on that Dr. Orchard. Dr. Adang, I know you touched on this just a little bit in your presentation, but if you'd like to expand at all on your own clinical treatment experience with stem cell transplant. And I'm just looking down at my notes and seeing that we heard a number of patients or really their caregivers expressing fear with graft-versus-host, septic shock and death. And so are those things that come up and are part of those discussions that you have or inform your considerations for treatment?

Laura Adang, MD, PhD (01:07:56):

Yeah. Thank you very much, James. And I feel the same as Barbara, Paul, and Adeline, where particularly with early MLD-

PART 2 OF 4 ENDS [01:08:04]

Laura Adang, MD, PhD (01:08:03):

... Barbara, Paul and Adeline, where particularly with early MLD, the evidence of both safety and advocacy for bone marrow transplant is strongly lacking, and I have concerns about sending patients down that road. If you go back to the PFDD and the powerful testimony shared by families, even when the bone marrow transplant was considered to be successful by the family, there were many mentions of, "It did not undo the damage that was already done. She has a new normal. We're satisfied. She has few limitations compared to where she would've been," but knowing the relentless and severe course of MLD, that would be not our goal for a therapeutic intervention.

(01:08:41):

We want to preserve function. Families that have had bone marrow transplant wrote in and said, "I feel bone marrow transplant has saved his life, but he's a five year old that only knows what he wants and cannot express himself, which leaves everyone involved frustrated." Another parent whose family underwent bone marrow transplant said, "I believe it took its toll, but it prolonged her life. She's now trached and vented 24/7. She cannot speak, but understand. She's totally dependent and cannot move or walk." While the transplant is successful from an engraftment standpoint, I think we need to be very mindful about having our benchmark for efficacy set by what is clinically meaningful to families. I worry that bone marrow transplant does not meet that bare minimum of a safe or effective treatment for early MLD.

James Valentine, JD, MHS (01:09:33):

Yeah. Thank you so much for everyone for reflecting on this, and I just feel compelled. We have that comment question box open for our audience today. We actually had Erica Barnes from Minnesota, an MLD mom, write in hearing this dialogue amongst our clinical experts here, "My daughter received a bone marrow transplant and she died from its complications. The best outcome we could hope for was that the BMT would simply cause her to die in slow motion from this disease because it does not stop the progression. I regret choosing the option."

(01:10:09):

I think that that aligns with what we had heard at the PFDD meeting as well, but I really appreciate all four of you reflecting on that topic from your clinical and research perspectives. I'd like to move us into another topic that comes out of some of what we heard at the PFDD meeting. We heard many parents of early onset MLD express a hope for earlier diagnosis in hopes of early intervention that would provide better outcomes for treatment if the treatment could have occurred earlier in progression.

(01:10:49):

The question for all of you is, when thinking about enrolling presymptomatic patients in a clinical trial, how predictable is the course of early onset MLD? How confidently can you predict whether a presymptomatic patient has early onset disease? Dr. Burton, perhaps we can start with you on this question in terms of the predictability of predicting, and then once someone does have early onset, how predictable is their course of disease?

Barbara Burton, MD (01:11:22):

Sure. Well, I think it matters a little bit whether you're dealing with a patient who is diagnosed pre-symptomatically because of an older sibling or because of newborn screening. Certainly, when we have a baby diagnosed who has an older affected sibling, we can predict with absolute certainty that the baby is going to have the same form of MLD that was seen in the sibling, and we know that the early onset forms have a very, very stereotypical course.

(01:11:56):

While you might have subtle variation and presentation in terms of several months of onset or some learn to walk and then lose the ability, a few never learn to walk, there are things like that, but ultimately, when they progress, it is absolutely stereotypical. These are patients with no enzyme activity. You can be absolutely certain when you're dealing with an older sibling. With newborn screening, which we have limited experience with thus far, I think we can predict that in most cases, we will be able to predict the phenotype based on the genotype because there are many, many gene mutations, now alleles, both for early infantile and juvenile MLD that have been defined in the literature, described in the literature.

(01:12:51):

We don't see the same genotype in patients with more than one phenotype. In other words, if a specific genotype has been associated with early onset disease, you can be absolutely certain that that's what you're going to deal with. The early onset patients typically have two null mutations, two mutations with no enzyme activity. The juvenile patients typically have one of those, and one with some residual. The adult patients have two alleles with residual and some activity, so they're good. Now, will we have patients with newborn screening where the genotype does not predict the phenotype? We absolutely will.

(01:13:35):

We have that with all of our lysosomal disorders for which we're now doing newborn screening, but just as we do with X-linked adrenoleukodystrophy, which is now on the recommended uniform screening panel, and we can never predict which boys are going to have cerebral ALD, we have ways of monitoring so that we can intervene very early. The model of the X-ALD, we do periodic MRI screening, and we would do the same with the patients with MLD. Through our close clinical surveillance, I think we have a way also of addressing that issue. I think there's no question in my mind that we need newborn screening for MLD, and we will be able to appropriately address all of the infants that are diagnosed through that testing.

James Valentine, JD, MHS (01:14:36):

Sure. Thank you so much, Dr. Burton. Dr. Vanderver, we want to bring you in on this, thinking about trials where we might want to enroll presymptomatic patients. How predictably can we identify those that would be early onset?

Adeline Vanderver, MD (01:14:54):

Yeah. I want to pick up where Barbara left off. Imagine yourself in the situation where you have a patient identified by a newborn screening or in a more today, now, immediate sense, identified because there're those first signs of developmental delay and increasingly, people are picking up children with presymptomatic or before the decline at least, through approaches like next gen sequencing for developmental delay. I think that again, there's a big difference in thinking about late onset and early onset.

(01:15:29):

When you're faced with a family, if you have a patient, you might not be able to say that they're going to develop symptoms at exactly within a month of when they're going to have that decline, but you should be able to, based on recently published evidence, based on genotype and enzyme levels, be able to say that in childhood, they're going to face inexorable progression of disease. In that situation, were you to have access to a therapy that might meaningfully be expected to change that child disease course, I think it would be reasonable to expect and to have a conversation with the family about acting at that time and not delaying an intervention for a time when the child is already clearly symptomatic, i.e., already declining at a point where you might no longer be able to halt the progression of the disease.

James Valentine, JD, MHS (01:16:16):

Okay. Yeah. Thank you so much, Dr. Vanderver. Dr. Adang, we would like to ask a similar question but also want to just continue to emphasize, if we're thinking about this as for a potential clinical trial, I think we've hit a lot on how much can we predict if someone will have early onset, but also then, for those same patients, can we predict what their clinical course would have been with confidence? I think this ties back to what we were discussing earlier in terms of the possibility of understanding how that compares to what would happen in the natural history of the disease.

Laura Adang, MD, PhD (01:16:56):

Yeah, thank you, James. I agree with my colleagues. The genotype- phenotype correlation for MLD is well established for the last 20 odd years, and there have been a series of papers that have helped us to underscore both that there are common mutations in MLD that represent the vast majority of cases that have been identified to date. Granted, once we get to newborn screening, that genotypic variation will expand, but the patients we know of today have standard variants and actually, a lovely paper done by the German LEUKONET group that was recently published underscored that almost 80% of patients carried at least one of the common mutations, and a third of their cohort actually was homozygous for that, and so, has a very clear, easy to define cohort.

(01:17:47):

We haven't seen the genotypic variability in MLD that we have with other lysosomal storage disorders, and I think that that's a really important point. Furthermore, the German LEUKONET group... Speaking of Samuel, I'm presenting your own paper to you. The German LEUKONET's group really did a beautiful job of underscoring yes, we can predict phenotype based on genotype in the majority of cases, but when we can't, we can rely on other biomarkers such as enzyme activity to accurately predict the subtype in cases pre-symptomatically when we don't have a clear genotypic indication.

(01:18:29):

I think it's a combination of information we're going to pull together, genotype, enzyme activity, and family history if it's available in order to be able to accurately subtype families. While it is a challenge, we will evolve with our understanding once newborn screening is widespread. With the information we have at hand, it seems like a very feasible task that with accuracy, we'll be able to determine the subtype of the vast majority of cases that we identify pre-symptomatically.

James Valentine, JD, MHS (01:19:01):

Yeah. Thank you Dr. Adang. I'd like to welcome Dr. Groeschel to the conversation. Just for your benefit, we're been talking about the fact that at the PFDD meeting, we heard for many parents for early onset MLD express a hope for earlier diagnosis in hopes that early interventions would provide better outcomes by being able to treat earlier in the progression. The question that some of your peers here have been expressing their thoughts around are, when thinking about enrolling presymptomatic patients in a clinical trial, how predictable is the course of early onset MLD? Can you confidently predict whether a presymptomatic patient has that early onset disease? Dr. Orchard, we haven't heard from you yet on this topic, so I'd like to see if you'd have something to add.

Paul Orchard, MD (01:19:51):

Well, I don't actually have that much to add over what others have said. Barbara's the geneticist and Laura and Adeline and Samuel have a lot of the natural history data that exists in terms of what to expect for these patients, but I would just reiterate the importance of being able to identify these patients by newborn screening because the vast majority of patients are not going to fully benefit from intervention

because we're diagnosing them too late, and whether that number is 80% or 90%, I think it's clear that unless we have newborn screening to be able to offer, virtually only the patients that are going to benefit are those that already had an affected sibling and that's just not adequate. It's clear to me that newborn screening is going to need to be developed quickly and that will save lives.
James Valentine, JD, MHS (01:20:50):

Dr. Groeschel, hopefully, now you heard a little bit about where we are in the conversation. As someone that is practicing in Germany where gene therapy is approved and certainly, have had a lot of experience treating early onset MLD patients, we'd love your perspectives on how confident we can predict whether a presymptomatic patient has that early onset disease, and if thinking about in a clinical trial setting, how confident do we feel that we know what their clinical course would have been absent intervention?

Samuel Groeschel, MD, PhD (01:21:30):

Yes. I can only underline what has been said already. We know that these early onset forms have such a rapid disease progression, rapid deterioration of motor and cognitive function that any treatment effect has to be very strong and early. We've seen that it is not easy even in presymptomatic cases with the hematopoietic stem cell transplantation, which is sometimes successful in later onset cases, but which is not successful in the early onset cases and therefore not an option, and with the introduction of the Libmeldy gene therapy, this is a game changer for MLD because we have a very effective treatment option and especially for the early onset forms, but if it helps for the early onset forms, it also helps, of course, for the later onset forms because if it changes so much in the early onset form, it is proof of principle that this is a very effective treatment.

(01:23:15):

When we have such an effective treatment option, then we need to diagnose this disease early, and as this has been said, newborn screening is very important in this situation because the storage material, the sulfatides, they accumulate very early from the beginning. We don't want to wait until the symptoms occur when these sulfatides damage the brain. We want to be very early, as early as possible. Newborn screening helps in making this diagnosis early. We have precise and specific diagnostic tools for newborn screening in MLD. At least from all the data that has been published so far, we know that it can detect very reliably these newborns with MLD.

(01:24:36):

We have only recently a diagnosed MLD patient in Germany from a pilot newborn screening project. Also, from this case, we can see that this diagnostic way works. The question was also whether we can predict whether we have an early onset form, and of course, we know certain genotype-phenotype correlations, we know that especially the early onset forms, the late infantile form, we know if the genetic variants are so severe that there's no enzyme function left, no residual enzyme activity left, that this causes the early onset form and then this, we can also measure with the enzyme activity level to predict this early onset form. With the later onset forms, there's uncertainty in the prediction of when the disease onset will be. Even within siblings in families carrying the same genotype, there's a certain variation in the later onset forms, but in the late infantile, early onset form, we can predict that very well. This is the form we also need to treat instantly.

James Valentine, JD, MHS (01:26:36):

Absolutely. Thank you so much, and I think nicely complimenting what we heard from your fellow panelists even before you joined there. Also, appreciate you commenting on stem cell transplant. That was something we talked about a little bit earlier in the discussion, so thank you for sharing some of your thoughts on that. I'd like to take us to another question for discussion. This is one that has been submitted from a colleague at FDA, Dr. Hussein Ezzeldin, and I appreciate the open ended-ness of this,

which is, "What is the greatest challenge you see in future clinical trials for MLD?" Of course, today we're thinking about all of that input we received at the externally-led patient-focused drug development meeting and what those most urgent and important needs are for this patient population that they expressed, but reflecting on that and thinking about the totality of your experience, would love some input on this. Perhaps Dr. Orchard, for this one, we'll start with you. What do you see perhaps as the greatest challenge for the future of clinical trials in MLD? You're on mute.

Paul Orchard, MD (01:27:59):

Sorry. I think there's a number of issues. Obviously, this is a rare disease, and if we have a narrow therapeutic window in terms of catching these patients early enough to make a difference, I think that's one of the key issues as we were just discussing. There is clearly some variability in terms of the disease. The phenotypes are variable and historically, the patient's own situation at the time that they were diagnosed can provide some complexity and whatnot here too. I think the outcomes... Part of it's because of the development of specific metrics that Laura and Adeline and others have put together, I think those things are relatively straightforward now. The outcome analysis piece I think is less of an issue, but being able to get meaningful numbers of patients at an early enough stage to be able to impact the disease is probably one of the bigger barriers that I would see.

James Valentine, JD, MHS (01:29:09):

Sure. Thank you very much. Dr. Vanderver, same question from our Dr. Ezzeldin on what you see as the greatest challenge.

Adeline Vanderver, MD (01:29:18):

I agree that the work of Samuel Groeschel and others in his group in Germany have provided us with really easy to administer and clear outcome measures through the GMFC-MLD and other similar tools. I agree also with Dr. Orchard that I think that patient numbers are going to be difficult because until we have widespread adoption of early diagnostic techniques, we're going to be in the situation we are now, which is that we're going to be diagnosing kids... In some cases, we'll be fortunate in diagnosing them at an early onset period, but most often, most patients will be diagnosed just too late.

(01:30:04):

Already, we're going to be taking a rare disease, we're going to be dealing with a small subset of those patients that are eligible for meeting inclusion criteria, and then my fear is that if you break things up into additional buckets so that you have multiple cohorts within a clinical trial, you're basically going to make clinical trials infeasible because you just will not be able to, within a timeframe that's reasonable for a clinical trial, be able to accrue patients in sufficient numbers to test multiple arms. I think we'll have to be really thoughtful about how we think about arms of clinical trials to make sure that we can get sufficient patient numbers that meet inclusion criteria for clinical trials.

James Valentine, JD, MHS (01:30:49):

Sure. Thank you very much Dr. Vanderver. Dr. Burton, how about you? What do you see as some of the biggest challenges?

Barbara Burton, MD (01:30:57):

Well, I couldn't agree more with what's just been said about the patient numbers and the challenge in finding appropriate patients, and particularly, if you're doing some sort of randomization. I think we have a challenge in front of all of us in terms of seeing clinical trials come forward for the later onset patients. I think Laura mentioned that in her talk, and we heard it also from the patients on the panel previously.

They are more challenging, of course, because of the variability of the disease being greater and also, the rate of progression being slower. Identifying appropriate endpoints for them is a challenge if we are to do trials in that population.

James Valentine, JD, MHS (01:31:51):

Sure. Thank you. Dr. Groeschel, what do you see as some of the greatest challenges for trials moving forward?

Samuel Groeschel, MD, PhD (01:32:04):

Maybe one of the challenges is also to make the treatment available to older onset forms to maybe adult onset forms when we have already proof that it works in the more severe forms. To make this treatment available also in later and onset forms, we need to... The problem is we need to wait longer until we can measure treatment effects. That makes it long lasting and complicated, although we already know the treatment works also for the later onset forms. Because this disorder is rare and certain late onset forms are, there are not many patients and we want to give them also the opportunity to have effective treatment options and designing trials then for these later onset forms is quite an effort and also, in a way, delays access to these treatment options. This is a challenge. Yeah.

James Valentine, JD, MHS (01:33:45):

Yeah. Thank you very much. Dr. Adang, I know you mentioned some of the challenges that you saw in your presentation, but anything you'd like to add to the conversation or emphasize?

Laura Adang, MD, PhD (01:33:57):

Yeah. Thank you. I agree with all of my colleagues. I think we have a challenge in MLD in that there is no standard of care for the early onset MLD and concurrent controls are both impractical and unethical, which means we really need to design clinical trials that rely on rigorous historical, non-concurrent control data. I think that's a challenge that our field is addressing, but it means we cannot rely on the traditional two arm comparator trials. We cannot have placebo control trials because they're both ethical and impractical. I'd also like to emphasize that the vast majority of patients that we know of are already symptomatic, again, because of the delay in diagnosis.

(01:34:39):

We have nothing to help them other than symptomatic relief, and so, having therapy development for this very challenging cohort, which is the vast majority of our patients, is something we should really be working towards. Although my dream is newborn screening and a curative or near curative disease modifying therapy earlier, that's not the majority of the population we have and need to help right now. I think we need to be working towards both directions.

James Valentine, JD, MHS (01:35:08):

Sure. Well, thank you all for reflecting on that and thank you Dr. Ezzeldin for that question. One final question that I'd like to raise for discussion as part of this broader discussion we're having about a patient-focused research agenda for drug development is something that Dr. Burton raised a little earlier, but very much resonates with what we heard from patients and caregivers at the PFDD, which raised a couple of different equity type concerns and issues. One of those was related to regional inequity and access to effective gene therapy and extrapolating from that, the possibility of patients with more or less financial means having access versus those who may not, but then also...

(01:36:08):

I think this also was mentioned by one of our panelists, inequity even in terms of accessing trial sites and expanded access within the United States, just given the limited number of expert trial sites that we have in MLD. What I'd like to ask our panel here is, is this, one, something that you agree with that there are these inequities? If so, do you have any ideas or see any opportunities for how we can collectively move forward to try to address some of these inequities? I'll just ask for this one, maybe to start, does anyone with a wave of a hand want to want kick us off? All right, Dr. Orchard, you go first, then we'll go to Dr. Vanderver.

Paul Orchard, MD (01:36:55):

I think there's a couple of considerations here. In the first place, there're biologic inequities too. We're looking for donors for patients if we're going to consider allogeneic transplantation. If you're looking for an unrelated donor, we can find a match donor for about 80% of the Caucasian population and about 50% of the Hispanic population and about 30 or 35% of the Black population. If you're going to mandate that somebody needs to get a transplant, then those issues end up being important as well, because if you're forcing someone to get a mismatched unrelated transplant, mortality just goes up from there as one might expect.

(01:37:44):

The other thing is it's much less burdensome on the family to offer autologous transplant with gene therapy than it is to do allogeneic transplant. There's many more complications. We require the families to be here longer. That's an issue too, and I think it's important to understand as well that there's a lot of transplant centers in the US, but if you're going to have a finite number of centers that would be offering a gene therapy trial, people would have to travel to get gene therapy, but they wouldn't necessarily have to travel to get their allogeneic transplant. They could stay much closer to home.

(01:38:24):

If people were, for instance, randomized to get allogeneic transplant, I would be concerned that they would say, "Well, I don't want to go through this far away from home. I can get my allo transplant two hours from here," and so, you may end up having people withdraw from your clinical trials because the difficulty for families to move somewhere for three or four months at a time is huge. We do what we can do to try to make that as easy on the families as possible, but it's extremely difficult. If you don't have a lot of resources to be able to help you do that, then that's going to skew your patient population somewhat as well.

James Valentine, JD, MHS (01:39:07):

Yeah. Thank you. Dr. Vanderver.

Adeline Vanderver, MD (01:39:13):

I was actually going to raise the same point about that biologic diversity piece, which I think is very important. I think another piece that we... May be in these complicated choices and rubrics that families are having to make when they're facing treatment decisions for their children that we haven't brought up yet are the other family members and in particular, the siblings of affected children. We follow several children in our clinic just right now.

(01:39:42):

This is literally a yesterday in-clinic issue and a week before in-clinic issue where you have siblings who are suffering from significant behavioral school-based difficulties because their parents have been absent from home, there might be an income difference and an income gap compared to what the family was experiencing before, because one parent has had to leave their work to care for the affected child, especially with these high morbidity interventions.

(01:40:10):

If you take that enormous burden on not just the affected child but on the family as a whole unit, and then you augment that with a difference in between a lower morbidity therapy and a higher morbidity therapy, you're just creating even more impact on those families to a point where it's just a degree of suffering for the entire family unit that becomes irrecoverable in some ways depending on the resources of the family.

(01:40:40):

That further impacts your diversity and equity issues because obviously, a family that's well resourced with tight family connections, with financial resources and with more socioeconomic wellbeing to begin with is better going to be able to withstand that compared to a family that might be less well-resourced at the beginning of this journey. It's going to make families have choices that are disparate as a result or have outcomes that are disparate as a result. I just think we need to think about not just the impact on the patient also as far as morbidity and mortality, but the entire family unit and their socioeconomic wellbeing.

James Valentine, JD, MHS (01:41:17):

Yeah. Thank you. Any other comments from our panel on this topic? Yes, Dr. Burton?

Barbara Burton, MD (01:41:25):

Yeah, I just want to say that we need expedited approval of new therapies for MLD to help address that equity issue. We just recently had a family who were able to pick up and move with their child and go to Milan and get gene therapy and another family that can barely get the transportation to come in for a clinic visit. When we have therapies that are approved in Europe, there's already a setup for tremendous inequities. I think we're desperate for therapies here. Families-

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Barbara Burton, MD (01:42:03):

I think we're desperate for therapies here. Families are desperate. We need to have expedited routes for approval for treatments for these diseases. We've already talked about the fact that these are patients and families that are willing to take on some risk of a therapy. They're willing to take on some risk that the therapy isn't really as efficacious as the preliminary data suggested is. Because without the therapy, their kids are going to die. It's 100% certain what's going to happen without it. If there's some uncertainty with it, that could be acceptable. I think we need to keep all of that in mind as we're looking at these new therapies. We need to get them out there now because kids are dying right now. They're going to be diagnosed today and they're going to go ahead and die because these families don't have the wherewithal to go to Milan. That's my big point.

James Valentine, JD, MHS (01:43:03):

Yeah. Well, I think that's a perfect place to end this first discussion of our day today. We hit on a wide ranging number of different patient-focused issues that were raised and talked about the implications of how that impacts clinical trials, drug development, and provability. At this stage, I'm going to turn it over to Maria to introduce our next topic of discussion.

Maria Kefalas, Ph.D (01:43:29):

Thank you, James. We're going to talk about one of the great ideas that came out of our PFDD was the urgent need for adult treatments and the enthusiasm, actually desperation to use, Dr. Burton's word, for

treatments for adults. We're going to have Mayo Clinic's Dr. Patterson, introduce some ideas and ways forward for doing this challenging, but absolutely, important research. Please let me introduce Dr. Patterson.

Marc Patterson, MD (01:44:03):

My name is Marc Patterson. I'm a child neurologist at Mayo Clinic in Rochester, Minnesota. I've had the privilege of participating in clinical research and caring for children with a variety of inherited metabolic diseases, particularly lysosomal diseases, including metachromatic leukodystrophy over the past 30 years. I appreciate the opportunity to speak to you today about adult onset metachromatic leukodystrophy. As you know, metachromatic leukodystrophy is an ultra rare lysosomal disorder associated with impaired activity of arylsulfatase A with subsequent accumulation of sulfatides in the central nervous system, peripheral nerves, urothelium, and gallbladder. As is the case for the majority of inherited metabolic diseases, the most severe phenotypes are associated with the most profound depression of enzyme activity and present in young children. In the case of metachromatic leukodystrophy, these presentations are dominated by motor dysfunction. Although cognitive decline is also a key feature of the illness, albeit one that may be difficult to measure in young children with substantial motor impairment. Patients with lesser degrees of reduced enzyme activity present later in life and have different phenotypes. Adult-onset disease accounts for about 10% of cases of metachromatic leukodystrophy. In other words, adults with metachromatic leukodystrophy represent a small and variable subgroup of this ultra rare disease. Two studies published in 2021 emphasized this point. An Italian cohort of 45 subjects with metachromatic leukodystrophy included four with adult-onset disease. A German study of 97 patients included just six with adult-onset disease. The majority of patients presenting in adulthood have predominant cognitive and/or psychiatric symptoms. Motor symptoms, when present at onset, predict a more rapid course, but more often do not appear until late in the course of adult-onset disease. It is worth noting in this regard that some juvenile- onset patients have predominant cognitive presentations without motor involvement and also tend to have a more slowly progressive course. Thus, the progression of metachromatic leukodystrophy is a function not only of age, but also of presenting predominant symptoms.

(01:46:50):

Adult-onset metachromatic leukodystrophy often presents mimicking schizophrenia or other major psychiatric illness. The psychiatric symptoms are often resistant to pharmacologic treatment adding substantially to the burden of this disease. Because metachromatic leukodystrophy is rare, the diagnosis is often missed sometimes for many years. In these circumstances, the slower progression of adult-onset disease may be outweighed by the large disease burden that is accumulated before the diagnosis is recognized. Because motor manifestations may be absent or subtle in adult-onset disease, the motor function-based instruments developed to measure disease progression in childhood-onset disease are typically not appropriate for adult-onset metachromatic leukodystrophy. Moreover, owing to the rarity and variability of presentation in adult-onset disease, it is not feasible to pursue traditional cohort studies for the development of standardized instruments. Instead, I would advocate for the use of tailored cognitive, psychiatric, adaptive, and quality of life measures to assess the burden of disease in adult metachromatic leukodystrophy. This is a situation where, for most patients, stabilization of disease progression and disease burden would be a realistic and attainable goal of disease-modifying therapy with patients serving as their own controls.

(01:48:27):

I would like to take this opportunity to emphasize that the burden of disease in metachromatic leukodystrophy is not confined to the effects on the individual with the illness. The social costs extend beyond the substantial direct expense of medical care to the opportunity costs or lost productivity, and participation by affected individuals plus the caregiver burden, which also includes opportunity costs and

psychosocial effects on caregivers and other family members. A recent international study of caregiver burden in metachromatic leukodystrophy published this year described the use of the EuroQol five-dimension instrument. The investigators found that caregivers suffered disproportionate anxiety or depression, and physical pain or discomfort confirming earlier studies in this disease. This is an important and often neglected aspect of the burden of neurodegenerative disorders, which I would argue should be taken into account in measuring the effects of therapy.

(01:49:33):

In addition to individualized clinical measures of the burden of disease in patients and caregivers, biomarkers offer complementary tools to assess disease progression and burden in adult metachromatic leukodystrophy. A Dutch study found that blood levels of neurofilament light chain and glial fibrillary acidic protein show great promise as non-invasive measures of disease burden and progression complementing findings in the cerebrospinal fluid. Similarly, a large cohort study of NMR based urinary metabolomics from tubing in identified N-acetyl-L-aspartic acid as a quantitative biomarker for neurodegeneration in metachromatic leukodystrophy. These developments are promising, but the challenge of adult onset metachromatic leukodystrophy remains substantial. There is no disease modifying therapy which is available to these patients. Hematopoietic stem cell transplantation, which may be helpful in presymptomatic or oligosymptomatic younger individuals is not applicable to symptomatic adults.

(01:50:40):

Now that a number of promising therapeutic modalities are under investigation in children and available in some jurisdictions, it is important that adults with metachromatic leukodystrophy also have the opportunity to receive the benefits of such therapies. I believe that we have an opportunity to forge a fruitful collaboration between the metachromatic leukodystrophy community and regulators by recognizing and embracing the unique qualities and challenges of adult metachromatic leukodystrophy in the fashion that I have briefly outline. I thank you again for the opportunity to participate today and look forward to the opportunity to continue to work together. Thank you.

James Valentine, JD, MHS (01:51:27):

Thank you so much, Dr. Patterson, for setting up this important discussion on opportunities for clinical trials and on adult onset MLD. Again, like Maria mentioned, this was just something that was such an important output from the PFDD meeting. We heard loud and clear that there's both an urgency for treatment, but also a huge degree of interest in this part of the population participating in clinical trials. So for this discussion, Dr. Patterson, you provided us a number of great ideas to get us started on how to address this unmet need and with the dearth of treatments and trials in MLD. So my question for the panel here is I want to keep this broad, whether it's something that's already been suggested by Dr. Patterson or something else, what do each of you see as the opportunities to help facilitate trials in this population? And Dr. Groeschel, perhaps for this session, we can kick it off starting with you.

Samuel Groeschel, MD, PhD (01:52:41):

Yes, it was a very good summary of the adult MLD from Marc Patterson which summarized or highlighted main points. I agree with everything that he said and can maybe underline again, it is probably, or it will be helpful to have good biomarkers and some were already mentioned, but also to understand better MRI changes because in the adult population you have already early MRI changes before onset of first symptoms, and that to really be able to detect any meaningful change in these trials and to be able to also use this as so get outcome measure. This is probably ... I just think that this is an important point that can help.

James Valentine, JD, MHS (01:54:22):

And Dr. Groeschel, just to follow up on that, do you see use of surrogate biomarkers that might inform an accelerated approval? Do you see that helping with specifically the challenge of just the slowly progressing nature of adult onset MLD and therefore the amount of time and follow up it would take to see clinical outcome differences? Or is it at all related to some of the variability in the clinical course from one adult onset patient to the next? Just trying to understand what is it that you think this helps solve, this kind of consideration of surrogate biomarkers?

Samuel Groeschel, MD, PhD (01:55:06):

Yes. One is to have endpoints to maybe see this, measure this stabilization that we want to achieve. And the other thing is also to understand this viability very early and to have realistic aims for treatment and to better predict these viable courses in the adult forms of MLD. As Mark Patterson said, there is early symptoms that can help, but then there's to detect these cognitive, more slowly progressing forms, but we also know from, or we hope to know with biomarkers, with imaging patterns or imaging parameters to understand, to predict this because there are also adult forms, as has been that they're not so slowly progressive. They can also have then within, but then a shorter timeframe motor function loss and deterioration. So, that would be important to predict that.

James Valentine, JD, MHS (01:56:48):

Sure. Thank you so much, Dr. Adang, maybe we can come to you next. Again, trying to brainstorm here, what are opportunities that we have to help overcome some of those challenges that Dr. Patterson so nicely outlined?

Laura Adang, MD, PhD (01:57:02):

Yeah, thank you Samuel for your summary. I would agree with everything that you said. I think the key is really using surrogate endpoints in the later forms of disease. And we have a threshold for rare diseases where MLD is both serious and life threatening. And that's true for the adult onset forms as well. It's just the chronicity of the disease and how it changes is slower than it is for the ultra rapid early forms of disease. And so using things like the established biomarkers, we have both the MRI biomarkers, but also even just the enzymatic biomarkers where we know that enzyme levels correlate with disease severity. And really using that as a surrogate endpoint for accelerated approval is an opportunity for us to be able to design a feasible clinical trial for the adult onset patients where we're not requiring 10, 15 years of disease evolution. So I think there are opportunities for us to use the guidance the FDA has provided us to design a feasible trial with appropriate surrogate endpoints.

James Valentine, JD, MHS (01:58:13):

Yeah. Thank you so much. Dr. Burton, would love your views on this topic as well.

Barbara Burton, MD (01:58:24):

I think I can be fairly short and sweet and just say that I agree with everything that's been said basically. I think the use of surrogate endpoints would be very important in a slowly progressive form like this. And I like the idea that we got from Mark about using the patients as their own controls, although that needs to be carefully considered and we need very, very careful guidelines in establishing that type of a design. But yes, I think we've had very good comments across the board.

James Valentine, JD, MHS (01:59:05):

Great. Thank you. Dr. Orchard, what opportunities do we have as we're thinking about clinical trials in adult MLD?

Paul Orchard, MD (01:59:18):

Well, so we'd be excited to be able to offer something to these patients. I mean, we've done transplant in at least several of the patients, outcomes haven't been great. And as people have mentioned, it's difficult to assess their progression. A lot of these patients are diagnosed in their early twenties, for instance, and it's unclear how quickly they're progressing. So any biomarkers that might help us with the extent of the disease or the rate of progression of the disease that might help us better understand the trajectory would be really useful. So I'm all in and trying to explore some of these biomarkers, whether they're plasma based or CSF based or imaging based or some combination of all of those to help us in designing these clinical trials, but we need to have something to offer these families. I think they've clearly made that point, and at least for now, [inaudible 02:00:25] transplant is the only thing out there, and I don't think any of us are excited about that in the future.

James Valentine, JD, MHS (02:00:31):

Sure. Dr. Vanderver, the final comment on this question of what do you see as some opportunities for this population?

Adeline Vanderver, MD (02:00:40):

Yeah, so I think I want to go back to the points that were made about the difficulty in understanding how to measure outcomes in the adult onset patients. And I think in order to frame that, I just want to remind everybody that this is a genetic disease that starts at birth in everybody. When you're actually manifesting symptoms is variable. And in the early onset patients, we know, again, the disease starts at birth. They have a period of development that might not meet completely typical trajectory, and then at some point there's a rapid decline. But the variability in that, because it's very early onset, is very limited, very predictable and very understandable. And that variability is measured within really a very tight window. The further away you get from that, obviously this disease has been progressing in these people their entire lives. They've been clinically progressing, but it's been progressing.

(02:01:34):

So the ideal situation for a clinical trial is you start everybody at the same start point. Everybody's hits go at the same time and you compare treatment versus non-treatment, but everybody's running the same race, but in adults, MLD, people are not running the same race because you don't know really when they've had pre-morbid subclinical presentation, especially of behavioral circumstances that can go on undetected for years, be attributed to just a quirky personality or a clumsiness. And then you really don't know when they get to clinical attention. You don't know when they started their race. You know it started at birth, but you don't know really when they started. So the ability in that circumstance to imagine that you're going to have a well-designed cohort controlled study is just not biologically feasible. And so you have to come up with adaptive approaches where you have to use either larger cohort studies of patients who are larger comparative groups that are not within the numbers feasible in a clinical trial setting as non concurrent controls. You have to use surrogate markers to try to get a sense of biologic possibility. And you have to metric things based on the own patient because anything else just doesn't physiologically work.

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

Yeah. Well, thank you. I do want to recognize Barbara [inaudible 02:02:50], an MLD mom who's written in with some questions that relate to the impacts of the adult onset being more slowly progressive and I hope that this discussion has helped answer some of your questions. I do want to follow up with our panel on this discussion, particularly around the possibility of accelerated approval, because if we get to a point where there is accelerated approval, one thing that's necessary is confirmation of clinical benefit. That of course is deferred post-approval through a confirmatory study that would be done in that setting, but we heard from Larry's summary, and I think this was even commented on a little earlier from this panel, that there's some differences in what are those primary key clinical manifestations that are most bothersome shifting really from in the earlier onsets motor for the later onset being cognition or perhaps behavior, some other things. And so I just like to invite volunteers to comment on, do you think we have tools that can evaluate those important aspects of the adult onset experience you that we could use an employ in a post-approval setting that would confirm benefit? Any takers from our panel on that? Just give me a little wave of a hand, although I might just pick on you then. So, all right, Dr. Adang. Thank you.

Laura Adang, MD, PhD (02:04:21):

I'm happy to talk on that. No, I think it is challenging because you are measuring something much more heterogeneous. The way the adult onset affects neurocognitive function manifests in different people, even if the pathophysiology is different. It can be more of a schizophrenia like phenotype or more depression like phenotype, I think to some of the clinical studies that have been done on the psychosocial impact long term of epilepsy, where they looked at job stability, marital stability, ability to complete higher level job performance skills. So I think there are ways, and I love Dr. Patterson's idea of doing more quality of life measures in looking at the day to day burden on how the adaptive skills are affected. We can measure things like motor function quite easily with great validated scales, but in the adult onset population, I think we need to reference back to what the families and patients are talking about, which is really the cognitive skills, the behavior function. We need validated skills to measure things that are outside of our typical MLD box, but pulling in more things in diseases such as dementia that have had validated outcome measures that have worked quite well to measure these more chronic diseases and how that disability progresses over time.

James Valentine, JD, MHS (02:05:53):

Sure. Thank you Dr. Adang. Any other thoughts from our panel on opportunities for those that confirming clinical data benefit when we get to that stage post and accelerated approval?

Paul Orchard, MD (02:06:07):

Well, it's definitely challenging, but I mean there are measures of executive function and whatnot that one can, and I'm no neuropsychologist clearly, but there are ways to get at those types of things. Part of the challenge here is that different patients are going to present in different ways and have different challenges. So it's not likely to be a uniform way of getting data that's going to be meaningful in every patient, but there are mechanisms to look at those types of things and potentially correlate those to biomarkers or imaging or other aspects of the disease as well. So I think it would be important to give some thought as to how we might do that. And again, having some of the neuropsychologists or others that are more adept at this weigh in on that would be useful.

James Valentine, JD, MHS (02:06:59):

Absolutely. Yeah, Dr. Vanderver.

Adeline Vanderver, MD (02:07:02):

Yeah. And here I think it might be good also to hear from Dr. Groeschel, but while we've talked a lot about the neurocognitive pieces and the challenges and providing metrics around that and the progression around that, a lot of these patients do ultimately develop also mobility issues. And so if you had an open-ended amount of time, and given some of the work that Dr. Groeschel's group has done on measuring, once motor and mobility impairment begins, how rapidly it can set in also sort of tracking those mobility challenges, which are sometimes easier to be objective about and easier to quantify, and getting a sense of whether or not you maintain physical independence in these individuals, I think would be both clinically meaningful and perhaps easier to measure in the long run as well. It would be hard to fit within the timeframe of a short trial, but once you have an open-ended observation period, easier to engage with.

James Valentine, JD, MHS (02:08:06):

Sure. And Dr. Groeschel, would you like to follow up on that? Since in that case, I didn't call on you, but Dr. Vanderver did.

Samuel Groeschel, MD, PhD (02:08:16):

Yeah. Yes, I totally agree with that. So to include cognitive and quality of life and other measures is even more important in the adult onset forms, but they also develop motor function issues at some point, and that's why this also has to be included. Yeah.

James Valentine, JD, MHS (02:08:51):

Yeah. Well, I want to thank all of you so much for the discussion today. The goal was not to come up with the answers to every one of these challenges, but to really begin to outline some options and opportunities for clinical trials and MLD moving forward. And I personally think that we accomplished that goal today, and I think our hope collectively is that this will be the start of an ongoing discussion with multiple stakeholders around these exact issues. So with that, I'm going to turn it over to Maria, who will be closing out the meeting.

Maria Kefalas, Ph.D (02:09:28):

Thank you, James. Thank you everyone. Thank you to all our panelists. Today's conversation has been a powerful way to integrate the perspectives we heard from the October 21st MLDELPFDD meeting into guidance for future MLD research and therapeutic development. Once we conclude, this program will be available immediately at the same webpage you're at now. We couldn't have done this meeting without our expert clinicians. Thank you to Dr. Laura Adang, Dr. Adeline Vanderver, Dr. Marc Patterson, Dr. Samuel Groeschel, Dr. Barbara Burton, and Dr. Paul Orchard. I would like to thank the FDA for allowing us to hold this novel addendum to our ELPFDD. We're incredibly grateful for everyone who turned out on October 21st and joined us today. We thought it was important to reflect on the tremendous input that our community provided to ensure that drug development and clinical trials are best supporting the needs of our patient community.

(02:10:28):

The insights our expert clinicians provided really did justice to these needs. Thank you to Larry Bauer and James Valentine for their participation in today's meeting and their guidance throughout the entire PFDD process. I'd like to take a few moments to summarize a few important points from what we heard today. Number one, the kinds of improvements we heard from gene therapy families at the PFDD meeting, which dramatically deviate from the natural history of early onset MLD are not the kinds of things that we need to measure against a concurrent control. Our patient families see the outcomes as life saving

and life changing. This is miraculous. Number two, patient families raise concerns about the morbidity and mortality of bone marrow transplants during the ELPFDD. Our experts explained that BMT is not standard of care in the early onset MLD population, not only because of safety issues, but also because of a lack of demonstrated efficacy.

(02:11:28):

As an advocate for a decade, I have never referred such a patient to a BMT. Indeed, we have worked tirelessly to get this population of patients to clinical trials. Number three, we heard today that we have an opportunity to leverage years of patient data that represent the natural history, given our strong understanding of the genotype phenotype relationship and other markers of progression for early onset MLD. As a patient community, we have tremendous faith in the expert clinicians we heard from today to diagnose MLD and refer eligible patients to the best treatments and clinical trials when appropriate. And number four, we heard loud and clear from the adult onset MLD community that they have also have unmet needs. Today, our experts put forth some valuable ideas that can help facilitate therapeutic development in this population, including biomarkers and accelerated approval. While all of these items present great opportunities to further MLD research, we can't forget to acknowledge the devastating unmet need of patients who need treatments now.

(02:12:38):

It has been eight months since the death of my daughter Cal, and my friends and family often ask me, why put myself through the pain and trauma of advocating for treatments and speaking to regulators when my child will never benefit. The answer for myself and all the other families you heard from today is that we are desperate to honor our loved ones by sharing our stories. More than anything else, I want to see a future where children and parents do not need to endure what my family have endured. That is why I am here speaking to you today. And I hope and pray if nothing else comes out of this meeting that our partners at FDA come to recognize the dedication of the doctors and scientists who have studied this disease and the tremendous knowledge we have harnessed for clinical trials. The patient community believes strongly that researchers have assembled all the tools they need to demonstrate the efficacy and safety of treatments.

(02:13:33):

Moreover, I want the FDA to remember the incredible unmet need. Two years ago, my husband died of cancer and as awful as his suffering was, it could not even touch what MLD patients like my daughter endure. The that the number that haunts me is that over a decade of living with MLD, my daughter Cal had 1,720 contacts with providers. I want you to take a moment to ponder the pain, suffering, and burden that number signifies. We simply cannot wait. We are ready to change what it means to have MLD. And finally, one last heartfelt thanks goes out to everyone who attended the ELPFDD and today's program. We look forward to moving forward, moving closer to newer and better therapies for the entire MLD community. Thank you.

PART 4 OF 4 ENDS [02:15:27]