PMD FOUNDATION
PELIZAEUS-MERZBACHER DISEASE

Patient Listening Session

presented to the FDA
August 22, 2023

AGENDA

- Welcome & Introductions (FDA Patient Affairs)
- PMD Foundation (Dave Manley)
- Reasons we requested a session
- What is PMD (Dr. Adeline Vanderver)
- Goals for treatments in PMD
- Clinician overview
- Patient / Caregiver Perspectives (Families)
- Summary (Dave Manley)
- Q & A (All)
- Closing Remarks (FDA Patient Affairs)

The PMD Foundation
Our Mission

- US-based 501(c)3 started in 2000
- www.pmdfoundation.org
- Proactively serve those affected by Pelizaeus-Merzbacher Disease (the PMD community) by supporting programs of **education, research, service and advocacy**.
- Identify sources of **medical care, social service, and genetic counseling**; establish a **communications network** among families
- Increase **public awareness**
- Information source for **health care providers**
- Promote **research** into causes, treatment, prevention and cure of PMD

Why we requested a listening session

Share knowledge with FDA staff on the complex issues of PMD, the various physical manifestations and the body systems that are affected.

Raise awareness among FDA staff on the:

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

Clinician Overview

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

- Attending physician in the Division of Neurology,
- Program Director of the Leukodystrophy Center
- Professor of Neurology, Perelman School of Medicine, University of Pennsylvania
- Jacob A. Kamens Endowed Chair in Neurologic Disorders and Translational Neurotherapeutics

Pelizaeus-Merzbacher Disease

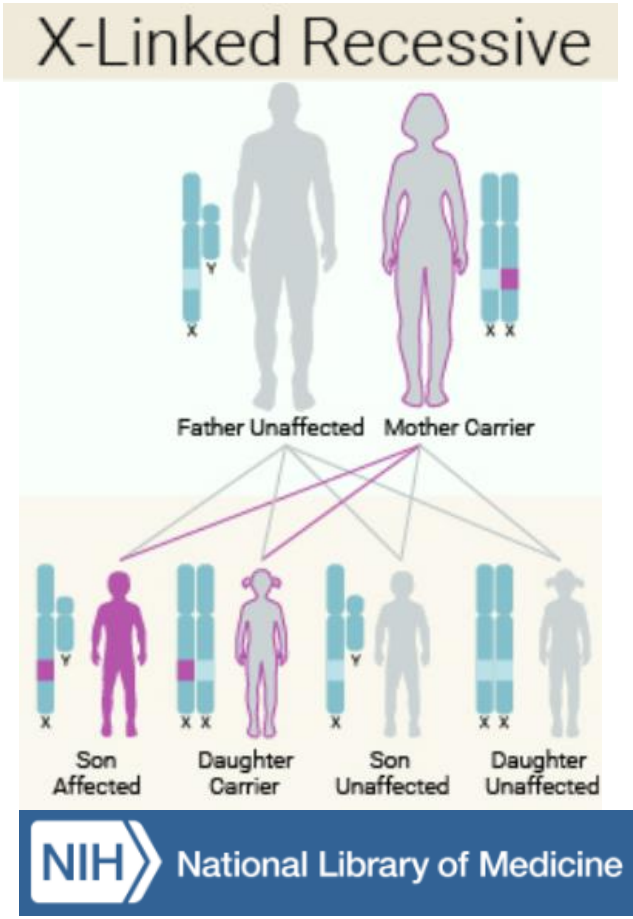
Overview

- The term 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***.
- Prevalence: 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)]

Pelizaeus-Merzbacher Disease

Genetics

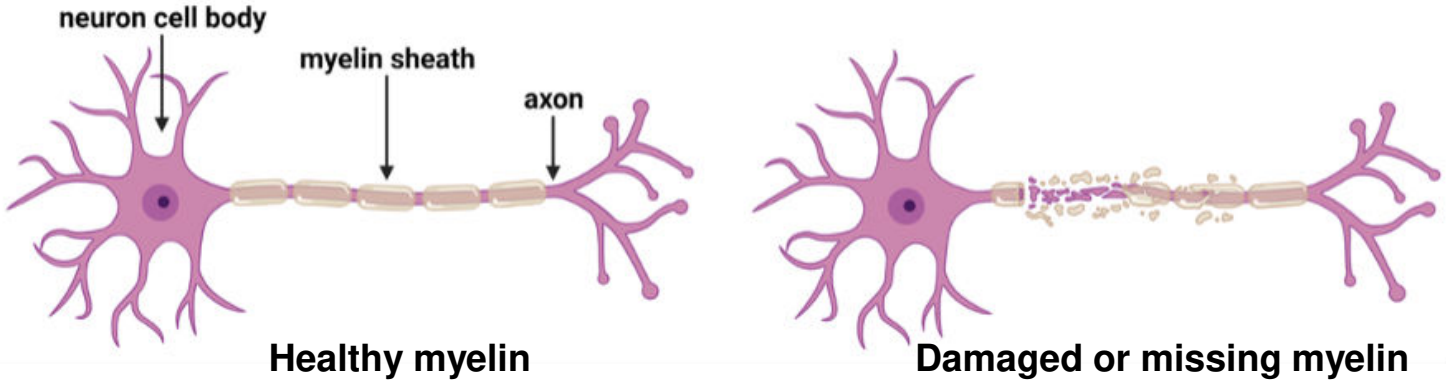
- Gene: Caused by mutations in the proteolipid protein 1 (*PLP1*) gene on the X chromosome
  - *PLP1* is exclusively expressed by oligodendrocytes, the myelinating cell of the central nervous system
  - *PLP1* encodes for proteolipid protein, which is a major protein component of myelin
- Inheritance: X-linked disease that affects boys (severely)
  - Female carriers may exhibit mild to moderate symptoms in adulthood
- Mutations: A wide spectrum of disease-causing mutations have been identified including missense, nonsense, splice site, and supernumerary copies.
  - 70% of PMD patients have duplication of the *PLP1* gene
- Diagnosis: Genetic testing is available to confirm the diagnosis and aid in family planning.
  - Misdiagnosis is common outside of major medical centers



Pelizaeus-Merzbacher Disease

Cellular & molecular mechanisms

- PMD affects myelination in the central nervous system.
- Mutations in *PLP1* induce stress and death of oligodendrocytes, the myelinating cells of the CNS.
- Loss of oligodendrocytes decrease myelin, the essential fatty substance that insulates and protects nerve fibers.
- When nerve fibers are not properly insulated, they can't communicate efficiently, leading to the motor and developmental symptoms of PMD.



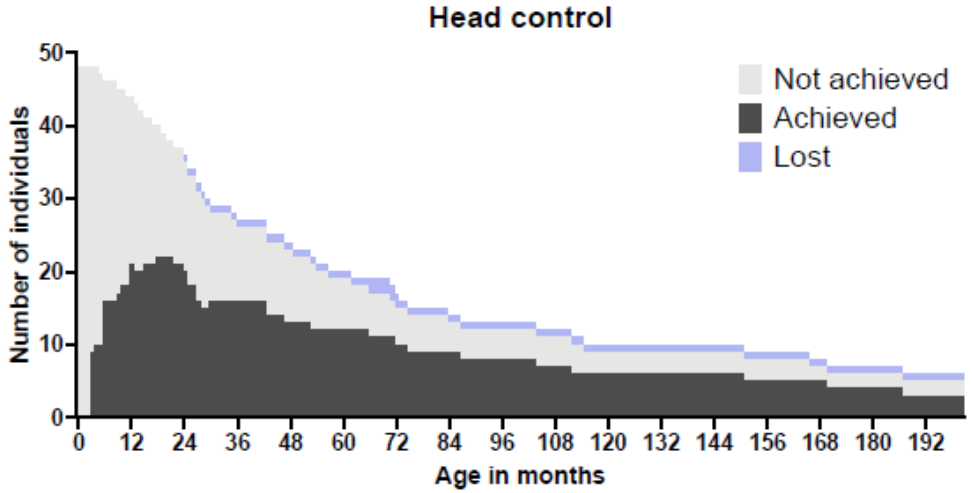
Pelizaeus-Merzbacher Disease

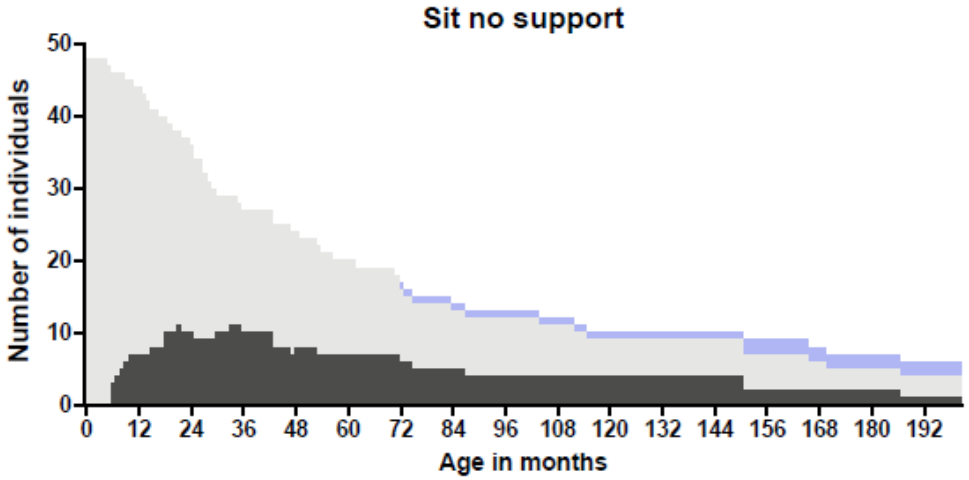
Presentation and symptoms

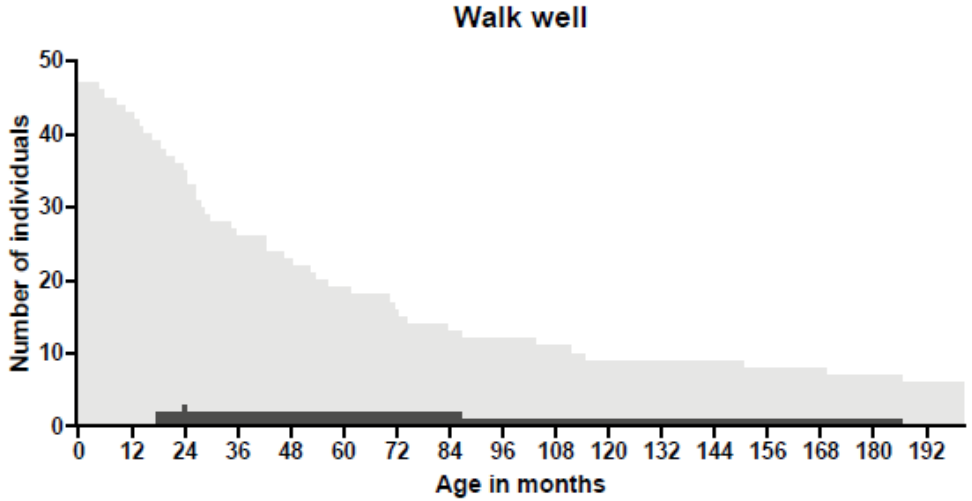
- Symptoms: PMD typically presents in infancy or early childhood.
- Affected individuals have nystagmus, spasticity, dystonia, head titubation, developmental delay, and difficulty with coordination and balance.
- The severity of symptoms may vary based on age of onset, but overall motor impairment is severe.
- PMD symptoms therefore affect children and young adults in profound ways.

Severe motor impairments affecting all aspects of developmental abilities

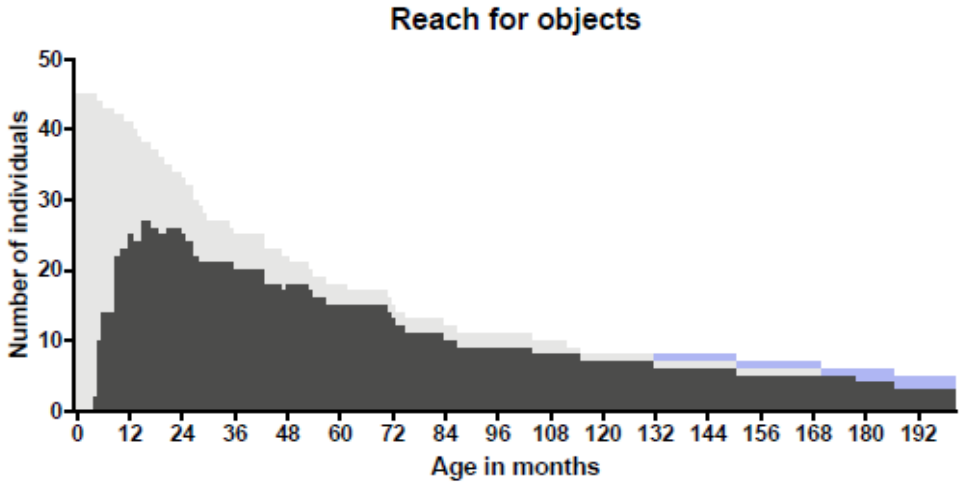


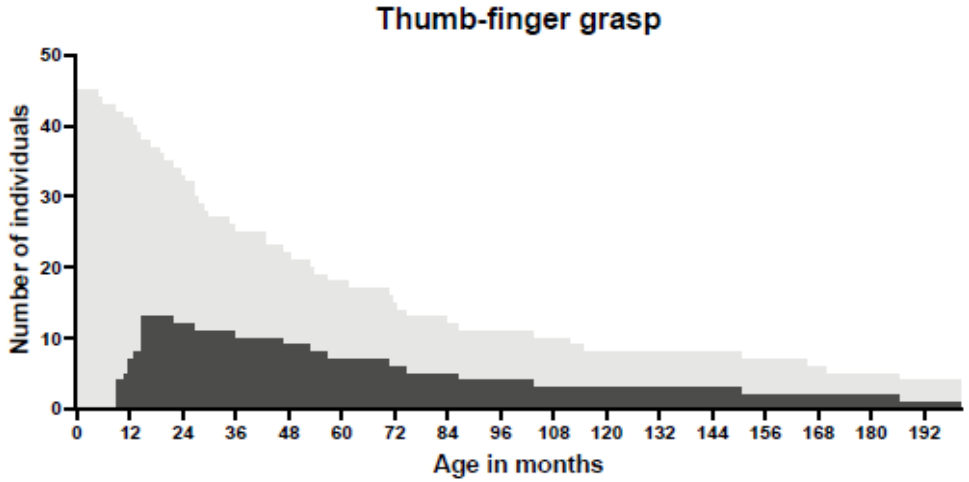


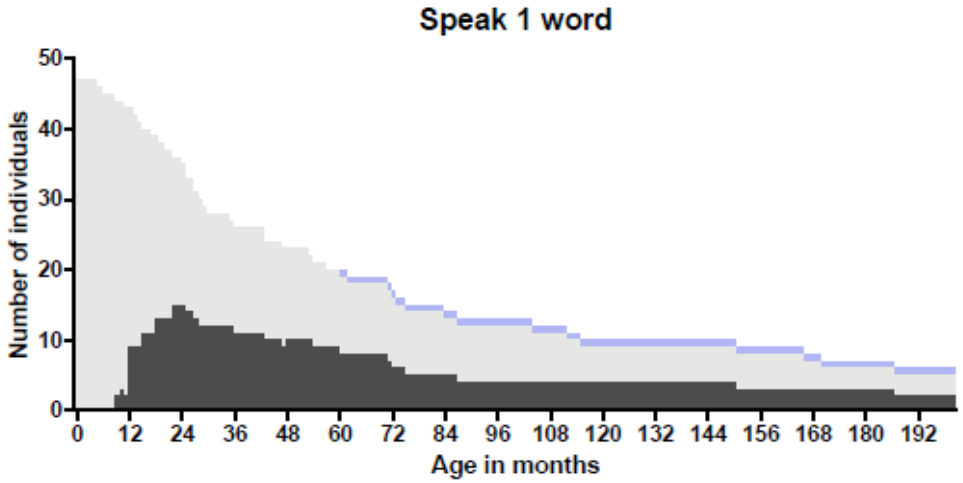


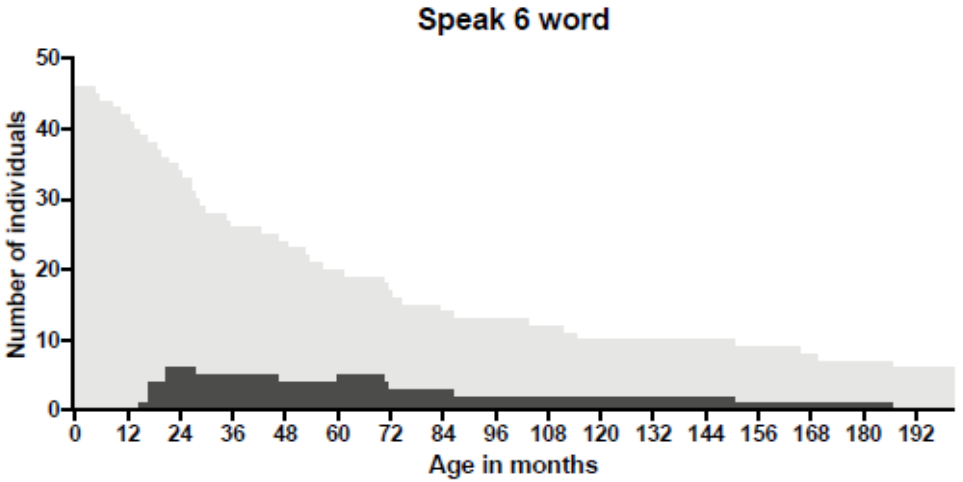


Severe motor impairments affecting all aspects of developmental abilities









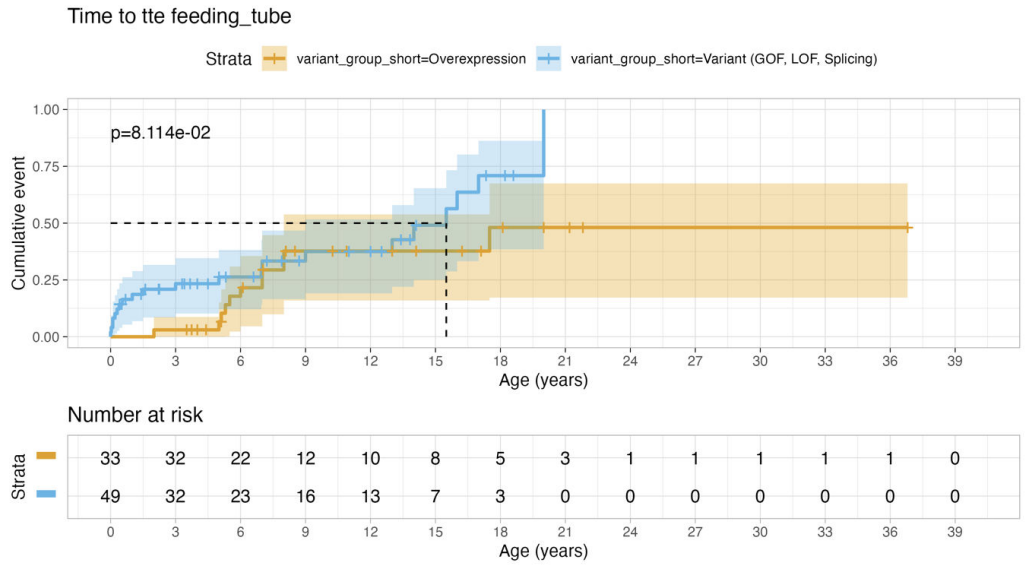
Pelizaeus-Merzbacher Disease

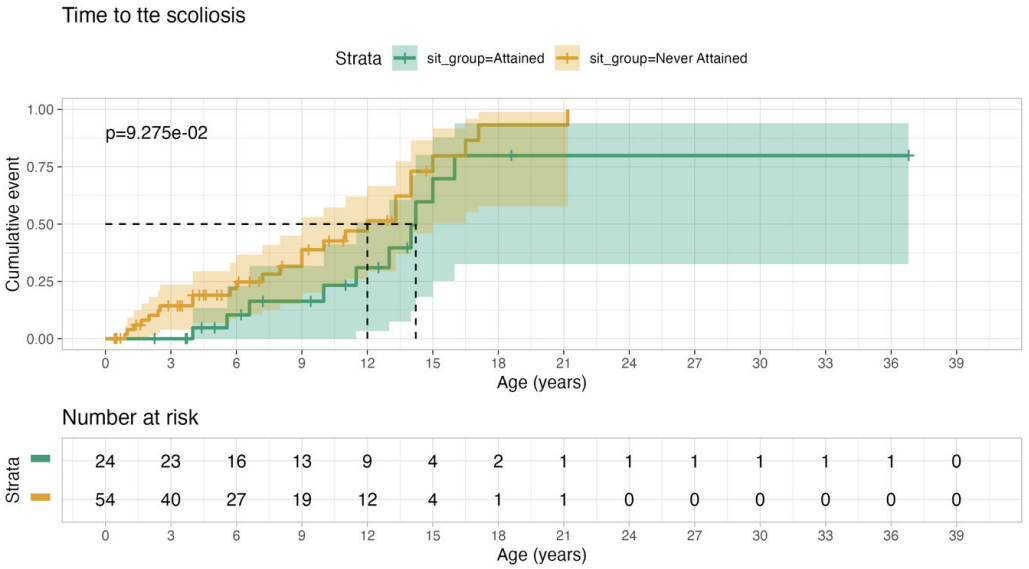
Common health problems

- 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)

Accumulation over time of significant health burdens

- A majority of our patients are needing support for feeding before the end of the 2nd decade
- Most are facing significant orthopedic and tone management surgeries such as hip reconstruction, baclofen pumps and spine fixation for scoliosis well before adulthood





Pelizaeus-Merzbacher Disease

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)
- 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.

Pelizaeus-Merzbacher Disease

Patient Perspectives

	Patient	Presenter	Relationship
1.	Jaden	Dave	Dad
2.	James	Paul	Dad
3.	Leonardo	Carlos	Dad
4.	Jack	Jeff	Dad
5.	Brian and Dylan	Rob	Dad
6.	Brant	Angi & Brandon	Parents

JADEN (Mexico, NY)

21 years old

Classic PMD diagnosis @ 18 months

<u>Primary symptoms</u>:

- Nystagmus
- Poor motor control (gross and fine)
- Non-verbal
- Non-ambulatory
- Incontinence
- Developmental delays



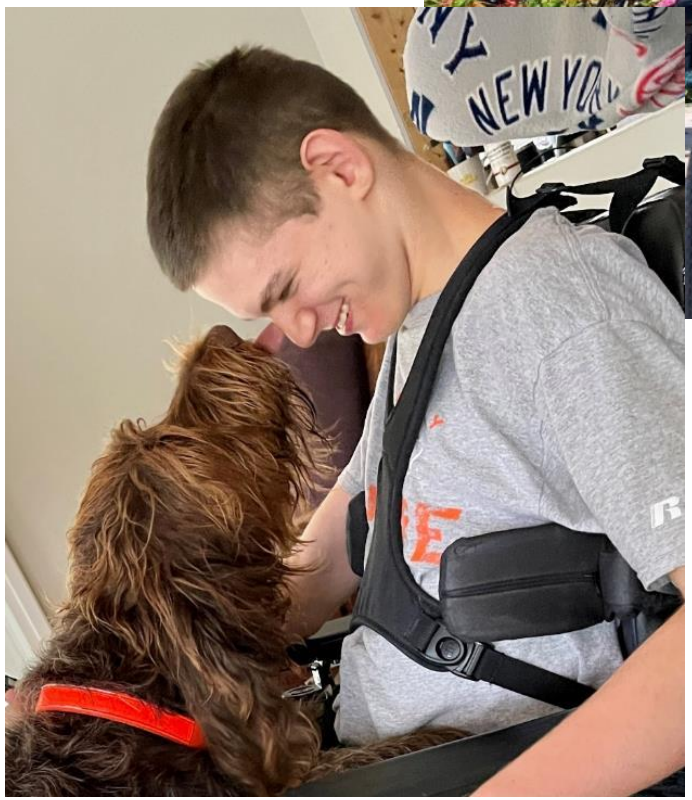
JADEN
Biggest challenges / impact

- Communication
- Accessibility
- Safety awareness
- Day-to-day care
- Adjusting every facet of our lives around Jaden’s care



JADEN
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

JADEN
Unmet medical need

<u>Long term concerns</u>:

- 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 Jaden will be in immediate crisis.

<u>Most significant unmet medical need</u>:

- As Jaden 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.



JAMES (Milton, VT)
33 years old
Classic PMD diagnosis @ 9 months

<u>Primary symptoms</u>:

- 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
- Significant reflux
- Osteopenia- high risk of fractures



JAMES
Biggest challenges / impact

- Communication is James' biggest challenge: making his needs and wants known is extremely challenging
- Mobility is dependent on caregivers (James is not able to drive a power chair) Requires specialized vehicle for transportation
- Feeding, hydration, and medication are all via G-tube, necessitates very careful caregiver management



JAMES Care

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
- 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



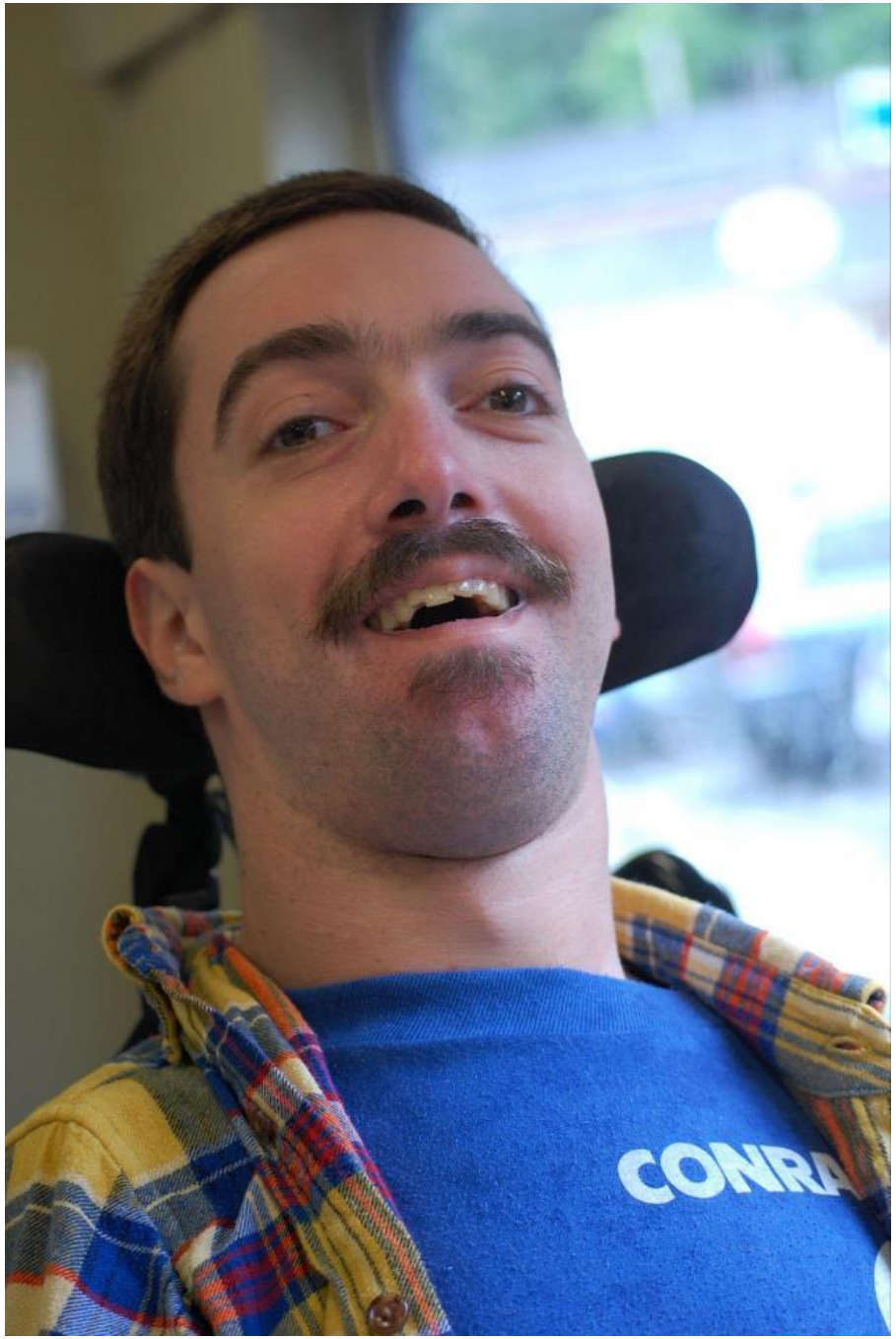
JAMES
Unmet medical need

<u>Long term concerns</u>:

- Spasticity and contractures
- Ongoing risk of fractures
- Feeding, reflux, managing secretions
- Communication and engagement/stimulation
- Positioning and comfort

<u>Most significant unmet medical need</u>:

- Treatment to reduce impact of PMD on James
- 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



LEONARDO (San Diego, CA)

10 years old

Classic PMD diagnosis @ 6 months

<u>Primary symptoms</u>:

- Ataxia
- Spasticity
- Hypoglycemia
- Hypotonia
- Nystagmus
- Muscle spasms
- Cognitive impairment
- Hip Dysplasia













LEONARDO
Biggest challenges / impact

- 100% dependent for all care (feeding, bathing, incontinence care)
- Non-verbal
- Non-mobile






LEONARDO
Care

<u>Past and current treatments</u>:
- Baclofen, Artane, Nightly Cornstarch

<u>Therapies</u>:
- Physical, Occupational, Speech

<u>Care Team</u>: SD Rady Children's
- Neurologist, Orthopedist
- Rehab, Metabolic, Endocrinologist,
- Pulmonology, Nutritionist









LEONARDO
Unmet medical need









<u>Long term concerns</u>:

- Leo's sister may be a carrier

<u>Most significant unmet medical need</u>:

- No treatment to prevent scoliosis
- No treatment to slow down progression of the disease

JACK (Robbinsville, NJ)
d. 15 years old
Conatal PMD diagnosis @ 4 months

<u>Primary symptoms</u>:

- Failure to thrive
- Breathing difficulties (laryngomalacia, vocal cord paresis)
- Seizures



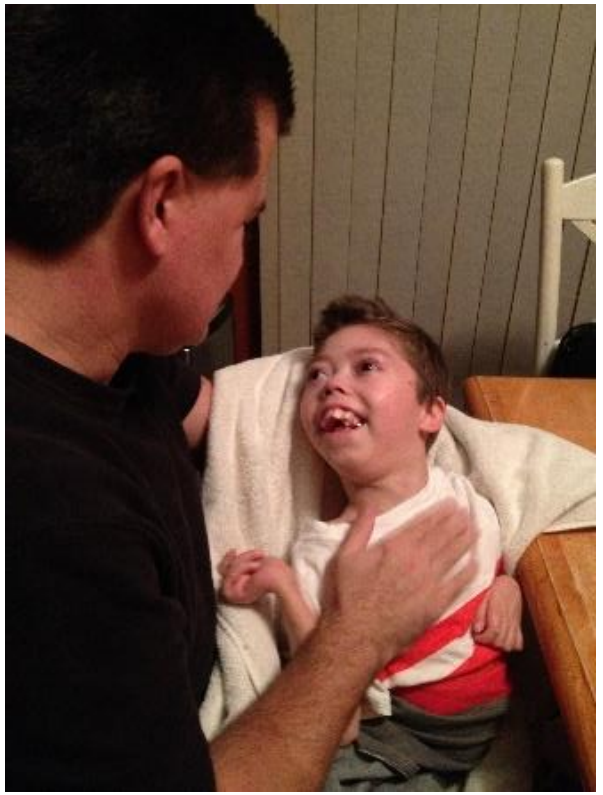




JACK
Biggest challenges / impact



- Completely dependent for all care
- Cannot hold his head up
- Completely non verbal
- Cannot crawl, roll over
- Severe scoliosis
- Much too sweet to put down





JACK
Care









<u>Past and current treatments</u>:

- G-tube for feeding
- Tegretol, Zanaflex, Valium
- Prilosec, Albuterol, Pulmicort
- Miralax

<u>Therapies</u>:

- Physical/speech/occupational

<u>Care Team</u>:

- CHOP (neuro, GI, ENT, seating) AI duPont (spasticity)

JACK
Unmet medical need

<u>Long term concerns</u>:

- Other family members may be carriers

<u>Most significant unmet medical need</u>:

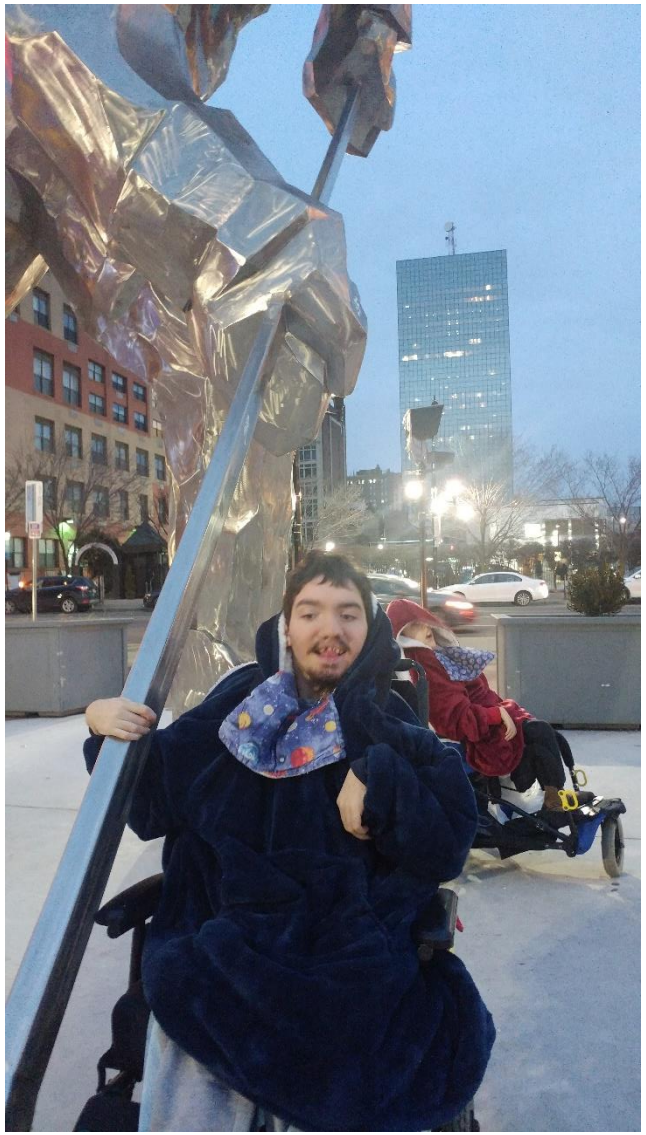
- No real treatment to extend the life of a conatal PMD patient



BRIAN and DYLAN (Franklin Square, NY)

Brian 27 years old, Dylan 20 years old

Classic PMD diagnosis @ Brian 8 years, Dylan 1 year





Primary symptoms:

- They are non verbal and reliant on others for all daily needs.
- No trunk control or use of extremities.
- Issues with congestion and constipation.

BRIAN and DYLAN
Biggest challenges / impact



- 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.



BRIAN and DYLAN
Care



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.

BRIAN and DYLAN
Unmet medical need

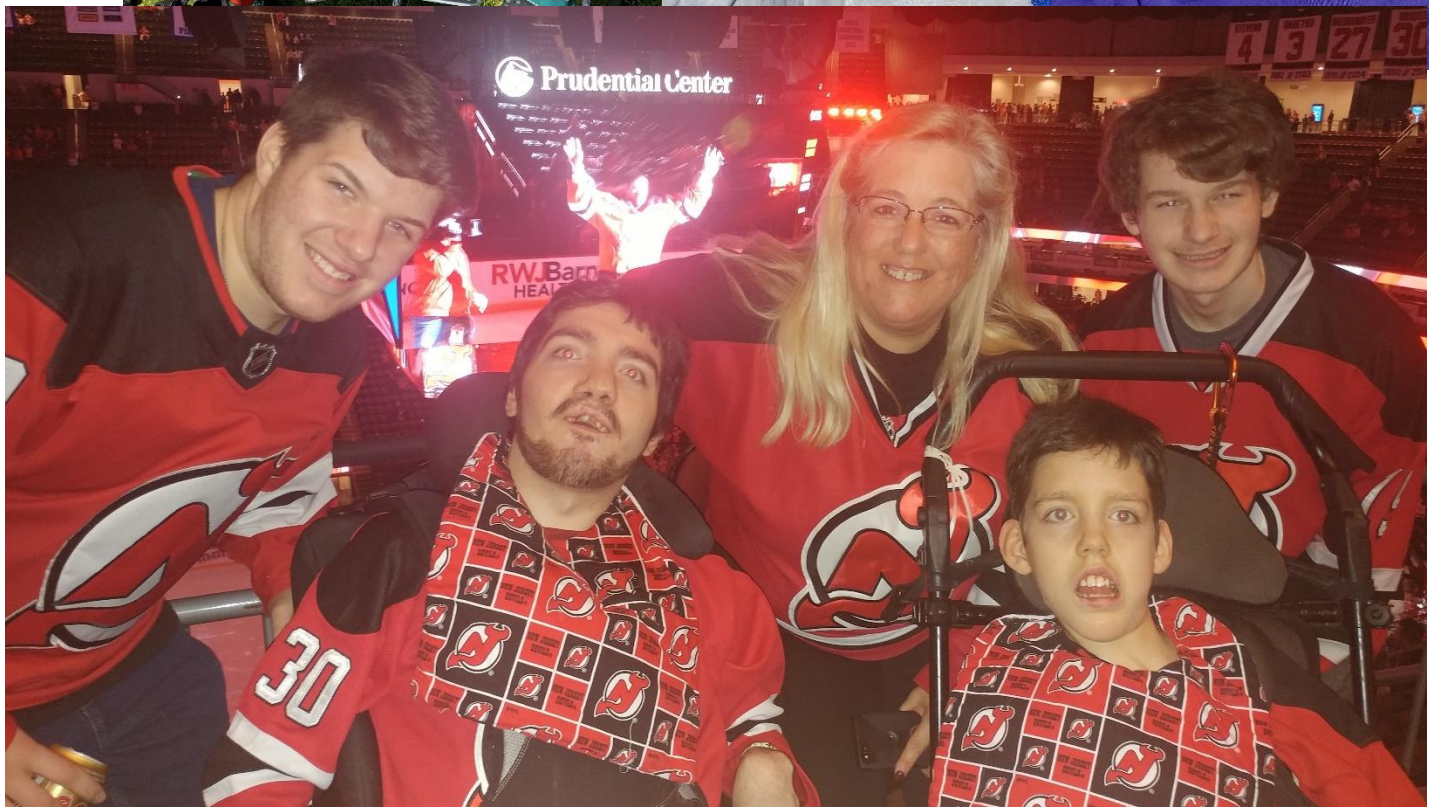






<u>Long term concerns</u>:

- life expectancy
- having them thrive
- keeping them out of the hospital
- keeping them comfortable and not in pain



<u>Most significant unmet medical need</u>:

- No treatment for the underlying cause

BRANT (Denham Springs, LA)

4 years old **today**

*Classic PMD diagnosis @ 13 months



Primary symptoms:

- Motor control
- Muscle spasticity
- Hypotonia
- Nystagmus
- Ataxia







*Might be between Conatal and Classic on the spectrum of PMD disease

BRANT
Biggest challenges / impact

- Completely dependent for all care
- Communication
- Constipation
- Dysphagia/Feeding Difficulties







BRANT
Care









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)

BRANT
Unmet medical need

<u>Long term concerns</u>:

- 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

<u>Most significant unmet medical need</u>:

- 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.



PMD Patient Listening Session Summary

- PMD affects multiple body systems
- 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-no FDA approved specific treatments
- Would like to have treatment that would slow or stop progression
- Would like treatment to 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 hopes for new benefits
- PMD can span generations and affect multiple family members

PMD Q&A



Thank you!

We are happy to answer all questions.