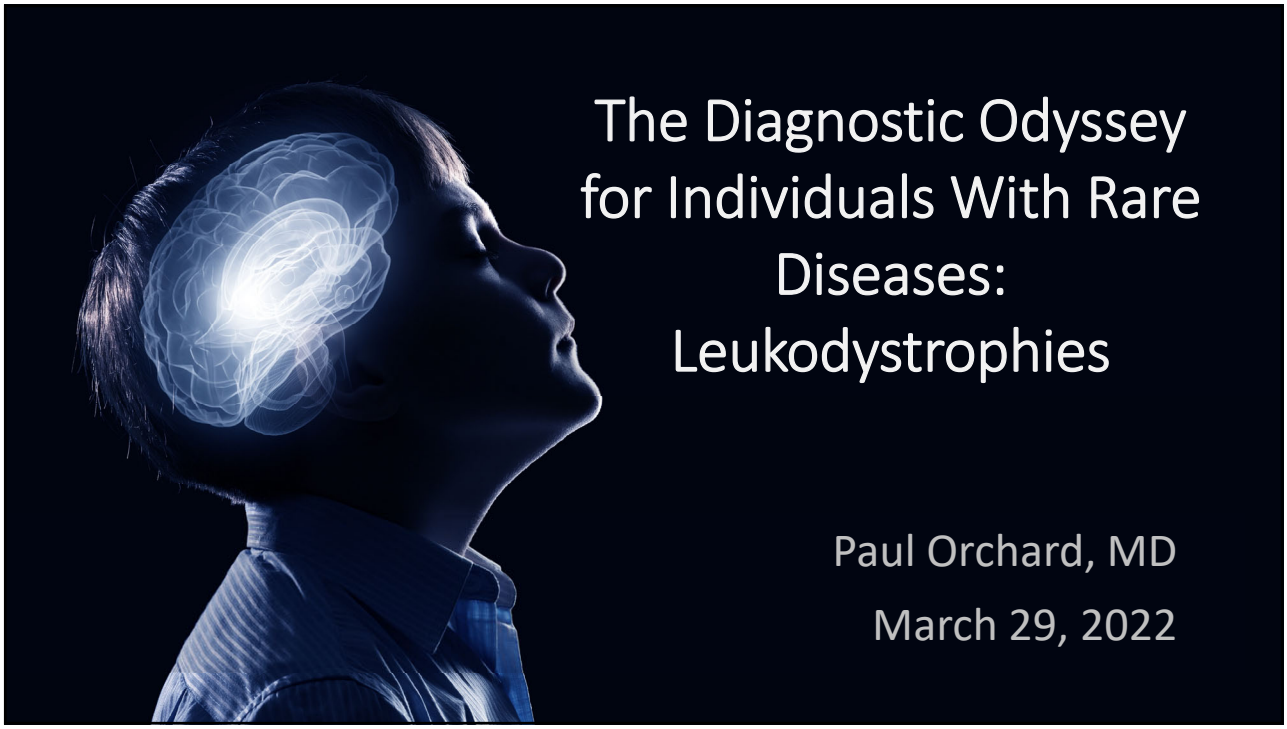


1

Disclosures:

- Dr. Orchard is a consultant or has clinical research support from Orchard Therapeutics (not my company), Immusoft, Bluebird Bio, Avrobio, Imel, Sanofi and Neurogene.
- We will be discussing off-label use of medications since some of these medications are being developed and are not yet approved for use in children.

2

For Discussion:

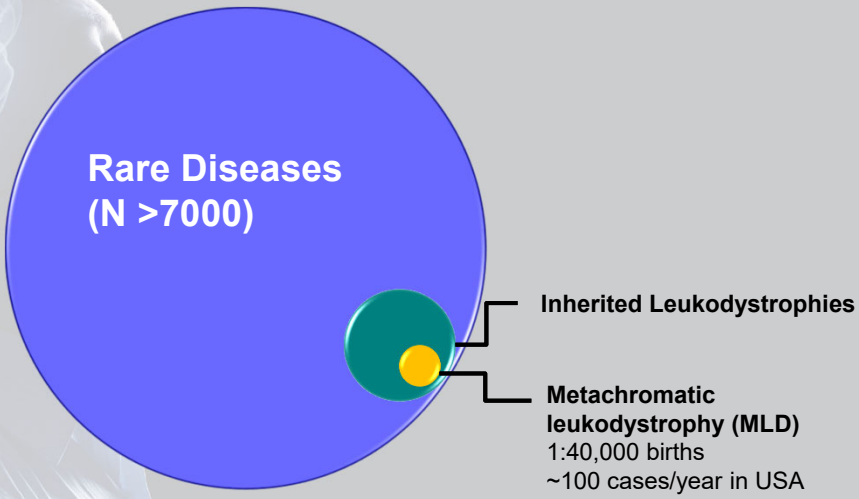
- Description of the inherited leukodystrophies
  - Metachromatic leukodystrophy, Krabbe, Adrenoleukodystrophy,
- How a diagnosis is established, and the diagnostic odyssey journey for patients and families
- Role of newborn screening
- Therapies
  - Allogeneic blood stem cell transplantation
  - Evolution to gene therapy
- What does this mean for those in the front lines? How does it relate to individual and caregiver(s) engagement in shared decision-making?

3

Inherited Leukodystrophies are Rare Disorders

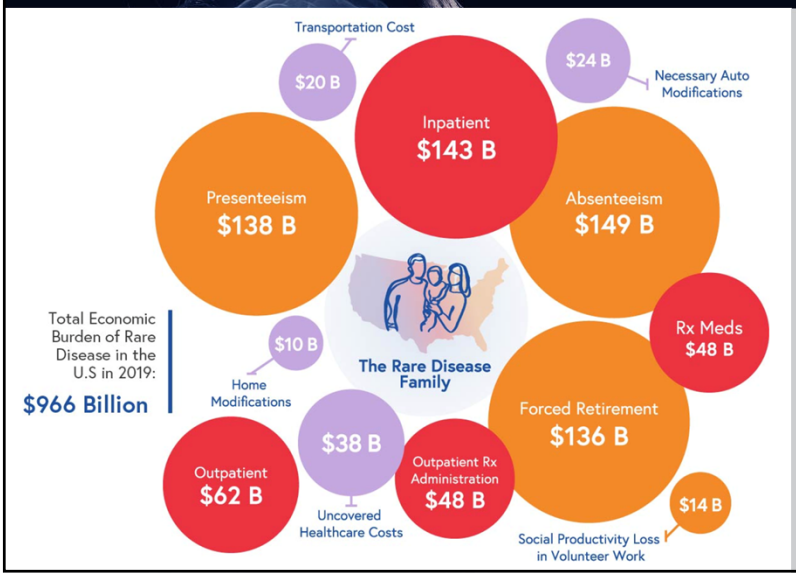
Rare Disease:
<200,000 affected in USA

Cost to Society ~1 trillion/year



4

Importance of Rare Disease in Society



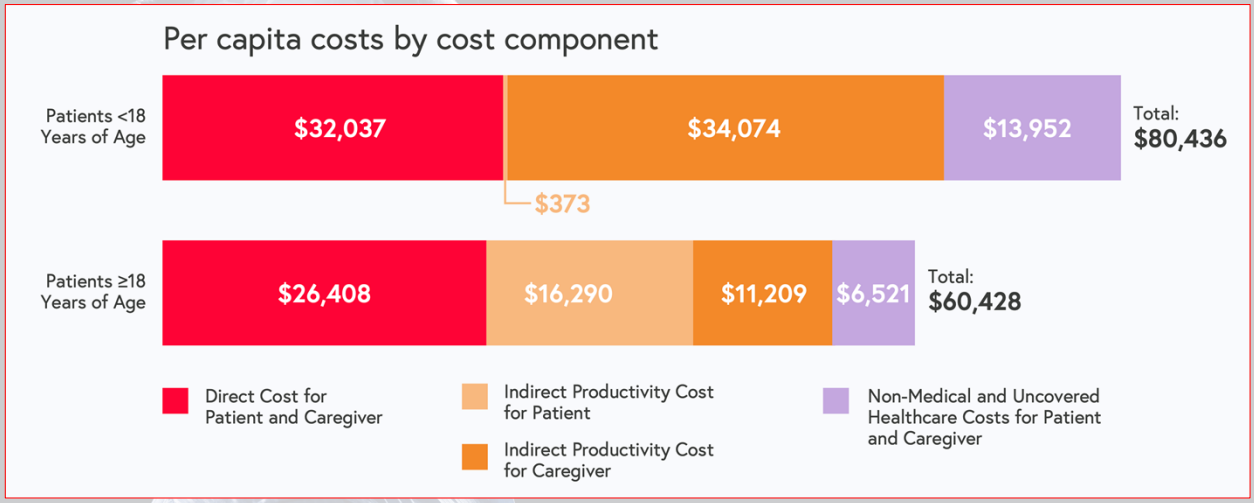
Study from Everylife Foundation
(<400 diseases represented)

- Direct medical costs
- Indirect; productivity
- Nonmedical/uncovered

Total ~1 trillion/year

5

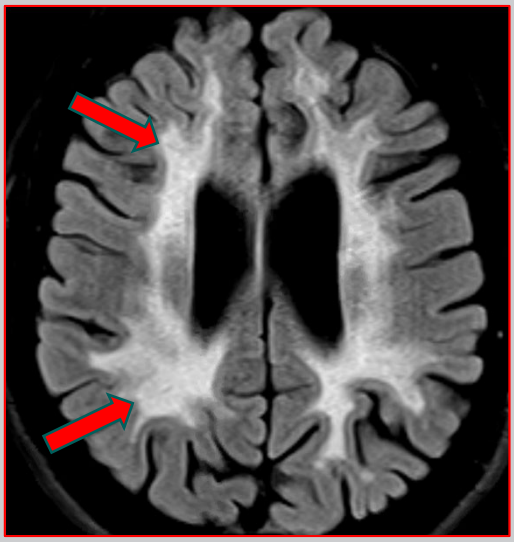
What is the Impact on the Average Rare Disease Family?



6

Metachromatic Leukodystrophy (MLD)

- MLD affects white matter of the brain
- Due to an enzyme deficiency (arylsulfatase A; ARSA)
- Accumulates sulfatides, which damages nerves
- Progressive, debilitating and lethal

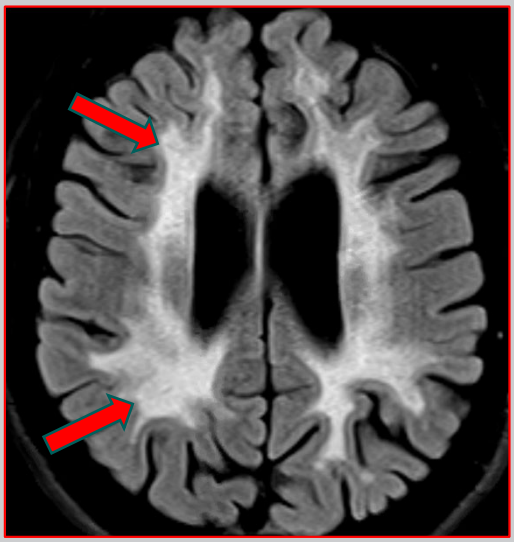


7

Metachromatic Leukodystrophy (MLD)

Several Phenotypes:

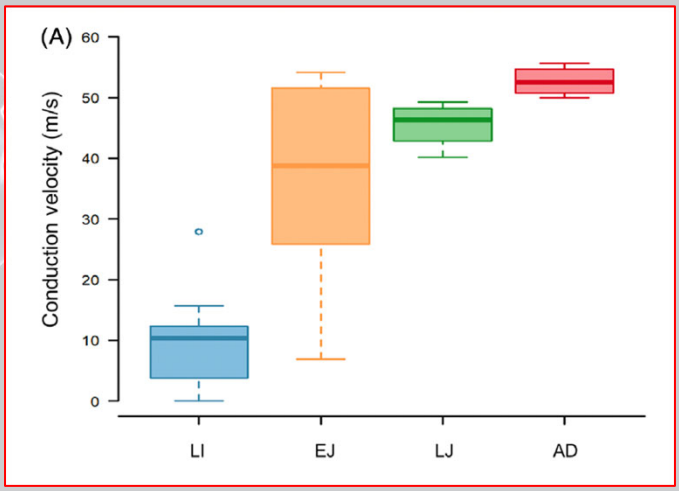
- Late infantile form (50%)
  - Onset <30 months; primary motor
- Juvenile form (30%)
  - 30 mon-16 years
  - Motor/cognitive issues
- Adult presentation (20%
  - Cognitive, executive function



8

Peripheral Nerve Dysfunction in MLD

Marked differences in the peripheral nerve function across phenotypes in MLD



Fumagalli: J Inherit Metab Dis. 2021;44:1151–1164.

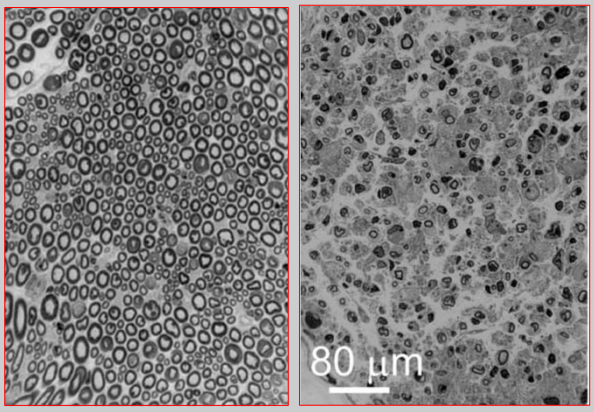
9

Globoid Cell Leukodystrophy (GLD; Krabbe)

- Similar to MLD, affects myelin in both the brain and peripheral nerves
- Another enzyme deficiency (galactocerebrosidase; GALC)
- Accumulates galactocerebroside and galactosylsphingosine; toxic
- Psychosine important in establishing the phenotype
- Progressive, debilitating and lethal

Control nerve

Krabbe nerve

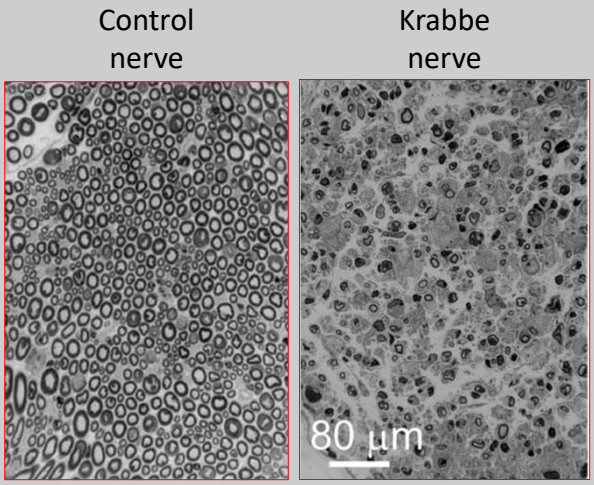


Images - Pan; Hum Gene Ther 2019 Sep;30(9):1039-1051

10

Globoid Cell Leukodystrophy (GLD; Krabbe)

- Infantile form (85%); <36 months
  - early to 12 mon, late to 36 mon
- Attenuated/later onset (15%)
- Infantile form rapidly progressive
- Newborn screening in limited states allows early intervention



Images - Pan; Hum Gene Ther 2019 Sep;30(9):1039-1051

11

Adrenoleukodystrophy

- Peroxisomal X-linked disorder
- Frequency ≈**1:17,000** boys
- Defect in ABCD1 gene; many described mutations
- Defective metabolism of very long chain fatty acids (VLCFA)
- High plasma VLCFA; diagnostic
- Newborn screening available

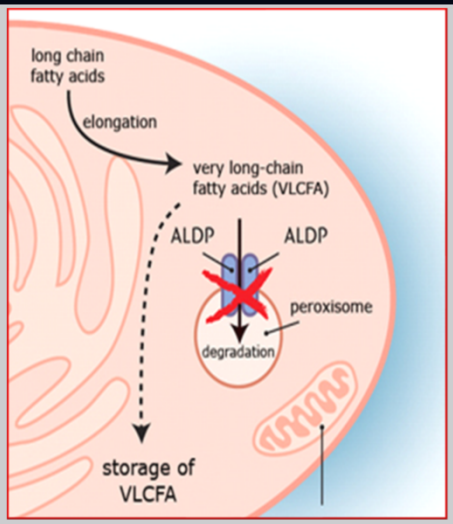


Figure: Dr. Kemp, Emma Children's Hospital, Amsterdam, Netherlands

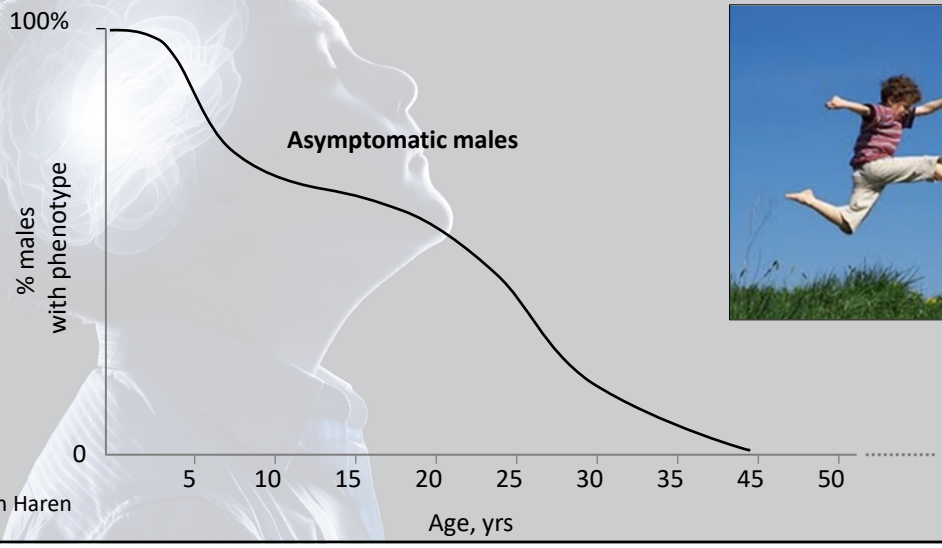
12

Adrenoleukodystrophy Phenotypes

• Childhood Cerebral ALD (C-ALD) 2.75-10 years; median age 7.2 years	30 - 35%
• Adolescent Cerebral ALD; 11-21 years	4 - 7%
• Adrenomyeloneuropathy (AMN) (40% develop C-ALD)	40 - 46%
• Adult C-ALD alone	2 - 5%
• Addisonian Disease alone	50%
• Asymptomatic: Decreases with age	Rare <40

13

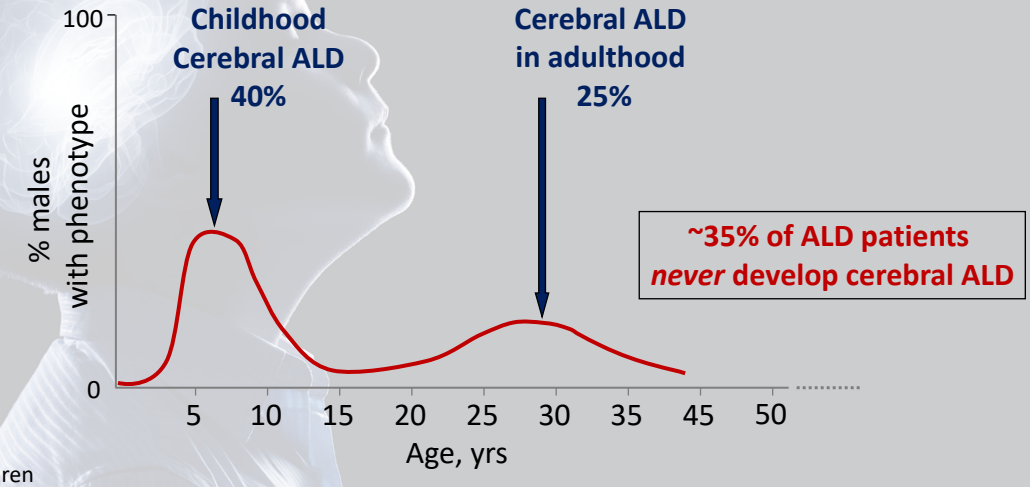
Adrenoleukodystrophy Phenotypes



From K. Van Haren

14

Development of Cerebral Disease in ALD

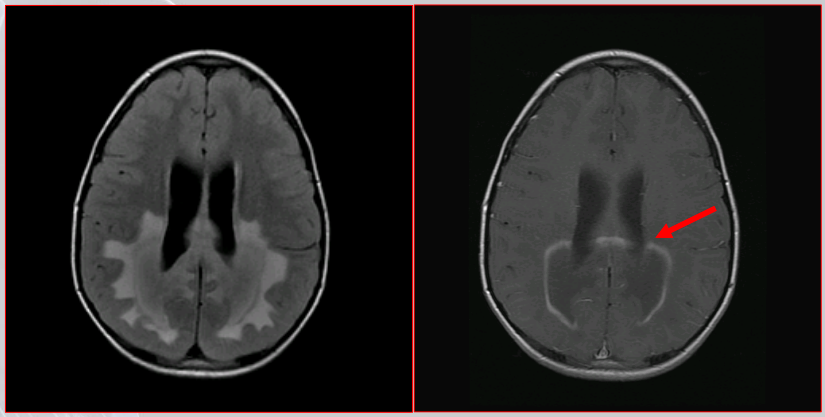


From K. Van Haren

15

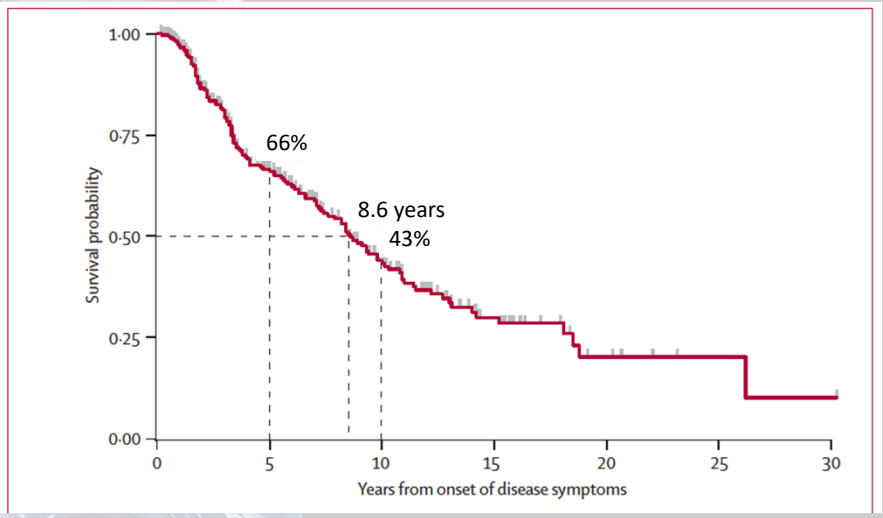
MRI Findings: Cerebral ALD

- 85% of disease is primarily occipital
- Affects vision, understanding of language
- Generally, is very advanced by the time of diagnosis



16

Cerebral ALD; Untreated Natural History



Online Metabolic & Molecular Basis of Inherited Disease, Chapter 131, XALD, 2011

17

Diagnosis; Inherited Leukodystrophies

1. MLD and Krabbe are recessive, lysosomal disorders
   - Generally no family history
   - MLD; ARSA activity decreased, mutations identified, accumulate sulfatide
   - GLD; GALC activity decreased, mutations identified, psychosine measured
2. ALD is peroxisomal, and is X-linked
   - May be a family history; brothers, cousins, uncles
   - NOT an enzyme deficiency; gene product in peroxisomal membrane
   - Very long chain fatty acid elevation; ABCD1 mutation
   - More recently C26 lysoPC assay

18

Achieving a Diagnosis in Rare Disease

Events Before Diagnosis of Rare Disease	Average
Number of Primary Care Providers Seen	4.2
Number of Specialists Seen	4.8
Number of Emergency Room Visits	3.7
Number of Hospitalizations	1.7
Number of Out-of-State Visits	2.4
Total:	**16.9**

Data from Rare Disease Impact Survey

19

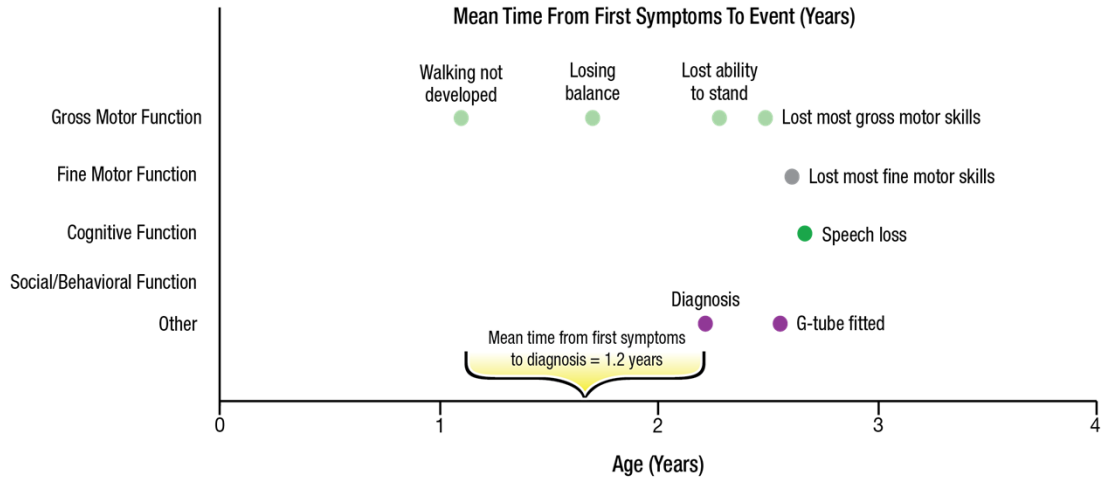
Achieving a Diagnosis in MLD

1. Providers may not suspect MLD as symptoms become evident
2. Misdiagnosis is common
3. Diagnostic delays can be long
   - On average **1.2 years from first symptom** in late infantile MLD
   - On average **3.7 years from first symptom** in early juvenile MLD
4. MLD is often diagnosed after the onset of symptoms and irreversible neurological damage
5. Pre-symptomatic diagnosis usually occurs only after an affected sibling is diagnosed

Harrington; Orphanet J Rare Dis 14.1(2019):89.

20

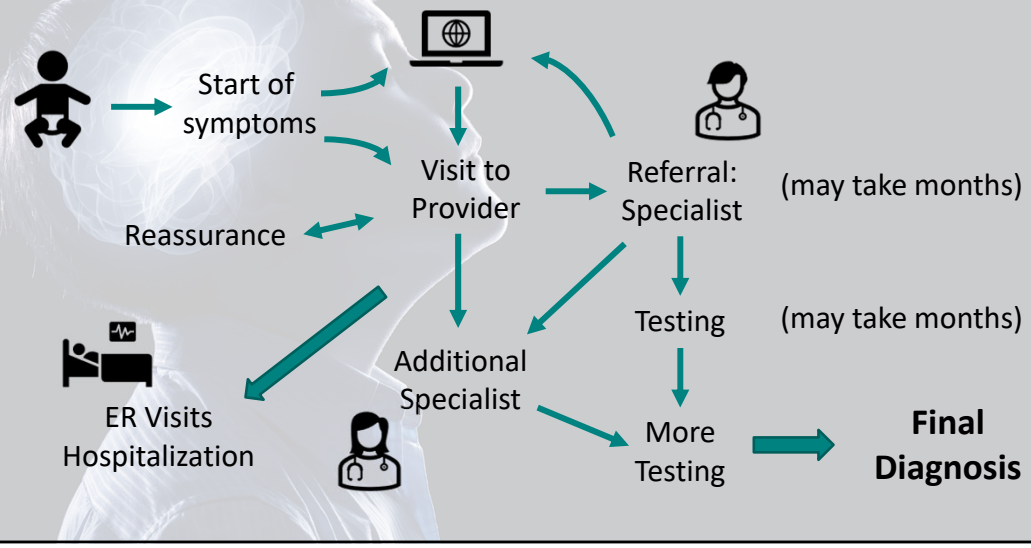
Achieving a Diagnosis in MLD



Fumagalli; Presented WORLD Conference 2021

21

Diagnostic Journey for Patients, Families

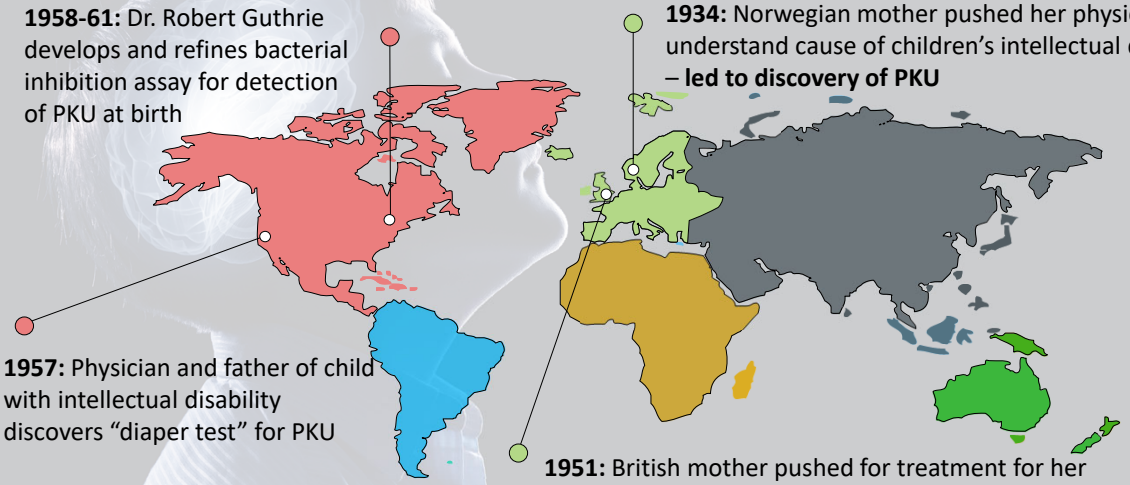


22

PKU, Newborn Screening, and the Role of Advocacy

1958-61: Dr. Robert Guthrie develops and refines bacterial inhibition assay for detection of PKU at birth

1934: Norwegian mother pushed her physician to understand cause of children's intellectual disability – **led to discovery of PKU**



1957: Physician and father of child with intellectual disability discovers "diaper test" for PKU

1951: British mother pushed for treatment for her child with PKU – **led to creation of phe-free formula**

23

Developing a System of Federal Guidance

2000

AAP

Calls for greater uniformity and national standards in Newborn Screening

2004

ACHDNC

HRSA Creates Advisory Council on Heritable Disorders in Newborns & Children

2005

HRSA/ACMG

Develop a Core Recommended Uniform Screening Panel (RUSP)

2008

NBS SAVES LIVES ACT

Expands role of ACHDNC to provide federal recommendations and provides funding for QA/QC/QI initiatives through HRSA and CDC

2020

ACHDNC

Currently, 6 diseases have been added using the ACHDNC mechanism

6

24

Background: Newborn Screening

Newborn Screening Programs are PUBLIC HEALTH programs

- Successful programs require knowledge and coordination from multiple stakeholders.

Newborn Screening Programs designed to detect TREATABLE conditions

- Disorders on the newborn screening panel must meet certain criteria

Newborn screening Programs are STATE-BASED

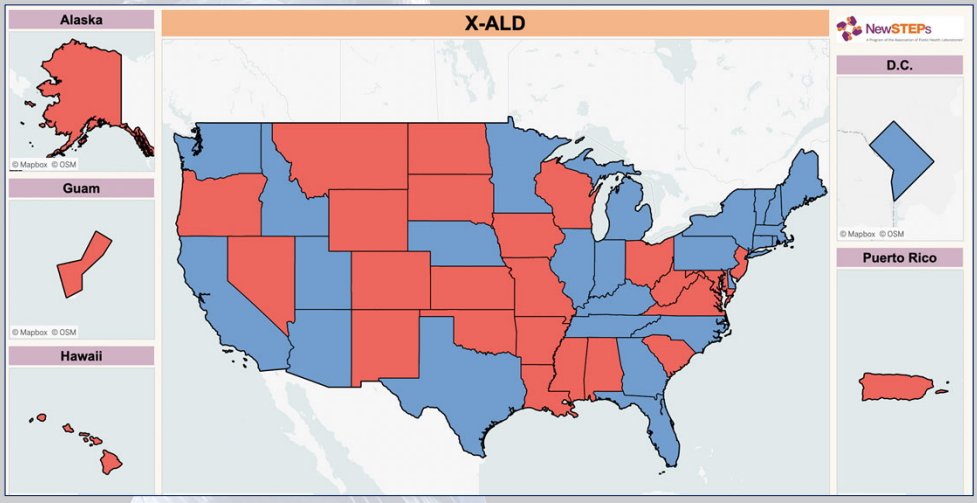
- Variations between Newborn Screening Programs exist from state-to-state.

25

How Disorders Get on the RUSP

26

Current Status: NBS for ALD



ALD on the RUSP

February, 2016

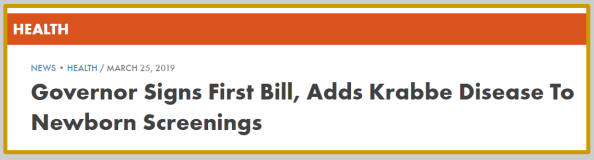
26 states now screening

https://www.newsteps.org/resources/data

27

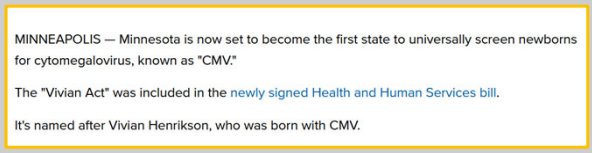
Why Do Discrepancies Exist?

- **Variations in:**
  - Ability to add diseases at state level
  - Public health funding and resources
- **Legislative Additions or Required Reviews**
  - Often for disorders not yet on the RUSP
  - Often sparked by family advocates
  - Often unfunded
- **RUSP is Recommended, but not *Required*…**
  - State must still approve and implement
  - Specific state concerns over some recent disease additions to the RUSP


HEALTH

NEWS • HEALTH / MARCH 25, 2019

Governor Signs First Bill, Adds Krabbe Disease To Newborn Screenings

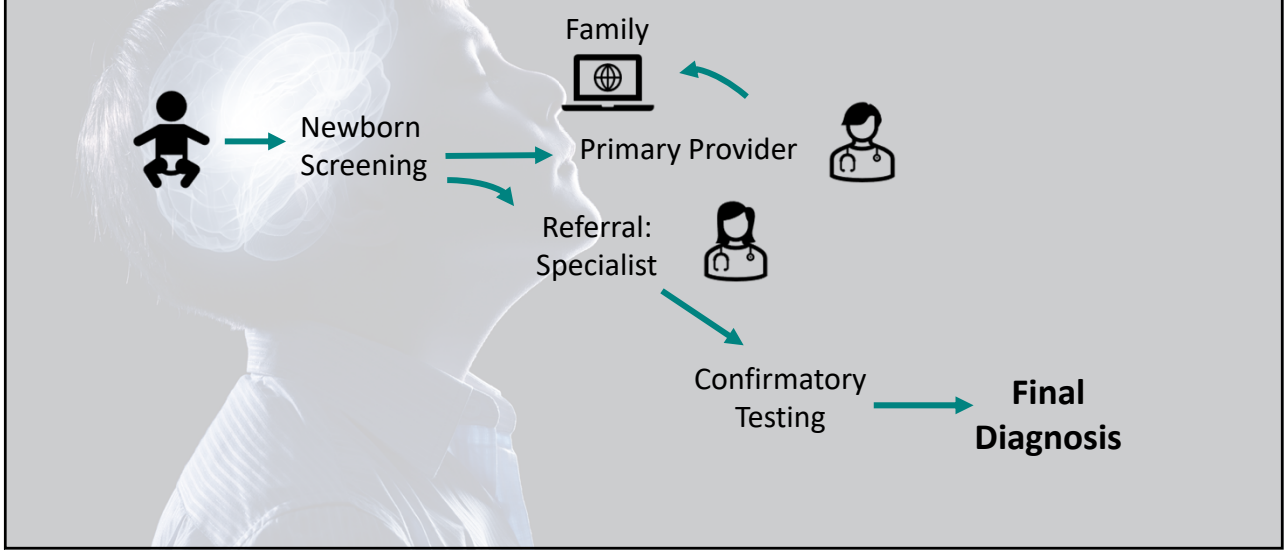

MINNEAPOLIS — Minnesota is now set to become the first state to universally screen newborns for cytomegalovirus, known as "CMV."

The "Vivian Act" was included in the newly signed Health and Human Services bill.

It's named after Vivian Henrikson, who was born with CMV.

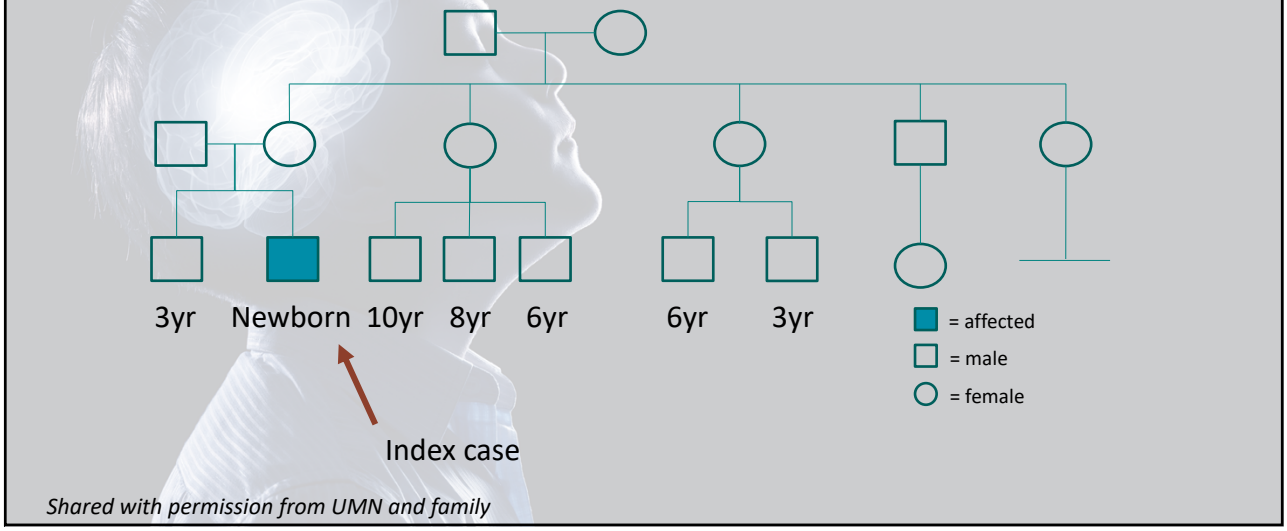
28

NBS: Diagnostic Journey for Patients, Families



29

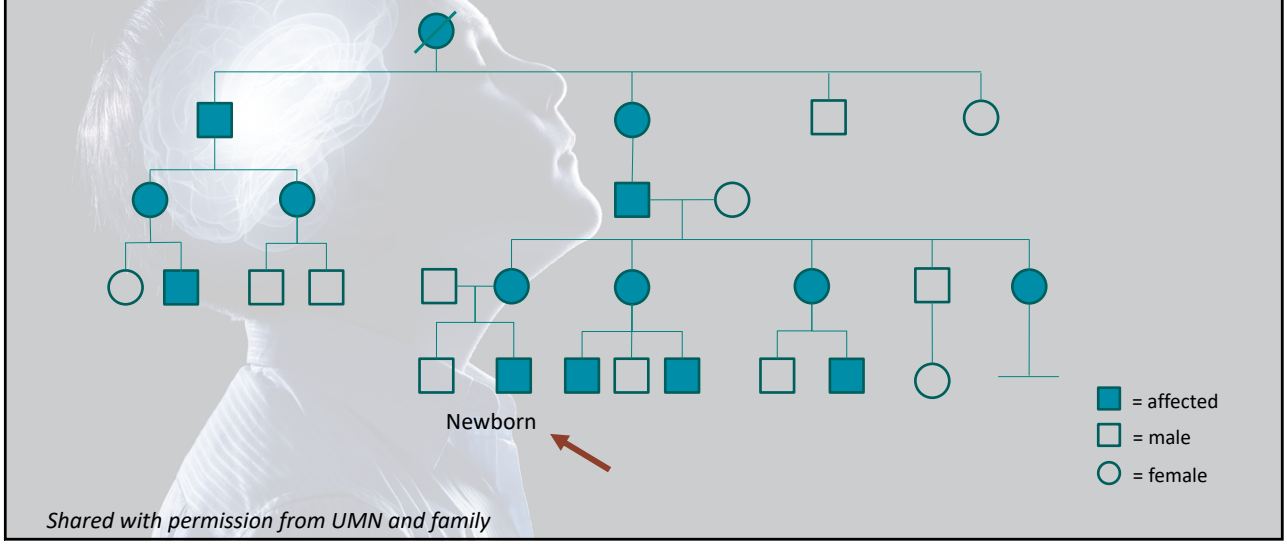
ALD NBS Case Example; Index Case



Shared with permission from UMN and family

30

ALD NBS Case Example; Index Case



Shared with permission from UMN and family

31

Monitoring ALD: Comprehensive Clinic

	ALD Dx	Y 1	Y 3	Y 9	Y 13	Y 17
Genetic Couns	Initial	As Needed				
ACTH/Cortisol	Every 4 months		Every 6 months			Yearly
Brain MRI		Yearly	Every 6 months		Yearly	
Adrenarchy				Yearly		
Neuropsychology			Yearly			
BMT Planning	Consider Early, Pre-Cerebral Disease					

Research Related to Comprehensive Clinic

1. Offer participation in ALD National Registry
   - Biorepository
   - Storage of MRI images
   - Data, phenotype development
2. Novel imaging research
3. Neuropsychology research

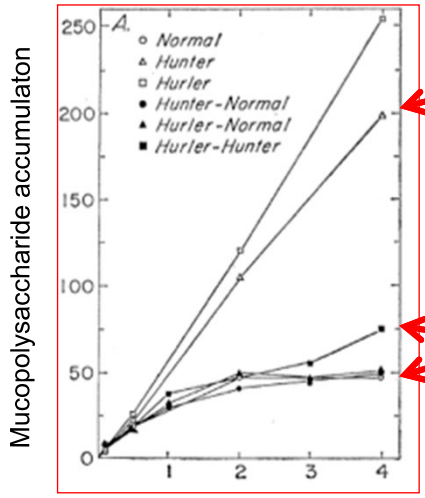
32

Therapy for Inherited Leukodystrophies

1. All the genes have been cloned; possible to provide enzyme infusions with pharmaceutic products
2. Enzyme are large molecules – do not penetrate the blood/brain barrier sufficiently
3. How can gene product be effectively delivered to the oligodendrocyte or Schwann cell?

33

Cross Correction Experiments; Lysosomal Disease



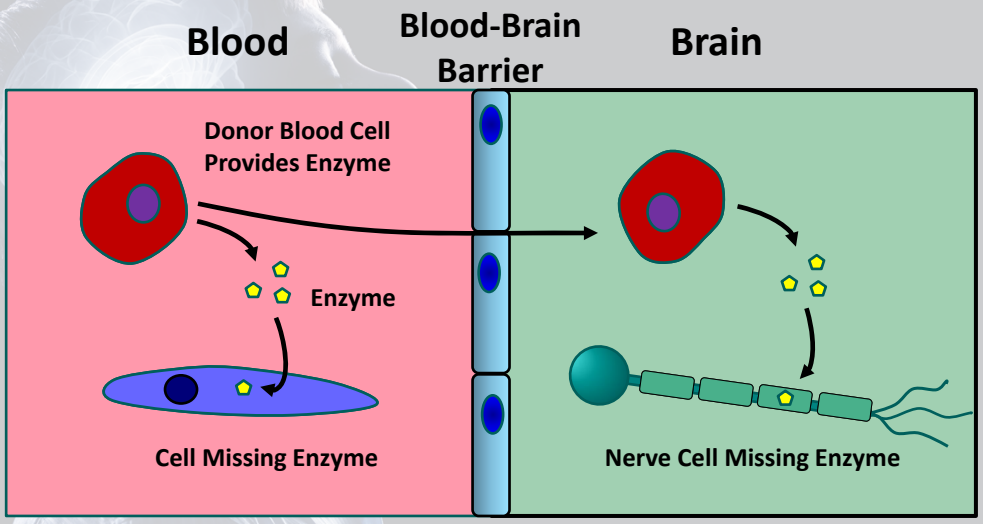
Hurler/Hunter cells alone

Hurler/Hunter Cells together, and with NL cells

Fratantoni, Hall, Neufeld. Science; 1968.162; 853: 570-2

34

Blood Stem Cell Transplantation



35

Hematopoietic Stem Cell Transplant (HSCT) Finding A Suitable Donor

Considering a transplant; start with HLA typing

Are there full siblings available?

- 1 in 4 chance each siblings is a match
- May be carriers; does that matter?

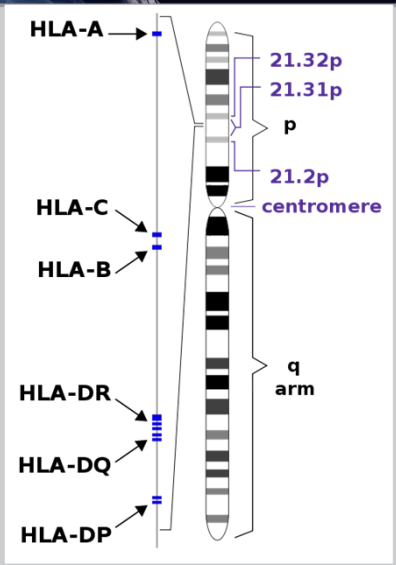
Find another source of blood stem cells

- Adult unrelated donors (URD)
- Unrelated cord blood (UCB)
- Haploidentical transplant (parent)

36

Overview; HLA Typing

HLA Complex Chromosome 6



Class I (all nucl cells)

A, B, C

Class II (nucl bld cells)

HLA-DP, DQ, DR

Determine number of Ag matches A, B, C and DRβ1:

Acceptability:

1. URD - 8/8 or 7/8
2. Cord blood - >5/8

37

Overview; HLA Typing

Recipient HLA Typed

↓

Preliminary Search via NMDP — **Electronic; free**

↓

Transplant Center; Formal Search — **Insurance; Consent; $$$**

↓

Confirmatory Typing

↓

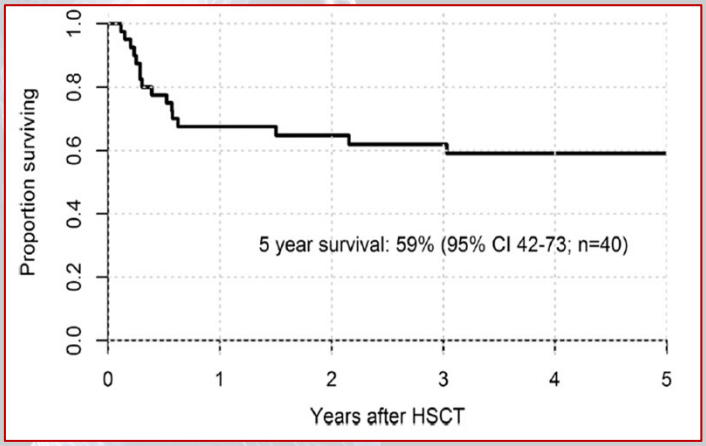
Cord – DONE!

URD Workup; PE, Labs; Months

38

Outcomes: Blood Stem Cell Transplant for MLD

Minnesota Data: Largest experience in MLD



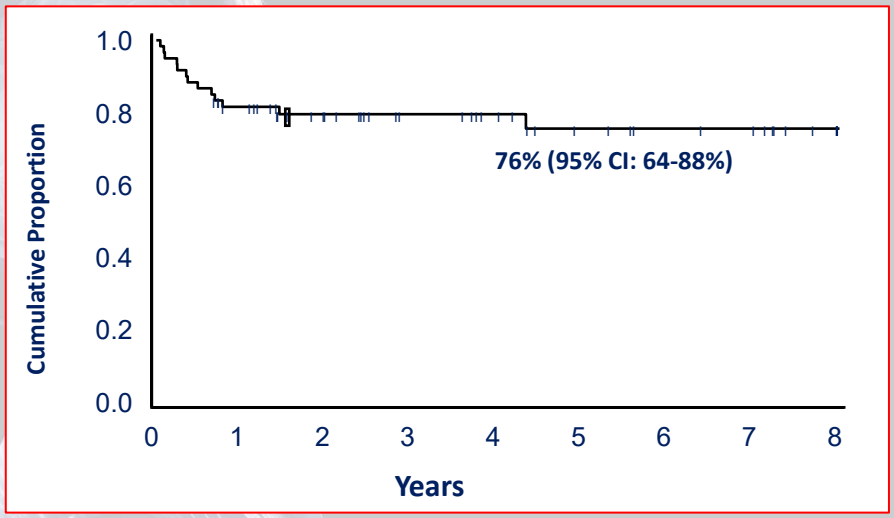
40% death rate 5 years after transplant

1. Transplant insufficient
2. Diagnosis too late

Boucher et al. Orphanet Journal of Rare Diseases (2015) 10:94

39

Overall Survival: All ALD Patients (n=60)



Miller, Blood, 2011; 18(7):1971-8

40

Assessing Functional Outcome: Neurologic Functional Score (NFS) Scale

Loes scoring: (0–34) Point system

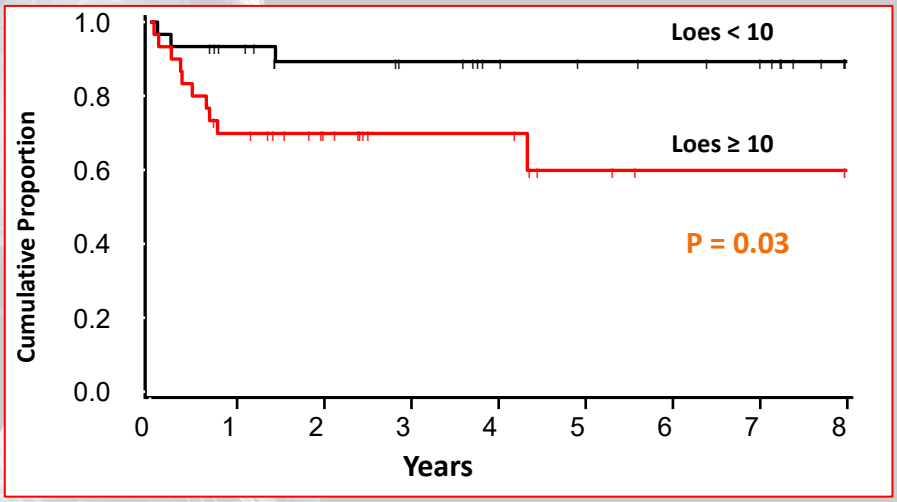
- parieto-occipital WM
- antero-temporal WM
- frontal WM
- corpus callosum
- visual pathways
- auditory pathways
- pyramidal system
- basal ganglia
- anterior thalamus

- **Increased involvement = higher score**
- **"Advanced disease" score is 9-10**

Loes et al. AJNR Am J Neuroradiol 1994;15:1761-1766

41

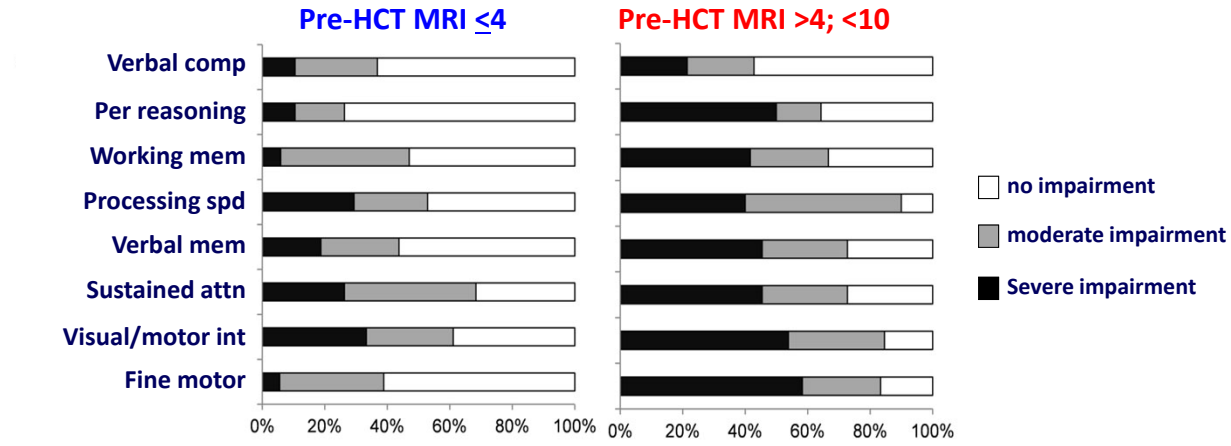
Survival by MRI Score; Early vs Late (Loes Score <10; N=30)



Miller, Blood, 2011; 18(7):1971-8

42

Standard Risk cALD Patients: Impairments at Most Recent Evaluation:



Pierpont; JAMA Neurology, 2017; 74 (6) 710-717

43

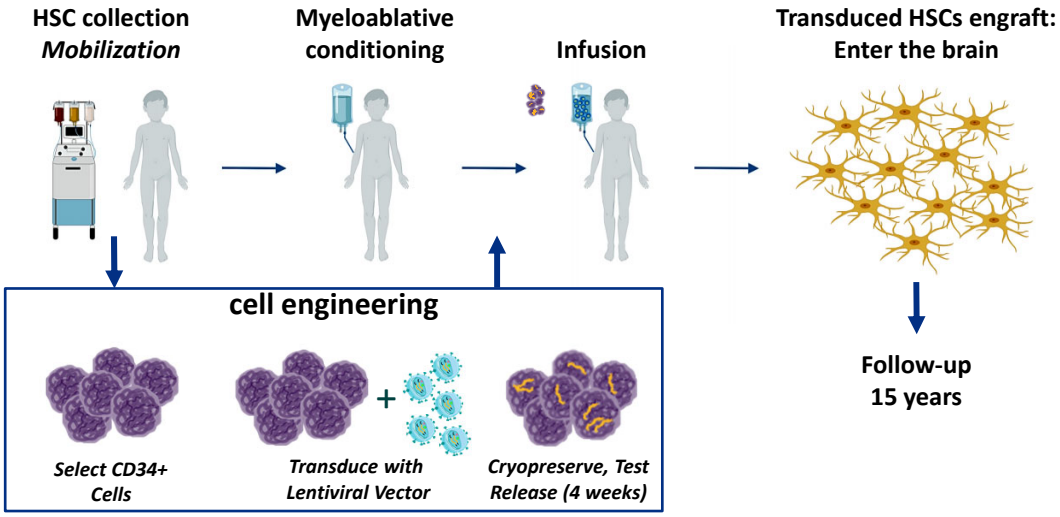
Other Therapeutic Options??

Gene Therapy in Development

1. **Ex vivo therapy – lentiviral mediated engineering of the patients own blood stem cells**
   - **Need to perform apheresis to obtain the cells**
   - **Manufactured in the lab**
   - **Requires chemotherapy to eliminate resident hematopoiesis**
2. **In vivo therapy – Adeno-associated virus based delivery**
   - **Virus injected into the spinal fluid**
   - **May be cisterna magna based delivery**
   - **Requires immunosuppression for some period of time**

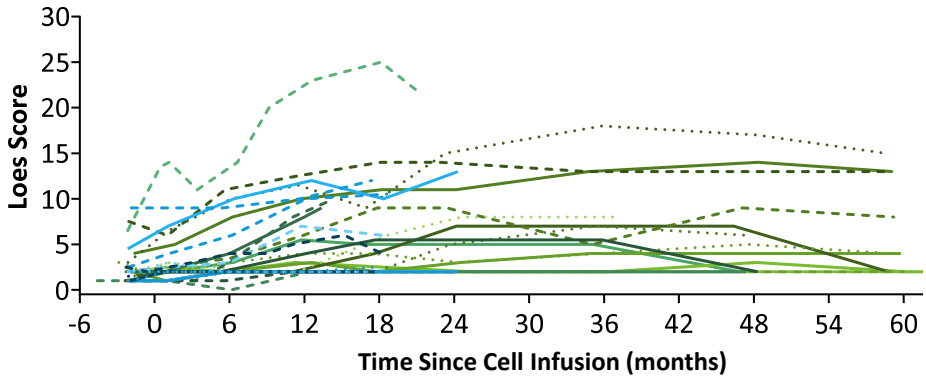
44

Lentiviral ex-vivo genetic engineering



45

MRI Stability Post Gene Therapy: ALD



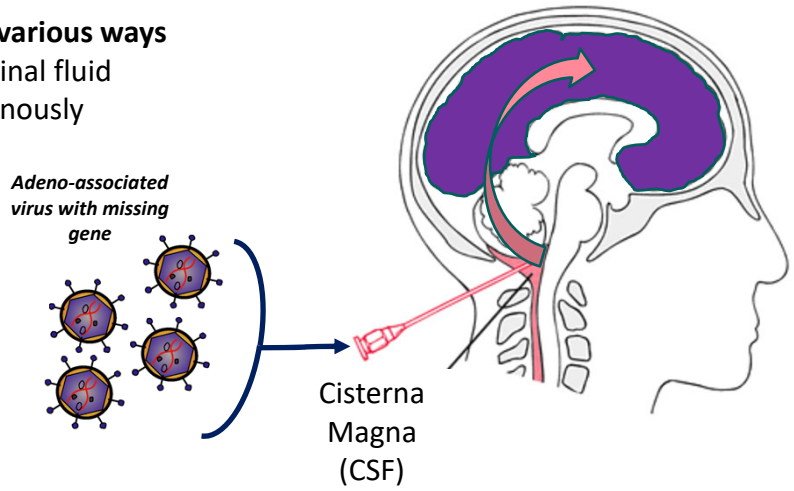
Presented at TCT Meeting; January 2021

46

Adeno-associated virus; direct injections

AAV delivered in various ways

- Directly into spinal fluid
- Infused intravenously



47

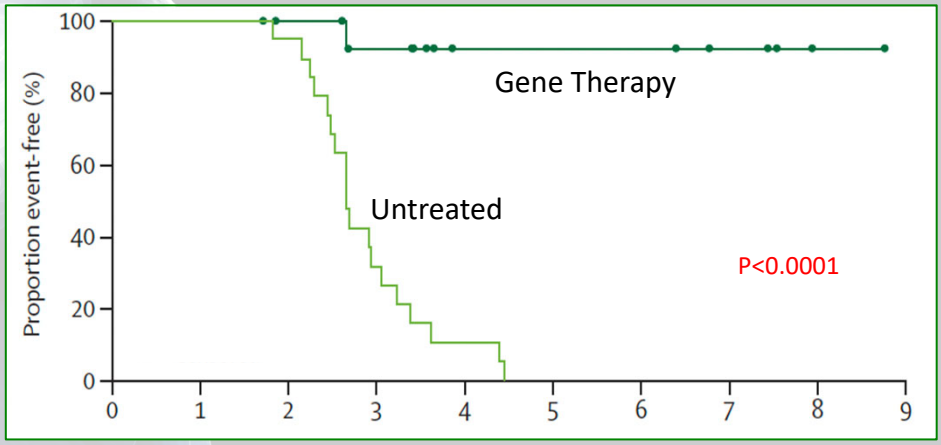
Status: Gene Therapy for Leukodystrophies

1. **Adrenoleukodystrophy**
   - 2 international lentiviral based gene therapy trials completed
   - Will be reviewed by FDA this year, possibly licensed in 2022
2. **Globoid cell leukodystrophy (Krabbe)**
   - Several trials now open using AAV as therapy
   - One trial in association with allogeneic transplantation
3. **Metachromatic leukodystrophy**
   - Lentiviral based therapy now approved in Europe; to be considered in the USA likely in 2023
   - Other approaches being considered as well

48

Survival Outcomes in MLD +/- Gene Tx

Survival/Lack of Severe Motor Impairment

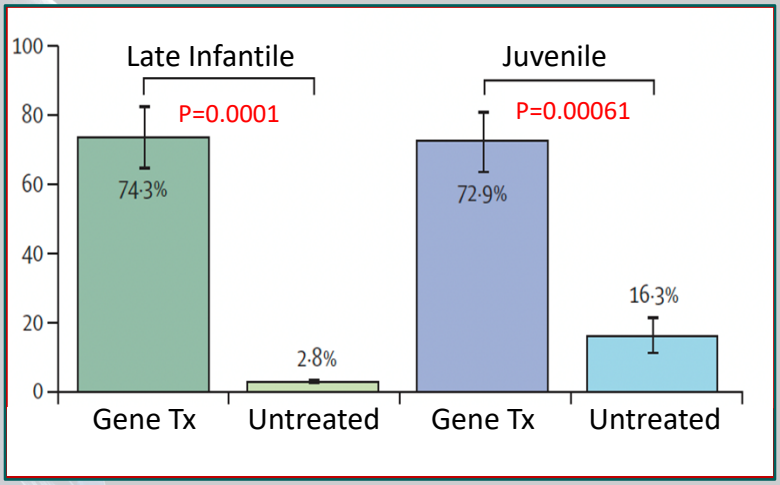


Fumagalli; Lancet 2022; 399: 372–83

49

Functional Outcomes in MLD +/- Gene Tx

Gross Motor Functional Measure (GMFM) 3 years



Fumagalli; Lancet 2022; 399: 372–83

50

Risks: Gene Therapy for Leukodystrophies

1. Will these therapies be safer than allogeneic transplantation?
   - Transplant mortality 15% by 100 days post
   - Autologous approaches likely 1-2%
   - AAV less clear
   - Late issues; myelodysplasia/leukemia
2. Will they be more effective than transplant?
   - For enzyme deficiencies, may deliver more than with transplant
   - Sustained?
3. How will we pay for them?
   - May be 2.5 – 3 million for cell product

51

How do families cope, make decisions?

1. Obtaining a new diagnosis turns the world of a family upside down
2. Determining the best path forward may be made with limited time and information
3. Insurance related questions loom large – especially if travel for care is required
4. The support structure of the family is extremely important
   - Family & friends, social work, primary providers
   - Shared decision making

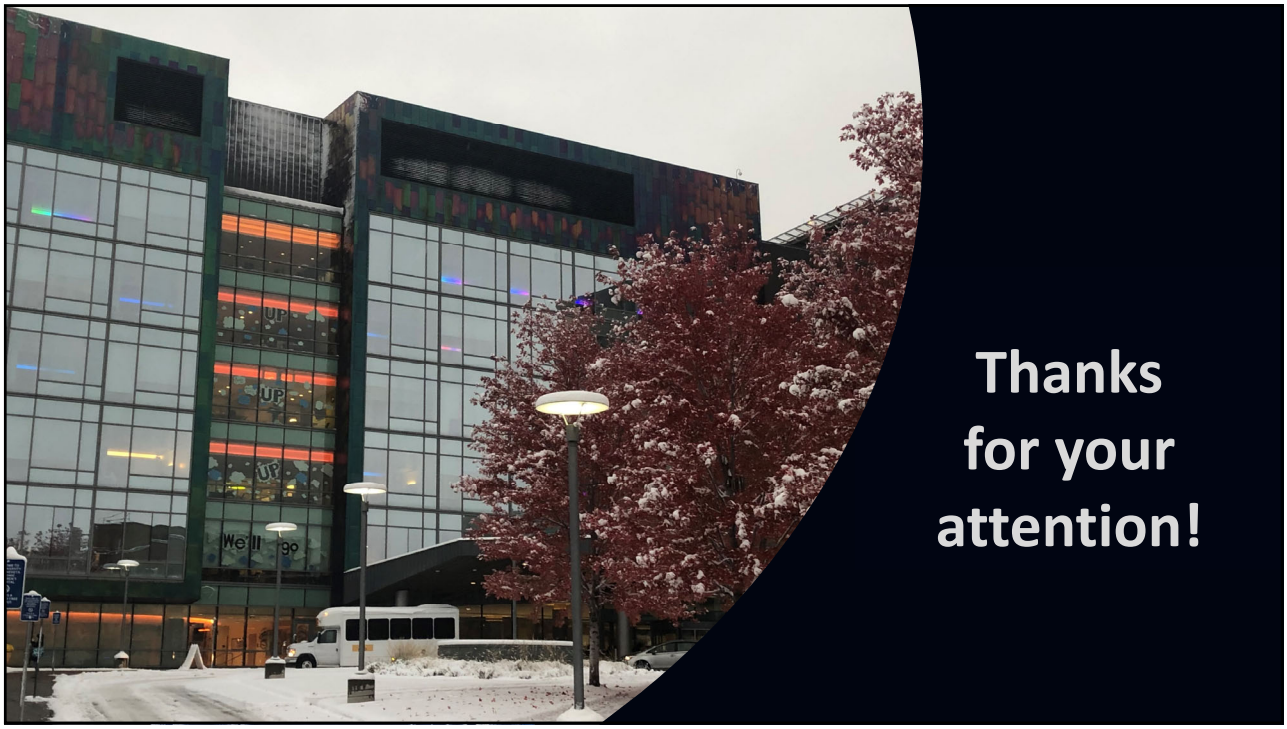
52

Summary: Inherited Leukodystrophies

1. ALD, MLD, GLD are progressive, lethal diseases of childhood
2. Making a diagnosis when symptomatic is too late
3. Newborn screening is the best means to achieve this
4. Blood stem cell transplantation is inadequate as therapy
5. New therapies are in development, yet early diagnosis remains critical

"Bring me a stem cell"

53



54

55