PMD FOUNDATION
PELIZAEUS-MERZBACHER DISEASE

Pelizaeus-Merzbacher Disease Patient-led Listening Session

August 22, 2023
1:00 – 2:30 PM

OBJECTIVES OF THE SESSION

- Educate FDA staff on the complex issues of Pelizaeus-Merzbacher Disease ("**PMD**"), and the variety of physical manifestations and body systems affected.

- Educate FDA staff on the serious impact of the disease manifestations on patients, the effects on quality of life, the current lack of FDA approved treatments, the tremendous unmet medical need, and preferences for treatments and outcomes.

SUMMARY OF TOPICS DISCUSSED

- Provide an overview of PMD from its 19th century discovery to the present-day understanding about genetics, cellular and molecular mechanisms

- Share the most common PMD health problems and goals of care for patients

- Describe symptoms and health effects most burdensome to people with PMD

- Describe symptomatic treatments of the disease and unmet medical needs

PATIENTS REPRESENTED

- Six patient caregivers presented and spoke about their experience representing nine patients diagnosed with various types of PMD.

MEDICAL PROFESSIONAL SPEAKER

- Dr. Adeline Vanderver, MD – Children's Hospital of Philadelphia

CONSULTANT

- Hyman, Phelps, & McNamara, P.C.

FDA DIVISIONS REPRESENTED

FDA staff from 18 different offices/divisions from 3 different Centers attended

Office of the Commissioner (OC) – 3 *offices*

- OC/OCPP/PAS – Office of Clinical Policy and Programs/ Patient Affairs Staff *(organizer)*
- OC/OCPP – Office of Clinical Policy and Programs
- OC/OCPP/OPT – Office of Clinical Policy and Programs/Office of Pediatric Therapeutics

Center for Biologics Evaluation and Research (CBER) – *3 offices/divisions*

- CBER/OCD – Office of the Center Director
- CBER/OCD/PS – Office of the Center Director/Policy Staff
- CBER/OTP/OCE/DCEGM/GMBII – Office of Therapeutic Products/Office of Clinical Evaluation/Division of Clinical Evaluation General Medicine/General Medicine Branch II

Center for Devices and Radiological Health (CDRH) – *5 offices/divisions*

- CDRH/OPEQ/OHTIII – Office of Product Evaluation and Quality/Office of Health Technology III
- CDRH/OPEQ/OHTIII/DHTIIIB – Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology III B
- CDRH/OPEQ/OHTIII/DHTIVB – Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology IV B
- CDRH/OSPTI/DAHRSSP/PSE – Office of Strategic Partnerships and Technology Innovation/ Division of All Hazards Response, Science and Strategic Partnerships/Patient Science and Engagement
- CDRH/OSPTI/DDH – Office of Strategic Partnerships and Technology Innovation/ Division of Digital Health

Center for Drug Evaluation and Research (CDER) – *7 offices/divisions*

- CDER/OCD – Office of the Center Director
- CDER/OCOMM/PASES – Office of Communications/Professional Affairs and Stakeholder Engagement
- CDER/OND/ODES/DCOA – Office of New Drugs/Office of Drug Evaluation Sciences/Division of Clinical Outcome Assessment
- CDER/OND/ON – Office of New Drugs/Office of Neuroscience
- CDER/OND/ON/DNI – Office of New Drugs/Office of Neuroscience/Division of Neurology I
- CDER/OND/ORDPURM/DRDMG – Office of New Drugs/Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine/Division of Rare Diseases and Medical Genetics
- CDER/OTS/OB/DBI – Office of Translational Sciences/Office of Biostatistics/Division of Biometrics I

Non-FDA Attendees

- Reagan Udall Foundation

AGENDA

1. **Welcome Remarks & Introductions** – FDA Patient Affairs
2. **PMD Foundation**
3. **Reasons we requested a session**
4. **What is PMD and Clinician Overview**
    a. Types of PMD and disease classification
    b. Clinical expert treating a number of patients with this rare disease will provide observations and insights about the patient burden and unmet needs from the lens of those patients she cares for in her practice.
5. **Patient Perspectives** – 6 Patients/Caregivers
6. **Summary**
7. **Open Discussion Q&A with FDA Centers & Offices**
8. **Closing Remarks** – FDA Patient Affairs

WELCOME by FDA PATIENT AFFAIRS

Brief welcome statement: we'll be hearing from patients, caregivers and advocates today. FDA staff attending from three FDA centers and the Office of the Commissioner. Financial disclosures read aloud.

PMD FOUNDATION

The PMD Foundation (**"PMDF"**) requested the patient listening session. PMDF is a 501(c)3 family-driven foundation that proactively serves those affected by Pelizaeus-Merzbacher Disease (the PMD community) by supporting programs of education, research, service, and advocacy. PMDF is dedicated to providing patients and their families with information about their disease and assistance in identifying sources of medical care, social service, and genetic counseling; establishing a communications network among families; increasing public awareness and acting as an information source for health care providers; and promoting research into causes, treatment, prevention and cure of PMD.

Our logo is a lighthouse. Before the Foundation was founded there was very little information available to newly diagnosed families. The information that was available was not always current or correct. The PMD Foundation provides a beacon for PMD families to unite and to get the information and direction they need to help navigate the difficult diagnosis of PMD.
www.pmdfoundation.org

REASONS WE REQUESTED A SESSION

We requested the patient listening session to share the complex issues of PMD, the various disease manifestations and the body systems that are affected. We wanted to share with FDA staff the serious impact and effects this disease has on the quality of life for the PMD patient as well as their caregivers. To be clear there are currently NO FDA approved treatments and there is a tremendous ongoing unmet medical need. We also shared our patient preferences for treatments and outcomes.

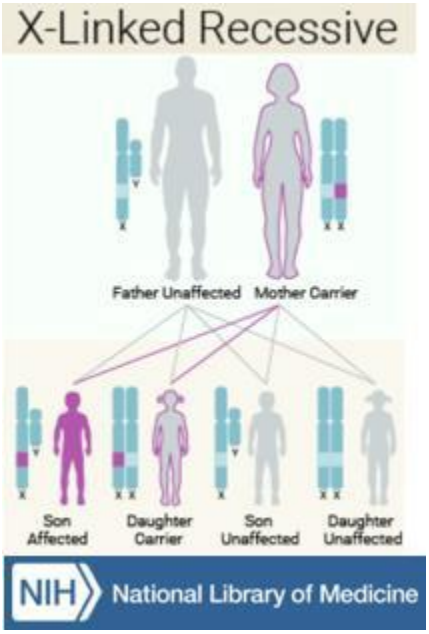
WHAT IS PMD and CLINICIAN OVERVIEW

PMD was first used in the 19th century to describe a disorder in children with little to no myelin (Drs. Friedrich Pelizaeus and Ludwig Merzbacher). Myelin is the insulating sheath around nerve fibers in the central nervous system and peripheral nervous system. Initially the term was used to describe all patients with hypomyelination, but specific genetic causes have been found for various disorder and this only refers to patients with changes in the gene PLP1. The prevalence is estimated at 1 in 200,000 to 500,000 individuals.
Types: **PMD is classified as classic or conatal based upon the severity and onset of symptoms**. Allelic disorders exist that are generally less severe than PMD [spastic paraplegia type 2 (SPG2)]

Genetics
PMD is caused by mutations in the proteolipid protein 1 (PLP1) gene.

The PLP1 gene, located on the X chromosome, is responsible for encoding the proteolipid protein. This protein is a primary component of myelin, an insulating coating essential for nerve signal transmission in the central nervous system. Notably, PLP1 is exclusively expressed by **oligodendrocytes**, which are the myelinating cells of the central nervous system.

PMD exhibits an **X-linked** inheritance pattern. Consequently, boys are severely affected. However, female carriers, while typically asymptomatic, can present mild to moderate symptoms in adulthood.

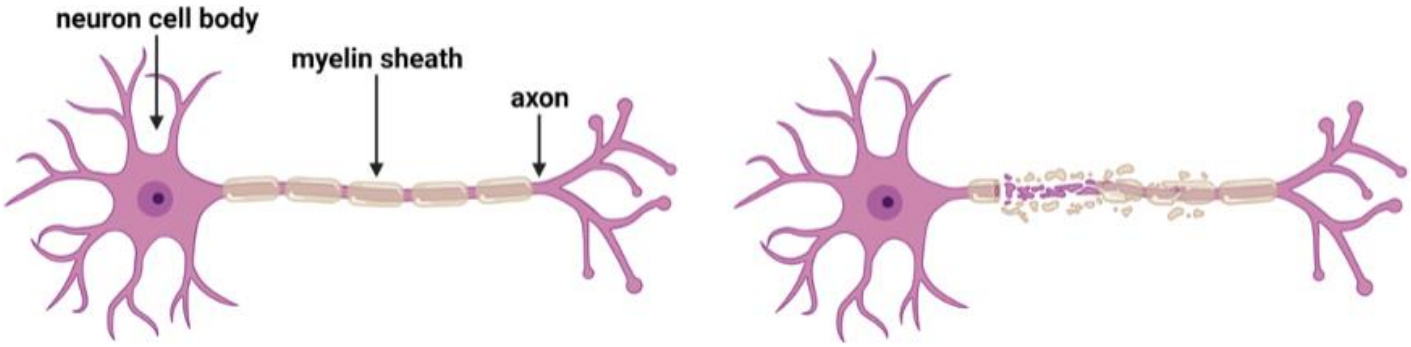


The genetic landscape of PMD is diverse. A broad spectrum of disease-causing mutations has been documented. These encompass missense, nonsense, splice site mutations, and even supernumerary copies. 70% of PMD patients possess a duplication of the PLP1 gene.

While genetic testing stands as a reliable method for diagnosing PMD, it's concerning to note the frequent misdiagnoses occurring outside established medical centers. As effective therapies come online, it will be important to have expanded and earlier testing.

Cellular & molecular mechanisms
Central to PMD's pathology is the compromised myelination within the central nervous system. Myelin, as you're aware, is a vital insulating substance, pivotal for the robust and efficient transmission of neural signals.

The molecular mechanisms of PLP1 mutations are well understood. All the various PLP1 mutations inflict considerable endoplasmic reticulum stress upon oligodendrocytes, and ultimately cause their death. These cells, which are exclusively found in the CNS, are responsible for the production of myelin.



A consequent reduction in oligodendrocytes leads to diminished myelin. And with insufficient insulation, neurons falter in their communication capabilities.

This disruption at the cellular level translates to the tangible motor and developmental manifestations we recognize as the hallmarks of PMD.

In essence, PMD can be perceived as a cascading chain of molecular disruptions, leading to tangible and often severe clinical outcomes.

Clinical practice point of view
One important barrier is around the ability of physicians to accurately diagnose individuals affected by PMD, and to support families around medical care early in the diagnostic process. Specifically, conatal patients may present acutely due to extreme hypotonia and may need complex early management decisions. Many patients have difficulty acquiring common early motor milestones which is non-specific and may not lead to appropriate early testing. MRI can be misleading early on when myelin is not yet complete and lead to misdiagnosis. Continued difficulties in using genotype to predict likely disease progression.

The motor impairments seen in PMD are amongst the most profound seen in the leukodystrophies, and result in only a fraction of affected persons achieving milestones beyond some of the very earliest, like smiling and head control. In data collected from individuals followed by our team, a relatively small percentage of persons achieve skills like independent sitting and can even lose previously acquired milestones over time. This degree of motor impairment results in complete dependence for care and limited ability to use adaptive equipment. These motor impairments affect not only gross motor skills, but also hand use and communication.

Common health problems
PMD patients face an array of health challenges. We observe a spectrum that spans muscular, gastrointestinal, respiratory, neural, and developmental realms.

Muscular manifestations include spasticity, hypotonia, and ataxia, leading to decreased control, balance, and coordination of limbs. Compounded by these, patients often face substantial movement challenges, ranging from basic actions such as crawling and rolling over to more complex motor functions. The inability to independently support the head or trunk and the presence of tremors.

From a gastrointestinal perspective, PMD patients grapple with issues like constipation, reflux, and incontinence. Concurrently, respiratory challenges such as laryngomalacia, excessive saliva, and potential need for a tracheostomy can arise. Dysphagia complicates feeding, and musculoskeletal issues, most notably scoliosis, can develop.

Neurologically, we see vision disturbances like nystagmus, potential seizures, and speech impediments, often leading to reliance on nonverbal communication. These neurological issues frequently necessitate specialized schooling. Furthermore, delays in growth, development, and comprehension become evident milestones.

In summary, PMD presents a multifaceted panorama of health complications, each amplifying the need for comprehensive medical support and interventions.

- Tight or stiff muscles (spasticity)
- Muscle weakness (hypotonia)
- Loss of muscle control, or coordination of arms/legs, head titubation (extra pyramidal movement abnormalities)
- Gastrointestinal Issues (e.g., constipation, reflux, bowel incontinence)
- Difficulty breathing (laryngomalacia, excess saliva, stridor or tracheostomy)
- Feeding issues (e.g., difficulty swallowing “dysphagia” and failure to thrive)
- Urogenital issues (incontinence, UTI)
- Musculoskeletal (scoliosis, fractures, osteopenia)
- Vision issues or abnormal eye movements (nystagmus)
- Seizures are possible
- Speech or communication difficulty “dysarthria” (nonverbal cues, min ability to speak or vocalize)
- Ability to access learning at least in part due to motor impairment and vision difficulties (specialized schooling or program)

Clinical Trial Landscape
No disease modifying therapy as of now. Treatments focus on relieving symptoms and improving quality of life. Ultimate goal is to restore oligodendrocyte numbers and myelination.

- Gene correction
- Oligodendrocyte transplants
- Suppress mutant protein (e.g., ASO)
- Reduce oligodendrocyte stress (ER stress)

There is ongoing research and clinical trial planning.

Goals of Care for PMD
Symptomatic treatments are also needed:

- Improve QOL (quality of life)
- Reduce pain
- Increase probability of survival
- Stabilization of tone to prevent orthopedic complications. Improve orthopedic/bone health
- Improvements in truncal stability to allow for better respiratory and GI care, and ability to use adaptive environments
- Earlier management of feeding challenges to improve nutrition and bone health
- Improved adolescent and young adult care to provide comprehensive pulmonary, GI and orthopedic management of disease complications as patients transition into adulthood.

PATIENT PERSPECTIVES

Six patient caregivers presented and spoke about their experience representing nine patients diagnosed with various types of PMD.

Caregiver 1, Father of 21-year-old diagnosed with Classic PMD at 18 months old

We were very fortunate to receive the diagnosis so early. Like many with PMD, our son was initially misdiagnosed with Cerebral Palsy. My wife and I had hoped to have additional children, however, my wife was tested and confirmed to be a carrier for PMD. Once we received the diagnosis, we elected not to have additional children for fear that they may be affected as well. Although my wife does not come from a large family, there was no history of this disease in her family as far back as anyone could remember.

For the past 21 years every hope and dream that my wife and I had for our future changed the day we received the diagnosis. Our entire lives have been reshaped around providing the best possible care for our son. He has had to endure 5 surgeries in the past 6 years due to the progression of the disease. These surgeries include a feeding tube, osteotomies on both of his hips, spinal fusion and the installation of an intrathecal baclofen pump to manage his pain and spasticity.

Our son is non-verbal, non-ambulatory, incontinent and relies on complete care and supervision for safety 24/7/365. We are very blessed in that though he has faced much adversity he has a smile and personality that will light up any room. He tends to go with the flow much better than we do. Due to his size, I have become the primary caregiver for him over the last 6-7 years. Throughout his time in public school, he has

required a one-to-one aid to assist in all of his activities. At school he received all of his therapies as well as his social interaction with peers. He has loved school all these years and they loved him as well. He has now aged out of school. Now that school has ended, he is with me 24/7/365. In addition to being his caregiver I am now also his Physical Therapist, Occupational Therapist, Speech Therapist and his social entertainment.

The worst symptom for all of us, I believe, is the fact that he is non-verbal. While we have tried many communication devices, because the disease affects his motor control there are really no good options. The inability for him to tell us what he needs, wants or how he is feeling leaves us to do our best to guess. I have become pretty good at knowing what he needs just by sounds or facial expressions and pure instinct. I can't imagine how frustrating it has been for him for 21 years to not be able to express himself to all those around him. This is especially difficult for us as caregivers that want to help when there is discomfort. You try your best not knowing if you are helping or actually making things worse.

The personal care required for him also makes it difficult for him and the caregivers. Requiring complete assistance must be frustrating for him. But it also means the caregivers' days are built completely around his schedule and routine. It takes an hour to get him up in the morning and in his wheelchair to start his day. He requires 3 tube feedings per day that take 1 ½ to 2 hours to complete. Due to the amount of fluid he receives, he also needs to be changed every 2 hours as he cannot tell you when he needs to be changed. This makes travel very difficult and going out in public in general difficult. At the end of the day, it takes an additional hour to get him ready for bed. Due to this schedule and the need to utilize the equipment in our home it is often easier to not leave the home. This leads to self-imposed isolation. In fact, I have not had a vacation since 2010 as it is actually more frustrating to try to go places and overcome the physical obstacles of his care than to just stay home. This is not great for him or the caregivers. However, as physically exhausting as the day-to-day care is. It becomes even worse when you disrupt the schedule and routine.

Now that he has aged out of school there are no good day programs that would be able to accommodate his needs in our county. So, I will be his full-time caregiver as I try to work a full-time job and also try to be a good husband. While we would be eligible to have some assistance come into the house that poses its own difficulties. While a physical break would be welcome, having a person lingering around our home caring for him takes away any privacy you may have so you cannot truly relax. So again, it is easier to just take care of him myself.

The biggest challenge that my wife and I have moving forward is finding a good long term care solution. Because we have no other children, there are no siblings to provide care if anything happens to me. I am the youngest of 8 children. My two oldest siblings have already passed. So, we have no family option to provide care in a crisis. Our biggest fear is him ending up in a hospital for months if anything happened to me and then being placed in the first (not the best) opening in a skilled nursing home. Should this happen, he would be surrounded by many 80–90-year-olds, perhaps with dementia, and would not be a good social environment for him to thrive. We live in great fear that he would be forced to live his remaining days in a bad situation should anything happen to me as my wife would not be able to care for him.

We pray that we will be able to see a treatment or a therapy in our lifetime even though it may not help him. But short of a complete cure, a treatment that would ideally allow for communication, and lessen the physical aspects of the disease which would allow for more independence and a better quality of life for those with PMD as well as the caregivers would be a victory. Though a treatment for my son due to his age is not realistic. If I think about the risks we would be willing to take, if there was an option available knowing what I know now and having the experience of living with PMD for 21 years, we would have been willing to

accept any risk that did not involve putting my son in more pain for the opportunity to give him a chance at a better quality of life that would give him more independence and joy.

Primary symptoms	Biggest challenges / impact	Care	Unmet medical need
Nystagmus Poor motor control (gross and fine) Non-verbal Non-ambulatory Incontinence Developmental delays	Communication Accessibility Safety awareness Day-to-day care Adjusting every facet of our lives around his care	**Past and current treatments**: Symptomatic only with therapies PT, OT, Speech, Vision **Therapies**: Has had 5 surgeries to fight the progression of the disease **Care Team**: Monitored by the Leukodystrophy Care Team at CHOP but is aging out	**Long term concerns:** I am the primary caregiver. As I age it is becoming more and more difficult to provide the physical daily care. If anything happens to me, my wife and son will be in immediate crisis. **Most significant unmet medical need:** As he ages out of school, being able to continue the therapies that he needs to avoid any regression and to fight the progression of the disease.

Caregiver 2, Father of 33-year-old diagnosed with Classic PMD at 9 months old

My son's form of PMD shows very severe motor impact, spasticity, hypotonia and muscle problems. He is not able to move himself around. He is not able to drive a power wheelchair at this point. He's had surgery for scoliosis and severe lordosis. He has a compromised swallowing reflex that required placement of a G tube when he was 13. Any kind of medication or feeding (even water) has to go through the G tube. My son had vocalizations a long time ago but never really any true speech. He had excellent support in school for 22 years. He has significant reflux that also causes a problem managing his secretions. He has very poor bone density his entire life and he remains at a very high risk for fractures, even by just moving him around.

Communication is the biggest challenge because he cannot speak, nor vocalize. We try to figure out his needs and wants and we did develop a sense for it. There are ways to ask him a question that he can respond to in a sort of minimal way if you know what you're looking for but really that's a hard one for us. His mobility is completely dependent on all of us who care for him as I said he's not able to drive a power chair anymore. I've got to have a specialized vehicle just to bring him to a doctor. He needed specialized transportation the whole time he was in school so that's an extra burden on the family for sure. All of his feeding, hydration, medication, everything in his G tube has to be managed very carefully. I'm changing those tubes out myself at home. It's just too frequent a thing to go to a doctor to do it. We manage all of the supplies for his feeding and make sure that his feeding schedule is very carefully maintained. It's a very tight schedule. He does 3 feeds during the day and an overnight feed using a pump at night.

My son has been through multiple orthopedic surgeries for hip dislocations. When younger, he had a femur fracture near the growth plate. He had major spinal correction when he was 14 where they put in a couple of rods, cables and many screws to hold everything together and to correct severe scoliosis that was extremely painful for him and was impacting his ability to breathe. At around 13 years old we went to Shriners in Montreal for infusions of pamidronate to try and plant some calcium in his bones. It was off-label, but Shriners had pioneered the technique on kids with osteogenesis imperfecta and it also worked on our son. There's still evidence today of the added calcium in his bones.

He's had an intrathecal baclofen pump since just before his spine surgery back in 2004. That's been a great thing in terms of managing his spasticity. It gets refilled a couple times a year. It gets replaced every five to six years which is yet another surgery. We continue to manage breathing difficulties for him with a couple of different inhalers. We have to control the oral secretions. Atropine drops help but don't fix the root of the problem. I am his physical therapist and his occupational therapist. I provide that range of motion for him several times a day. We use a supine stander every day. He has various splints. He's got dynamic ankle foot orthotics (DAFOs). He's got hand splints to prevent contractures and that's important just to keep him comfortable. His care team starts with me but there are a lot of people involved. We have caregivers coming into the home every day. I work full time in a school system for the entire school year. If a caregiver does not come, I have to leave work and come home that day to be that care provider.

Our long-term concerns include managing his spasticity and watching out for any contractures in the muscles. The fracture risk remains very high all the time with just moving him around. There is risk in going out anywhere. Managing the feeding and reflux is 100% of the time day and night around the clock care. I'm much older now and I don't know what I will do to care for him in the future. I don't want to see him end up in a nursing facility. I don't think that's a good situation for him. I don't know what that future holds and that's a concern for me. I would love it if he could communicate better. Keeping him engaged and stimulated is an ongoing process that all caregivers work together to make happen. It's always an ongoing need to keep him correctly positioned and comfortable. We're always looking at changing things and upgrading things. In terms of unmet medical need, we really need some treatments to reduce the impact of PMD. Again, my son is almost 34 so realistically treatment is going to be limited. If there is any possibility that future trials can allow for older patients that would be awesome even if it's not technically part of the study. Any treatment that can help him is absolutely worth it. I would make a very liberal accounting of the risk in terms of improvement for him because I am getting older and concerned for his future.

Primary symptoms	Biggest challenges / impact	Care	Unmet medical need
Severe motor impact: hypotonia, spasticity and muscle spasms, no independent movement, scoliosis/lordosis Compromised swallowing reflex, requires gastronomy tube for feeding No speech or vocalizations	Communication is his biggest challenge: making his needs and wants known is extremely challenging Mobility is dependent on caregivers (He is not able to drive a power chair) Requires specialized vehicle for transportation	**Past and current treatments:** Multiple orthopedic surgeries: hip dislocation, femur fracture, major spinal correction (rods, cables) Pamidronate infusion (off label, at Shriners' Montreal) age 13-18 Intrathecal baclofen pump to manage spasticity	**Long term concerns:** Spasticity and contractures Ongoing risk of fractures Feeding, reflux, managing secretions Communication and engagement/stimulation Positioning and comfort **Most significant unmet medical need:** Treatment to reduce impact of PMD on him.

Significant reflux Osteopenia- high risk of fractures	Feeding, hydration, and medication are all via G-tube, necessitates very careful caregiver management	Managing breathing difficulties with fluticasone and albuterol; secretion control with atropine as needed **Therapies:** Parent-administered physical therapy, use of supine stander, range-of-motion exercises Use of foot orthotics and hand splints daily to prevent contractures **Care Team:** Parents, multiple caregivers, primary care doctor, neurologist, physiatrist, gastroenterologist, orthotist, ophthalmologist, nutritionist, equipment support	Hope that any future treatment trials will allow for older patients. Even small gains would be worth potential risks Aging primary caregiver and care manager (father) impacts his long-term care and quality of life

Caregiver 3, Father of 10-year-old diagnosed with Classic PMD at 6 months old

My son was born in 2013. Our youngest of three children. From the moments we first laid eyes on him, we were in love. He was a beautiful baby with nothing out of the ordinary. Lower weight than our other two children, but within the healthy range. He latched on for breastfeeding, no nystagmus, no stridor. We picked his name, got his pictures, completed all the necessary paperwork, and only the hearing test remained. That test sent us down a path we have not looked back from again. He was diagnosed with Auditory Neuropathy Spectrum Disorder (ANSD), later nystagmus, followed by hypotonia, and lately hypoglycemia. At around 6 months old an MRI and then a blood test provided the answers to our search. We went for a voyage and a storm was brewing on our path. The feeling of loneliness and desperation is still profound to this day. Death is a problem none can solve, but we uncovered its name as it lurked inside our son's body: PMD (Pelizaeus-Merzbacher Disease).

A search on medical journals about PMD provided us symptoms and diagnosis. It read: "Clinical signs usually include some combination of nystagmus, stridor, spastic quadriparesis, hypotonia, cognitive impairment, ataxia, tremors. Seizures and perinatal stridor are rare signs and are typically seen only in the most severe cases. Severe [PMD] is often fatal during the first decade of life, typically due to respiratory complications." This is a progressive disease that is going to cut our son's life short and make our living days frightful. Our

neurologist provided us with no lighthouse for navigational aide, nothing to steer away from dangerous waters. There is no cure, there are no medical trials, there is little to grab onto out there. But she did say make him happy. Love him. And that's what we have done as we joined a Facebook community of parents, and later the PMD Foundation whose lighthouse symbol gives hope to future children and parents.

My brother-in-law passed away in 2017 at 43 years old, the same day my son turned 4 years old. He had been diagnosed with CP all his life. After learning about PMD, I put two-and-two together, and a week before he passed away, he was given the PMD diagnosis officially. My son's cousin is 3 months older than him, whom I helped get tested for PMD because he was not meeting his milestones and the family was told things will be normal by 18 months. He was diagnosed at 15 months with PMD. Our extended family has 3 boys affected with this condition. I also have a daughter that needs to be tested for PMD as a carrier. This condition has been, is, and will be a part of our lives.

During the time since PMD was discovered 130 years ago, the world has been able to conceive ways to communicate globally, fly through the skies and set foot on the moon. Yet, my son cannot send a signal from his brain to his legs noise free. We spend most of our time traveling to therapies (physical, occupational, speech) and doctor appointments (neurology, orthopedics, endocrinology), that treat symptoms and attempt to make our sons' life a bit more about living. I have flown my son or reached out to experts in leukodystrophies in Northern California, Philadelphia, Washington, Japan, scratching for nuggets of information that can extend or improve my son's life. I have put my son through the few available trials, therapies, or corrective surgeries. I have investigated options like removing his immune system and bone marrow through extreme chemotherapy, inject stem cells through his heart, spinal cord, or directly into his brain. His future will likely include spinal surgeries (like my brother-in-law) to add metal rods to straighten his back and reduce the possibility of future spinal breaks or bends that could puncture other organs. I am willing to put my son on a phase 3 trial with 90%+ chance of survival, hoping it will make my son's daily life functionally better in the long run.

He has already had a bilateral hip surgery and is likely to need it again. My brother-in-law choked on small piece of meat that required to puncture his trachea as a life saving measure. Botox injections, and a lifetime of pills to minimize his ataxia and spasticity are already a part of his life, while his future holds scoliosis, seizures, and feeding through a g-tube. Our daily routine includes hours of stretching, constantly re-positioning him from the couch, to his wheelchair, to his stander, to his activity chair, to his walker, to his bed, to lying flat on the floor. We learn to communicate with him through signs, sounds, and a communication device. We check his glucose and ketones weekly. We feed him special minced meals with soft consistency, we clothe him, and bathe him. We battle with insurance, doctors, and the school system to provide him the necessary support, which includes a one-on-one aide that is strong enough to lift him; outspoken enough to advocate for his needs; trustworthy to invade his private area and change his diapers, and hyper-vigilant so that he does not choke on his food or vomit. We give him 8oz of cornstarch every night like clockwork because otherwise the energy wasted by his tense muscles through the night will lower his glucose levels to the low 20s and 30s. We have had several of these scares as we carried his almost lifeless body to the emergency room. A regular cold affects his breathing, and we must stay alert through the night to make sure he is still breathing along giving him pulmonary therapy with our cupped hands. Humidifiers, nebulizers, air purifiers, and keeping a comfortable home temperature are all part of our daily life.

My son can unlock discoveries in the study of myelin. Our lives have become a kind of Sherlock Holmes detective novel always in the lookout for signs of hope. As parents, we would gift our son

our legs, our brains, our hands, our voice, everything until there is nothing else to give, if that would replace what he's missing. We hold hope for a cure, and if not a cure, at least treatments that would stop or slow down the progression of his disease, specially help to avoid scoliosis and epileptic seizures and improve his communication. Our family would look to participate on trials that would not opt him out of future treatments. The question for us, will it be early enough to make a difference in our son's life? Or on our daughter's life, who could be a potential carrier. In the meantime, we will live, not just survive. We will love him until our dying days. Thank you.

Primary symptoms	Biggest challenges / impact	Care	Unmet medical need
Ataxia Spasticity Hypoglycemia Hypotonia Nystagmus Muscle spasms Cognitive impairment Hip dysplasia	100% dependent for all care (feeding, bathing, incontinence care) Non-verbal Non-mobile	**Past and current treatments:** Baclofen, Artane, Nightly Cornstarch **Therapies:** Physical, Occupational, Speech **Care Team:** SD Rady Children's Neurologist, Orthopedist Rehab, Metabolic, Endocrinologist, Pulmonology, Nutritionist	**Long term concerns:** His sister may be a carrier **Most significant unmet medical need:** No treatment to prevent scoliosis No treatment to slow down progression of the disease

Caregiver 4, Father of deceased 15-year-old diagnosed with Conatal PMD at 4 months old

My second child was born 7½ pounds and 20 inches long in 2000 through a full-term, normal pregnancy and delivery. The moment he was born he let out a screeching sound, stridor. The doctor quickly scoped his throat for any physical obstruction and calmly said "Take him home and bring him to my office on Monday (4 days later). I'll scope his throat and that requires an automatic overnight stay". As we celebrated his birth and held him that first day, I noticed how his eyes would circle around as if he was struggling to focus on me or objects in the room. His head would move to compensate for his nystagmus. No matter. I just thought he's a newborn. Nothing could stop the joy of having my first son.

Four uneventful days later, we brought him to that ear nose and throat (ENT) appointment and prepared for 1 overnight. We knew he wasn't eating as well as his older sister did when she was first born, but we weren't concerned yet. The ENT said he has some floppy throat cartilage and likened it to drinking through a straw that collapses instead of staying sturdy. "He'll grow out of it" he said. During the routine overnight stay a nurse thought his breathing was not good even though there was no cyanosis. We battled a bit, but he was admitted to the ER for further testing. Then our lives bent sideways. We spent the next 19 days in 2 hospitals, including Children's Hospital of Philadelphia (CHOP). He had tons of x-rays and blood tests, an echocardiogram, a head CT scan, a brain MRI, a barium swallow and chest x-ray, a PH reflux test, a spinal tap, a blood transfusion, a bronchoscopy and two laryngoscopies (not to mention being intubated for 13

days) and barely missed getting a tracheostomy ... only to conclude that his brain, heart, lungs, trachea and blood vessels are all normal. He had caught RSV in the hospital. Oh, and he has vocal cord paresis. We took him home and prepared to live normal lives again.

[Caregiver 4 stated his opinion that Pelizaeus Merzbacher Disease and all leukodystrophies should be included in newborn screening. Several doctors missed the PMD clinical symptoms of stridor, nystagmus, laryngomalacia and vocal cord paresis. The expense and agony of many diagnostic tests could have been avoided.]

Then he simply failed to thrive. It was torture – did he have a silly vitamin deficiency? Am I supposed to give him something basic that can end his discomfort and allow him to grow? Three months later, I brought him to CHOP and was referred to Genetics. The department chief made an impossible call. He said, "I think he has Pelizaeus Merzbacher disease, and we need to draw a blood sample and send it to a special Indiana lab for analysis". I said, "whatever disease you just said, how many patients have you seen?" To my horror, Dr. started counting on his fingers and said, "well in my 25 years of practice as a geneticist and neurologist, he would be my 9th PMD patient". His blood went off to Indiana and I went home to scour the web. PMD was doom but everything I read matched his symptoms. The diagnosis was confirmed and the prognosis was death within the first year.

I quit my job, bought funeral plots and prepared to have the most festive, most awesome celebration of his life for the entire year. He was placed on hospice. We had all of the nasty little medicines in the home. And then … a year passed, two years passed … three … and he was kicked out of hospice. What helped the most to support him? We did a great job of regimenting his day and taking care of his symptoms (with medicine, love, and around-the-clock attention). He could not walk, talk, roll over, hold his head up and barely had any gross motor control whatsoever … but he could SMILE and there's something very peaceful about him. He can non-verbally communicate if you are willing to look and listen. We thumbed our noses at PMD and lived our best lives.

Besides his breathing issues through laryngomalacia and vocal cord paresis, his most serious early symptom was the seizures. They never registered on any electroencephalogram (EEG) or sleep study, but they were regular and started getting longer and more intense. Healthcare professionals were stumped. My son was scared and in pain. His face would contort and freeze and his eyes would twitch. He would start crying because he knew it was coming. [A video of his son having a seizure was played for the group.]

It was another PMD parent who told me about carbamazepine (Tegretol). That was the miracle drug he needed. He took it 3 times a day for 15 years. Sadly, it knocks him out 2-3 hours, but he needs it, or he will have seizures. He also could not take it on an empty stomach. He became primarily tube-fed. At 1 year old he was 11 lbs. 4 oz.

As more symptoms appeared, we regimented his day around the following medicines:
tizanidine (Zanaflex) and a tiny dose of diazepam (Valium) for spasticity. Omeprazole (Prilosec) for acid stomach. Carbamazepine (Tegretol) for seizures. Not daily, but the slightest respiratory issues were treated with nebulizers, albuterol or budesonide (Pulmicort). Saliva/secretions are a constant battle that carry choking risk. He keeps his head tilted to the right because it's the best position to maximize his airway. Polyethylene glycol (MiraLAX) for motility.

Over the years, he developed severe scoliosis. He is too small to be a candidate for back surgery or to fix hip sockets.

I know patients with the classic form of PMD can live many decades. Patients like my son with this conatal form need gene therapy, stem cells, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and emerging therapies to live that long. We need early translational intervention.

My son died unexpectedly of respiratory failure in 2015. [The speaker shared pictures of his smiling son just 48 hours prior to his death.]

I would have been willing to try CRISPR, down regulating PLP, gene therapy or stem cell treatments. Anything that could've produced gain in function, not just gain in myelin. I would've taken the most risk for something that could have improved his breathing, communication or muscle strength and control (like being able to hold his head up). I probably would not try anything that had greater than 20% chance of death or serious side effects. And, it would have been a tough decision to enroll him in any clinical trial earlier than Phase 3, especially if that disqualified him from potential future treatments. I've worked in pharma for 22 years and I look at treatments for rare, incurable disease a bit differently than medicines that control blood pressure, for example. I believe we need to increase the incentives for companies who are willing to invest in rare diseases like PMD and grant them some leeway with trial designs due to the lower patient population and necessary risk associated with impacting the central nervous system.

My daughter may be a carrier. Her blood has never been tested for PMD. If I am ever blessed with a grandson, I pray that he is healthy or has a real PMD treatment option that can extend his life. The unmet medical need could not be greater.

Primary symptoms	Biggest challenges / impact	Care	Unmet medical need
Failure to thrive Breathing difficulties (laryngomalacia, vocal cord paresis) Seizures	Completely dependent for all care Cannot hold his head up Completely nonverbal Cannot crawl, roll over Severe scoliosis Much too sweet to put down	**Past and current treatments:** G-tube for feeding Tegretol, Zanaflex, Valium Prilosec, Albuterol, Pulmicort MiraLAX **Therapies:** Physical/speech/occupational **Care Team:** CHOP (neuro, GI, ENT, seating) AI duPont (spasticity)	**Long term concerns:** His sister may be a carrier **Most significant unmet medical need:** No real treatment to extend the life of a conatal PMD patient

Caregiver 5, Father of two boys (27 and 20-years-old) diagnosed with Classic PMD at (8 yrs. and 1 yr.)

My wife and I have four sons: PMD son1 (27) Healthy son (25), Healthy Son (22), and PMD son2 (20). All of them are currently living at home.
We had thought our life was changing when a sonogram in 1996 revealed that PMD son1 would be born with a bi-lateral cleft lip and palate. Our research indicated that it could be fixed soon after birth and he would

be able to live a normal life. We were prepared to face that challenge. PMD son1 was born at 41 weeks. We were not surprised when he was brought to the neonatal ICU shortly after birth. Shortly on, we noticed that he had nystagmus, a shaking of the eyeballs. He never reached any developmental milestones. We had no idea what was wrong. This was the worst part. Neither of us has a family history of neurological disorders, although I had an aunt with a cleft palate. We went to several doctors in an attempt to find a diagnosis. We were first told that it could be a birth injury due to him being born one week late and having meconium in the amniotic fluid. That could have been aided by the bi- lateral cleft palate. We also tested for a multitude of other diseases. PMD son1 was always happy and cognizant of everything around him. He just had poor head control and couldn't drink or eat unassisted.

PMD son1 received physical, occupational, and speech / feeding therapy. However, none of these therapists or the physicians knew what they were treating. They just considered it to be "cerebral palsy-like.) This continued for the next seven years. We continued with our team of doctors for him. We were seeing a plastic surgeon and a prosthodontist for his face, and a neurologist, orthopedist, physiatrist, ophthalmologist, gastroenterologist, nutritionist, cardiologist, as well as regular visits to his pediatrician.

My wife gave birth in 2003 to our 4th son (PMD son2). It was her fourth Cesarean section. I was excited to meet the new member of the family. I just had a feeling in my gut that something wasn't right by just looking at him. I'm not sure if it was parental instinct or the experience at PMD son1's birth which I had suppressed, but I just noticed something was wrong. I went over to my wife and she asked about him while she was getting her tubes tied. I told her, "I think we might have another PMD son1 on our hands." Her look at me said it all.

PMD son2 went into the neonatal intensive care unit (NICU) and was discharged with us a few days later. His neurological development mirrored PMD son1, but not their personalities. PMD son1 was a lovable child that would smile at everyone that would come up to him. PMD son2 knew what he wanted and made sure you knew it, and had a sarcastic smile, even at a young age.

In 2004, my son's neurologist took a blood sample that was sent to Baylor University for a fluorescence in situ hybridization (F.I.S.H.) test. We got the positive results for PMD on a Saturday. PMD son1 and I flew to Indianapolis the following Wednesday for a meeting of the PMD Family Support group. I was surprised to see adults with the disease, and meet some of the most knowledgeable, caring, and down to earth parents I have ever met. We felt at home and relieved that it was not a death sentence.

Fast forward to the present. The six of us are living with PMD. It affects the entire family. Our PMD sons are reliant on us for all daily life skills. They cannot sit up or eat and drink unassisted. They cannot be left home alone. One son works in Connecticut but lives at home to help us out. It is increasingly difficult to lift them. Durable medical equipment has been able to help. PMD son1 was also hospitalized twice in 2023 for pulmonary issues, including getting a chest tube inserted.

Both of our PMD sons attended a special needs school with PMD son1 graduating at age 21. He now attends a day program for disabled adults. They realize they are different from the abled population but that doesn't affect their personalities. They enjoy travelling up to their grandparent's lake house, going to hockey games, and meeting new people.

They each have their own choices in what television shows to watch, who sits where in the van, and which setting to have the air conditioner on. They are non-verbal, but we know what they want. They definitely let us know!

We started sending them to a summer sleep-away camp for the disabled in around 2016. They love it. PMD son2 will let out an angry cry when we come to visit, because he thinks we are picking him up. Camping trips have to be to accessible sites, it is difficult to go to events together as a family. We are happy to send them back to camp after a three-year hiatus. The staff at Camp is wonderful. We were only worried for them the first year.

My wife and I are realists. Any new therapeutic that comes out will probably not affect our boys, but anything to keep them comfortable and extend their lives would have to be considered. I am more concerned about future generations. PMD in my family will end with this generation, as we do not have the girl we always wanted.

Primary symptoms	Biggest challenges / impact	Care	Unmet medical need
They are non-verbal and reliant on others for all daily needs. No trunk control or use of extremities. Issues with congestion and constipation.	Physical reliance on others for all aspects of life. Emotional family issues. Their other brothers needed to be caretakers in their early teens. Need to keep them comfortable and healthy. Possibility of hospitalization at any time.	**Past and current treatments:** PT, OT, Speech therapy, home aides Special needs school and day program for socialization **Therapies:** In home physical therapy Respiratory therapy with cough assist, suction machine, the vest **Care Team:** Immediate family with mother working as in-house aide. Dr. visits with gastro, pulmonology, orthopedic, neurology.	**Long term concerns:** life expectancy having them thrive keeping them out of the hospital keeping them comfortable and not in pain **Most significant unmet medical need:** No treatment for the underlying cause

Caregiver 6, Mother and Father of 4-year-old diagnosed on spectrum between Conatal and Classic PMD at 13 months old

I am mom to my son who is now four years old, who is the center of my universe. He is fiercely loved by my husband and I, his older sisters, and everyone who is uniquely blessed to know him. He is a sufferer of Pelizaeus-Merzbacher Disease. The day of our son's diagnosis at thirteen months of age was the hardest day

of our lives. That day, we were informed that our beautiful baby boy, for whom we had so many hopes and dreams, would likely never walk, or talk. We were told that his condition was incurable, and that it would require constant care, management, and therapy if he was to have any true quality of life. The outlook was grim. We were told that our baby boy, whose life had only just begun, would, in all likelihood, perish in the first decade of his life.

Though our son was still alive, and though we knew that we still had many precious years with him ahead of us, it still felt like a death sentence had been handed down. It felt as if his life was already over before it had even had the chance to begin. Yes, we had time, but not enough time and he would never live anything that resembled a "normal" life due to no treatments being available. We grieved—for ourselves, for our family, and for him most of all, trapped unfairly in a little body that his brain simply couldn't communicate with effectively. An innocent prisoner.

My son is completely dependent on myself and a handful of trusted others. Every single aspect of his day-to-day existence, even the simplest task, requires attention, supervision, and assistance. Every need that he has as a human being cannot be met without my help. There is nothing that my son can do on his own. He can't play the way that other children his age can. He can't feed himself. He can't move independently, even from one room to the next. He is non-verbal (though he manages to get his point across in his own unique way), basically every single day of his life is a struggle against himself.

I currently attend outpatient therapy sessions with him eight times a week—these include occupational, physical, and speech therapies—along with any other medical appointments he may have scheduled during any given week. We semi-annually consult with a team of specialists at the Children's Hospital of Philadelphia and these visits conclude with a sedated procedure where he is administered botulinum toxin type A (Botox) and phenol injections to help with muscle spasticity. In our hometown, most of the doctors we encountered had never heard of PMD before meeting us, so we must travel to medical centers with greater expertise. When he was originally diagnosed, the genetics doctor classified him as conatal type because she was unfamiliar with PMD and because he had symptoms at birth, she considered him to be a worst case scenario, but once we were seen by the specialty team at CHOP it was described to us that the disease is more like a spectrum and they consider him to be somewhere in the middle.

My husband and I both work out of necessity. My husband does the bulk of his daily at-home therapy routines with him. I arrange my work schedule to accommodate my son's very full therapy schedule. His condition requires a great deal of patience, along with consistent, near-constant management. Because of the degenerative nature of PMD, any negligence, however slight, on our part would likely result in the worsening of his symptoms. PMD does not stop, and it does not take breaks. Therefore, neither can we.

The outpouring of love we and our son receive from our friends and family is truly miraculous. My husband's and my parents have given a great deal of their personal time in order to be there for us so that my husband and I can prioritize our son and devote our focus and attention to his care.

We always have, and always will, see our son as a blessing. I have never questioned, not even for a moment, if my life is better because I get to share it with him. I know that it is, but the emotional, financial, and physical toll of his illness on our family cannot be exaggerated. His motor control and fine motor skills prevent him from walking and developing physically as a typical 4-year-old would. His fine motor skills make it difficult to use many communication devices to communicate to others as well.

Just this month we received the news that his biological sister is also affected as she is carrier like me. We have not shared this information with her as we feel like it's a lot to process for someone her age, so we will save that conversation with her for another time.

The outlook, according to every expert and every text on the subject, is bleak. They say that my son--who is so full of life, who charms everyone he meets without saying a word, whose tireless will and unbreakable spirit battle daily, mightily, against the limitations of his body, whose personality shines through his disability, and whose smile could melt even the iciest heart—could have his life cut short if a treatment isn't developed to stop the progression of PMD. My prayer is that a treatment will come before it's too late and that he will be a candidate to receive such treatment. If a treatment was developed that would give a possibility of longevity and better quality of life, we would be willing to accept all risk to give him that chance. To give our family and generations to come, hope. Thank you!

Primary symptoms	Biggest challenges / impact	Care	Unmet medical need
Motor control Muscle spasticity Hypotonia Nystagmus Ataxia *Might be between Conatal and Classic on the spectrum of PMD disease	Completely dependent for all care Communication Constipation Dysphagia/Feeding Difficulties	**Past and current treatments:** Sedated Phenol and Botox injection procedures every 5-6 months Milk of Magnesia, Glycerin Suppositories **Therapies:** physical, speech, occupational **Care Team:** CHOP (Neuro, Ophthalmology, Orthopedic, Physiatrist) Home (Neuro, Ophthalmology, Orthopedic, Pulmonary, Gastroenterology)	**Long term concerns:** His sister is a carrier (confirmed) Aging grandparents being unable to help in the future Our physical abilities to be able to support him in the future as we age ourselves **Most significant unmet medical need:** A treatment that would help him overcome some of the PMD hardships. Something that would help him become verbal, freely move about and/or add years to his life that can be cut short from disease progression.

SUMMARY

PMD affects multiple body systems.

There is a huge burden of care as most kids need complete care and have no communication skills.

Current treatments are mostly off label and treat the variety of symptoms; there are no FDA-approved specific treatments for PMD.

The PMD community would like to have a treatment that would slow or stop disease progression, prevent hospitalizations and early death.

Families expressed a desire to participate in research and would generally tolerate a large amount of risk in a clinical trial with hope for new benefits.

PMD can span generations and affect multiple family members.

In summary of our time today, we defined PMD.

We heard from one of the most respected clinicians in the world on PMD and Leukodystrophy.

We heard from 6 families who presented what PMD looks like for the patient and the caregivers.

We heard from a father as he spoke about his son now 33 and the fear for the future.

We heard from a father about his son soon to be 22 who just aged out of school and is also concerned about the next chapter and about the long-term future.

Then we heard from a father and learned about his son who is 10 years old and has the most severe form of PMD and is also from a multiple generation PMD family.

We heard from a father who has had to experience the loss of his son who surpassed all expectations but passed away at the young age of 15. The loss of a child is a pain no parent ever imagines or wants to feel.

Then we heard from the father of two boys with PMD. The difficulties they have faced as caregivers has been double what other caregivers have faced.

And finally, we heard from a mom and dad about their son who is now 4 years old and still at the very beginning of their journey.

Our hope is that these stories share what it is like living with PMD for the patient and caregivers at the various stages of our lives. Some of us realistically do not have any viable treatment options due to age, but we pray that for the younger PMD patients in our community and for future families that there is still time. For those of us that have run out of time, we are here for these other families that still have hope.

OPEN DISCUSSION Q&A with FDA CENTERS & OFFICES

FDA shared their appreciation for the families being so open and honest to share their stories with the FDA.

FDA Staff from CDER, Division of Neurology I:

Thanked everyone for taking the time to come and speak with us. Said the stories were really impactful and it's really helpful to hear directly from the caretakers of patients to understand what daily struggles are like. Stated FDA really appreciates it and 'we hear you.' Stated FDA is committed to working with rare diseases and to try and find treatments for this devastating disease. There is some variability in PMD family stories but consistency with communication and motor challenges. What is the one thing that would be most impactful for a treatment to address?

Caregiver 4: For his son with the severe conatal form of the disease, he couldn't hold his head up and that was extremely impactful. Newborns are delicate and you have to support their head at all times, and they had to do that for his son for 15 years which was scary, but also a pleasure because you get to hold him. Would like to see any treatment that improves muscle control and stability; gain gross or fine motor control.

Caregiver 3 agreed with **Caregiver 4**. Improving communication is important because parents don't always know from their child when they are hurting or what hurts. It's even more problematic when communicating with doctors. Secondly, for my brother-in-law who passed away a few years ago, who had 40 years of living with PMD, he had scoliosis and had metal rods inserted which became infected and in time that infection went all over his spinal cord. They had to remove them. I've seen how painful even getting that can become, although it can be helpful for many children who need it. But this surgery can be very painful and requires improvement. Thirdly, improving mobility and anything that helps them move around.

Caregiver 2: Fixing the oligodendrocyte problem is most impactful because the broken communication link from the brain to the rest of the body affects all PMD patients. (All families agree with this statement.)

Caregiver 3 raised the importance of newborn screening. Dr. Vanderver mentioned PMD prevalence appears to be one in 200,000 to 500,000. In our database, we know approx. 100 children in the US, so we are not identifying the population even at the 1 in 500k estimate. Even if we knew 300 in 300 million that is one in a million. So, I'm sure there's more but we're not identifying them. And if we're not, then that also hurts in terms of rare diseases not having enough population for research studies. Having newborn screening and not being misdiagnosed with CP like my brother-in-law would be very, very helpful for us to have better screening and much quicker diagnosis of the condition. More frequent screening is needed to accurately understand the prevalence and help the true PMD population receive care. It would also help doctors make an earlier diagnosis when they see a PMD patient.

FDA Staff from OC, Office of Pediatric Therapeutics: We facilitate pediatric activities across the agency. I will ensure that points you've shared today are conveyed to my colleagues. Some of you spoke about the risk you're willing to accept and it seemed to be a variety of percentages. Could you expand more on whether you would be willing to accept severe or life-threatening risks for your child? Why or why not?

Caregiver 1: We don't know what to expect in a treatment, but it depends on the child's overall health and prognosis. The more robust and healthy a PMD child is, the less risk we'll take. As you can see with my son over my shoulder here, he is a very robust young man other than having PMD. So, for a family like ours, we

would definitely have to weigh the risks involved versus perhaps a family with a child similar to **Caregiver 3** and others who have the more severe form of PMD, they might be more willing to tolerate greater risk.

Caregiver 3: Yes. I think that is exactly right. It depends on the situation in terms of what the available treatment is and how the treatment could potentially improve our son's life and in what ways. That is why you see a wide range of people saying like **Caregiver 4** that they wouldn't accept more than 20% risk of death. I say 10% risk of death.

It depends on what the treatment would be able to do. We would accept greater risk for greater reward and greater risk for children with poorer prognosis.

Maybe there's a CRISPR gene therapy modifying the PLP-1 gene, which we've heard as parents that modifying the gene may actually help them to have a better life. There are children out there with a modified gene that have PMD that have even gone to college that have a null mutation and not a duplication or triplication like many of our children here today.

Caregiver 4: We become very educated about PMD because it's our family member. It's our child. We love them and we want to know what's wrong with them. That's why it's excruciating for us, that before we get a diagnosis some families have waited years to learn what's even wrong with their child. That's even more painful in my mind. Don't get me wrong, having a PMD diagnosis is bittersweet. Knowing the diagnosis at least lets you focus onto something so that you can study the disease, you can learn about it. You learn about any treatments that are out there on the horizon to make that risk assessment. It becomes your lifestyle. Every parent would research diligently to understand any potential treatment and HOW exactly it would work to provide the treatment; to understand scientifically very clearly how it gets us to the expected treatment result. A higher probability of technical success leads to an acceptance of greater risk. I have no formal scientific training, but I could talk with you all day long about misfolded proteins in the oligodendrocytes causing apoptosis and lack of myelination and the broken signal going from the brain out to the motor neurons which prevents our children from being able to move the way that they should.

We learn these things and then learn about the opportunities that are out there in science on the horizon to provide a treatment or take a chance at a treatment. It is enormously scary to think of injecting something into somebody you love who is your family member. But you also know the prognosis which for my son was one year, and he lived 15 years. Even though he came to the end very unexpectedly, even at 15, because that regimentation and living that lifestyle for so long you start to know whether there's an acute health threat that you must treat or not.

Caregiver 5: My oldest has been in the hospital 3x this year. We started making preparations because we did not know if he would live. The risk we are willing to take does take into account that PMD life is even more fragile than normal. Even a treatment that will keep PMD children happy has importance. We are glad there is a family support group to help us bounce ideas off each other.

Caregiver 1: There is a lot of guilt that comes as a caregiver. Is the treatment for the child, or for the convenience of the caregiver? The decision comes down to individual situations, but most families would be aggressive if quality of life is improved.

Caregiver 6: I agree 100%

CLOSING REMARKS

FDA Patient Affairs: Thank you to PMD families and for being brave and sharing your stories. Thank you to FDA staff for attending this PLS. Patient Affairs wants to stay in contact with the PMD community. We are the doorway to the FDA for patients, caregivers and patient organizations. Please contact us anytime at: PatientAffairs@fda.gov

DISCLAIMER

Discussions in FDA Patient Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects The PMD Foundation's account of the perspectives of patients and caregivers who participated in the Patient Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of Pelizaeus-Merzbacher Disease, health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire Pelizaeus-Merzbacher Disease patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.