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.
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?

Inherited Leukodystrophies are Rare Disorders

Rare Disease:
<200,000 affected in USA

Cost to Society
~1 trillion/year

Rare Diseases (N >7000)

Inherited Leukodystrophies

Metachromatic leukodystrophy (MLD)
1:40,000 births
~100 cases/year in USA
Importance of Rare Disease in Society

Study from Everylife Foundation
(<400 diseases represented)

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

Total ~1 trillion/year

What is the Impact on the Average Rare Disease Family?

Per capita costs by cost component

Patients <18 Years of Age
- Direct Cost for Patient and Caregiver: $32,037
- Indirect Productivity Cost for Patient: $34,074
- Non-Medical and Uncovered Healthcare Costs for Patient and Caregiver: $13,952
- Total: $80,436

Patients ≥18 Years of Age
- Direct Cost for Patient and Caregiver: $26,408
- Indirect Productivity Cost for Patient: $16,290
- Indirect Productivity Cost for Caregiver: $11,209
- Non-Medical and Uncovered Healthcare Costs for Patient and Caregiver: $6,521
- Total: $60,428
Metachromatic Leukodystrophy (MLD)

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

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
Peripheral Nerve Dysfunction in MLD

Marked differences in the peripheral nerve function across phenotypes in MLD


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

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

Adrenoleukodystrophy

- Peroxisomal X-linked disorder
- Frequency \( \approx 1:17,000 \) 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
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

From K. Van Haren
Development of Cerebral Disease in ALD

- Childhood Cerebral ALD: 40% of males
- Cerebral ALD in adulthood: 25% of males

From K. Van Haren

MRI Findings: Cerebral ALD

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

~35% of ALD patients never develop cerebral ALD
Cerebral ALD; Untreated Natural History

![Survival curve showing 66% survival rate at 8.6 years with 43% survival at 10 years.](image)

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

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
Achieving a Diagnosis in Rare Disease

<table>
<thead>
<tr>
<th>Events Before Diagnosis of Rare Disease</th>
<th>Average</th>
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</thead>
<tbody>
<tr>
<td>Number of Primary Care Providers Seen</td>
<td>4.2</td>
</tr>
<tr>
<td>Number of Specialists Seen</td>
<td>4.8</td>
</tr>
<tr>
<td>Number of Emergency Room Visits</td>
<td>3.7</td>
</tr>
<tr>
<td>Number of Hospitalizations</td>
<td>1.7</td>
</tr>
<tr>
<td>Number of Out-of-State Visits</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>16.9</strong></td>
</tr>
</tbody>
</table>

Data from Rare Disease Impact Survey

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.*
Achieving a Diagnosis in MLD

Fumagalli; Presented WORLD Conference 2021

Diagnostic Journey for Patients, Families

Start of symptoms
Reassurance
ER Visits
Hospitalization
Visit to Provider
Referral: Specialist
Testing
Additional Specialist
More Testing
Final Diagnosis

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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.

Developing a System of Federal Guidance

2000

AAP
Calls for greater uniformity and national standards in Newborn Screening.

2005

HRSA/ACMG
Develop a Core Recommended Uniform Screening Panel (RUSP).

ACHDNC

2020

ACHDNC
Currently, 6 diseases have been added using the ACHDNC mechanism.

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

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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.

---

How Disorders Get on the RUSP

1. Submit nomination package
2. HRSA reviews package
3. Nomination & prioritization workgroup review
4. **Full committee vote** to go to condition evidence review
5. If “yes”, Evidence Review Workgroup evaluates
6. **Full committee vote** to add condition to RUSP
7. If “yes”, recommend to Secretary of HHS to add to RUSP
8. Secretarial decision to add or not add condition to RUSP

- 9 months ≤ 180 days
Current Status: NBS for ALD

ALD on the RUSP
February, 2016
26 states now screening

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
NBS: Diagnostic Journey for Patients, Families

Newborn Screening → Family
Primary Provider
Referral: Specialist
Confirmatory Testing → Final Diagnosis

ALD NBS Case Example; Index Case

Index case

Shared with permission from UMN and family
ALD NBS Case Example; Index Case

Shared with permission from UMN and family

Monitoring ALD: Comprehensive Clinic

<table>
<thead>
<tr>
<th></th>
<th>ALD Dx</th>
<th>Y 1</th>
<th>Y 3</th>
<th>Y 9</th>
<th>Y 13</th>
<th>Y 17</th>
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</thead>
<tbody>
<tr>
<td><strong>Genetic Couns</strong></td>
<td>Initial</td>
<td></td>
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<tr>
<td><strong>ACTH/Cortisol</strong></td>
<td>Every 4 months</td>
<td>Every 6 months</td>
<td>Yearly</td>
<td></td>
<td></td>
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<tr>
<td><strong>Brain MRI</strong></td>
<td>Yearly</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Adrenarchy</strong></td>
<td>Yearly</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Neuropsychology</strong></td>
<td></td>
<td></td>
<td>Yearly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BMT Planning</strong></td>
<td>Consider Early, Pre-Cerebral Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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
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?

Cross Correction Experiments; Lysosomal Disease

Cross Correction Experiments; Lysosomal Disease

Fratantoni, Hall, Neufeld. Science; 1968.162; 853: 570-2
Blood Stem Cell Transplantation

**Blood**
- Donor Blood Cell
- Provides Enzyme
- Enzyme
- Cell Missing Enzyme

**Blood-Brain Barrier**

**Brain**
- Nerve Cell Missing Enzyme

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 sibling 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)
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

---

**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
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

Overall Survival: All ALD Patients (n=60)

76% (95% CI: 64-88%)

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


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

![Survival Curve](image)

- Loes < 10
- Loes ≥ 10

P = 0.03

### Standard Risk cALD Patients:

**Impairments at Most Recent Evaluation:**

<table>
<thead>
<tr>
<th></th>
<th>Pre-HCT MRI ≤4</th>
<th>Pre-HCT MRI &gt;4; &lt;10</th>
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</thead>
<tbody>
<tr>
<td>Verbal comp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per reasoning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working mem</td>
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<td>Processing spd</td>
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<td>Verbal mem</td>
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<td></td>
</tr>
<tr>
<td>Sustained attn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual/motor int</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine motor</td>
<td></td>
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</tr>
</tbody>
</table>

- No impairment
- Moderate impairment
- Severe impairment

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

### 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
Lentiviral ex-vivo genetic engineering

HSC collection
Mobilization

Myeloablative conditioning

Infusion

Transduced HSCs engraft:
Enter the brain

Follow-up
15 years

Select CD34+ Cells

Transduce with Lentiviral Vector

Cryopreserve, Test Release (4 weeks)

MRI Stability Post Gene Therapy: ALD

Presented at TCT Meeting; January 2021

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Adeno-associated virus; direct injections

AAV delivered in various ways
- Directly into spinal fluid
- Infused intravenously

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
Survival Outcomes in MLD +/- Gene Tx

Survival/Lack of Severe Motor Impairment

Gene Therapy

Untreated

P < 0.0001

Fumagalli; Lancet 2022; 399: 372–83

Functional Outcomes in MLD +/- Gene Tx

Gross Motor Functional Measure (GMFM) 3 years

Late Infantile

Juvenile

P = 0.0001

P = 0.00061

Gene Tx

Untreated

Gene Tx

Untreated

Fumagalli; Lancet 2022; 399: 372–83
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

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
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”

Thanks for your attention!
March 29, 2022

The Diagnostic Odyssey for Individuals With Rare Diseases: Leukodystrophies

Q&A