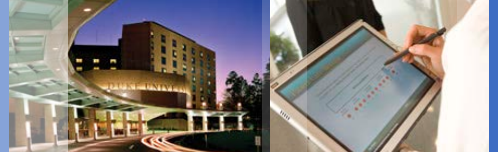
Duke Clinical Research Institute

Newborn Screening for X-linked Adrenoleukodystrophy (X-ALD): Update from the Condition Review Workgroup

Alex R. Kemper, MD, MPH, MS

May 12, 2015



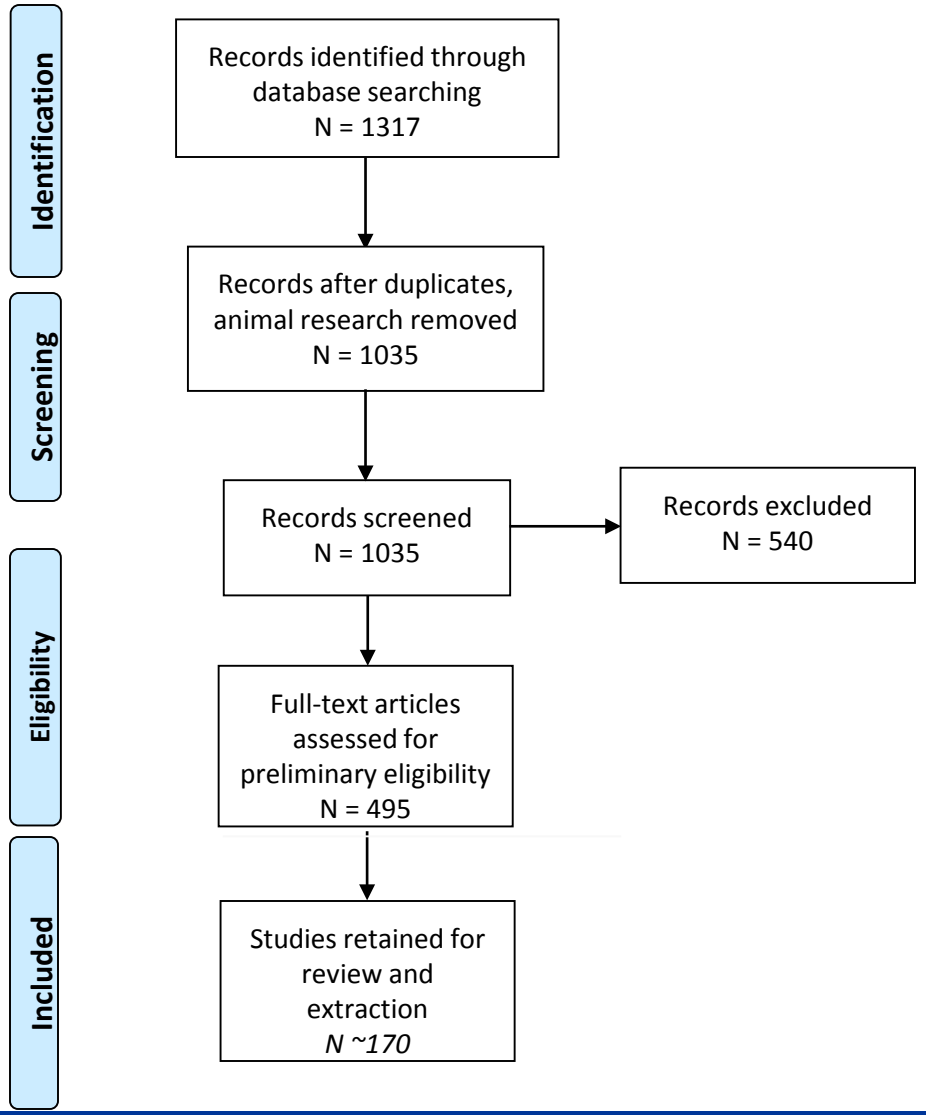
Overview: X-Linked Adrenoleukodystrophy (X-ALD)

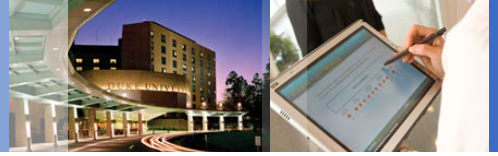
- Peroxisomal disorder affecting the adrenal cortex and the central nervous system (CNS)
- Broad phenotype spectrum ranging in onset and severity from childhood through adulthood
- Primarily affects males (across the spectrum). Female heterozygous carrier can develop symptom onset in adulthood
- Most common peroxisomal disorder
- Estimated X-ALD incidence in the U.S.:
  - *1 in 21,000 newborn males*
  - *1 in 14,000 newborn females are carriers*

Systematic Evidence Review: Published Literature – Through ~November 2014

- Keywords: *("Adrenoleukodystrophy"[Mesh]) OR ("Adrenoleukodystrophy"[tiab]) ("Adrenoleukodystrophy/therapy"[Mesh]) OR ("X-ALD"[tiab]) OR ("very long-chain fatty acids"[All Fields]) OR ("VLCFA"[tiab]) OR ("Lorenzo's oil"[Supplementary Concept]) OR ("Lorenzo's oil"[tiab]) AND ("animals"[Mesh] NOT "humans"[mesh]) AND Limits: English.*
- Articles through PubMed, EMBASE, & CINAHL since database inception (1317)
- Articles screened for relevance (987)
- Articles assessed for initial eligibility (495)
- Articles retained for data extraction & synthesis ~170 (*pending final exclusions*)
- Screening by two independent reviewers

Figure 1. Preliminary PRISMA Diagram of Published Literature Search





NBS for X-ALD Condition Review Focus

- Primary target of review: childhood forms detected at screening
  - *Cerebral ALD – symptomatic and asymptomatic [later-onset] at birth*
  - *Adrenal insufficiency/Addison's only*
- Secondary screening targets – counts of female carriers detected, other disorders (Zellweger's, other peroxisomal disorders)
- Exclude evaluating expected outcomes of early diagnosis of adult-onset conditions (AMN, female heterozygote ALD)

X-linked Adrenoleukodystrophy (ALD)

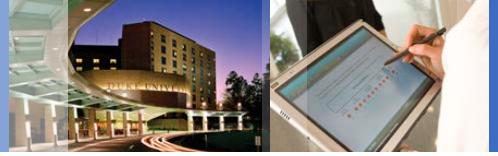
Genetics:

- ABCD1 = single causative gene of X-ALD, maps to Xq28. ABCD1 gene encodes adrenoleukodystrophy protein (ALDP), which facilitates transport of very long-chain fatty acids (VLCFA) into peroxisomes. ALDP deficiency impairs VLCFA beta-oxidations, leading to elongation of VLCFA.
- *>600 mutations identified* (**http://www.x-ald.nl**)*; most are unique*
- *No genotype-phenotype correlation, even within families*

Screening: Dried-blood spots – laboratory study conducted by Mayo Clinic (~100,000 samples), prospective screening in MD (~5,000 newborns)

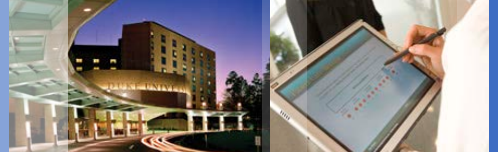
Diagnosis: ABLD1 mutation analysis, measurement of VLCFAs in plasma, MRI ("Loes Score")

Treatment(s): HSCT, Steroid/Adrenal hormone replacement therapy, Gene therapy



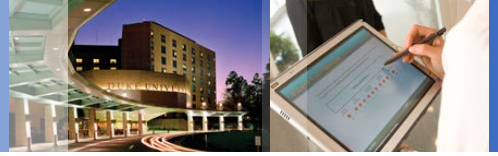
X-ALD Phenotype Spectrum

	CHILDHOOD				ADULT	
	Cerebral ALD (CALD) *(about 90% of C-CALD also have adrenal insufficiency)			**Adrenal Insufficiency*** ("Addison's Only)	**Adrenomyelo-neuropathy** (AMN)	**Women with X-ALD**
Onset Age (Yrs)	2.5–10	10–21	>21	>2	>18	Mostly >40
Frequency (%)	CHILD **31 – 35**	ADOL **4 – 7**	ADULT **2 – 5**	*(prevalence decreases with age)*	**40 - 46**	unknown symptomatic
Progression	Rapid			–	Slow	Slow
Myelopathy	Extensive	Some	Possible	–	+	+
Brain MRI - White matter lesions	Extensive			–	Some	Occasional-Rare
Behavioral & Cognitive Disorder	Extensive	Some	Possible		– (+ *if cerebral involvement*)	Very rare
Peripheral Neuropathy		Rare	Possible	–	Sensory-motor, axonal	+ / -
Life Expectancy *(untreated)*	Death within a few years after onset					



X-ALD Newborn Screening

- Measurement of C26:0 lysophosphatidylcholine (26:0-lyso-PC)
- Detected in dried-blood spots (DBS)
- Small pilot and validation studies suggest
  - *low false-positive rates*
  - *High-throughput feasibility*
  - *Unclear sensitivity (false-negative rate)*
- Primary Screening Methods:
  - *Tandem mass spectrometry (MS/MS)*



Current X-ALD Newborn Screening

- **Legislative Approval:**
  - ***NY, CT,*** *and* ***NJ*** *State Newborn Screening–2013*
  - ***NY NBS – Live screening since December 2013***
- **States considering X-ALD screening:**
  - ***CA*** *– Proposed legislation to mandate NBS for ALD moving forward, April 2014*
  - ***MD*** *– proposed to add ALD in 2014, pending funds and state lab changes*
- Mayo Clinic Comparative Effectiveness of Screening study (100,000 NBS from CA), *final results pending*.

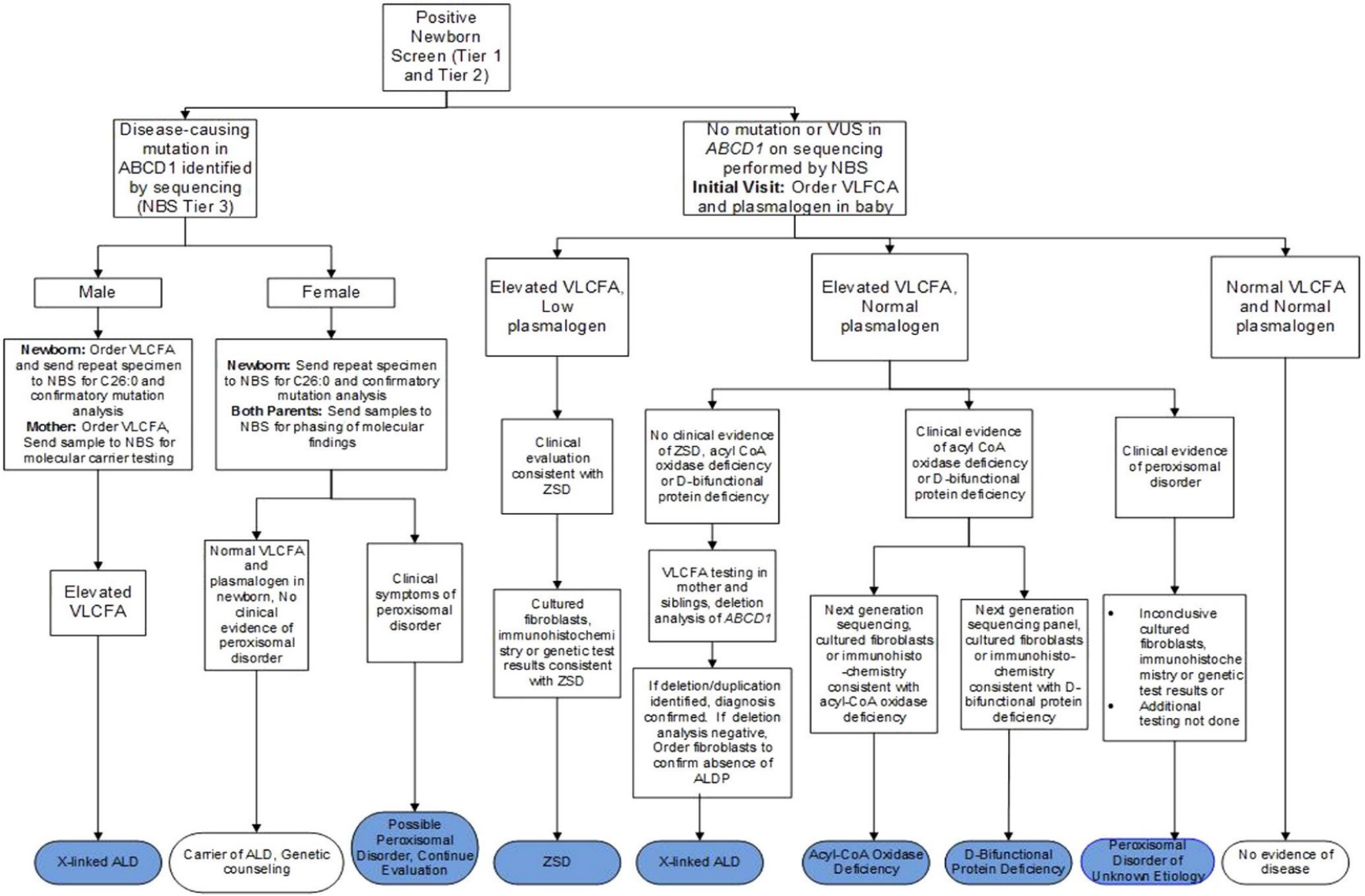
(State NBS for ALD updates ongoing)

NY State NBS Program: "3-Tier" Screen for X-ALD

Dates: *Dec 30, 2013 to present, >300,000 newborns screened*

Tier - Screening Activity		Rate Definition
TIER 1	MS/MS for C26:0 LPC	Re-test rate (same specimen)
TIER 2	HPLC & MS/MS for C26:0 LPC	Repeat rate (independent specimen)
⇨ Mutation analysis of ABCD1 gene, in-house ⇨ Referral also for confirmatory testing		
(screening results removed; manuscript is in preparation)		

NY NBS Short-term Follow Up Algorithm: Tier 3 & Referral

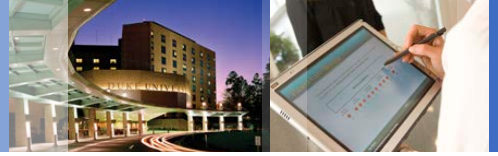


B.H. Vogel et al. (2015). Newborn screening for X-linked adrenoleukodystrophy in New York State: Diagnostic protocol, surveillance protocol and treatment guidelines. *Molecular Genetics and Metabolism, in press*.

Establishing the X-ALD Diagnosis

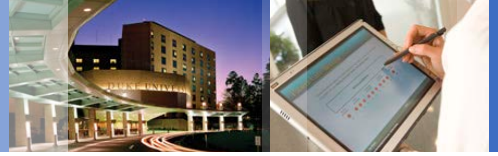
- **Increased Very long-chain fatty acids**
  - *Most important laboratory assay is VLCFA concentration in plasma*

- **X-ALD diagnosis – ABCD1 mutations**
  - *DNA diagnostic test for X-ALD involving non-nested genomic amplification of the ABDC1 gene, followed by sequencing and analysis with fluorescence.*
    - *affected X-ALD newborns may have known gene mutations from mutation analysis, OR gene deletions and other abnormities which require further genetic analysis – gene mutation analysis alone may not ID all cases*



Establishing the X-ALD Diagnosis *(cont')*

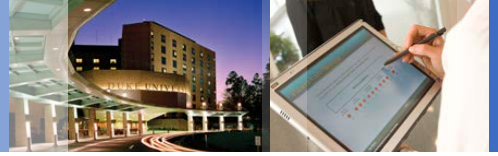
- **Clinical Assessment**
  - **Neuroimaging -** *Brain MRI/(& Loes severity scale for MRI) – always abnormal in neurologically symptomatic males*
  - **Clinical Symptoms - Child Cerebral ALD (Boys)**
    - *ADD symptoms, signs of dementia, difficulties understanding spoken language, progressive disturbance in behavior, coordination, handwriting, vision, other neurological disturbances*.
    - *Primary adrenocortical insufficiency co-occurs in ~90% of Cerebral ALD (with additional diagnostic confirmation)*
  - **Asymptomatic**
    - *May show ABCD1 mutations, but be asymptomatic in infancy and require follow-up and monitoring*



Management of Presymptomatic X-ALD

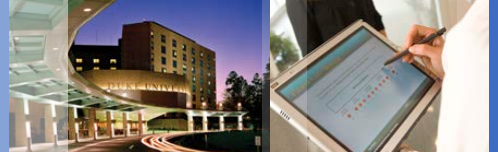
- *Ongoing follow up care for early detected, presymptomatic X-ALD patients to monitor for disease progression*
- *Management protocols of follow up care for X-ALD patients established*
- *Brain magnetic resonance imaging (MRI) has been found to be a reliable marker for disease progression/cerebral involvement*
- *Loes Score – MRI disease severity rating established to inform progression and need for transplant*
- *Referral to endocrinologist specialists to monitor adrenal function*

Engelen et al. 2012. X-linked adrenoleukodystrophy: Clinical presentation and guidelines for diagnosis, follow-up and management. *Orph J Rare Dis. 7*



Primary Treatment Strategies

- **Hematopoietic Stem Cell Transplantation (HSCT)**
  - *May reduce risk or progression of neurological degeneration in early stage CALD*
- **Adrenal Cortisol Replacement therapy**
  - *Necessary for adrenocortical insufficiency "Addison's disease" to prevent adrenal crisis*
  - *No effect on neurological symptoms*
- **Gene Therapy for X-ALD**
  - *Not standard care, Experimental*
  - *2 successful case studies in France (2 7 yr old boys, early CALD), cerebral disease progression halted after 14-16 mos*

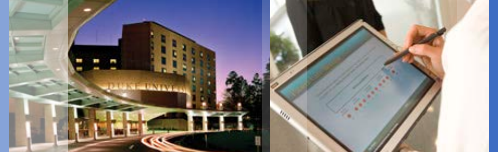


5-year Survival for Childhood Cerebral X-ALD, With and Without Transplant

C-CALD (Historical Controls)	No Transplant (n=283)	Transplant ---
5-year survival	66%	---
Deaths by 5 years (Mean age at death)	46% (12.3 years)	

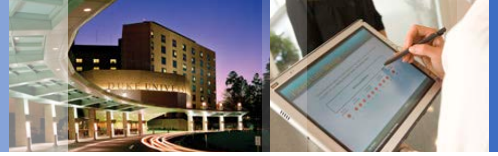
C-CALD (Early stage)	No Transplant (n=30)	Transplant (n=19)
5-year survival	54%	95%
		**p=0.006

Mahmood et al. 2007. Survival analysis of HCT for childhood cerebral X-linked ALD: A comparison study. *The Lancet, 6,* 687-692.



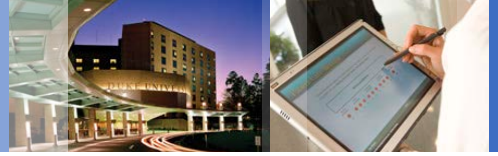
Decision Modeling Population Level Outcomes

- **Decision Modeling…*in progress***
  - Technical Expert Panel (TEP) assembled
  - 3 expert panel meetings scheduled



Decision Modeling Population Level Outcomes

TEP	Date	Objectives
TEP 1	14 APR 2015	1. Determine natural history and epidemiology with usual clinical detection 2. Discuss screening and diagnostic confirmation process 3. Identify key outcomes of X-ALD 4. Identify standard treatments and treatment effectiveness 5. Review initial draft of decision tree model for X-ALD
TEP 2	*14 MAY 2015*	• *Review updated model structure* • *Review probability inputs*
TEP 3	*11 JUN 2015*	• *Review preliminary results*



Decision Modeling Population Level Outcomes (*cont.*)

Next Steps:

- Develop/refine Decision Model Structure
- Translate key parameter inputs from evidence review
- Project population outcomes

Public Health System Impact Assessment for X-ALD

Association of Public Health Laboratories

PHSI Background

- The Secretary of HHS Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) makes recommendations to the Secretary, HHS, about what conditions should be included in the RUSP
- These recommendations are based on
  - The certainty of net benefit
  - The feasibility and readiness of implementing comprehensive screening
- Feasibility and readiness is based, in part, on an assessment of the public health system impact

Aims/Goals

- Inform the ACHDNC
- Opportunity to
  - Understand the “real world” barriers and facilitators related to screening
  - Identify research gaps
  - Conduct a needs assessment
  - Evaluate opportunity costs
  - Share practices that can ultimately improve implementation

Guiding Philosopy

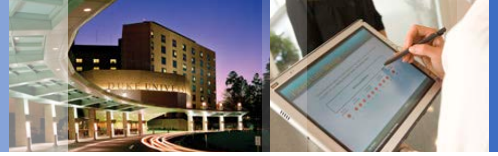
- All states can provide useful information about public health impact
- We need to provide useful, high-quality data to the ACHDNC within a short period of time
- We cannot burden state public health officials
- We need to provide information to states to facilitate the process
- This is a critical opportunity to assure that the ACHDNC is aware of issues at the state level

Progress

- Key informant interviews with state NBS programs that are screening or have mandates to screen
- Development of Fact Sheet for X-ALD Screening Methods
- Development of X-ALD public health system impact assessment survey

Next Steps

- Distribute survey to NBS program directors in all 50 states, DC and PR via email
- Period to complete: May 13 to June 17, 2015
- Educational X-ALD webinar on May 14 at 2 pm ET
- Report to ACHDNC: July/August 2015



Thank You!

Questions?

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Presentation Contact:

Alex R. Kemper, MD, MPH, MS
alex.kemper@duke.edu