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

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SACHDNC Meeting
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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 ($\geq C_{22}$).

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:**

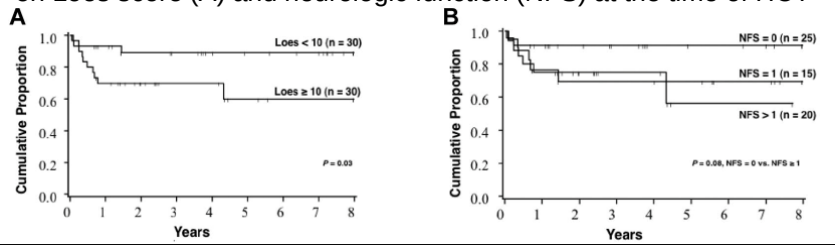
  contrary to X-ALD noninflammatory distal axonopathy involving mostly the long tracts of the spinal cord
- **Phenotype:**
  - progressive spastic paraplegia (often misdiagnosed as primary progressive MS or hereditary spastic paraparesis)
  - 20% of males with AMN will develop cerebral ALD later
- **Diagnosis:**
  - 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

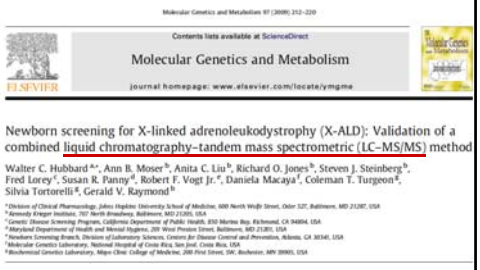


- **Prognosis better when treatment started early (NBS!)**

Miller WP et al. Blood 2011, 118: 1971-8

X-ALD


Available online at www.sciencedirect.com
ScienceDirect
Molecular Genetics and Metabolism 89 (2006) 185–187
Brief Communication
Combined liquid chromatography–Tandem mass spectrometry as an analytical method for high throughput screening for X-linked adrenoleukodystrophy and other peroxisomal disorders: Preliminary findings
Walter C. Hubbard, Ann B. Moser, Silvia Tortorelli, Anita Liu, David Jones, Hugo Moser

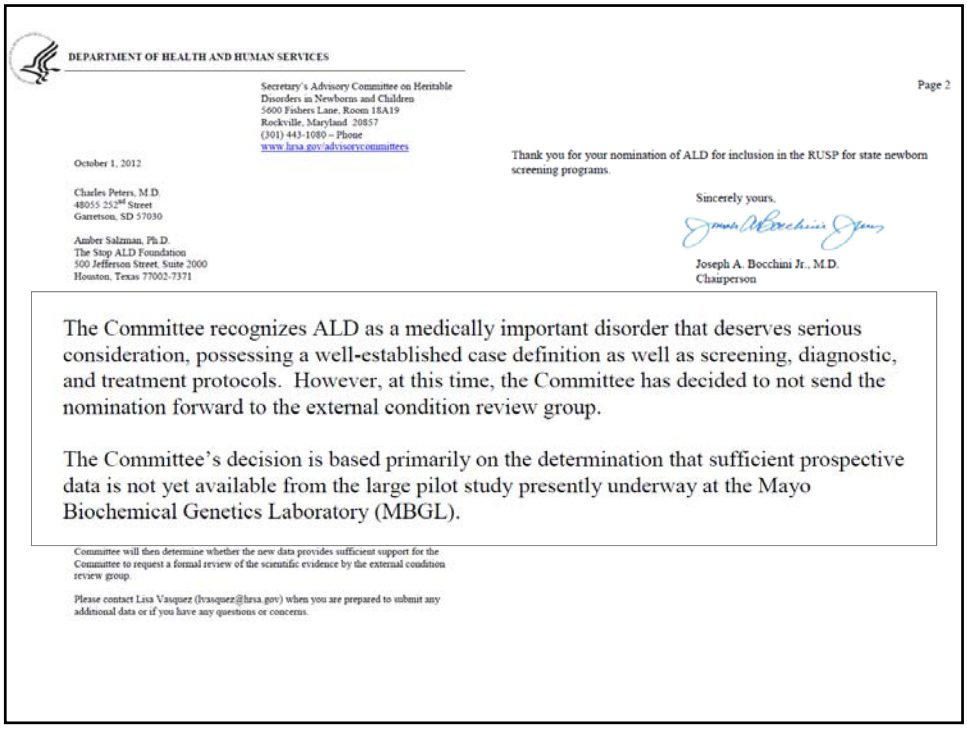

Molecular Genetics and Metabolism
journal homepage: www.elsevier.com/locate/ymgme
Newborn screening for X-linked adrenoleukodystrophy (X-ALD): Validation of a combined liquid chromatography–tandem mass spectrometric (LC–MS/MS) method
Walter C. Hubbard, Ann B. Moser, Anita C. Liu, Richard O. Jones, Steven J. Steinberg, Fred Lorey, Susan R. Panny, Robert F. Vogt Jr., Daniela Macaya, Coleman T. Turgeon, Silvia Tortorelli, Gerald V. Raymond

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



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Secretary's Advisory Committee on Heritable
Disorders in Newborns and Children
5600 Fishers Lane, Room 18A19
Rockville, Maryland 20857
(301) 443-1080 – Phone
www.hrsa.gov/advisorycommittees

October 1, 2012

Charles Peters, M.D.
48055 252nd Street
Garretson, SD 57030

Amber Salzman, Ph.D.
The Stop ALD Foundation
500 Jefferson Street, Suite 2000
Houston, Texas 77002-7371

Thank you for your nomination of ALD for inclusion in the RUSP for state newborn screening programs.

Sincerely yours,

Joseph A. Bocchini Jr., M.D.
Chairperson

The Committee recognizes ALD as a medically important disorder that deserves serious consideration, possessing a well-established case definition as well as screening, diagnostic, and treatment protocols. However, at this time, the Committee has decided to not send the nomination forward to the external condition review group.

The Committee's decision is based primarily on the determination that sufficient prospective data is not yet available from the large pilot study presently underway at the Mayo Biochemical Genetics Laboratory (MBGL).

Committee will then determine whether the new data provides sufficient support for the Committee to request a formal review of the scientific evidence by the external condition review group.

Please contact Lisa Vasquez (lvasquez@hrsa.gov) when you are prepared to submit any additional data or if you have any questions or concerns.

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

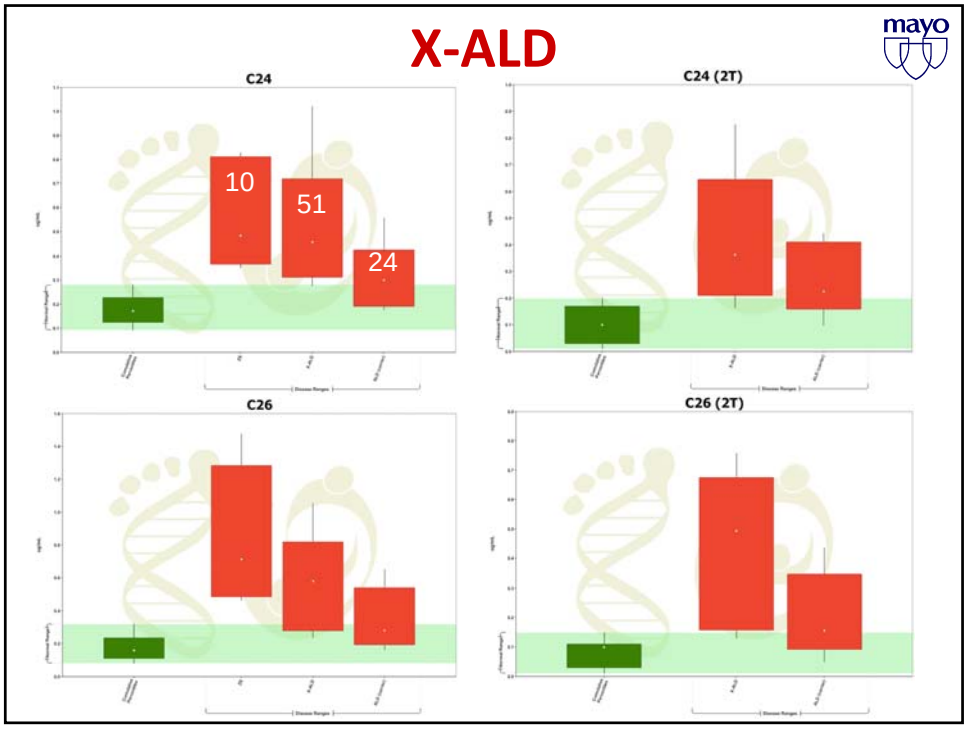
Fred Lorey

John Hopwood

Shire for a generous gift of galactocerebrosidase

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.

DISORDER	MS/MS	Immunocapture	Dig. Microfluidics
Fabry disease	+	+	+
Gaucher disease	+	+	+
Krabbe disease	+	+	+
MLD		+	
MPS I	+	+	+
MPS II		+	
MPS IIIA		+	
MPS IIIB		+	
MPS VI		+	
Mucolipidosis II/III		+	
MSD		+	
Niemann-Pick A/B	+	+	+
Pompe Disease	+	+	+
Wilson disease		+	
Aceruloplasminemia		+	
Menkes disease		+	
Friedreich Ataxia		+	
X-Adrenoleukodystrophy	+		
Zellweger spectrum dis.	+		
Acyl-CoA oxidase def.	+		
Bifunctional protein def.	+		



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

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Status of NBS for X-ALD

- **USA:**
  - **NY: NBS for X-ALD started in NY on 12/30/2013.**
  - **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:

DISORDER Group	Prevalence	FPR	PPV
X-ALD	1 : 21,250 boys	0.02%	18%
AA/OA/FAO (Mayo)	1 : 1,900	0.02%	68%
AA/OA/FAO (US avg.)	?	0.46%	18%

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 NBS programs already screening for X-ALD participate in R4S Laboratory Performance Database (https://www.nbstrn.org/research-tools/lab-performance-database).
- Recommend that ACMG develop ACT SHEETS and algorithms (www.acmg.net) for X-ALD and relevant peroxisomal disorders.