Metachromatic Leukodystrophy (MLD) Voice of the Patient Report

Incorporating outcomes from both:

MLD Externally-Led Patient Focused Drug Development (EL-PFDD) Meeting - October 21, 2022
Adjunct MLD Scientific Meeting: Integration of the Patient Perspective into Therapy Development for MLD - November 18, 2022

Meeting hosted by: Cure MLD, The Calliope Joy Foundation, MLD Foundation, The United Leukodystrophy Foundation and the Global Leukodystrophy Initiative

Submitted to: The U.S. Food and Drug Administration (FDA)

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Metachromatic Leukodystrophy *Voice of the Patient* Report

The Metachromatic Leukodystrophy (MLD) Externally-Led Patient Focused Drug Development (EL-PFDD) meeting was organized and hosted by a collaboration of MLD patient advocacy groups and researchers including Cure MLD, The Calliope Joy Foundation, MLD Foundation, The United Leukodystrophy Foundation (ULF), and the Global Leukodystrophy Initiative (GLIA). This *Voice of the Patient* report was prepared on behalf of these organizations as a summary of the insights shared by patients and families during the MLD EL-PFDD meeting conducted virtually on October 21, 2022. This report also contains expert reflections gathered at the Adjunct MLD Scientific Meeting on November 18, 2022, where a panel of MLD expert clinicians reacted to the issues, needs, hopes, and desires raised by families at the MLD EL-PFDD meeting.

Authors and Collaborators: This report was prepared and submitted on behalf of MLD Foundation, ULF, The Calliope Joy Foundation, GLIA and Cure MLD, by Maria Kefalas, PhD, founder of The Calliope Joy Foundation, Melanie Rumbel and Marly McGowan, Program Managers, Cure MLD, Dean Suhr, co-founder and president of MLD Foundation, and Teryn Suhr, co-founder and Executive Director of MLD Foundation. Cure MLD contracted with Chrystal Palaty from Metaphase Health Research Consulting Inc. for assistance in writing this report.

Consulting Partners include James Valentine, Esq., and Larry Bauer, RN, MA, from Hyman, Phelps & McNamara, P.C.

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Dedication:

The EL-PFDD and this *Voice of the Patient* report are dedicated to Calliope Joy, whom we have lost to MLD, who we dearly love and deeply miss, as well as all of those affected with MLD – past, present, and yet to come – and their families. It is our sincere desire that the information and passion expressed by families in this report is impactful and will be put to good use to improve the lives of MLD patients and their families.

"Our families have taught me that miracles do not happen because we wish for them or pray for them, or even because we deserve them. They must be earned through sacrifice and hard work. And I believe our families have suffered and sacrificed enough. We have earned our miracle." - Maria Kefalas

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Executive Summary and Key MLD Meeting Insights

The Metachromatic Leukodystrophy (MLD) Externally-Led Patient Focused Drug Development (EL-PFDD) meeting held on October 21, 2022 was organized and hosted by a collaboration of MLD patient advocacy groups and researchers. The meeting represented an important opportunity for the MLD community to share patient, family and caregiver perspectives on the challenges and unmet treatment needs of those who live with MLD every day.

MLD is a devastating and relentlessly progressive neurological disease, affecting the entire body. Most patients with this lysosomal storage disorder live less than a decade after diagnosis. Early presenting MLD subtypes are the most severe and predictable forms of the disease and progress most rapidly, often presenting with motor dysfunction first. Eventually, these children become "locked in" and depend on their caregivers for everything. The late onset MLD subtypes often initially present with behavior challenges and cognitive impairment in adolescents and adults, with a slower and more unpredictable progression.

As part of the EL-PFDD process, an Adjunct MLD Scientific Meeting, "*Integration of the patient perspective into therapy development for MLD",* was held on November 18th, 2022. At this meeting, key MLD clinical and research experts discussed the issues identified by the families during the EL-PFDD meeting. Both the October and November 2022 meetings were held virtually to enable as many community members to participate as possible and to allow many different voices to be heard.

The patient and caregiver perspectives gathered from the October 21st EL-PFDD meeting are summarized in this *Voice of the Patient* report and highlighted with expert reflections gathered at the November 18th Adjunct MLD Scientific Meeting. The information in the *Voice of the Patient* report may be used to guide therapeutic development and inform the FDA and other regulatory partners' benefit-risk evaluations when assessing therapies to address MLD. The hope is that this information will catalyze earlier diagnosis, more efficacious treatments, and ultimately a cure for all those affected by MLD.

Cure MLD, The Calliope Joy Foundation, MLD Foundation, ULF and GLIA have provided this report to the FDA, government agencies, regulatory authorities, medical products developers, researchers, academics, and clinicians, and it is publicly available for the many stakeholders in the MLD community.

The following MLD themes and insights were distilled from both the October 21, 2022 MLD EL-PFDD meeting and the November 18, 2022 Adjunct MLD Scientific meeting:

Key MLD EL-PFDD Meeting Insights

1. **Metachromatic leukodystrophy, or MLD, is a rare and progressive neurologic disease with devastating impacts**. Most patients with this lysosomal storage disorder live less than a decade after diagnosis. Some families include multiple affected family members.
2. **Unfortunately, most MLD families endure long diagnostic odysseys, with an MLD diagnosis made long after the appearance of initial symptoms which prevents access to viable therapies**. Earlier forms of MLD usually present first as mobility challenges, and progress rapidly from onset. Later presenting forms of MLD are less predictable, generally first presenting with cognitive and behavioral changes which may be initially hard to recognize as MLD.
3. **Most MLD patients experience devastating symptoms including regression, a loss of communication, impaired mobility and balance challenges, feeding and GI motility, and cognitive and behavioral challenges**. Additional MLD symptoms include muscle tone issues, muscle cramps, seizures, pain and irritability, respiratory issues, vision issues, incontinence, anxiety, depression, fatigue, gallbladder abnormalities, fine motor issues, drooling, temperature regulation, neuropathy, renal issues, and scoliosis.
4. **Earlier diagnosis is necessary.** Newborn screening for MLD will ensure that children with MLD can be identified presymptomatically and be eligible for life-saving gene therapy, among other potentially curative therapies. For all other patients, the time from the first symptoms to diagnosis must be shortened so that patients will gain more benefit from earlier therapeutic intervention.
5. **MLD profoundly impacts quality of life for patients and their entire families.** Patients are completely dependent on their caregivers, and most cannot be left unattended. Younger patients are at risk of aspirating and choking. Older patients are socially isolated and a risk to themselves. Caregivers worry that their loved one will be unable to breathe and will die prematurely, that their loved one will experience uncontrolled pain, and that communication and responsiveness will decrease.
6. **Disease modifying therapies for MLD now exist and when delivered early, are potentially life-changing.** Gene therapies and enzyme-replacement therapies now offer hope; however, only presymptomatic and minimally symptomatic patients are eligible. Financial and geographic barriers result in treatment inequity. During the EL-PFDD meeting, many parents compared the lives of siblings who received therapy with those who had not.
7. **There is an urgent need for treatments for MLD patients across the spectrum of disease, especially for those who are already symptomatic, including adult patients**. Currently, patients rely on a very large number of different treatments and medications to control and manage symptoms and for comfort at the end of life. These palliative care options are not curative and will not slow or stop the progression of MLD.
8. **Leveraging existing data and using novel clinical trial designs will allow more MLD patients to be treated.** Experts recommended methods for measuring meaningful improvement in systematic patients such as non-comparator trials with historical patient data or using patients as their own controls.

Metachromatic leukodystrophy overview and treatment landscape[1]

Metachromatic leukodystrophy, or MLD, is a relentlessly progressive neurological disease, affecting the entire body. This ultra-rare lysosomal storage disease is caused by reduced activity of arylsulfatase A (ARSA), a lysosomal enzyme. Low ARSA activity results in an accumulation of sulfatides in the central nervous system, peripheral nerves, urothelium and gallbladder.

MLD is a genetic disease that starts at birth for all patients. Genotype-phenotype correlations for MLD are well established, with many genetic variants well described in the literature. The disease has four subtypes differing by the level of ARSA impairment, which influences age of onset, severity, and heterogeneity in disease course. Early onset MLD subtypes have the most severe phenotypes and are caused by a profound impairment of ARSA activity, while the late onset MLD subtypes present later in life, have less severe subtypes and lesser degrees of ARSA activity depression. The four subtypes present and are detailed as:

- **Late infantile MLD**. This is the most common and the most severe form of MLD, typically caused by two null variants, resulting in no to very little ARSA enzyme activity. Onset is early, with the first symptoms manifesting before two and a half years of age, typically are observed between 12 and 18 months. Following a typical developmental trajectory, children begin to experience motor dysfunction, and difficulties with sitting and walking. This is followed by a rapid and severe loss of neurologic function, and a plethora of other symptoms described later in this report. This MLD subtype has a very narrow window of disease onset, a homogenous disease course with little variation in symptoms and outcomes between patients.
- **Early juvenile MLD**. This subtype presents between two and a half and eight years of age and is also considered an early onset form of MLD. Individuals experience a rapid onset of motor symptoms followed by a rapid decline. The age of onset, symptomatology, and rate of disease progression vary more than with late infantile MLD.
- **Late juvenile MLD.** Symptom onset in late juvenile patients generally presents between eight and 16 years of age. Juvenile patients typically have one null variant with some residual enzyme activity. These patients experience cognitive symptoms upon initial presentation followed by motor skill loss, and have a slower and more variable disease progression compared to late infantile and early juvenile patients.
- **Adult onset MLD**. Patients with this MLD subtype are a small and variable subgroup, accounting for an estimated 10% of MLD cases. It is likely that more adult patients exist, yet are undiagnosed or misdiagnosed. Adult patients typically have two ARSA alleles with residual enzyme activity. The first symptoms, which are often cognitive or behavioral in nature, can emerge anytime from the age of 16 years until well into adulthood. Symptoms

[1] Adapted from presentations delivered at the EL-PFDD by **Dr. Laura Adang** and **Dr. Adeline Vanderver,** and the Adjunct MLD Scientific Meeting by **Dr. Marc Patterson.**

can manifest as personality changes or anxiety and often mimic schizophrenia or another major psychiatric illness, including depression. Motor symptoms, when present at onset, predict a more rapid course, but usually do not appear until late in the course of adult onset disease. Although adult patients experience a slower and much more variable disease progression compared to other subtypes, a large disease burden usually accumulates before diagnosis. As with the other subtypes, those with adult onset MLD also die prematurely.

MLD diagnosis is relatively straightforward, consisting of both biochemical and genetic analyses. Biochemically, the levels of urinary sulfatides and ARSA enzyme activity are measured, and the *ARSA* gene is sequenced. The classic diffuse demyelination observed with MLD can be visualized with MRI. However, prior to an official MLD diagnosis, patients are often in the medical system for months, presenting to multiple specialists including orthopedics, neurology, ophthalmology.

Historically, the only treatment option for MLD was hematopoietic stem cell transplant (HSCT), with variable results, particularly in early onset MLD subtypes. More recent MLD treatment and management approaches include gene therapy and enzyme replacement therapy through intrathecal delivery, but these therapies are typically limited to pre- or early-symptomatic patients. Gene therapy was approved by the European Medicines Agency in 2021 and has Pre-Approval Access status in the United States. The therapeutic options for symptomatic patients and patients with later onset MLD remain very limited, even in the context of clinical trials.

Overview of the meetings and this report

MLD EL-PDFF, October 21, 2022

The Metachromatic Leukodystrophy (MLD) Externally-Led Patient Focused Drug Development (EL-PFDD) meeting held on October 21, 2022 was organized and hosted by a collaboration of MLD patient advocacy groups including Cure MLD, The Calliope Joy Foundation, MLD Foundation, ULF and GLIA. The meeting represented an important opportunity for the MLD community to share patient, family and caregiver perspectives on the challenges and unmet treatment needs of those who live with MLD every day. Panelists, callers, and discussion included all forms of MLD as well as families with and without various therapies. The meeting agenda is in **Appendix 1**, meeting demographics are shown in **Appendix 2**, meeting discussion questions are in **Appendix 3**, names of panelists and callers are listed in **Appendix 4**, and online polling results from Topics 1 and 2 are included in **Appendix 5**. To include as many voices as possible, an online comment submission portal was open for four weeks after the meeting. Selected comments are included in the body of this *Voice of the Patient* report, and all submitted comments are included in a separate PDF.

Adjunct MLD Scientific Meeting, November 18, 2022

A follow-up scientific meeting, entitled "*Integration of the Patient Perspective into Therapy Development for MLD*" was held on November 18th, 2022. This meeting enabled a panel of MLD experts to 1) reflect on the patient perspectives that were shared at the October 21, 2022 MLD EL-PFDD meeting, and to 2) share the available tools and potential opportunities to ensure that drug development and clinical trials best support the needs of MLD patients. Expert Reflections derived from comments made during the Adjunct MLD Scientific Meeting are included in **Appendix 6.** The Adjunct MLD Scientific Meeting agenda is in **Appendix 7**, and biographies of the expert clinicians and researchers are listed in **Appendix 8**.

Voice of the Patient report

The patient and caregiver perspectives gathered from the October 21, 2022 EL-PFDD meeting are summarized in this *Voice of the Patient* report. Key points and discussion outcomes from this meeting are included as "Expert Reflections" throughout this report. The information in the *Voice of the Patient* report may be used to guide therapeutic development and inform the FDA and other regulatory partners' benefit-risk evaluations when assessing therapies to address MLD. The hope is that this information will catalyze earlier diagnosis, more efficacious treatments, and ultimately a cure for all those affected by MLD.

Cure MLD, The Calliope Joy Foundation, MLD Foundation, ULF and GLIA have provided this report to the FDA, government agencies, regulatory authorities, medical products developers, researchers, academics, and clinicians, and it is publicly available for the many stakeholders in the MLD community. The input received from the October 21, 2022, EL-PFDD meeting reflects a wide range of MLD experiences, however not all symptoms and impacts may be captured. The final *Voice of the Patient* report, an accompanying PDF document of submitted comments, as well as videos of both meetings and meeting transcripts are available at https://MLDpfdd.org/.

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TOPIC 1: Living with MLD – Symptoms and Daily Impact of MLD

During the EL-PFDD meeting, patients and caregivers shared their experiences of living with MLD, the impacts of the disease on their daily lives, and worries for the future. During the meeting, several key themes emerged that were not captured via the polls. Key themes, online poll results, and selected patient and caregiver quotes are presented below.

Key Theme: Most MLD families endure long diagnostic odysseys, with an MLD diagnosis made long after the appearance of initial symptoms. Earlier onset forms of MLD are characterized by mobility challenges and relentless progression from onset. Children are sometimes initially misdiagnosed with cerebral palsy or ADHD. Parents are devastated to find that there are no therapies to cure the disease or halt disease progression once symptoms appeared.

> "*Loie was initially diagnosed with cerebral palsy and when the symptoms seemed to be getting worse during her second year, the doctors conducted additional testing. …We received the MLD diagnosis and were told to spend as much quality time together with Loie as she would likely not live beyond the age of five. No treatment options were available for our beautiful daughter*." – Matthew, father of Loie, who passed away at the age of three and a half years from late infantile MLD
>
> Following a nine-month odyssey, *"We received her MLD diagnosis the day after her second birthday. Within a month, she had lost her remaining milestones. Adeline had no treatment options available since she was too far progressed. We have watched as MLD has stolen more and more from her. She now suffers from chronic respiratory failure, seizures, is non-ambulatory, can no longer speak and is completely dependent upon us for everything*."- Victoria, mother of two children living with late infantile MLD, two-year-old Oliver who received gene therapy and six-year-old Adeline who did not

Key Theme: Diagnosis of adult onset MLD is also protracted, as adults present with bewildering cognitive and behavioral symptoms often misdiagnosed as mental health challenges. Adult onset disease has a slower progression and adults suffer for years or decades before receiving an MLD diagnosis. Tragically, some are not diagnosed until after they have children of their own.

> Joel is 42 years old. *"He first showed symptoms of MLD at age 24 with changes in his behavior. He would forget how to do things he once knew how to do or would have inappropriate behavior in public. He became withdrawn and was not his normal, funny, happy, and witty self. He would get lost when driving and was unable to hold a job after a while*." - Heather, 35-year-old sister of Joel and one of four siblings living with adult onset MLD

"My daughter was a competitive dancer, varsity athlete, award-winning artist and high achieving student who graduated with honors from high school. At age 16 with plans of becoming a surgeon, we saw social awkwardness and difficulty remembering or discerning truth versus something she thought about. Now, she cannot draw a smiley face, retain what she reads, follow steps, like getting dressed or remember things from one moment to the next. She cannot live independently, and we grieve what she has lost and worry about the future progression." - Debbie, mother of a 22-year-old daughter Alyssa with late juvenile/adult onset MLD

"Kris went 15 years misdiagnosed. From age 18 to 33, she was diagnosed with various mental health disorders - and on various medications. Not one psychiatrist suggested there could be a physical cause for the cognitive symptoms she was displaying as well as changes in her personality, academic, and athletic ability." - Mary, mother of 43-year-old adult daughter, Kris living with adult onset MLD

Poll Q1 & Q2

MLD is a devastating disease, characterized by regression, a loss of speech/communication, mobility/balance issues and many other symptoms.

Meeting attendees used online polling to select all the MLD-related health challenges that they or their loved one experienced, and then to select the three most troublesome. Each MLD symptom alone is devastating, and yet poll respondents selected an average of *nine* symptoms that their loved one experienced. Poll results are in **Appendix 5**, **Q1** and **Q2**. Each of these symptoms profoundly impacts activities of daily life, so many of these impacts are also included below with patient quotes.

Regression is a defining characteristic of MLD

Although not included as a poll response option, regression was mentioned by almost every speaker and is one of the most devastating aspects of this disease. Patients with earlier presenting forms of the disease experience very rapid regression, losing all voluntary movement and requiring complete care in a short period of time.

"Shortly after Loie's diagnosis, her health started to rapidly decline. She lost the ability to walk, talk, sit up, and eat through her mouth." - Lauren, mother of Loie, who passed away at the age of three and a half from late infantile MLD

"At the time of diagnosis [at age three], we already had witnessed Liviana, our once vibrant, hilarious, beautiful daughter regressing in abilities at a startling pace. Our child, who started walking at 11 months old, suddenly struggled to walk across the room, scooting on the ground instead. Her early and impressive vocabulary was dwindling rapidly." - Amy P., mother of three children with late infantile MLD, 12-year-old

Giovanni and eight-year-old Cecilia who both received gene therapy and Liviana with no therapies who passed away at the age of five

"*MLD came suddenly and dramatically to our family. One year was all the time it took from the onset of first symptoms to being fully caregiver dependent. … His diagnosis of a degenerative terminal condition was shocking and the knowledge that there were only symptom management therapies available heartbreaking."* - George, father of 11-year-old Ronan, living with early juvenile MLD

Horrifyingly, many MLD patients are aware of their regression and loss of abilities.

"*Before losing his speech, Ronan was aware that his life was changing and he shared how frustrating and sad he was at losing his abilities. Upon reflection, I think he knew for some time before we did, that he was facing a challenge, unlike those around him*."- George, father of 11-year-old Ronan, living with early juvenile MLD

"Amelia lived for eight years as a healthy girl until she started having difficulty in school and then led to difficulty walking. We are watching our daughter slowly die. Our daughter is upset. Amelia does not understand why her legs used to work and now they do not. …This is cruel and inhumane to watch our daughter go through this with no available medication." - Krystle, mother of 10-year-old Amelia, living with early juvenile MLD

"I've had dark and fearful moments of not wanting to live. I'm wholly aware of what has happened, what can happen, and what is to come with this disease. I've lost a brother to MLD and I'm watching two more wither away. There's not a day that goes by that I don't wake up and think about MLD. I struggle with the knowledge and everyday moments are impacted." - Heather, a 35-year-old woman, one of four siblings living with adult onset MLD

Mobility/ balance impairments

Loss of mobility and balance is often the first symptom of early onset MLD. Patients experience challenges with ambulation, loss of floor mobility and then the inability to sit upright. Some parents also described tremors and the loss of fine motor skills.

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

"*His gait had changed, and he began intermittent toe walking. His fine motor coordination was becoming noticeably impaired. It was apparent that this was not ADHD*." - George, father of 11-year-old Ronan, living with early juvenile MLD

Willow's first symptoms were mobility challenges. "*Before the diagnosis, we noticed Willow was always very clumsy. She would stumble when walking or fall off of her stool. In daycare, she occasionally got accident reports where she fell into the bushes or hit her head*." - Michelle, mother of six-year-old Willow living with early juvenile MLD

IMPACTS: Mobility/Balance. The inability to walk impacts all activities of daily living including outdoor activities, recreation, participation in sports and ultimately independence. Diminishing mobility skills can impact the ability to socialize, form relationships or play with others.

"Physically, he had hiked four miles in June, he was diagnosed in July, and by October, he was fully wheelchair-bound. It was incredible how swiftly MLD removed Ronan's capabilities." - George, father of 11-year-old Ronan, living with early juvenile MLD

"*When I was eight years old in third grade, I had a little tremor in my hand when I was brushing my teeth or eating. I also had trouble stopping my bike when I was riding. I couldn't seem to hit the baseball that year because I always swung too late."*- Corrine, speaking on behalf of her son Trent, who passed away at the age of 29 from late juvenile MLD

Swallowing/Gastrointestinal Issues (GI)

For many living with MLD, challenges with feeding, swallowing or constipation, choking, low gut motility, and weight loss are their most troublesome symptoms. Swallowing issues can often lead to coughing and choking, and many eventually rely on gastric tubes for nutrition and hydration. Many described frequent vomiting.

"Insufficient swallowing is the scariest symptom because she could choke. Loss of muscle control compacts this significantly. In order to provide nutrition, Willow had a G-tube placed. …Even with preventative measures and use of scopolamine patches, we remain on 24-hour alert with a suction machine because of asphyxiation precaution." - Michelle, mother of six-year-old Willow living with early juvenile MLD

Loie experienced GI pain as she became intolerant to her formula. "*Within just six short weeks of diagnosis, Loie received a G-tube for feeding. … We struggled with motility, gas buildup, and a significant overgrowth of bacteria within her digestive system. … Loie would tolerate each formula for a few weeks until she could not. The GI issues would worsen each time. … All we wanted to do was feed Loie as she constantly struggled with pain and discomfort."* - Lauren, mother of Loie, who passed away at the age of three-and-a-half from late infantile MLD

"My son Cathal lived a short and painful life. … The most difficult symptoms he endured after his rapid decline, age two and three, were gut pain from digesting and passing his liquid feedings and the muscle spasticity he suffered from. He cried more than any child should." - Les, father of Cathal, who passed away at age six from late infantile MLD and Ciarán, who received gene therapy and is now six

"*Nutrition was a huge challenge with a slow gut motility. Every day was a constant battle to figure out if he was tolerating [his food], if we could be mixing it up by changing formulas, volume rate, et cetera*." - Kristin, mother of Grayson who passed away at five years old from late infantile MLD

IMPACTS: Swallowing/Gastrointestinal Issues (GI). The inability to eat affects the ability to eat together as a family and to socialize with others. Those with adult onset MLD also have challenges with understanding that they are hungry or are unable to feed themselves.

"As a family we like to bond over food - going out to eat, having cookout parties, trying new places. Used to bring a lot of joy but another thing we are no longer able to do." - Lexi, mother of a four-year-old son living with late infantile MLD

"They couldn't get me to swallow. My parents could not handle watching me not being able to eat while they sat and ate dinner with the food falling out of my mouth that they fed me. I'd lost a lot of weight." - Corrine, speaking on behalf of her son Trent, who passed away at the age of 29 from late juvenile MLD

The symptoms that affect him most now are his loss of his communication and his overall ability to take care of himself, such as feeding and bathing and toileting. Joel is a shell of the person he once was. He was kind, funny." - Heather, 35-year-old sister of Joel and one of four siblings living with adult onset MLD

Loss of communication/speech

Speech and communication losses are one of the most devastating symptoms of this disease; with the loss of speech and communication, parents and family members suffer the loss of their loved one's personality, laughter, and smiles.

"Before she was diagnosed, she was talking, she was laughing, she was silly, she was sassy, bossy, and fun. And shortly after she was diagnosed around three, we had her G-tube placed and from there, she lost her ability to speak, and about six months later, lost her ability to laugh. And then shortly after that, we saw her last smile. So that's been probably the biggest devastation." - Tara, mother of nine-and-half-year-old Cece, living with late infantile MLD

"For Daniel, the last three years of his life, he couldn't move. … We had the blinking, one for yes, two for no, but that was inconsistent, and it was really hard to determine exactly whether or not he really was responding to questions. … Daniel also lost the ability to laugh and smile pretty early on and that was really difficult because we really had no way to tell how he was doing or having him respond." - Susan, mother of Daniel, who passed away at the age of seven years from late infantile MLD

IMPACTS: Communication/Speech. Loss of communication was a top MLD impact selected in the polls and described by parents and caregivers. Once patients with MLD lose the ability to speak and to communicate, they no longer have the ability to choose what they want and can no longer tell their caregivers if something is wrong or if they are in pain.

"MLD took from her the ability to communicate to us, so we have to rely on her heart rate monitor to tell us if she must be in pain. …We have to guess what she's thinking, how she's feeling, and we have to be her voice. We have to decide whether she likes something or not. I decide that she likes pink, she probably likes orange, but we try the best we can without her being able to tell us whether she's in pain, what's hurting, is she comfortable, is she not?" - Tara, mother of Cece, a nine-and-half-year-old girl living with late infantile MLD

"The loss of speech is devastating. This makes communication difficult as she lacks the fine motor skills to use an iPad as a method of communication. We primarily use thumbs up and thumbs down. She loved to sing and now takes several minutes to get a sentence out. People assume she is dumb because she can't speak. She is still extremely intelligent and has a lot to say, but her body lacks the mechanics to speak at a normal pace. It frustrates her to speak at turtle speed." - Jennifer, mother of eight-year-old Jana living with early juvenile MLD

"Communication is definitely the hardest thing to lose. … she lost her ability to talk completely almost exactly a year after she was diagnosed. …In the beginning, we had much more ability, she was still mobile then, so she could raise her hand or a leg to respond to questions. And that has decreased to the point where she is only capable of blinks now. … We know that she can understand and think and the inability to express herself in any way, it's torturous. … We know she's still in there." - Debbe, mother of 12-year-old Annabel, living with early juvenile MLD

Impaired communication also impacts individuals living with late onset MLD.

"Something could be hurting her and she wouldn't necessarily tell us. She doesn't offer information because that requires initiating. For example, if we ask her if she's hungry,

'Yes. I'm starving', but she'll never tell you or offer that she's hungry."- Debbie, mother of a 22-year-old daughter Alyssa with late juvenile/adult onset MLD

"He became quiet and lost his witty, funny/jokester personality. … Joel is now 42 years old and non-verbal. I would give anything to be able to speak with him again. While his decline increased, I slowly lost my brother and my best friend even though he is still alive." - Heather, 35-year-old sister of Joel and one of four siblings living with adult onset MLD

Respiratory issues

Weakened muscles lead to respiratory issues. Issues with swallowing, vomiting, and choking can lead to aspiration and infection.

Lybie can't swallow, which causes her to cough. "*She's coughing on a good day maybe a handful of times. On a bad day, every two or three minutes and we got to suction and be on top of her. And she definitely needs 24/7 monitoring because of that sole symptom."*- Tyler, father of four-year-old Lybie, living with late infantile MLD

"*His breathing was labored, and he needed oxygen to survive*." - Shanna, mother of Gavin, who passed away at five years old from early juvenile MLD

"Every time he would vomit, we would have to be perpetually concerned that that was going to have led to an aspiration pneumonia, make sure his airways were clear. So, it was a real struggle, and it was really painful for him." - Susan, mother of Daniel, who passed away at the age of seven years from late infantile MLD

IMPACTS: Breathing Independently. Many individuals living with MLD rely on supplemental oxygen. For some, respiratory issues lead to death.

"*Just the ability to breathe, something you or I take for granted. Because it's so easy. 24/7 oxygen, her nose bleeds almost every day. Heartbreaking."* - Kelsey, mother of Teagan, who passed away at six years old from late infantile MLD

"*Eventually, I developed a respiratory infection and my lungs were collapsing. My mom got home from work and my dad had taken me to the doctor that day. She was on the phone to get hospice started for me and she looked over at me and I wasn't breathing. I'd lost the ability to cough for the last couple of weeks of life and we thought maybe a mucus plug was blocking my airway, but I passed away very quietly without struggling on December 11th, 2019, 19 years after diagnosis*." - Corrine, speaking on behalf of her son Trent, who passed away at the age of 29 from late juvenile MLD

Tone, muscle cramps, rigidity, pain and irritability

Although tone/muscle cramps/rigidity and pain/irritability were separate poll responses, they were closely aligned in the poll results and the caregiver comments were closely related.

> "*Her muscle spasms got worse over time and it was very rapid progression over the course of the first six months of her disease. … When she has a lot of spasms, she gets very tired and it can cause vomiting, and therefore she's very distressed and we have to help her with suctioning. We never know when it's going to happen. … On the days where she was very rigid, I cannot hold her and have her feel that we're with her."* - Asmahan, mother of six-year-old Norah, living with late infantile MLD

> "*One of the worst symptoms that my daughter has is the tone and muscle spasms. … She screams in pain, her arm sticks out straight. I can feel her shoulder blades sticking out her back. Her leg gets so tight that she cannot control it to bend it. It is always difficult to figure out what is causing the tone to kick in extra. It could be being cold, being scared, not feeling well, constipation. When the tone kicks in so bad, she screams and becomes unable to communicate*." - Jennifer, mother of eight-year-old Jana living with early juvenile MLD who received gene therapy

Pain was often described as being uncontrollable. In addition to the pain caused by muscle spasms and GI issues, parents described other significant sources of pain including neuropathic pain and pain from gallbladder inflammation.

> "*In addition to GI issues, a significant portion of her discomfort was due to constant nerve pain. We tried to manage the pain. A cocktail of medications was given to her around the clock to try and address her issues. It was a struggle to find the right combination of medication in order to provide Loie with some semblance of comfort*." - Lauren, mother of Loie, who passed away at the age of three and a half from late infantile MLD

> *"Now she is in such pain from her legs being curled up in the fetal position. They can't be straightened out. ... As of this date, she is in a wheelchair and in such pain from MLD. Any help would be welcomed."*- Cindy, mother of Karen aged 42 who is living with adult onset MLD

Symptoms such as tone, rigidity and pain profoundly impact all aspects of daily living including **sleeping**, **sitting**, **eating** with the rest of the family, and **traveling**. Each of these impacts (sleeping sitting, eating and travelling) were selected in poll question 3.

> *"One of the things that has been very impactful for us is the amount of muscle spasms that she has …The way that affects her now is she's not comfortable sitting in the same position all the time. She can not really move, but it can feel that it gets tense in her neck and most likely in her legs. And she's always in that very tense position. ... [This influences] getting her into the car seat, what wheelchair we have to use, how she sits, how she sleeps. And over time it gets worse because the more strain you put on your muscles, the more stiff it gets over time. … [This even impacts] where she can sit when*

we're in the living room, when we're having dinner, we want her to share the experience of dinner with us." - Asmahan, mother of six-year-old Norah, living with late infantile MLD

Pain not only profoundly impacts quality of life for the individual living with MLD but also the quality of life for parents and caregivers.

"Grayson was in constant pain and uncomfortable. It was hard to enjoy life when he was constantly hurting and all he wanted was to be home and in his safe place." - Kristin, mother of Grayson who passed away at five years old with late infantile MLD

"It was hard for my parents to see me in pain." - Corrine, speaking on behalf of her son Trent, who passed away at the age of 29 from late juvenile MLD

Cognitive or memory issues

Cognitive and memory issues are often one of the first symptoms experienced by individuals with later onset MLD subtypes.

At the age of seven, "*At the beginning of his school year, his concentration began to diminish and he started demonstrating some slightly awkward social behaviors, so we treated Ronan for ADHD."* - George, father of 11-year-old Ronan, living with early juvenile MLD

"In my family, we have the adult onset form of MLD. Our mind is taken much sooner in my experience than our bodies. The hardest impact is watching the individual's slow cognitive decline. In the beginning of my brother Joel's onset, I watched him slowly exhibit this, as he would forget how to complete tasks, become disoriented, and confused." - Heather, 35-year-old sister of Joel and one of four siblings living with adult onset MLD

"*Typically, he does well and then he's got a plateau for a while and then something happens, usually an illness. … We see a decline and then he will ramp back up, but never quite makes it back to that baseline. … He's at a new plateau level*." - Pam, mother of a 26-year-old son living with adult onset MLD

Behavioral issues

Behavioral issues are complex. They are particularly an issue for those with the older onset forms of MLD. The combination of behavior and cognitive issues can result in safety concerns.

"When we're in public with her, we have to make sure that she doesn't wander off. We've actually just added a GPS tracker. I wish they made them small enough to solder onto a medic alert bracelet, to be honest, because when they have some of these behavioral symptoms, they would be likely to take it off or somehow remove it." - Debbie, mother of a 22-year-old daughter Alyssa with late juvenile/adult onset MLD

"He's vulnerable. We have to keep an eye on him 24/7." Because Evan looks normal, *"There's a vulnerability that goes along with it that makes the world kind of an unsafe place for them."* Evan needs constant direction. *"Whether it's showering, whether it's going to the garage and getting a hammer, whether it's getting dressed appropriately for the weather."* - Linda, mother of 29-year-old Evan, living with adult onset MLD

"He has a lot more social issues, trusting people that he shouldn't necessarily trust, financial problems, things of that sort. But then also mixed in there with the falling and seizures. … When he was much more mobile, we had issues with him wandering. He got in an Uber with somebody and decided to go 45 minutes away to a bar. … So it's a big safety concern." -Pam, mother of a 26-year-old son living with adult onset MLD

IMPACTS: Social Interactions/Friends. As cognitive and behavioral problems intensify, social isolation becomes an enormous problem for adults living with MLD.

"*I see isolation of not having friends anymore, people not coming around anymore, him not being able to have organizations or groups that typically adults his age would have as far as peer support, job support, things like that. And a lot of the struggles that go with that*." - Pam, mother of a 26-year-old son living with adult onset MLD

"*My husband is only 29 years old, now has a whole life of being cognitively impaired ahead of him and has to spend most of his days alone and confused at home. I have to work, and will probably always have to work long hours because he cannot, and he can't go out on his own because he gets lost*." - Margaret, wife of 29-year-old Michael, living with adult onset MLD

"Due to this [cognitive] decline, he lost various labor jobs and relationships with his peers." - Heather, 35-year-old sister of Joel and one of four siblings living with adult onset MLD

Other MLD-related health concerns

Other health concerns selected in the polls include **seizures**, **vision issues/blindness** and **incontinence**. Other MLD-related health concerns not included in the polls but discussed during the meeting or described in the comments include anxiety, depression, fatigue, tremors, ocular defects, neuropathy, gallbladder abnormalities including carcinoma of the gallbladder, fine motor issues, drooling, immune system issues, temperature regulation, neuropathy, renal issues, scoliosis and nosebleeds.

Poll Q3

MLD quality-of-life impacts are profound, not only for patients but for their entire families.

Using online polling, families and caregivers selected the top three specific activities of daily life that their loved ones are unable to do or struggle with due to MLD. Poll results are shown **in Appendix 5, Q3.** The top impacted activities of daily life were consistent with MLD symptoms and include communication, walking/mobility, feeding/eating/swallowing and social interactions/friends, and were integrated in the section above.

Key Theme: Individuals living with MLD are completely dependent on their caregivers.

> "*Gabby is unable to walk, speak, eat, or participate in any activities of daily living. She is completely dependent on her parents and caregivers. She is constantly monitored by machines and needs rescue interventions such as pulmonary treatments and oxygen to help her breathe and assistance such as catheterization and suppositories to help her void*." - Nicole, mother of four-year-old Gabby, living with late infantile MLD

> "*His present condition is such that now, four years since symptoms began, he has no voluntary motor function. There are no areas of independence in his life. He cannot move, he cannot eat, toilet, or speak. He is also challenged with blindness, neuropathy, and seizures. He requires wheelchairs, lift systems, internal feeding appliances, and supplemental oxygen*." - George, father of 11-year-old Ronan, living with early juvenile MLD

Although those with adult onset MLD may not initially require as much care or medical intervention as those with earlier forms of the disease, they too are unable to live independently because of cognitive or behavioral issues.

> *"She's not independent. She will never be able to live independently, we don't believe. So, just making sure that she's safe and making sure that she can get through activities like toileting, bathing, dressing, anything that requires a sequencing of tasks is a challenge."* - Debbie, mother of a 22-year-old daughter Alyssa with late juvenile/adult onset MLD

> *"Due to cognitive decline, Anja cannot live independently. If she's home alone, I never know if she'll actually eat lunch and I know she won't do anything smart because I always have to involve her."* - Barbara, mother of Anja, living with adult onset MLD

Key Theme: MLD impacts family members, family dynamics, and family relationships. Many described "families divided", as parents had to care for children with MLD and their siblings separately. Many families experience financial hardships when having to give up work to care for loved ones.

> "*We struggled with balancing the needs of a child with a terminal disease, the needs of a six-year-old boy - Loie's brother, Owen - and our marriage. These are items for which no prescription can be provided. It should be considered a symptom of the disease.*" - Matthew, father of Loie, who passed away at the age of three and a half years from late infantile MLD

> "[MLD] *Can change the entire family unit. … Dave and I are often forced to divide and conquer. One of us can take our oldest daughter, Ava, along with Keira to do activities, but one of us always has to stay with Livvy whose life revolves around her sisters. She's sad when they're away and she lights up upon the return."* - Kendra, mother of two girls living with late infantile MLD, Keira, a two-year-old who received gene therapy and Olivia, four years old, who did not

Many patients and parents suffer from profound grief, mental health issues and several mentioned suicidal ideation.

> *"I struggle with the mental health effects of all of the loss we have endured in our family. I struggle with the knowledge of what is to come for others and myself if we are not able to expand treatment options to include anyone, regardless of age, in gene therapy trials. There has not been a day that goes by where I do not think about MLD. It is the persistent dark cloud hovering in the sky on a sunny day."* - Heather, a 35-year-old woman, and one of four siblings living with adult onset MLD

> *"The loss of her life is painful for the entire family. The grief bubbles up when least expected. Her siblings feel the pain of missing growing up with their sister beside them."* - Aria, mother of a daughter who passed away from late infantile MLD

> "*Ten years ago when my daughter Cal was diagnosed, I had no idea how I would survive watching my daughter lose everything. … As I sank into a suicidal despair, the only thing that got me out of bed was holding onto the idea that the children who came after Cal would not suffer as she did."* - Maria, mother of Calliope Joy who passed away at age 12 from late infantile MLD

Other MLD impacts

Other important activities of daily life impacted by MLD that were selected in the polls include **traveling, sleeping**, **attending school/education**, and **sitting**. Although traveling was relatively low in the polls as an activity of daily living impacted by MLD, it generated a great deal of comments about the amount of equipment required, the rigidity that prevents comfortable traveling, and unexpected medical challenges that may result from travel.

> *"We had the opportunity to travel to visit her grandparents over this summer. I did have in the airplane to ask the person sitting right in front of me to not recline their chair, otherwise they were crushing her legs because there wasn't way for her to have them*

sitting in the right position." - Asmahan, mother of six-year-old Norah, living with late infantile MLD

Kelsey described the MLD-related barriers to camping and being in the outdoors. "*She requires 24/7 oxygen, suction machine, pulse/OX monitors, CBT treatments and all of the things. So that in itself is quite taxing. Her weakened immune system, that's a really big one."* Kelsey described how quickly things deteriorated after a recent trip. *"She ended up intubated after a nine-minute code. …She ended up with aspiration pneumonia and a mucus plug blocked her airway and she was exhausted, so her heart stopped for nine minutes*." - Kelsey, mother of Teagan, who passed away at six years old from late infantile MLD

"Now, our lives are spent at home. We can't risk Livvy getting COVID ... or shorten her time with us even more. Family vacations have come to a halt aside from our annual checkups for Keira in Italy, but that doesn't include Livvy because the trip would be too hard on her." - Kendra, mother of two girls living with late infantile MLD, Keira, a two-year-old who received gene therapy and Olivia, four years old, who did not

Poll Q4

Families have many worries for the future as MLD's unrelenting progression spares no one; worries about increased suffering and dying prematurely top the list.

Parents' MLD experiences were reflected in their many worries. Using online polling, caregivers and family members selected their top three worries about their loved one's condition in the future. Top worries were all related to their loved one's increased suffering and premature death, including their inability to breathe, uncontrolled pain, and decreased communication/ responsiveness. A second major category of worries concerned future care. Poll results are shown **in Appendix 5, Q4** and described below.

Managing care long term and needing increased nursing or hospice support

Many parents worried about how they would care for their child in the future. They shared their concerns about no longer being able to lift their child, their child "aging out" of the pediatric care system, and challenges finding caregivers, especially for older and adult patients.

"I worry about what I'll do when Willow's too heavy for me to carry. - Michelle, mother of six-year-old Willow living with early juvenile MLD

"A lot of our fear for the future is if he outlived us because we're aging … What happens to them when they've outlived their pediatric diagnoses and caregivers and physicians?" - Pam, mother of a 26-year-old son living with adult onset MLD

"We have a lot of problems finding caregivers or ancillary staff to help us. At first, we were still working, my husband had to take basically an early retirement to help manage his care. Now, just the struggle of trying to find [medical] caregivers who will help us is hard." - Pam, mother of a 26-year-old son living with adult onset MLD

Progressive loss of abilities and other worries about diminishing quality of life

Families described many fears about the **progressive loss of abilities** and the emergence of new symptoms including **scoliosis/hip dysplasia** which may require reconstructive surgeries, **eating/feeding issues** and **walking/mobility** issues.

"One worry about the future is Willow's scoliosis becoming so bad that she'll need reconstructive surgery or getting to a point where surgery is no longer viable." - Michelle, mother of six-year-old Willow living with early juvenile MLD

"My fear about [my brother] getting older is the gradual loss of more of the functions he's still able to do, such as swallowing or walking. My fears for him are also my fears for myself." - Heather, a 35-year-old woman, and one of four siblings living with adult onset MLD

Increased suffering and premature death

Parents and caregivers' top worries include their loved one's **inability to breathe**, **premature dying**, **uncontrolled pain** and **decreased communication and responsiveness**. At the meeting, several spoke about their children or siblings who passed away from MLD.

"I'm concerned about her respiratory wellness, and I fear the need of a trach one day" - Michelle, mother of six-year-old Willow living with early juvenile MLD

"What we're worrisome for us right now with Olivia is her breathing. She easily can choke on her drool, we are having to use a suction machine a lot more. We often wonder if she'll be awake when we walk in her room in the morning or did she choke in the night. So those are real and regular concerns for us." - Kendra, mother of two girls living with late infantile MLD, Keira, a two-year-old who received gene therapy and Olivia, four years old, who did not

TOPIC 2: Current and Future Treatments for MLD

In the second part of the EL-PFDD meeting, MLD families discussed the different treatment approaches and management strategies that they had used to address the devastating symptoms of MLD. They described treatment drawbacks and shared their perspectives on ideal future MLD therapies. Key meeting themes, online poll results, and select patient and caregiver quotes are presented below.

Key Theme: Gene therapy has the potential to change everything for MLD families. This was the most poignant message from the EL-PFDD meeting, as MLD families compared the experiences of children living with MLD with those of a younger sibling who received gene therapy. In all cases, the first child followed the typical and tragic trajectory of late infantile MLD, with regression, loss of abilities and sometimes death. In all cases, the child who received gene therapy experienced a drastic reduction in MLD symptoms.

> "*My experience, I suppose is of both sides of the coin in terms of treatment and non-treatment. Ciarán is six now. He's the age that Cathal died. At the age of three, Cathal was completely paralyzed. …But Ciarán has grown to meet all the milestones. He has some nerve damage. He walks slowly, he kind of drags his feet a little. He wears splints on his lower legs. But other than that, he's an absolutely fine, healthy, and thriving six-year-old boy*." - Les, father of Cathal, who passed away at age six from late infantile MLD and Ciarán, who received gene therapy and is now six

> "*I can tell you without a doubt that gene therapy has helped Oliver. While the therapy did not result in an absolute outcome, he is thriving and growing each day, and we are hopeful for his future. … He is now the same age as my daughter was when she could no longer stand or walk. …During the time that Oliver should have been regressing and showing nerve damage, he was not*." - Victoria, mother of two children living with late infantile MLD, two-year-old Oliver who received gene therapy and six-year-old Adeline who did not

The most impactful statement came from Giovanni, a 12-year-old boy who received gene therapy at the age of 11 months, and spoke about his older sister Liviana, who has passed.

> "*It is strange to hear when my mom talks about MLD because I just feel like a normal 12-year-old kid. … I like to play games online with my friends, hang out at their houses, play with my cats, and sometimes play games with my siblings. We like to go watch the sunset and go camping with my dad too. … I remember my sister Liviana. … I had gene therapy, and she couldn't because she had already had MLD. … My parents told me that Liviana said I was her best friend. I think it is sad that my best friend isn't here anymore.*

> *… She would be starting high school this year*." - Giovanni, a 12-year-old boy who received gene therapy for MLD at the age of 11 months

Despite gene therapy's lifesaving potential, strict eligibility requirements limit access. Many individuals diagnosed with MLD do not qualify for gene therapy, as it is limited to presymptomatic or minimally symptomatic patients with late infantile or early juvenile forms of the disease. While gene therapy can halt further progression, it cannot reverse symptoms in those who are already symptomatic. In some cases, mildly symptomatic children decline further while waiting for treatment.

> Jennifer's daughter was mildly symptomatic and declined further while waiting for gene therapy. As a result, she still requires a great deal of support. *"She now requires adaptive equipment, daily medications and therapies. Despite this, we are beyond grateful that this disease has stopped progressing and that our daughter is still with us. Most importantly, our daughter is grateful to be alive and is happy."* - Jennifer, mother of eight-year-old Jana living with early juvenile MLD who received gene therapy

Gene therapy can inflict a burden on patients and families. The decision to subject an infant to this therapy is a very difficult one as the conditioning procedure is physically demanding and long, and the risk of potential side effects can be extreme.

> "*The thought of chemotherapy, months in isolation in a hospital and knowing Oliver would be immuno-compromised was scary, but we had to do it. We had to give all over this opportunity despite the risks. We did not want to see him suffer like his sister. To potentially be able to live his life not trapped inside his own body, free of seizures, and to be able to breathe without machines and constant respiratory therapies, gene therapy could be his miracle and we could not pass it up*." - Victoria, mother of two children living with late infantile MLD, two-year-old Oliver who received gene therapy and six-year-old Adeline who did not

Many of the families who received this therapy had to raise half a million dollars and move to the clinical trial site in Milan, Italy (many during the pandemic). Furthermore, extended medical travel with one family member inflicted stress on other siblings when their parents were absent from home.

> *"Unfortunately, the only place we could receive this life changing treatment was in Milan, Italy, thousands of miles from home. It meant a six-month relocation for Oliver and myself away from family, which meant missing out on precious time and memories, especially of those which involved Adeline, who is already living up borrowed time."* - Victoria, mother of two children living with late infantile MLD, two-year-old Oliver who received gene therapy and six-year-old Adeline who did not

Patients who receive gene therapy still require a great deal of follow up. This includes regular visits to gene therapy specialists, which are costly and time intensive.

> "*Oliver is followed by neurology, BMT, his team in Milan, physical and occupational therapists."* - Victoria, mother of two children living with late infantile MLD, two-year-old Oliver who received gene therapy and six-year-old Adeline who did not

Despite the drawbacks from gene therapy's eligibility, travel, and subtype requirements, most families see it as a beacon of hope for the community. Caregivers described how willing they were to take on these burdens if it meant a different outcome for their loved one with MLD.

> "*For me, there isn't a gray area with MLD and gene therapy. We lost my sister at five years old and here I am thriving and enjoying my 12th year of life."* - Giovanni, a 12-year-old boy who received gene therapy for late infantile MLD at the age of 11 months

> *"When I think of an ideal treatment for MLD, gene therapy would absolutely be it, hands down. As a parent, I would gladly give up five months of my life to endure a treatment that would provide a normal life for my child."* - Kendra, mother of two girls living with late infantile MLD, Keira, a two-year-old who received gene therapy and Olivia, four years old, who did not

> "*Gene therapy is the only solution to this disease. And that has to be coupled with the rollout and implementation of newborn screening for MLD. And that's the end game in my mind, to be able to identify at birth and immediately treat with gene therapy. We'll leave the problems of MLD behind for the majority and should be the vision of the future*." - Les, father of Cathal, who passed away at age six from late infantile MLD and Ciarán, who received gene therapy and is now six

Key Theme: Some MLD families have also tried enzyme replacement therapy (ERT) and hemopoietic stem cell transplantation (HST) to halt disease progression. Enzyme replacement therapy (ERT) involves an infusion of active ARSA enzyme administered intrathecally. Clinical trials are underway. Many families reported that ERT has slowed progression.

> "*Little did we know that our expectations would be far exceeded. … ERT has helped Radha remain stable without further regression and has even helped her regain some previously lost skills. She has not required hospitalization since enrollment in the ERT trial. … This treatment has given her an opportunity for life and living that I thought she had once lost*." - Sonal, mother of six-year-old Radha, living with late infantile MLD

> *"We believe that receiving ERT has significantly slowed down further progression. … She was one of the oldest children to be accepted into the trial and was already far progressed - she had lost everything and was completely dependent for all of her care."* - Melanie, mother of eight-year-old Noelle, living with late infantile MLD

Enzyme replacement therapy is not a cure for MLD and has a number of drawbacks. Clinical trials are currently limited to minimally symptomatic patients with late infantile disease. Locations for ERT administration are also limited.

> "*Livvy needed to exit the clinical trial due to complications with the internal port. After the port was removed, she was the happiest we had seen her in a really long time, but by then she'd already lost the ability to walk, talk, and eat on her own*."- Kendra, mother of two girls living with late infantile MLD, Keira, a two-year-old who received gene therapy and Olivia, four years old, who did not

ERT requires weekly administration and is not always easy on the patient or the family.

> *"We've been fortunate that Radha has had no side effects from the enzyme infusions to date. We spend our Friday mornings at the trial clinic site for two-and-a-half hours, then carry on with the rest of our day. I could not imagine a smoother process which has had such an immense impact*." - Sonal, mother of six-year-old Radha, living with late infantile MLD

> *"ERT has slowed the progression down but did not stop it. We travel over an hour to have her infusions done every week. …It's been so hard on her and the family. She cries and is uncomfortable the day of and the day after her infusions. It's hard to watch her and I can't stop the pain*." - Kayla, mother of six-year-old Alexandria, living with late infantile MLD

Hematopoietic stem cell transplants (HST) are not curative but are thought to slow MLD deterioration. In the absence of any other therapeutic options, many symptomatic individuals living with MLD have tried HST. Some reported positive results.

> *"My child had a bone marrow transplant using umbilical cord stem cells that saved his brain. It's been four years since diagnosis. He is now five years old. Currently Brooks can't talk or walk. As he grows, he continually loses physical function but thanks to the transplant his brain remains intact."* - Stacy, mother of five-year-old Brooks, living with late infantile MLD

> *"As hard as bone marrow transplant was compared to the gene therapy, 110% worth it. Both of my boys, the seven-year-old who was three when he had his gene therapy, he has absolutely no symptoms of MLD to this day. And then my other son who's nine and was five when he was diagnosed, he still has some progression in his limbs, but it was there before and we're not seeing that increase in the four years since transplant."* - Amy W., mother of two children living with early juvenile MLD, a seven-year-old who received gene therapy and a nine-year-old son who received a bone marrow transplant

> *"Evan was transplanted … almost 10 years ago, 2013. And he has a terrific quality of life physically. There's almost a thing he can't do. He can drive a golf ball, he can play goalie,*

he can skate out, he fishes, he can really physically do just about everything [but] cognitively, [he is] significantly impaired." - Linda, mother of 29-year-old Evan, living with adult onset MLD

Patients sometimes progress further while waiting for the transplant and during the time it takes for the enzyme levels to increase.

"*When she received her bone marrow transplant in November, she was still pretty functional, but we did see that decline in function throughout her bone marrow transplant. Independence went down significantly, dressing herself, putting on shoes and socks, writing, just all of these basic things she was no longer able to do on her own."* - Cache, father of two daughters with late juvenile MLD, three-year-old Hazel who received gene therapy and 10-year-old Lia who received a bone marrow transplant

"We're grateful for the transplant because it did stop the progression. …Her hand no longer tremors, her mouth no longer moves. It is very difficult the first two years after transplant, but for us it was successful so far." - Mary, mother of 43-year-old Kris, living with adult onset MLD, who was transplanted at 33 years of age

Side effects include graft versus host disease (GVHD) and even death.

"We would make the decision to do the transplant again because there was no other treatment option available. But it was very dangerous and Michael will now have graft vs. host disease for the rest of his life. Of course, having GVHD and having the chance of halting the progression of MLD is better than letting it run its course. But I hope someday that those with adult onset MLD will have the option of gene therapy." - Margaret, wife of 29-year-old Michael, living with adult onset MLD

"We were very optimistic about the stem cell transplant and the actual treatment was successful for my son, but he ultimately died of graft versus host disease. Although the BMT treatment was successful with ARSA, he was far too progressed in the peripheral nerves to be successful. We knew all the risks, but we just wanted to save our son." - Shanna, mother of Gavin, who passed away at five years old from early juvenile MLD

"*Unfortunately, Darcee passed away shortly after an experimental bone marrow transplant*." – Dean, father of two daughters with late juvenile MLD, Darcee who passed at age 10 and Lindy living with no therapies at 42 years

Some MLD families opted not to proceed with HST because of the downsides.

Trent's parents eventually decided against HST. "*After much research by my mom, very little information on the success of bone marrow transplants was found. The information showed a 30% chance of dying from the transplant and if it took, it would be at least 18 months before there might be any effect shown. In the meantime, the difficult process of*

the BMT may accelerate the disease process." - Corrine, speaking on behalf of her son Trent, who passed away at the age of 29 from late juvenile MLD

Despite the risks, some were grateful for any opportunity to help their loved ones.

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

"She had two BMTs. I believe it took its toll, but it prolonged her life for sure. She is trach/vented 24/7, can't speak but understands. She is totally dependent and cannot move or walk." - Pat, mother of Maddigan who passed away at 25 years old from late infantile MLD

Poll Q5

In the absence of an approved curative therapy, MLD patients require many medications. Demand intensifies as the disease progresses, especially for those with earlier presenting forms of MLD.

Using the online polling, patients and caregivers selected all the different types of medications that they or their loved one used (either currently or previously) to treat the symptoms associated with MLD. Half of poll respondents selected all the medications in the poll, as shown in **Appendix 5, Q5**. The top medications in the polls that were selected by most families include (in descending order): **antispasmodics**, **pain medications**, **dietary/nutritional supplements**, **seizure medications**, **gut motility** and **sleep medications.** Parents described their desperate attempts to control their child's symptoms and to give them some relief from the pain.

"As she worsened, her treatment plan had to change. What initially started as only Baclofen for spasticity and CBD lotions for muscle pains has now turned into eight medications on a daily basis, and two additional medications are needed. Livvy now receives Baclofen three times a day for spasticity; Gabapentin three times a day for neuropathy; levetiracetam two times a day to keep seizures at bay; Sulfatrim once a day to keep UTIs away; Clonidine and melatonin to help her have a painless rest each night; THC twice a day for pain and anxiety and glycopyyrolate three times a day for drooling. For the moments when she's screaming in pain and because she can no longer speak to tell us what's causing it, we have to use day Diazepam as needed, which is also on deck for seizures. When that doesn't do the trick, we have to use morphine." - Kendra, mother of two girls living with late infantile MLD, Keira, a two-year-old who received gene therapy and Olivia, four years old, who did not

"She's taking Baclofen for tone, Gabapentin for nerve pain, Sinemet for tremors, Cremalax for bowel issues, Bactrim as part of her transplant, Zyprexia settles her at night. She has a G-tube as she cannot swallow fast enough to take the volume of medication by mouth. She's in OT, PT and speech therapies, several times a week. We try to incorporate exercise to keep her from getting stiff. Our whole life is modified at this point." - Jennifer, mother of eight-year-old Jana living with early juvenile MLD who received gene therapy

Other medications selected in the polls including **respiratory/breathing medications**, **anti-anxiety medications**, and **CBD and other cannabis products**. Other medications and medical treatments that were not mentioned in the polls but described during the meeting include: antidepressants, antiemetics, as well as medications for ADHD, bipolar disorder, and allergies.

Poll Q6

Most individuals living with MLD require extensive therapy and other supports to move, to eat, and even to breathe.

Using the online polling, patients and caregivers selected all the different types of therapies/supports their loved one has used (currently or previously) to help manage the symptoms of MLD. Each poll respondent selected an average of 7.6 different therapies and supports. Poll results are presented in **Appendix 5, Q6**. The top two approaches tied in the polls included **wheelchair, cane and walker**, and **physical therapy**, followed by **occupational therapy** and **leg/hand braces**.

Parents described how much mobility and personal equipment is required for their children, as well as adapted vehicles.

"*Others have talked about the amount of equipment necessary that you have to move with you if you want to go anywhere. It's essentially a mobile PICU."* - Susan, mother of Daniel, who passed away at the age of seven years from late infantile MLD

"*She became wheelchair bound probably at five and later she was on a trach-vent-feeding tube shunt, had to have spinal fusion. … We had the adapted van and we had a wheelchair. We had a wagon with all of our extra supplies."* - Pat, mother of Madigan, who passed away at the age of 25 of late infantile MLD

"I had a neck support brace when I couldn't hold my head up anymore and leg braces to keep my feet from drooping. …My parents bought a wheelchair van for my last two years of life and always took me on walks, to church, and any place we could go with my wheelchair." - Corrine, speaking on behalf of her son Trent, who passed away at the age of 29 from late juvenile MLD

Parents also described the extensive **physical and occupational therapy** that their children required in addition to numerous specialist consults.

> For recovery from a bone marrow transplant, "*We've been mainly focusing on physical and occupational therapy. And with these two treatments, we're noticing small but noticeable improvements over the past several months. … She's still not to able to do things independently, but she's getting faster at putting on her clothes with coaching, riding a tricycle with coaching*." - Cache, father of two daughters with late juvenile MLD, three-year-old Hazel who received gene therapy and 10-year-old Lia who received a bone marrow transplant
>
> Livvy, *"receives physical therapy once a week, music therapy once a month, and due to staffing issues, she hasn't been able to receive OT and SLP therapies once a week as usual. This has rendered her augmentative communication device almost useless. Her hospice nurse also visits us every two weeks for checkups, and they now deliver all of her medications to our home*." - Kendra, mother of two girls living with late infantile MLD, Keira, a two-year-old who received gene therapy and Olivia, four years old, who did not

Most individuals with MLD require **feeding supports**. This can include g-tube placement as well as feeding therapy.

> "*We've gone through food therapy so she can now eat anything that she wants. She's able to swallow liquids, she still swallows slowly, but she can enjoy eating now. We still have a G-tube for supplemental nutrition and just because she takes a large volume of medications every day, that's just too much by mouth*." - Jennifer, mother of eight-year-old Jana living with early juvenile MLD who received gene therapy
>
> *"My parents also decided to put in a feeding tube at age 15 as I was slowly starving. This was the second hardest decision as they didn't want to prolong my disability, but they couldn't get me to swallow. … Once I got a feeding tube, I quickly gained weight and filled out and continued to grow. I was a big guy and grew to six feet, four inches and probably 190 pounds."* - Corrine, speaking on behalf of her son Trent, who passed away at the age of 29 from late juvenile MLD

Other therapies/supports selected in the polls included **speech therapy** and **assisted communication devices/methods, respiratory supports,** including supplemental oxygen or tracheostomy, **aqua therapy**, **naturopathic therapies** and **urinary catheters**. These were not discussed at great length during the meeting. Other therapies/supports not included in the polls but mentioned during the meeting include: **physical comforts**, such as being held and resting in specialized chairs; **surgery**, such as gallbladder removal, Nissen fundoplication to reduce acid reflux, spinal fusion therapy; **extensive home modifications** such as ramps and equipment including hospital beds, lifts, and rolling shower.

> *"Beyond the pain medications available, Lauren and I would hold Loie 12 to 16 hours a day to help ease the pain and discomfort. Most of the pictures we have of Loie during her last year with us are of Loie sitting on our lap, or laying on our chest. It seemed to*

calm her." - Matthew, father of Loie, who passed away at the age of three and a half years from late infantile MLD

"My parents had to add a bedroom to our house since we had no bedrooms on the main level. Ramps were also added to get into the house. We had a stander, a hospital-type lift bed, a rolling shower chair, and portable lift systems added so my parents could care for me. I had foam booties and a foam mattress pad to keep away bed sores, which we had problems with on my heels." - Corrine, speaking on behalf of her son Trent, who passed away at the age of 29 from late juvenile MLD

Key Theme: Patients with adult onset MLD often face cognitive and behavioral issues which necessitate constant care and supervision. Treatment options thus far have been limited.

"I have not had any treatments due to the likelihood of severe after-effects, cognitive decline, infertility and the possibility of death." – Heather, a 35-year-old woman, and one of four siblings living with adult onset MLD

"*But really since she's had her diagnosis, there is nothing. None of those medications worked, number one, and there really aren't any treatments. She's not in need of physical therapy, occupational therapy, speech therapy. She mostly needs monitoring of her activities*." – Debbie, mother of a 22-year-old daughter Alyssa with late juvenile/adult onset MLD

Poll Q7 + Q8

Treatment inequity is a top drawback of MLD therapy.

Barriers to treatment include limited availability and accessibility, high costs, and a lack of efficacious options for some populations. During the EL-PFDD meeting, online polling was used to select the top three drawbacks of current MLD treatment approaches, which indicated that there is a lack of equity with regards to MLD treatments. Poll results are presented in **Appendix 5, Q8**, and described below.

Limited availability or accessibility of the treatment

Limited availability or accessibility of the treatment was the top treatment drawback selected in the polls. There were many reasons for this including ineligibility due to existing symptoms, MLD subtype, and geographical constraints. For example, many gene therapy families who spoke at the meeting had travelled to Milan for treatment in clinical trials, but this is not easily accessible for US based families.

"The difficulty of our experience with Giovanni's gene therapy was the practical, logistical, and psychological. It was relocating our family to Milan, Italy for six months, missed work, financial burden and stress, cultural and language barriers, stress, fear of the unknown, which will never go away, and the follow-up visits where you relive it all

over again." - Amy P., mother of three children with late infantile MLD, 12-year-old Giovanni and eight-year-old Cecilia who both received gene therapy and Liviana, no therapies, who passed away at the age of five years

"There is no guarantee in any treatment and gene therapy, which is a beacon of hope for the MLD community, is not available for adults like my two brothers and myself living with MLD. The only treatment, specifically for adults, is no treatment, and to put it plainly, I'm terrified." - Heather, a 35-year-old woman, and one of four siblings living with adult onset MLD

High cost or copay, not covered by insurance

This is a drawback of many of the therapies including gene therapy, where patients described having to raise a half-million dollars. Other parents described how they were financially devastated by all the equipment and therapies and by having to leave their employment to care for an affected child.

"*We lost Cal earlier this year in March. Over her 10 years living with MLD, she had over 1,720 confirmed provider contacts. Please take a moment to ponder what that number says about the emotional, physical, and financial toll of caring for a child with MLD.*" - Maria, mother of Calliope Joy who passed away at 12 years old from late infantile MLD

"My wife and I haven't been able to work consistently because they got treatment roughly the same time. My wife went to Italy, I stayed here and moved to Salt Lake City to be with my other daughter. She was being treated. That's a huge thing." - Cache, father of two daughters with late juvenile MLD, three-year-old Hazel who received gene therapy and 10-year-old Lia who received a bone marrow transplant

Many MLD families also indicated that supportive care treatments they have utilized were **not very effective at treating the target symptoms** or **treat some, but not all of the symptoms.** This is fairly consistent with the results of the poll question 7, which asked caregivers and patients to select how well their current treatment regimen treats the most significant symptoms of MLD, **Appendix 5, Q7**.

For the last three years of Daniel's life, *"It was mostly just trying to make him comfortable and for a long period of time, that was really difficult and almost impossible. …The tone, muscle cramps, rigidity, and pain, and irritability were among the most difficult because we really had almost no way to control those symptoms. They were somewhat managed with clonidine and diazepam and other things, but really, our doctors seemed to be at a loss and we were too."* - Susan, mother of Daniel, who passed away at the age of seven years from late infantile MLD

"*Our experience is that all symptom reduction therapies, OT, PT, AFOs, et cetera, or medications that don't reduce the myelin degenerative processes may slow symptoms*

for a while, but they don't improve underlying disease processes. They give some comfort to the patient for a time, but they don't provide hope." - George, father of 11-year-old Ronan, living with early juvenile MLD

"I'm one of those that selected 'none of the therapies help'. We did the PT, we did the OT, we did the speech therapy, we've done meds. There really isn't anything. This is just where we're at. And so to live it, to accept it but to still advocate I think is where I'm at." - Linda, mother of 29-year-old Evan, living with adult onset MLD

Other treatment drawbacks selected in the polls include **side effects, route of administration**, and **requires too much effort and time**. Parents described how medication side effects like drowsiness and respiratory suppression were necessary trade-offs for pain and seizure control. They also described how HST and gene therapy may cause secondary side effects such as sterility.

"*[My daughter] did not qualify for any of the clinical trials or treatments. So essentially, she is sustained with medications and with that there are side effects. So when you look at it as a big picture, there's days where it's okay, we're controlling her seizures or her dystonic episodes. But now we are on a scary edge of suppressing her respiratory system and which already struggles daily being that she needs 24/7 oxygen support."* - Kelsey, mother of Teagan, who passed away at six years old from late infantile MLD

"*We feel that her medications manage her symptoms somewhat, but wish that her quality of life was better and that she was less drowsy. Drowsiness is a big trade off that she experiences to control her pain and seizures."* - Melanie, mother of eight-year-old Noelle, living with late infantile MLD

A significant drawback that was also mentioned throughout the meeting but not captured in the polls, was **the length of time it takes for therapies to take effect**.

"Bone marrow transplant, it was several months after the transplant before Lia was able to make enough of the enzyme to be able to start fighting back the MLD... And when you have MLD, which is a rapidly progressing disease every minute, every day, every week counts. It's the difference between being able to continue to walk and being in a wheelchair." - Cache, father of two daughters with late juvenile MLD, three-year-old Hazel who received gene therapy and 10-year-old Lia who received a bone marrow transplant

Poll Q9

MLD families desperately want a cure or at least some hope for a cure.

Using online polling, caregivers and patients were asked to select the top three things that they would look for in an ideal therapy for MLD, short of a complete cure. The poll results are shown

in **Appendix 5, Q9** and are discussed further in this section. Parents had a hard time selecting just three things that they could have, as all of these are important to address.

Key Theme: **There is an immediate and devastating unmet need for widely accessible disease modifying treatments.** While gene therapy has been profoundly impactful in modifying the course of MLD progression, it has strict eligibility and geographical constraints. Many parents would **tolerate a great deal of risk** for their child in exchange for a chance at curing the disease.

> *"As a parent and primary caregiver of a patient with advanced MLD, our risk tolerance is extremely high. … Our family would take big risks to treat the myelin erosion if there are solutions considered or developed for trial or implementation in the future in advanced cases."* - George, father of 11-year-old Ronan, living with early juvenile MLD

> *"We would risk death. This is a horrific, terminal disease. We would be willing to try anything in order to get some quality of life back. We have nothing to lose at this point. Death is inevitable with this disease. I want the FDA to know how desperate many families are for these new treatments such as gene therapy. I want them to know that it wouldn't be fair to exclude kids who have had ERT or transplants in the upcoming clinical trials. We've done everything humanly possible to help our son. We can't be forgotten."* - Stacy, mother of five-year-old Brooks, living with late infantile MLD

> *"We are often asked, 'How did you decide to go to Italy with so much unknown and the potential risks?' We knew painfully the risk of doing nothing. The potential of seeing our son gradually lose every learned milestone, losing the sound of his voice and knowing that we, my husband and I, and our two older children would not only lose Liviana, but also Giovanni. Of course, as a former researcher, I thoroughly read the medical literature. I sought to understand all I could about gene therapy and asked questions of our local physician and the doctors in Milan. What I learned reinforced our decision that the only certainty would be the outcome of not treating Giovanni, which is certain death."* - Amy P., mother of three children with late infantile MLD, 12-year-old Giovanni and eight-year-old Cecilia who both received gene therapy and Liviana, no therapies who passed away at the age of five years

MLD families want a treatment that slows or stops the disease progression, not only for those with early onset disease but for those with late onset disease as well.

A treatment that slows or stops the disease progression was the top option selected in the poll. Parents expressed a strong need for a treatment for those who are already symptomatic.

> *"I definitely picked stopping or slowing the progression of disease. I find it frustrating that the late juvenile and adult onset patients or people who have already started showing symptoms don't even have the option to try the gene therapy or the enzyme replacement therapy or potentially even the emerging options. I feel like that part of the population, the MLD population, really doesn't have any choices other than the*

transplant option."- Debbie, mother of a 22-year-old daughter Alyssa with late juvenile/adult onset MLD

"Regarding future drug development, I feel that research emphasis should be placed on management and treatment of those who are currently symptomatic in order to decrease morbidity and mortality." - Sonal, mother of six-year-old Radha, living with late infantile MLD

Parents want a treatment that leads to increased communication, engagement, and responsiveness.

The second choice for an ideal therapy selected in the polls was a therapy that could increase communication, engagement, and responsiveness. The need for improved communication reflects that the loss of speech/communication was the most troublesome MLD-related health concern and impact.

"Communication is the biggest [wish for a future treatment]. I often had to interpret non-verbal signs to understand what a problem was or where pain was. Ways to help a child express themselves would be so helpful to a tired parent who is afraid of missing something that they can't let others help out of fear." - Jennifer, mother of Emma who passed at seven years old from early juvenile MLD

"The most burdensome symptom for Brooks is the inability to communicate. Brooks's brain remains stable since his stem cell transplant in 2018. His brain knows what he wants, but his body can't tell us." - Stacy, mother of five-year-old Brooks, living with late infantile MLD

Other options that were selected in the poll for ideal treatments included improvements to just about every single MLD symptom including: **longer lifespan**; **increased ability to walk or increased mobility**; **reduced pain**; **improved or retained voluntary movement**; **improved eating/swallowing/motility**; **improved ability to breath independently**; and **reduced spasticity and tone.**

"Improvements in oral intake, head control, gut motility and hypertonicity can help alleviate suffering and further decompensation. Improvements in these and other similar issues should be the primary endpoints of future clinical trials involving symptomatic patients as opposed to the achievement of gross motor milestones, which is less realistic and has a less significant clinical impact." - Sonal, mother of six-year-old Radha, living with late infantile MLD

Incorporating Patient Input into a Benefit-Risk Assessment Framework

Each FDA approval decision involves a scientific determination that the benefits of a drug outweigh the risks. The FDA uses a Benefit-Risk Assessment Framework which provides the context for drug regulatory decision-making and includes valuable information for weighing the specific benefits and risks of a particular medical product under review.

Patient information includes two major areas of patient experience. The first, Analysis of Condition, includes the burdens of the disease and the impacts on patients' daily lives. This helps to describe the seriousness and life-threatening nature of what patients live with on a day-to-day basis. The second, Current Treatment Options, includes patients' perspectives on the adequacy of available therapies. This helps to define the degree of unmet medical need that exists when treating the most significant burdens of the disease.

Table 1 speaks to the challenge of having a lifelong disease burden that patients living with MLD endure. It serves as the proposed introductory framework for the Analysis of Condition and Current Treatment Options to be adapted and incorporated in the FDA's Benefit-Risk Assessment. This may enable a more comprehensive understanding of this unique condition for key reviewers in the FDA Centers and Divisions who would be evaluating new treatments for MLD. The data resulting from this meeting may help inform the development of MLD-specific, clinically meaningful endpoints for current and future clinical trials, as well as encourage additional investigations into treatment options.

The information presented captures the perspectives of caregivers caring for patients living with MLD presented at the October 21, 2022 EL-PFDD. Note that the information in this sample framework is likely to evolve over time.

TABLE 1 Metachromatic Leukodystrophy Benefit-Risk Table

	EVIDENCE AND UNCERTAINTIES	CONCLUSIONS AND REASONS
ANALYSIS OF CONDITION/ IMPACTS ON ACTIVITIES OF DAILY LIVING	**Metachromatic leukodystrophy (MLD) is a rare and progressive neurologic disease with devastating impacts**. Most patients with this lysosomal storage disorder live less than a decade after diagnosis. Some families include multiple affected family members. **Most MLD families endure long diagnostic odysseys, with an MLD diagnosis made long after the appearance of initial symptoms**. Earlier forms of MLD usually present as mobility challenges and progress rapidly from onset. Later presenting forms of MLD are less predictable, generally presenting with cognitive and behavioral changes which may be initially hard to recognize as MLD. **Most MLD patients experience devastating symptoms including regression, a loss of communication, impaired mobility and balance challenges, feeding and GI motility, and cognitive and behavioral challenges,** as well as many other MLD-related symptoms.	**MLD profoundly impacts quality of life for patients and their entire families.** Patients are completely dependent on their caregivers, and most cannot be left unattended. Younger patients are at risk of aspirating and choking. Older patients are socially isolated and a risk to themselves. Caregivers worry that their loved ones will be unable to breathe and will die premature death, that their loved one will experience uncontrolled pain, and that communication/ responsiveness will decrease. **Earlier diagnosis is necessary.** Newborn screening for MLD will ensure that children with MLD can be identified presymptomatically and be eligible for life-saving gene therapy or other emerging therapies. For other patients, the time from the first symptoms to diagnosis must be shortened, so that patients will gain more benefit from early therapeutic intervention.
CURRENT TREATMENT OPTIONS/ PROSPECTS FOR FUTURE TREATMENTS	**Disease modifying therapies for MLD now exist and when delivered early, are potentially life-changing.** Gene therapies and enzyme-replacement therapies are now offering hope; however, only presymptomatic and minimally symptomatic patients are eligible. Financial and geographic barriers result in treatment inequality. During the EL-PFDD meeting, many parents compared the lives of siblings who have received therapy with those who had not.	**There is an urgent need for treatments for MLD patients across the spectrum of disease, especially for those who are already symptomatic**. Patients rely on a very large number of different treatments and medications to manage symptoms and for end of life comfort. These palliative care options are not curative and will not slow or stop MLD progression. **Leveraging existing data and using novel clinical trial designs will allow more MLD patients to be treated.**
	See the Voice of the Patient report for a more detailed narrative.	

Acknowledgements

We wish to thank many organizations and individuals for their support and involvement in this important initiative.

Thank you to the FDA for attending and hearing our voices and perspectives at both the October 21, 2022 MLD EL-PFDD meeting and the November 18, 2022 Adjunct MLD Scientific Meeting. We are incredibly grateful for these opportunities to share our experiences with you. Thank you to Dr. Sairah Thommi for attending and for emphasizing just how important the voices of our patients and families are for those who oversee the drug development process. Thank you to our FDA liaisons, Shannon Sparklin from the Patient-Focused Drug Development Staff and Karen Jackler from CBER for helping us plan these meetings.

We thank our expert clinicians for their support during the EL-PFDD meeting and again at the Adjunct MLD Scientific Meeting. Thank you, Dr. Laura Adang and Dr. Adeline Vanderver, for providing the MLD Clinical and Treatment Overviews at the EL-PFDD meeting. Thank you, Dr. Laura Adang, Dr. Barbara Burton, Dr. Samuel Gröeschel, Dr. Paul Orchard, Dr. Marc Patterson and Dr. Adeline Vanderver for being part our expert panel. We appreciate your commitment to serving our MLD patients and to finding a cure.

Thank you to Larry Bauer and James Valentine for their support and guidance throughout the entire PFDD process. Thank you to the production team at Dudley Digital Works for their hard work and for ensuring that our voices were heard.

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We would like to acknowledge the members of our organizing committee, Erica Barnes, Dean Suhr, Teryn Suhr, Bob Rauner, and Maria Kefalas. A special thanks to Cure MLD's Melanie Rumbel and Marly McGowan.

To the many MLD families who have shown incredible vulnerability and courage in sharing their stories, our gratitude goes to you. To recount the most traumatic thing that has ever happened to you and do it repeatedly, is a gift to the scientists, doctors, researchers, FDA reviewers, and to future MLD families. Thank you for sharing your insights, providing the patient voice to help inform clinical trial design and therapeutic development. Thank you also those that have participated in our natural history studies, as well as our international collaborators from major academic institutions around the world. Please know that your voices are tremendously important, and the impact of your participation cannot be overstated.

Appendix 1: MLD EL-PFDD Meeting Agenda, October 21, 2022

10:00 am – 10:05 am Welcome
Dean Suhr, MLD Foundation

10:05 am -10:15 am FDA Opening Remarks
Dr. Sairah Thommi, Division of Clinical Evaluation & Pharmacology/ Toxicology OTAT, CBER – FDA

10:15 am – 10:30 am MLD Clinical Overview
Laura Adang, MD, PhD, Children's Hospital of Philadelphia

10:30 am -10:35 am Introduction and Meeting Overview
James Valentine, JD, MHS, Meeting Moderator

10:35 am – 10:45 am Demographic Polling

Session 1 – Living with MLD Symptoms and Daily Impact

10:45 am -11:10 am Patient/Caregiver Panel 1

1:10 am – 12:30 pm Audience polling & moderated discussion – including telephone call-ins and written comments

12:30pm- 1:00 pm Lunch

Session 2 – Current and Future Treatments for MLD

1:00 pm – 1:10pm Treatment Overview
Adeline Vanderver, MD
Children's Hospital of Philadelphia

1:10 pm -1:35 pm Patient/Caregiver Panel 2

1:35 pm -2:45 pm Audience polling & moderated discussion – including telephone call-ins and written comments

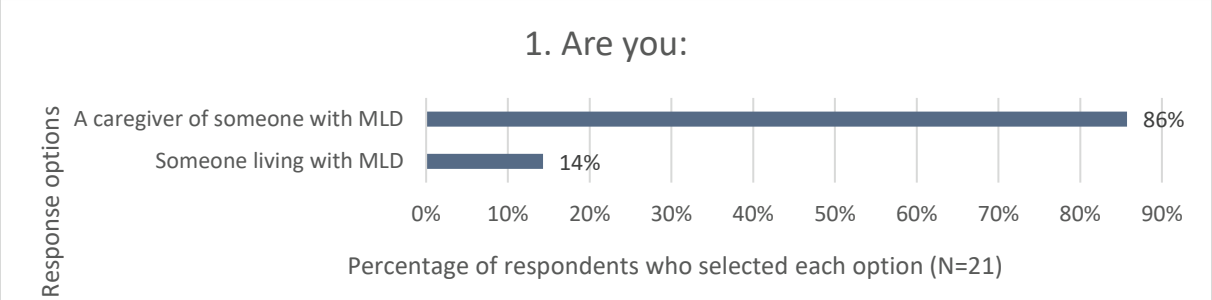
2:45 pm -2:55 pm Summary Remarks – Larry Bauer, RN, MA

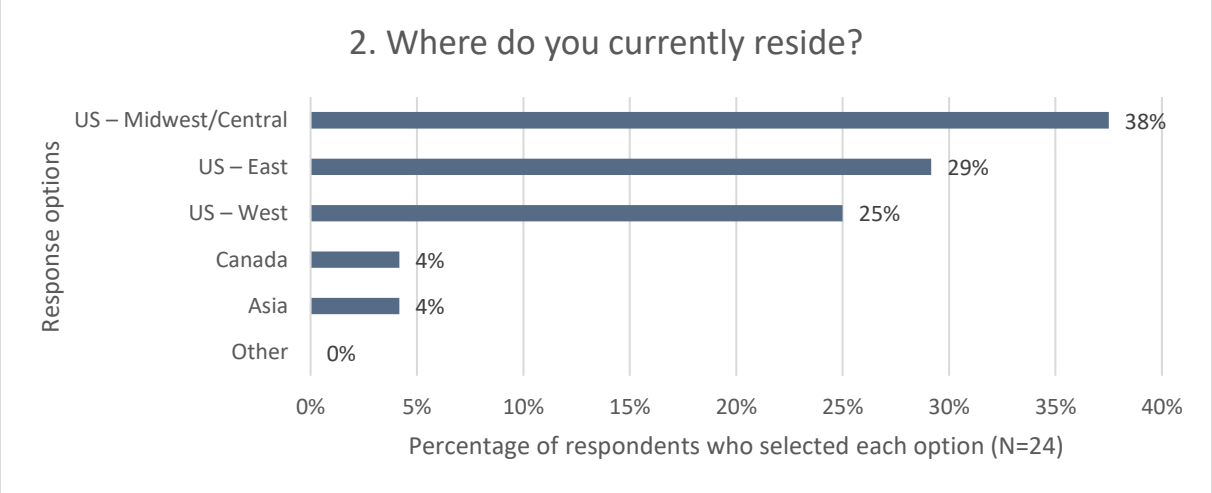
2:55 pm- 3:00 pm Closing Remarks
Maria Kefalas, PhD, The Calliope Joy Foundation

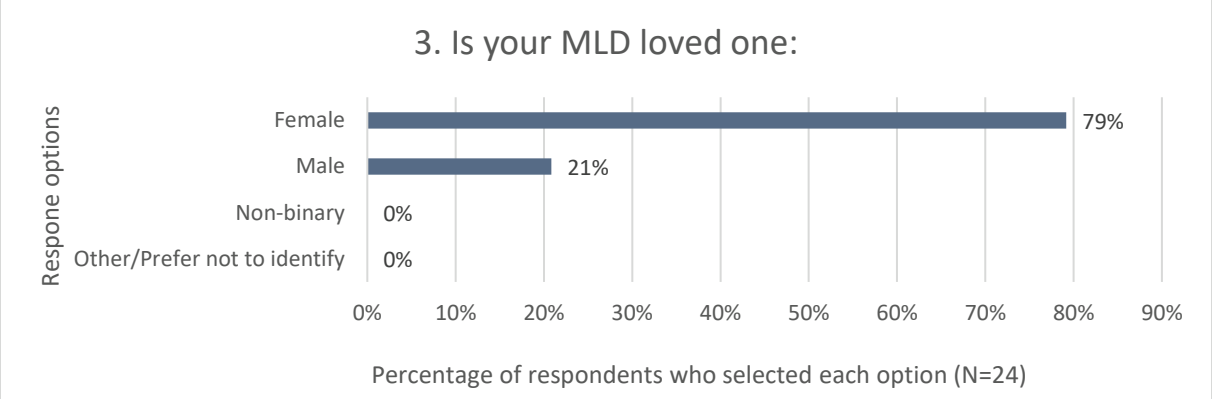
Appendix 2: MLD EL-PFDD Meeting Demographic Poll Results

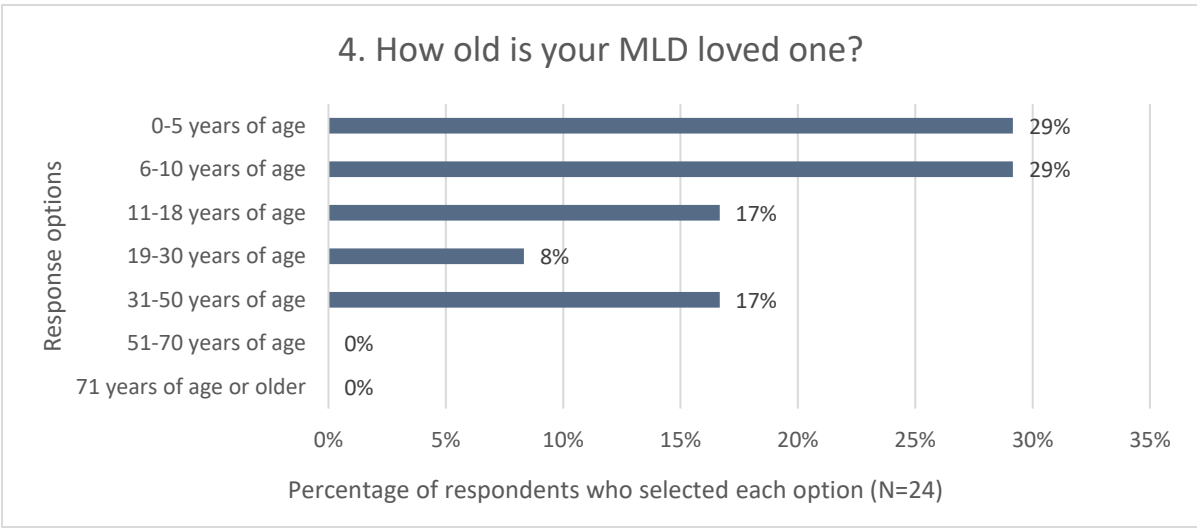
The graphs below include patients, parents and caregivers who chose to participate in online polling. The number of individuals who responded to each polling question is shown below the X axis (N=x).

While the response rates for these polling questions is not considered scientific data, it provides a snapshot of those who participated in the MLD EL-PFDD meeting. Note that meeting demographics are dynamic and may have changed as more individuals joined the meeting.








4. How old is your MLD loved one?
Response options
0-5 years of age
6-10 years of age
11-18 years of age
19-30 years of age
31-50 years of age
51-70 years of age
71 years of age or older
29%
29%
17%
8%
17%
0%
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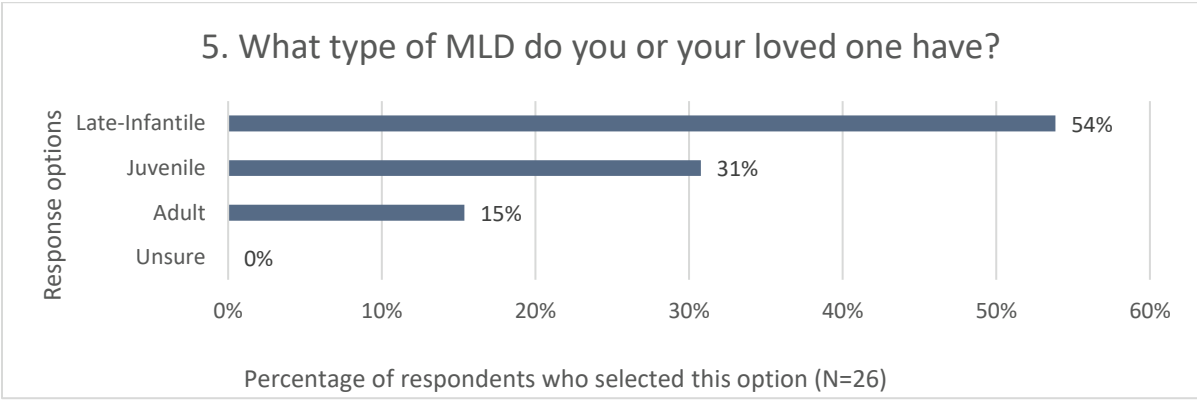
0%
5%
10%
15%
20%
25%
30%
35%
Percentage of respondents who selected each option (N=24)


5. What type of MLD do you or your loved one have?
Response options
Late-Infantile
Juvenile
Adult
Unsure
54%
31%
15%
0%
0%
10%
20%
30%
40%
50%
60%
Percentage of respondents who selected this option (N=26)

Appendix 3: MLD EL-PFDD Meeting Discussion Questions

Topic 1: Living with MLD: Symptoms and Daily Impacts

1. Of all the symptoms and health effects of MLD, which 1-3 symptoms have the most significant impact on your loved one's life?

2. How does MLD affect your loved one on best and on worst days? Describe your best days and your worst days.

3. How has your loved one's symptoms changed over time? How has their ability to cope with the symptoms changed over time?

4. Are there specific activities that are important to your loved one that they cannot do at all or as fully as they would like because of MLD?

5. What do you fear the most as your loved one gets older? What worries you most about your loved one's condition?

Topic 2: Perspective on Current and Future Approaches to Treatment

1. What are you currently doing to manage your loved one's MLD symptoms?

2. How well do these treatments treat the most significant symptoms and health effects of MLD?

3. What are the most significant downsides to your loved one's current treatments and how do they affect daily life?

4. Short of a complete cure, what specific things would you look for in an ideal treatment for MLD? What factors would be important in deciding whether to use a new treatment?

Appendix 4: MLD EL-PFDD Panel Participants and Meeting Speakers

Session 1 Discussion Starters

- George, father of 11-year-old Ronan, living with early juvenile MLD
- Michelle, mother of six-year-old Willow living with early juvenile MLD
- Matthew and Lauren, parents of Loie, who passed away at the age of three and a half years from late infantile MLD
- Corrine, mother of Trent, who passed away at the age of 29 from late juvenile MLD
- Heather, a 35-year-old woman, and one of four siblings living with adult onset MLD

Session 1 Zoom Panel

- Susan, mother of Daniel, who passed away at the age of seven years from late infantile MLD
- Tara, mother of nine-and-half-year-old Cece, living with late infantile MLD
- Tyler, father of four-year-old Lybie, living with late infantile MLD
- Debbe, mother of 12-year-old Annabel, living with early juvenile MLD
- Kelsey, mother of Teagan, who passed away at six years old from late infantile MLD

Session 1 Callers

- Vijay, father of a daughter living with early juvenile MLD
- Asmahan, mother of six-year-old Norah, living with late infantile MLD
- Kendra, mother of two girls living with late infantile MLD, Keira, a two-year-old who received gene therapy and Olivia, four years old, who did not
- Pam, mother of a 26-year-old son living with adult onset MLD

Session 2 Discussion Starters

- Kendra, mother of two girls living with late infantile MLD, Keira, a two-year-old who received gene therapy and Olivia, four years old, who did not
- Sonal, mother of six-year-old Radha, living with late infantile MLD
- Victoria, mother of two children living with late infantile MLD, two-year-old Oliver who received gene therapy and six-year-old Adeline who did not
- Gary, father of six-year-old Celia Grace living with early juvenile MLD, the first child to receive gene therapy in the United States
- Amy P., mother of three children with late infantile MLD, 12-year-old Giovanni and eight-year-old Cecilia who both received gene therapy and Liviana, no therapies who passed away at the age of five years
- Giovanni, a 12-year-old living with late infantile MLD, who received gene therapy

Session 2 Zoom Panel

- Cache, father of two daughters with late juvenile MLD, three-year-old Hazel who received gene therapy and 10-year-old Lia who received a bone marrow transplant
- Debbie, mother of a 22-year-old daughter Alyssa with late juvenile/adult onset MLD
- Amy W., mother of two children living with early juvenile MLD, a seven-year-old who received gene therapy and a nine-year-old son who received a bone marrow transplant
- Pat, mother of Maddigan, who passed away at the age of 25 year from late infantile MLD

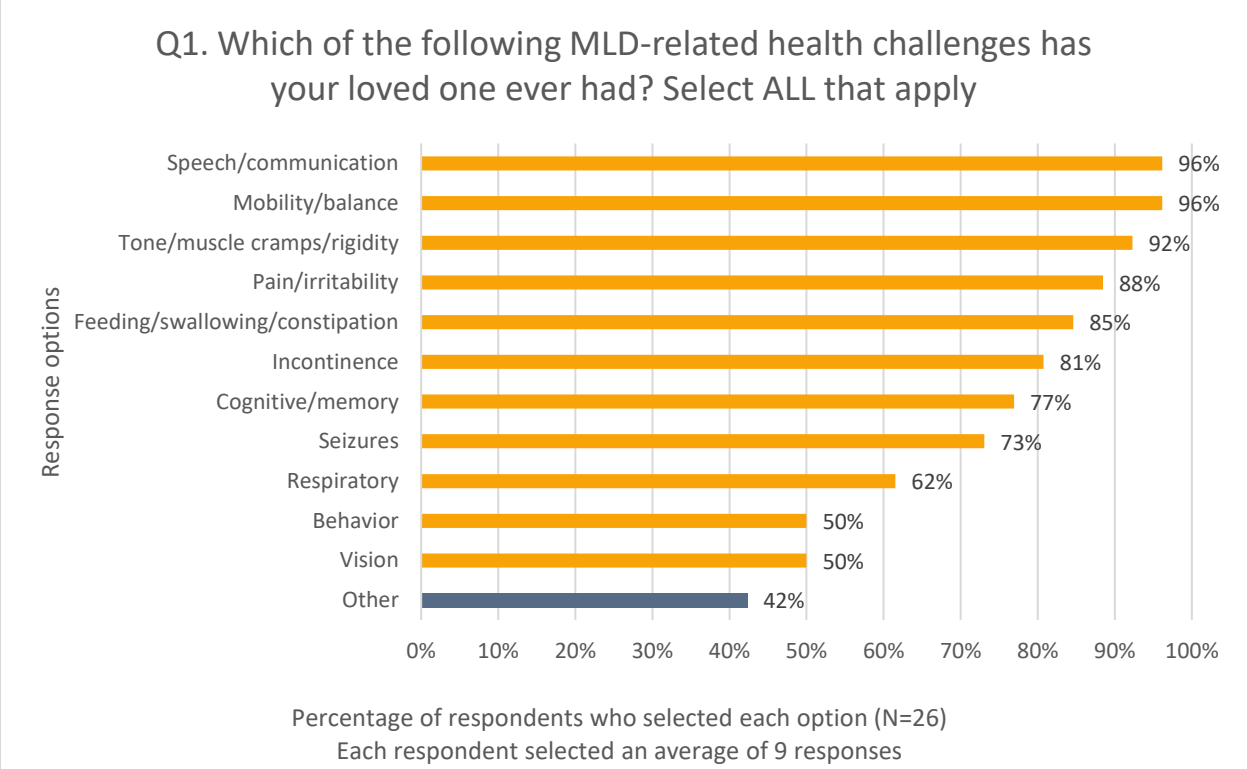
Session 2 Callers

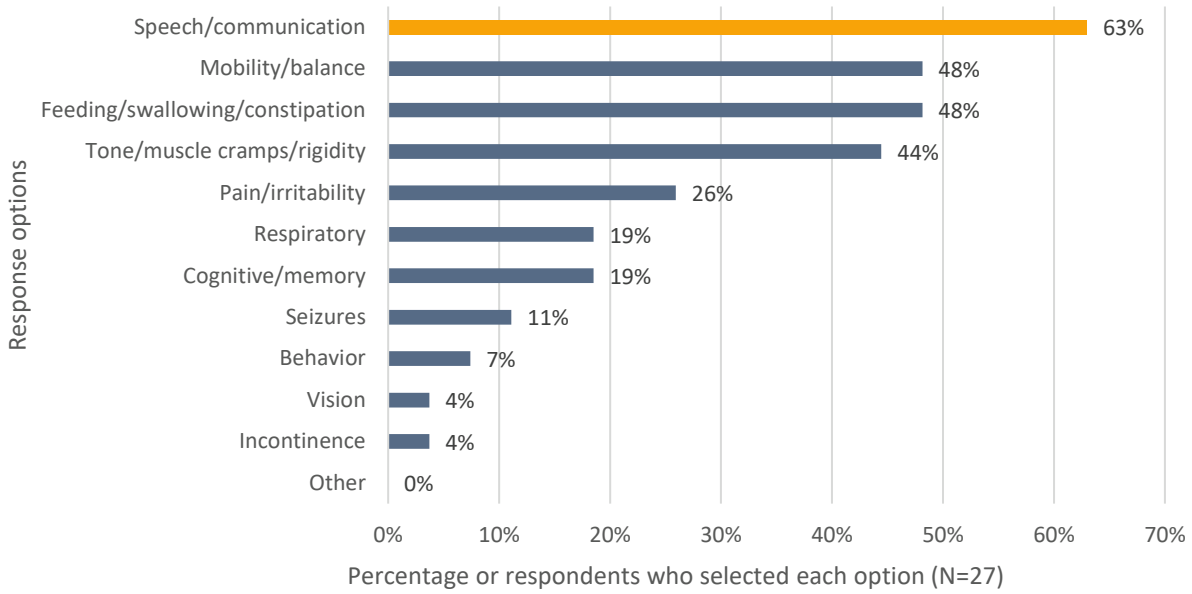
- Kelsey, mother of Teagan, who passed away at six years old from late infantile MLD
- Les, father of Cathal, who passed away at age six from late infantile MLD and Ciarán, who received gene therapy and is now six
- Kassie, mother of six-year-old Celia Grace living with early juvenile MLD, the first child to receive gene therapy in the United States
- Linda, mother of 29-year-old Evan, living with adult onset MLD
- Mary, mother of 43-year-old Kris, living with adult onset MLD who was transplanted at 33 years of age
- Jennifer, mother of eight-year-old Jana living with early juvenile MLD who received gene therapy

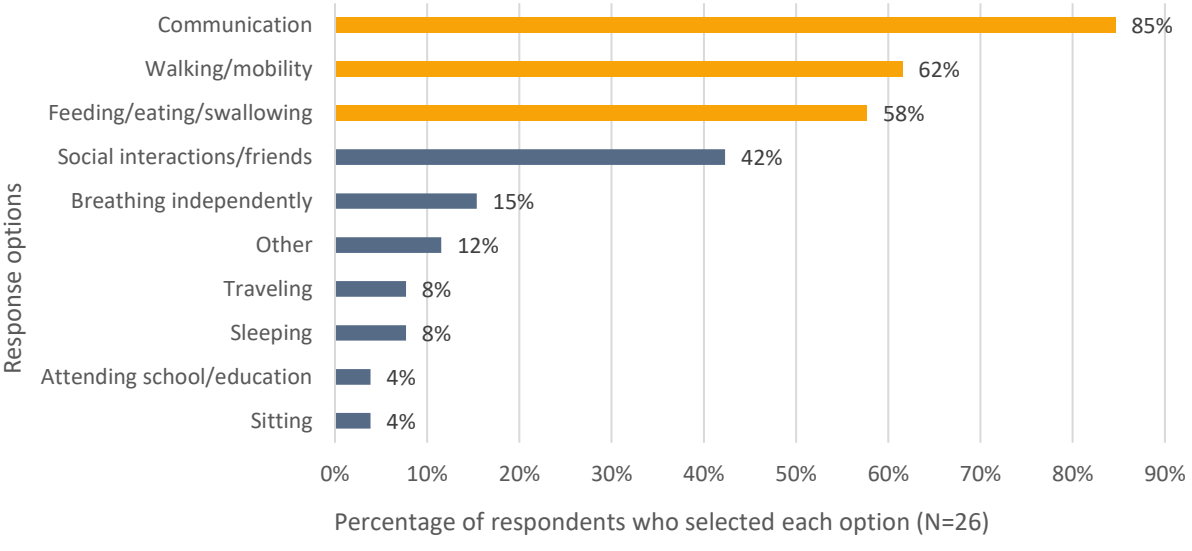
Appendix 5: MLD EL-PFDD Meeting Poll Results

The graphs below include patients, parents and caregivers who chose to participate in online polling. The number of individuals who responded to each polling question is shown below the X axis (N=x).

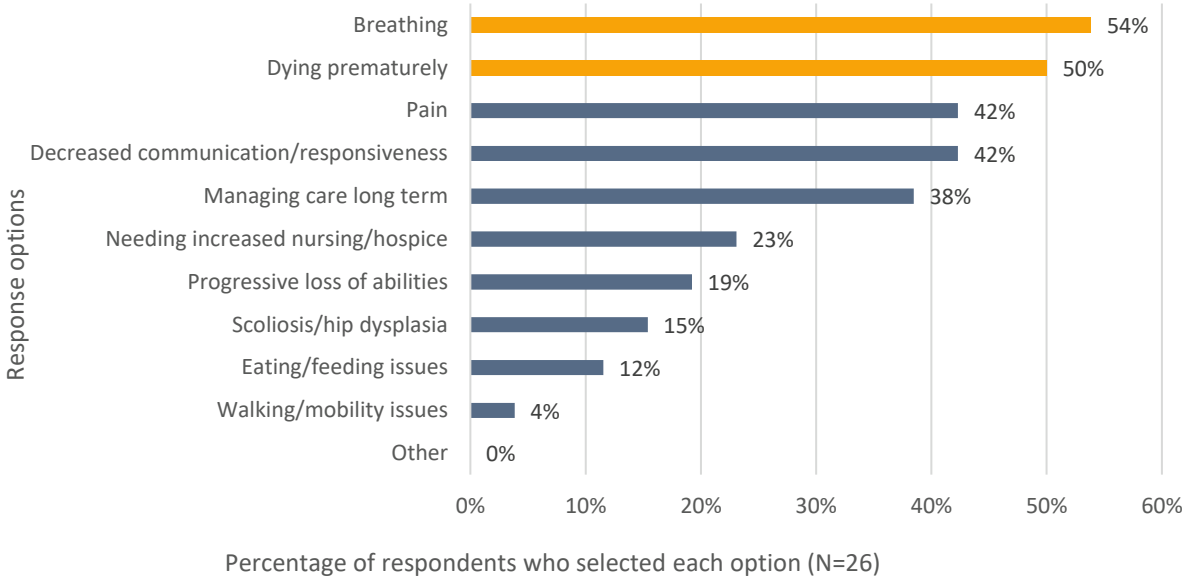
The responses for these polling questions are not considered scientific data but intended to show preferences and to complement the patient comments made during and after the meeting. Response options selected by 50% or more of respondents are shaded in **yellow**.




Q2. What are the most troublesome MLD-related health challenges your loved one has ever had? Select TOP THREE
Response options
Speech/communication 63%
Mobility/balance 48%
Feeding/swallowing/constipation 48%
Tone/muscle cramps/rigidity 44%
Pain/irritability 26%
Respiratory 19%
Cognitive/memory 19%
Seizures 11%
Behavior 7%
Vision 4%
Incontinence 4%
Other 0%
0% 10% 20% 30% 40% 50% 60% 70%
Percentage or respondents who selected each option (N=27)

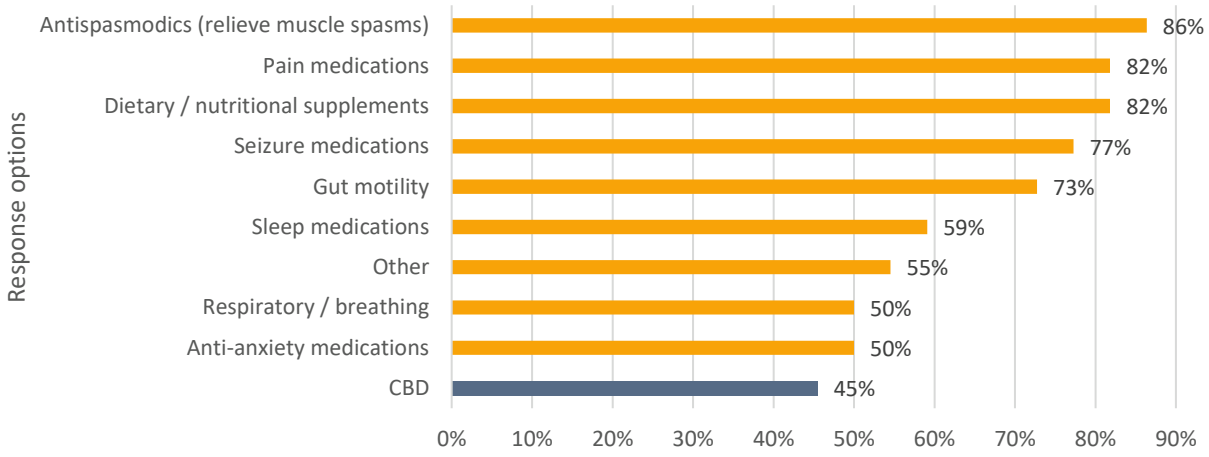

Q3. What specific activities of daily life that are important to YOUR LOVED ONE are they NOT able to do or struggle with due to MLD? Select TOP THREE
Response options
Communication 85%
Walking/mobility 62%
Feeding/eating/swallowing 58%
Social interactions/friends 42%
Breathing independently 15%
Other 12%
Traveling 8%
Sleeping 8%
Attending school/education 4%
Sitting 4%
0% 10% 20% 30% 40% 50% 60% 70% 80% 90%
Percentage of respondents who selected each option (N=26)

Q4. What worries you most about your loved one's condition in the future? Select TOP THREE



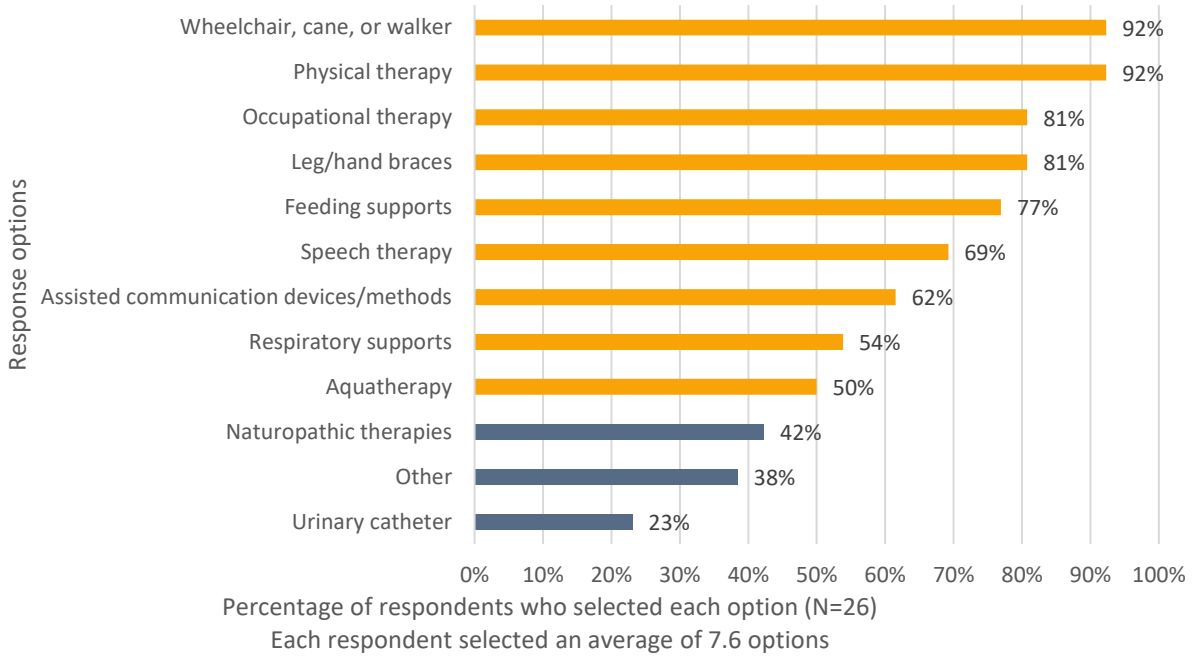
Percentage of respondents who selected each option (N=26)

Q5. What types of medications has your loved one used (currently or previously) to treat symptoms associated with MLD? Select ALL that apply

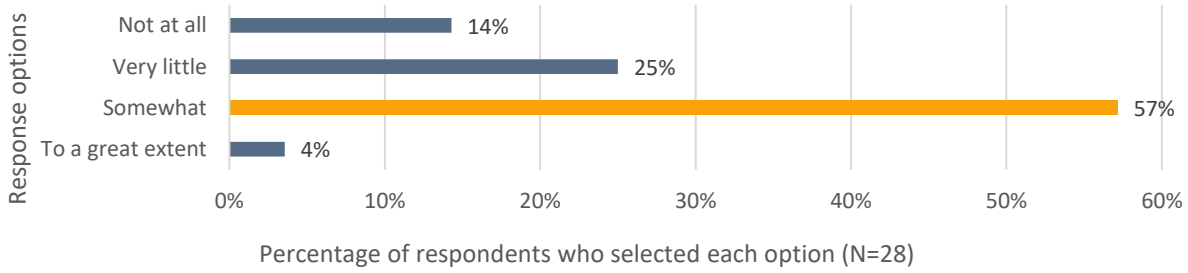


Percentage of respondents who selected each option (N=22)
Each respondent selected an average of 6.6 options

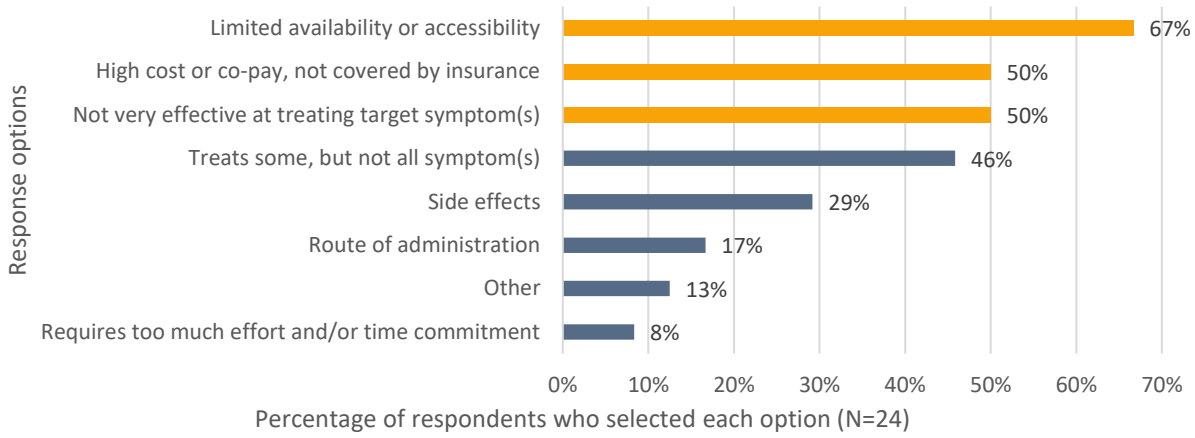
Q6. Which therapies/supports has your loved one used (currently or previously) to help manage the symptoms of MLD? Select ALL that apply



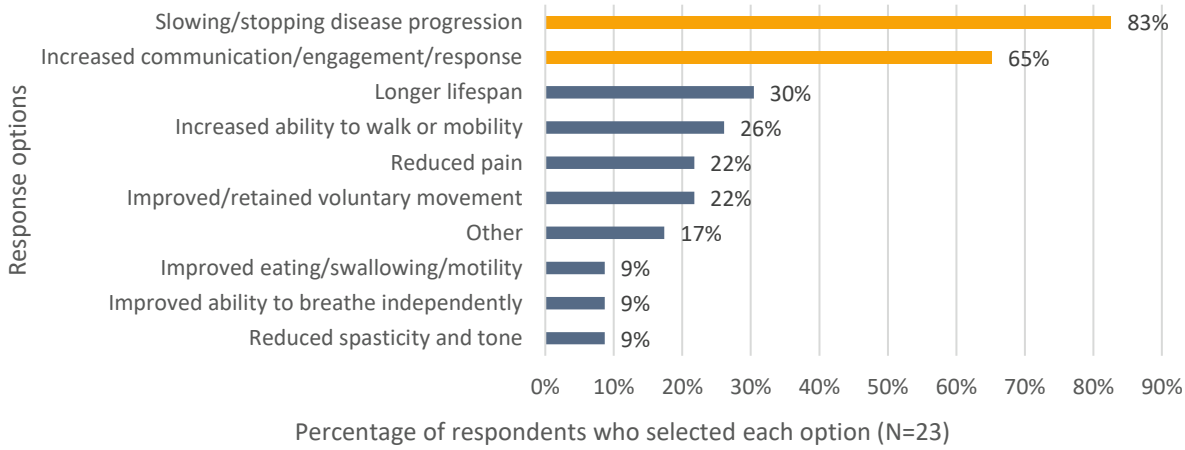
Q7. How well does your current treatment regimen treat the most significant symptoms of MLD?



Q8. What are the biggest drawbacks of your current approaches to treatment? Select up to THREE



Q9. Short of a complete cure, what would you look for in your ideal therapy for MLD? Select TOP THREE



Appendix 6: EXPERT REFLECTIONS

The following seven Expert Reflections were derived from comments made during the Adjunct MLD Scientific Meeting on November 18, 2022. The Adjunct MLD Scientific Meeting agenda is in **Appendix 7**, and biographies of the expert clinicians and researchers are in **Appendix 8**.

Expert Reflection 1: Earlier means of diagnosis, such as newborn screening, is required to help alleviate MLD burden of disease.

The experts who attended the Adjunct MLD Scientific Meeting discussed what they heard from families at the EL-PFDD meeting: **MLD symptoms are severe and the impacts of this disease on both patients and their families are profound**.

MLD burden of disease is not confined to the devastating effects on the individual with the illness. Families are forced to make complicated choices when they are facing treatment decisions for their children; these choices impact other family members, particularly siblings of affected children. Caregiver burden includes opportunity costs, lost productivity and psychosocial effects on caregivers and other family members. A recent international study demonstrated that MLD caregivers suffer disproportionate levels of anxiety, depression, physical pain, and discomfort. The MLD burden of disease includes the substantial direct expenses of medical care as well as societal costs. All of these things need to be considered when measuring the effects of therapy.

MLD has a very early neurotherapeutic window. Time between disease onset and diagnosis is a challenge for many rare diseases. Unfortunately, this is particularly challenging for a rapidly progressive disorder such as early onset forms of MLD, where motor and cognitive functions deteriorate rapidly. Indeed, it is incredibly rare for a non-symptomatic child with MLD to be diagnosed, yet this early diagnosis is necessary for the gene therapy and other definitive therapies to be optimally effective or curative. Newborn screening for MLD will be a crucial piece for MLD therapies. With early diagnosis of non-symptomatic patients and expanded access to therapies in the US, experts believe MLD will become a managed and treatable condition. Until newborn screening for MLD is implemented, the only patients to benefit from gene therapy and other potentially curative therapies are those who already have an affected sibling.

Newborn screening will permit more children to be treated with curative intent. The efficacy of earlier treatment was demonstrated by the gene therapies applied to presymptomatic younger siblings. Newborn screening will also allow a greater MLD disease understanding especially regarding genotype-phenotype variations.

MLD Expert Recommendations:

- **Newborn screening for MLD must be developed and implemented immediately to ensure the presymptomatic diagnosis of all individuals with this disease**. The existing reliable, precise and specific diagnostic tools for newborn screening in MLD need to be widely implemented.
- **More timely diagnosis is required for individuals who are experiencing symptoms.** This includes individuals with later forms of the disease, so that they too may potentially benefit from therapies.

Expert Reflection 2: Hematopoietic stem cell therapy for MLD is controversial.

The experts who attended the Adjunct MLD Scientific Meeting discussed what they heard from families at the EL-PFDD meeting: **HST was the only treatment option available for many, especially later diagnosed or more symptomatic patients. Parents described how difficult it was to make the HST treatment decision. Even in the very best-case scenario, HST does not offer a cure and only slows MLD-related deterioration. Some patients experienced GVHD, septic shock and death.**

Although HST was considered to be one of the only treatment options for years, there is little scientific evidence to support this approach, and existing studies have demonstrated very limited efficacy even in early diagnosed patients. Experts agreed that bone marrow transplant does not meet that bare minimum of a safe or effective treatment for patients with MLD, especially the early onset population. In addition, HST has significant safety issues, including a high mortality rate of 10-20%, depending on the patient's situation and availability of well-matched donors. Although it may modify the course of MLD, it is not curative, and patients still progress and deteriorate.

MLD Expert Recommendation: Experts agree that stem cell transplants can no longer be considered a treatment option for presymptomatic MLD patients, because of lack of evidence, safety issues, and lack of efficacy. Clinical trial opportunities offer far better outcomes than HST. HST may be considered in the early diagnosed juvenile or adult patient who has no other options. For those who are not eligible for a clinical trial, symptomatic support is recommended.

Expert Reflection 3: Adult onset MLD patients have an urgent need for treatment options.

The experts who attended the Adjunct MLD Scientific Meeting, discussed what they heard from families at the EL-PFDD meeting: **Those with adult onset MLD urgently need efficacious therapies and have an enormous degree of interest in participating in clinical trials.**

All therapy development to date has targeted the earlier onset forms of the disease, leaving few options for those with later onset forms of MLD. Slower disease progression and greater disease variability makes selection of appropriate endpoints more challenging. Experts discussed ways to make gene therapy, among other therapies, available to patients with later onset forms of MLD. This included clinical trials which would not only offer potentially beneficial therapies to those enrolling in the trials in the short term but may eventually lead to the approval of therapies for these patients in the long term. In order to enable clinical trials for later onset MLD, the experts discussed some of the tools and needs outlined at the EI-PFDD meeting:

- Biomarkers offer complementary tools to assess disease progression and burden in adult MLD populations
- Measuring cognitive skills and behavior function is important in adult onset MLD to determine progression and stabilization
- Motor function-based instruments may still be appropriate in adult patients
- Adaptive clinical trial designs are required for adult onset MLD patients, including non-concurrent controls

MLD Expert Recommendation: Clinical trials and treatments, which consider surrogate endpoints, would be valuable for the adult MLD patient population. We have an opportunity to forge a fruitful collaboration between the MLD community and regulators by adapting to the unique challenges of adult MLD.

Expert Reflection 4: Treatment inequity for MLD needs to be addressed.

The experts who attended the Adjunct MLD Scientific Meeting, discussed what they heard from families at the EL-PFDD meeting: **Families are desperate for therapies for their loved ones, yet barriers to treatment have created a lack of equity with regards to MLD treatments.**

Experts discussed equity concerns and issues.

- With HST, there are biological inequities in finding a matched donor. Currently, for allogeneic transplant, a match can be found 80% of the time for the Caucasian population, 50% in the Hispanic population, and 30-35% in the Black population.
- Given the limited number of expert trial sites for MLD, patients experience regional inequity and access to effective gene therapy and other potentially curative therapies. This can exclude patients from lower financial means from having access to therapy.
- Gene therapy is currently recommended only for presymptomatic patients with late infantile and early juvenile MLD or very mildly symptomatic patients with early juvenile MLD who are still able to walk independently and without overt cognitive decline. Individuals with late juvenile MLD may have access to a gene therapy clinical trial outside the U.S., and only in presymptomatic or very early symptomatic stages.

MLD Expert Recommendation: Many treatment inequities can be addressed through the expedited approval of new MLD therapies.

Expert Reflection 5: All MLD patients, especially those who are already symptomatic, require treatments that can slow or stop disease progression.

The experts who attended the Adjunct MLD Scientific Meeting, discussed what they heard from families at the EL-PFDD meeting: **Parents want a treatment for the vast majority of patients with MLD who are already symptomatic.**

Experts acknowledged hearing parents' incredible distress of watching a child deteriorate neurologically, slip away from the family, and lose the ability to communicate all the while knowing that there is nothing they can do and nothing their doctors can do to stop that process. Parents clearly communicated they understand and are willing to accept the risks of emerging therapies.

The introduction of gene therapy is a game changer for MLD. While gene therapy has demonstrated efficacy for those who are presymptomatic, this treatment also has the potential to stop further disease progression in individuals who are showing early symptoms of MLD.

MLD Expert Recommendation: Gene therapy clinical trials for symptomatic and later onset forms of MLD, including adult onset MLD, are needed.

Expert Reflection 6: Novel clinical trial design is an opportunity to further MLD research and therapeutic approvals.

The experts who attended the Adjunct MLD Scientific Meeting discussed what they heard from families at the EL-PFDD meeting: **MLD families regard gene therapy outcomes as miraculous, with the outcomes that deviate dramatically from the natural history of MLD, and would like this option to be available for all MLD patients.**

Clinical trials offer potentially efficacious treatment options to meet an unmet need for therapies for symptomatic MLD patients, including adults. For decades, the gold standard for scientific evidence was the randomized, double blind, concurrently controlled trial. Measuring gene therapy outcomes against a concurrent control is both impractical and unethical. As MLD is a rare, life-threatening disease with a profound unmet medical need, alternate types of trial design may be appropriate to demonstrate efficacy. These include single arm trials with external or natural history controls and trial designs to accommodate small patient numbers.

MLD has years of published, rigorously conducted retrospective and prospective longitudinal natural history study data as well as large case series. Prospective natural history studies have rigorously captured the post-diagnosis disease course, and retrospective history documents the earlier pre-diagnostic stages to understand optimal timing for therapeutic interventions. This

can permit the use of a non-concurrent historical control when investigating any prospective interventions for MLD.

MLD Expert Recommendation: Because MLD is a rare, life-threatening disease with a profound unmet medical need, alternate types of trial designs are appropriate to demonstrate treatment efficacy. This may include single arm trials with an external or natural history control.

For the use of a non-historical control for single arm trials, MLD information must be obtained from natural history studies. It is imperative that well-defined standard operating procedures are implemented, including protocols to ensure the rigor of retrospectively collected data. The retrospective natural history studies must include patients representing a wide spectrum of disease severity phenotypes.

Expert Reflection 7: Considering alternative clinical trial endpoints that reflect disease modification may expand MLD research opportunities.

The experts who attended the Adjunct MLD Scientific Meeting discussed what they heard from families at the EL-PFDD meeting: **The patient community believes strongly that researchers have already assembled all the tools they need to demonstrate the efficacy and safety of treatments**. **The patient community expressed their hopes that the next generation of children affected by MLD do not have to suffer in the same way, as treatments are developed that are effective at controlling what is important to families.**

Therapeutic options for symptomatic patients or later onset patients remain very limited. For these patients, the current expectation of a "cure" should be revised to an expectation of disease modification as a clinical trial endpoint.

The FDA's guidance emphasizes that it is critical to understand the aspects of disease that are meaningful to the patient and their families in order to assess the effectiveness of a therapy. Patient and community input have an important role in defining outcomes for MLD disease modification that are meaningful for patients.

Outcome evaluations need to include family and caregiver impacts. An important and often neglected aspect of the burden of neurodegenerative disorders involves the impact on caregivers. MLD has very strong published evidence for this burden, which was further supported by the testimonies of families at the EL-PFDD. Burden of disease can be measured using individualized clinical measures in patients and caregivers, such as self-reported quality of life instruments, like the EuroQol five-dimension tool.

Motor and communication impairment can be measured. Unlike in many rare diseases, well characterized, disease-appropriate outcome measures for MLD exist. Motor dysfunction is a predominant early feature in early onset MLD. The Gross Motor Function Classification in MLD

(GMFC-MLD) is a tool that has been validated to longitudinally assess neurologic function of gross motor skills, both retrospectively and prospectively. This is a meaningful outcome measure from clinical, parent and patient perspectives. Similarly, communication disturbance is an early distinguishing feature of MLD. Many well-established and clinically validated tools exist for this, such as the Expressive Language Function Classification in MLD (ELFC-MLD).

Other important disease features must be considered for evaluation. Parents and caregivers described many other disease features that are critically important in the day to day lives of patients and families alike. Clinical outcome assessments can include measures of how patients feel and function, with neuropsychological cognitive and behavioral measures. Outcome measures for MLD pain, tone, feeding, nutrition, seizures and behaviors have been developed and will soon be validated.

MLD Expert Recommendation: We have an opportunity to create a patient-centric research landscape by conducting trials that reflect outcomes valuable to patients and caregivers. We need to select appropriate endpoints for clinical trials, including the use of surrogate and intermediate clinical endpoints. In addition to motor and communication function, other disease features, like family and caregiver impacts, are critically important in the daily lives of patients and families alike and need to be considered.

Appendix 7: Scientific Workshop Agenda, November 18, 2022

11:00 am- 11:05 am	Opening Remarks *Maria Kefalas & James Valentine*
11:05 am-11:20 am	Recap of EL-PFDD: What's Important to MLD Patients/Caregivers *Larry Bauer*
11:20 am-11:30 am	Framework for Integrating the Patient Voice into Drug Development *James Valentine*
11:30 am-11:45 am	Landscape Analysis of Tools to Evaluate What's Important to MLD Patients *Dr. Laura Adang*
11:45 am-12:30 pm	Discussion: Setting a Patient-Focused Research Agenda for Drug Development Tools Moderator: *James Valentine* Key Opinion Leaders: *Drs. Laura Adang, Barbara Burton, Samuel Gröeschel, Paul Orchard, Marc Patterson, Adeline Vanderver*
12:30 pm-12:40 pm	Opportunities to Conduct Clinical Trials in Late-Onset MLD *Dr. Marc Patterson*
12:40 pm- 12:55 pm	Discussion: Perspectives on Facilitating Clinical Trials in Late-Onset MLD Moderator: *James Valentine* Key Opinion Leaders: *Drs. Laura Adang, Barbara Burton, Samuel Gröeschel, Paul Orchard, Marc Patterson, Adeline Vanderver*
12:55 pm-1:00 pm	Closing Remarks *James Valentine*

Appendix 8: Expert Clinician and Researcher Biographies

Laura Adang, MD, PhD, Children's Hospital of Philadelphia

Dr. Laura Adang is an Assistant Professor of Child Neurology at the Children's Hospital of Philadelphia specializing in the care of children with leukodystrophies. Dr. Adang is a magna cum laude graduate of the University of Georgia's Foundation Fellowship scholarship program and a graduate of the Medical Scientist Training Program at the University of Virginia, where she received both her M.D. and Ph.D. Her graduate work in the laboratory of Dean H. Kedes M.D. Ph.D. characterized the immune evasion mechanisms of herpesvirus infections. Her work has been published in Cell, Journal of Clinical Investigations, and Journal of Virology, among others.

After graduating from the University of Virginia, she completed her pediatrics and child neurology residencies at the Children's Hospital of Philadelphia and the University of Pennsylvania. During her training, her research explored the seasonal trends of NMDA receptor encephalitis in children. She has completed additional fellowship training in multiple sclerosis and leukodystrophies as well. Her primary clinical focus is the care of children with white matter disorders and neuroinflammatory conditions. She is an active member of the Child Neurology Society.

Barbara Burton, MD, Lurie Children's Hospital

Dr. Barbara K. Burton is a Professor of Pediatrics at the Northwestern University Feinberg School of Medicine and Co-Director of the Leukodystrophy Care Center in the Division of Genetics, Birth Defects and Metabolism at the Ann & Robert H. Lurie Children's Hospital of Chicago. She is Board certified in Pediatrics, Clinical Genetics and Clinical Biochemical Genetics. Her clinical and research interests are focused on inborn errors of metabolism and newborn screening. Dr. Burton is an investigator in numerous natural history studies and clinical trials of new therapies for various metabolic disorders, including the MLD and MPS disorders. She has published over 200 peer-reviewed articles, 50 chapters in books and is an editor of two textbooks. Dr. Burton served for four years as a member of the Secretary's Advisory Committee on Heritable Disorders in Infants and Children, the federal advisory committee that makes recommendations regarding newborn seeing in the US and currently serves as Chairman of the Newborn Screening Advisory Committee of the Illinois Department of Public Health.

Samuel Gröeschel, MD, PhD, University Children's Hospital Tuebingen

Dr. Samuel Gröeschel is consultant pediatric neurologist in Tübingen, Germany, and expert in leukodystrophies. He is a PI of the German MLD natural history study. His center offers MLD treatment options like enzyme replacement therapy, hematopoietic stem cell transplantation

and gene therapy. As an MLD expert, he coordinates the European MLD guideline, is active in the MLD Initiative, the Leukodystrophy group of the European Reference Network for Rare Neurological Disorders as well as Scientific Advisor for the European Leukodystrophy Association.

Paul Orchard, MD, University of Minnesota

Dr. Paul Orchard is a Professor in the Department of Pediatrics at the University of Minnesota and serves as the Medical Director of the Inherited Metabolic & Storage Disease Program. He is interested in the use of hematopoietic stem cell transplantation (HST) and other cellular therapies for inherited metabolic diseases, as well as combination therapy in order to improve outcomes. He also has been exploring methods to modify the transplant process to decrease the toxicity associated with transplant, as well as the use of gene therapy approaches.

His research interests include:

- Hematopoietic cell transplantation of genetic disorders, including methodology to reduce transplant related toxicity and graft failure This includes the development of reduced intensity preparative regimens and defining risk factors affecting outcomes following transplantation.
- The biology of lysosomal and peroxisomal disease, including the mucopolysaccharide (MPS) disorders and the inherited leukodystrophies. This includes identification of biomarkers that can be used to define risk populations as well to assess the impact of therapeutic interventions.
- The potential for combination therapies to improve outcomes.
- Development of multi-disciplinary and multi-institutional databases to assess a better understanding of natural history, biology, and the analysis of outcomes.

Marc Patterson, MD, Mayo Clinic

Marc C. Patterson, M.D., is currently a professor of neurology, pediatrics and medical genetics at May Clinic College of Medicine and Science. He previously served as Chair of the Division of Child and Adolescent Neurology and Director of the Child Neurology Training Program at Mayo Clinic (2008-2017). He also served as Director of Pediatric Neurology at Columbia University College of Physicians and Surgeons and Morgan Stanley Children's Hospital of New York from 2001 to 2007. His research and practice are focused on rare diseases in children, including:

- Neurogenetics and developmental disorders
- Neurometabolic disorders in general
- Niemann-Pick disease, type C
- Other lysosomal diseases (including glycoproteinoses)

- Mitochondrial cytopathies
- Congenital disorders of glycosylation

These are areas in which he has published more than 300 peer-reviewed papers and book chapters. He has presented widely throughout the United States and internationally, both to professional and lay organizations. Dr. Patterson has received funding support from NIH, industry and private foundations. He is currently an editor for the Journal of Inherited Metabolic Disease. He became editor-in-chief of the Journal of Child Neurology on Jan. 1, 2014, and subsequently editor-in-chief of its open-access sister journal, Child Neurology Open.

Adeline Vanderver, MD, Children's Hospital of Philadelphia

Dr. Vanderver conducts translational research on leukodystrophies and leukoencephalopathies in order to refine clinical diagnostic tools and accelerate the development of therapeutic treatments. Along with her team of researchers, Dr. Vanderver aims to define novel homogeneous groups of patients with previously unclassified leukodystrophies and to uncover the genetic causes of these disorders; establish the molecular disease mechanisms in selected known leukodystrophies; assess the validity of advanced genetic sequencing techniques in the diagnosis of these disorders; and develop the next generation of therapeutic clinical trials through natural history and biomarker discovery studies.

She is also Program Director of CHOP's Leukodystrophy Center of Excellence (LCE), which is focused on creating new standards of care for children with leukodystrophies by advancing leukodystrophy gene discovery, creating new therapies, and supporting and advocating for patients and their families. In parallel with this strong clinical program, Dr. Vanderver's preclinical and clinical research projects aim to discover molecular therapeutics that target the genetics of leukodystrophy subtypes. In addition to her clinical and research efforts, Dr. Vanderver leads the Global Leukodystrophy Initiative, an advocacy group that includes parents, clinicians, and researchers, to raise disease awareness and ensure that patients receive appropriate social and medical support.