Nomination and Prioritization Workgroup Report on X-Adrenoleukodystrophy (X-ALD)

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Nomination of X-ALD

Proponent: - Charles Peters, MD
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Advocate Organizations:
- The Stop ALD Foundation
- ALD/AMN Global Alliance
- Be A Hero Become a Donor
- Cure ALD
- Fight ALD
- The Myelin Project
- Run4ALD
- ELA
- ULF
X-ALD

• X-linked recessive

• Prevalence:
  ▪ 1 in 21,000 males
  ▪ Ca. 65% of carrier females develop disease by 60 years old
  ▪ Most common peroxisomal disorder

• Etiology:
  ▪ Mutations in ABCD1 gene
  ▪ ABCD1 encodes peroxisomal membrane protein ALDP, a transmembrane transporter of VLCFA (≥C_{22}).

X-ALD

• Pathophysiology:
  ALDP deficiency > impaired VLCFA peroxisomal beta-oxidation (~30% of normal) > accumulation of VLCFA-CoA esters in cells causes oxidative stress and oxidative damage to proteins, microglial activation and apoptosis

• Phenotypes:
  ▪ adrenocortical insufficiency (Addison-only)
  ▪ cerebral demyelinating form of X-ALD (cerebral ALD)
  ▪ adrenomyeloneuropathy (AMN)
  ▪ variants can occur within same family
  ▪ no phenotype/genotype correlation
Cerebral X-ALD

- Phenotype:
  - Insidious onset (often misdiagnosed as ADHD)
  - First symptoms not before 2.5 years of age
  - Progressive inflammatory demyelination within the brain
  - Severe cognitive and neurologic disability > vegetative state and death within 2-5 years after onset

- Diagnosis:
  - VLCFA in plasma
  - Molecular genetic analysis of ABCD1 in women (15% will have normal VLCFA)
  - Family investigations

Adrenomyeloneuropathy (AMN)

- Pathology:
  Contrary to X-ALD noninflammatory distal axonopathy involving mostly the long tracts of the spinal cord

- Phenotype:
  - Progressive spastic paraplegia (often misdiagnosed as primary progressive MS or hereditary spastic paraparesis)
  - 20% of males with AMN will develop cerebral ALD later

- Diagnosis:
  - VLCFA in plasma
  - Molecular genetic analysis of ABCD1 in women (15% will have normal VLCFA)
  - Family investigations
**X-ALD**

**Treatment options:**
- hormone replacement
- Lorenzo’s oil
- Hematopoietic cell transplantation (HCT)

**Probability of survival after HCT for boys with cerebral ALD (n=60) based on Loes score (A) and neurologic function (NFS) at the time of HCT**

![Graph showing probability of survival after HCT for boys with cerebral ALD](image)

- Prognosis better when treatment started early (NBS!)


**X-ALD**

**BIOMARKERS: C_{20} - C_{26} Lysophosphatidylcholines (LPC)**

**Modified:**
- from LC-MS/MS to FIA-MS/MS
- from 3.0 to 1.5 min/sample
- multiplex with testing for 6 LSDs

Dr. Silvia Tortorelli
Mayo’s NBS Study for LSDs, Wilson Disease, Friedreich Ataxia and X-ALD

- Implement all assays available for testing of DBS for up to 13 LSDs, Wilson disease, Friedreich Ataxia and X-ALD;
- Conduct a prospective NBS study of 100,000 blinded DBS with the goal to identify an effective and efficient testing approach;
- Evaluate approaches to rapidly confirm a presumptive diagnosis applying biochemical and molecular genetic analyses;
- Build a web site to gather data and provide analytical protocols, reference and disease ranges, and guides to result interpretation.*

*emulate the Region 4 Genetics Collaborative MS/MS Data Project
Mayo’s NBS Study
Sponsors & Supporters

This project has been funded in part with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services (Contract #HHSN275201000017C), the Newborn Screening Translational Research Network (NBSTRN; subcontract #HHSN275200800001C 01), and a generous gift from The Legacy of Angels Foundation.

<table>
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<tr>
<th>DISORDER</th>
<th>MS/MS</th>
<th>Immunocapture</th>
<th>Dig. Microfluidics</th>
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<tr>
<td>Fabry disease</td>
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<td>Gaucher disease</td>
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<td>MLD</td>
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<td>MPS I</td>
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<td>Bifunctional protein def.</td>
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Status of Mayo’s NBS Study for X-ALD

Samples tested: 85,000

1st Tier MS/MS
(LPCs + 6 LSDs)
Abnormal (1%): 640 ♀ + 274 ♂

2nd Tier LC-MS/MS
(LPCs)
Abnormal:
25 ♀ + 10 ♂
0.03% ♀ + 0.01% ♂

ABCD1 genotyping*
X-ALD: 1 ♀ + 2 ♂

*other peroxisomal disorders not excluded
Status of NBS for X-ALD

• USA:
  ▪ CT/NJ: legislation passed for NBS for X-ALD.
  ▪ CA: legislature is considering NBS for X-ALD.

• Elsewhere:
  ▪ Netherlands: NBS for X-ALD (males only) under consideration

Summary (1)

• X-ALD is a serious medical condition.
• Natural history of X-ALD seems well known.
• X-ALD does not require initiation of treatment in the newborn period!
• DBS based assays are available using LPCs as a disease marker.
• LPCs are not specific for X-ALD but also elevated in other peroxisomal conditions (secondary targets?) and (many) female carriers.
Summary (2)

- A pilot study of 100,000 de-identified samples is being completed at Mayo Clinic.
- Mayo took a two-tier approach. 2nd tier test could be done locally or regionalized.
- **Preliminary** findings from Mayo’s Study:

<table>
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<th>DISORDER Group</th>
<th>Prevalence</th>
<th>FPR</th>
<th>PPV</th>
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<tbody>
<tr>
<td>X-ALD</td>
<td>1 : 21,250 boys</td>
<td>0.02%</td>
<td>18%</td>
</tr>
<tr>
<td>AA/OA/FAO (Mayo)</td>
<td>1 : 1,900</td>
<td>0.02%</td>
<td>68%</td>
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<td>AA/OA/FAO (US avg.)</td>
<td>?</td>
<td>0.46%</td>
<td>18%</td>
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Nomination of X-ALD for NBS

- **Recommendation to DACHDNC** -

- **Initiate** External Evidence Review because:
  - In 2012 SACHDNC already stated that X-ALD is an important condition to be considered but pilot studies were lacking at the time.
  - Mayo pilot study suggests an appropriate NBS approach exists.
- **Recommend** that ACMG develop and algorithms (www.acmg.net) for X-ALD and relevant peroxisomal disorders.