Duke Clinical Research Institute

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

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Alex R. Kemper, MD, MPH, MS

August 27, 2015





Condition Review Workgroup (CRW)

CRW Members	Role	Institution
Alex R. Kemper, MD, MPH, MS	Chair, Clinical Pediatrician, USPSTF	Duke University
Jeff Brosco, MD, PhD	Pediatric /NBS Bioethicist, and Regional Title V Services	Mailman Center for Child Development CMS South Region (Florida's Title V Agency) Pediatrics Bioethics Committee, Jackson Health System
Anne M. Comeau, PhD	State NBS Public Health Program	New England NBS Program, University of Mass Medical School
Nancy S. Green, MD	Clinical Pediatric – Hematology Specialist	Department of Pediatrics, Columbia University Medical Center
Scott Grosse, PhD	Federal Advisor, Health Economist	Nat'l Center on Birth Defects & Developmental Disabilities, CDC
Jelili Ojodu, MPH	Public Health Impact Task Leader	NBS & Genetics, Association of Public Health Laboratories
Lisa Prosser, PhD	Decision Analysis Leader, NBS Health Economist	Health Management & Policy/ SPH; Pediatrics/Univ of Michigan Med School
Susan Tanksley, PhD	State NBS Public Health Program	Newborn Screening Laboratory TX Department of State Health Services
Jennifer Kwon, MD	Clinical Pediatric Neurologist, LT follow up	Clinic for Inherited Metabolic Diseases, Golisano Children's Hospital, U of Rochester
K.K. Lam, PhD	Project Leader	Duke University
Fred Lorey, PhD	*Committee Representative for X-ALD Review*	Genetic Disease Screening Program California Department of Public Health
Donald Bailey, PhD	*Committee Representative for X-ALD Review*	Early Childhood Development RTI International



Outline

- Highlight key findings from the systematic evidence review and supplemental data analyses
- Describe the anticipated bounds of benefit and harm
- Summarize the capability of state newborn screening programs to offer comprehensive screening for X-ALD



Overview: X-Linked Adrenoleukodystrophy (X-ALD)

- Peroxisomal disorder affecting the adrenal cortex and the central nervous system (cerebral demyelination and spinal cord/peripheral neuropathy)
- Broad phenotype spectrum ranging in presenting symptom, severity and age of onset (~1 year through adulthood)
- Male (hemizygote) X-ALD – about 90% affected with significant, multi- symptom involvement, with onset from 1 year through adulthood.
- Female (heterozygote) X-ALD – based on 46 women in the Netherlands, age range 22-76 years (average 48 years) in a referral center (Engelen et al., 2014)
  - *Symptoms – 18% < 40 years; up to 88% in women by 60 years; symptoms ranged from myelopathy, peripheral neuropathy, fecal incontinence*



Prevalence of X-ALD in the U.S.

All X-ALD cases	**1 in 16,900**
Male X-ALD	*1 in 42,000*
Female X-ALD	*1 in 28,000*

- based on clinical referral and extended family testing of males

Bezman et al., 2001. Adrenoleukodystrophy: incidence, new mutation rate, and results of extended family screening. *Ann Neurol*, 49(4), 512-517



Prevalence of X-ALD in Males

Study Authors & Year	Country/ Region	Base Years	Male X-ALD Hemizygotes per 100,000
Clinical Detection			
Kirk et al., 1998	Australia	1981 - 1996	1.6
Di Biase et al., 1998	Italy	1990 - 1995	3.6
Takemoto et al., 2002	Japan	1990 - 1999	2 - 3.3
Stradomska et al., 2009	Poland	1994 - 2004	2.9
Jardim et al., 2010	Brazil	2002 - 2007	2.8
Clinical Detection + Extended Family Screening			
Bezman et al., 2001	U.S. *(KKI, Mayo)*	1996 - 1998	2.38



X-ALD Clinical Spectrum

	CHILDHOOD - Males			ADULT (Males)		Females
	Adrenal Insufficiency	**Cerebral ALD (CALD)** *(about 90% of C-CALD also have adrenal insufficiency)		CALD	**Adrenomyelo -neuropathy** (AMN)	**Women with X-ALD**
Onset Age (Yrs)	>1 - 13	2.5–10	10–21	>21	>18	Adulthood
Frequency (%)	**60-90** *(~10% AI only)*	CHILD **31 – 35**	ADOL **4 – 7**	ADULT **2 – 5**	**40 - 46**	(est ~1.5 to 2.5 times male frequency)
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 3 years after onset*				



Genetics of X-ALD

- 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 elevation of VLCFA.
- *>600 mutations identified* (http://www.x-ald.nl)*; most are unique*
- *No genotype-phenotype correlation, even within families*



X-ALD Newborn Screening

- Measurement of C26:0 lysophosphatidylcholine (26:0-lyso-PC) as marker for VLCFA in DBS
- Tandem mass spectrometry (MS/MS)
  - High Performance Liquid Chromatography (HPCL)
  - Can be multiplexed – Krabbe disease and Pompe disease (NY)
  - CDC Proficiency Tests Expected Fall 2015
- Small technical validation and pilot studies
  - *Low number of positives (X-ALD, other peroxisomal disorders, false positives)*
  - *Expected to detect about 80-90% of heterozygote females*
  - *High-throughput feasibility*



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*
  - Because of the lack of genotype-phenotype correlation, this is not required to establish the diagnosis. However, this information can be of use to specialists and is a component of the NY newborn screening program



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

- **Clinical Assessment**
  - **Neuroimaging -** *Brain MRI / Loes severity scale – always abnormal in neurologically symptomatic males*
  - **Clinical Symptoms**
    - *ADHD 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 X-ALD*
  - **Asymptomatic**
    - *May have ABCD1 mutations and elevated VLCFA but be asymptomatic and require follow-up and monitoring*



Treatment Strategies

- **Hematopoietic Stem Cell Transplantation (HSCT)**
  - *Requires either matched-related donor (ideally non-heterozygote) or closely matched cord blood (overall, 95% will have cord-blood match)*
  - *May reduce risk or progression of neurological degeneration in early stage CALD*
  - *Risk of Graft-versus-Host disease depends on the match, age, prophylaxis*
  - *Risk of mortality for non-cancerous conditions ~5% within the first few years*
  - *Risk of failure to engraft (likely small)*
- **Adrenal Cortisol Replacement therapy**
  - *Necessary for adrenal insufficiency*
- **Gene Therapy for X-ALD**
  - *2 successful case studies in France (Two 7-year-old boys, early CALD), cerebral disease progression halted after 14-16 months. Clinical trial underway.*
- **Lorenzo's Oil**
- **N-acetyl-L-cysteine**
  - *Case series suggests that it can help with advanced brain involvement*

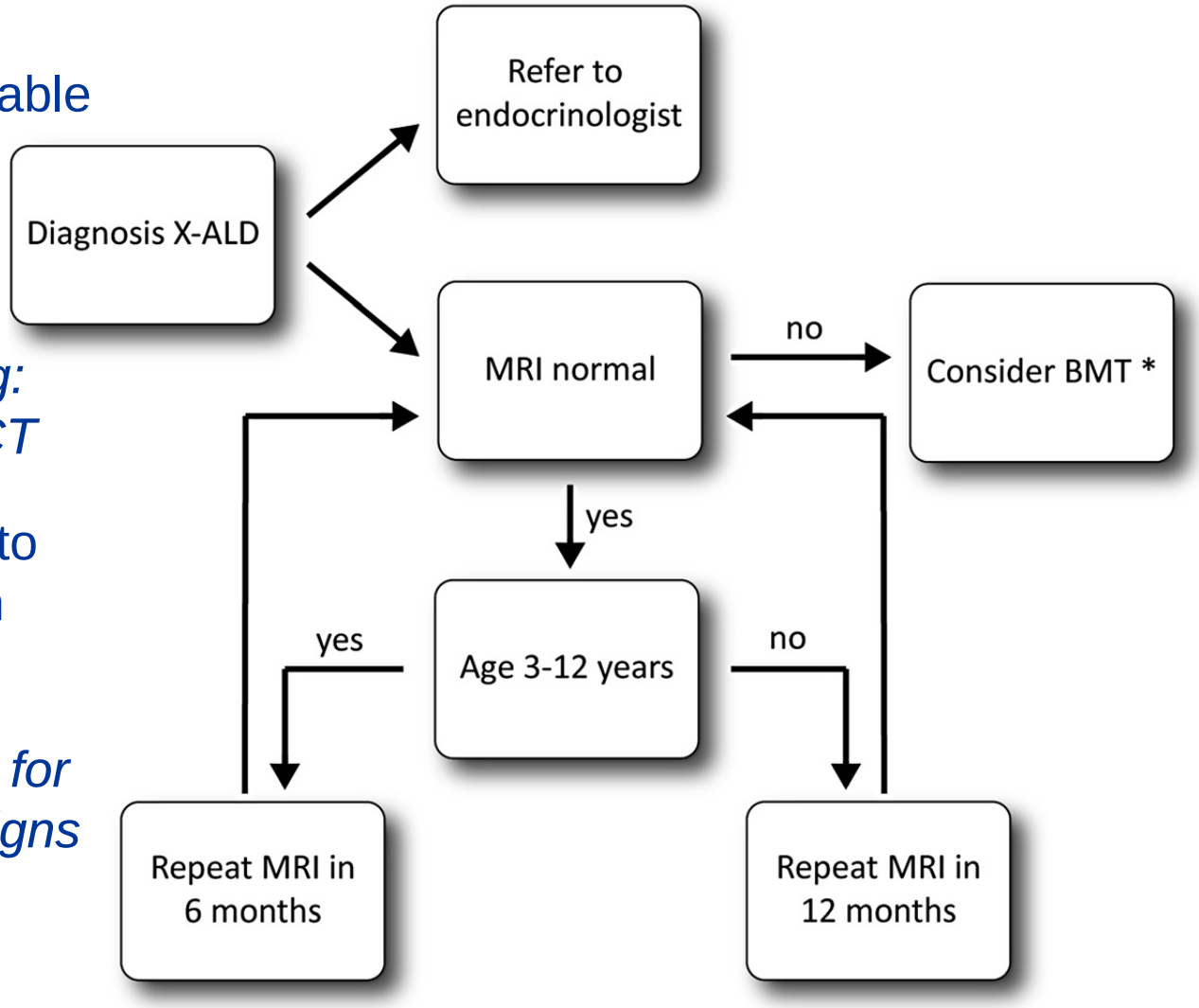
Management of Presymptomatic X-ALD

- MRI is sensitive and reliable marker for disease progression

  Loes Score – MRI disease severity rating: <9 recommend for HCT

- Endocrinologist referral to monitor adrenal function

  Serum ACTH levels, ACTH stimulation test for used to detect early signs

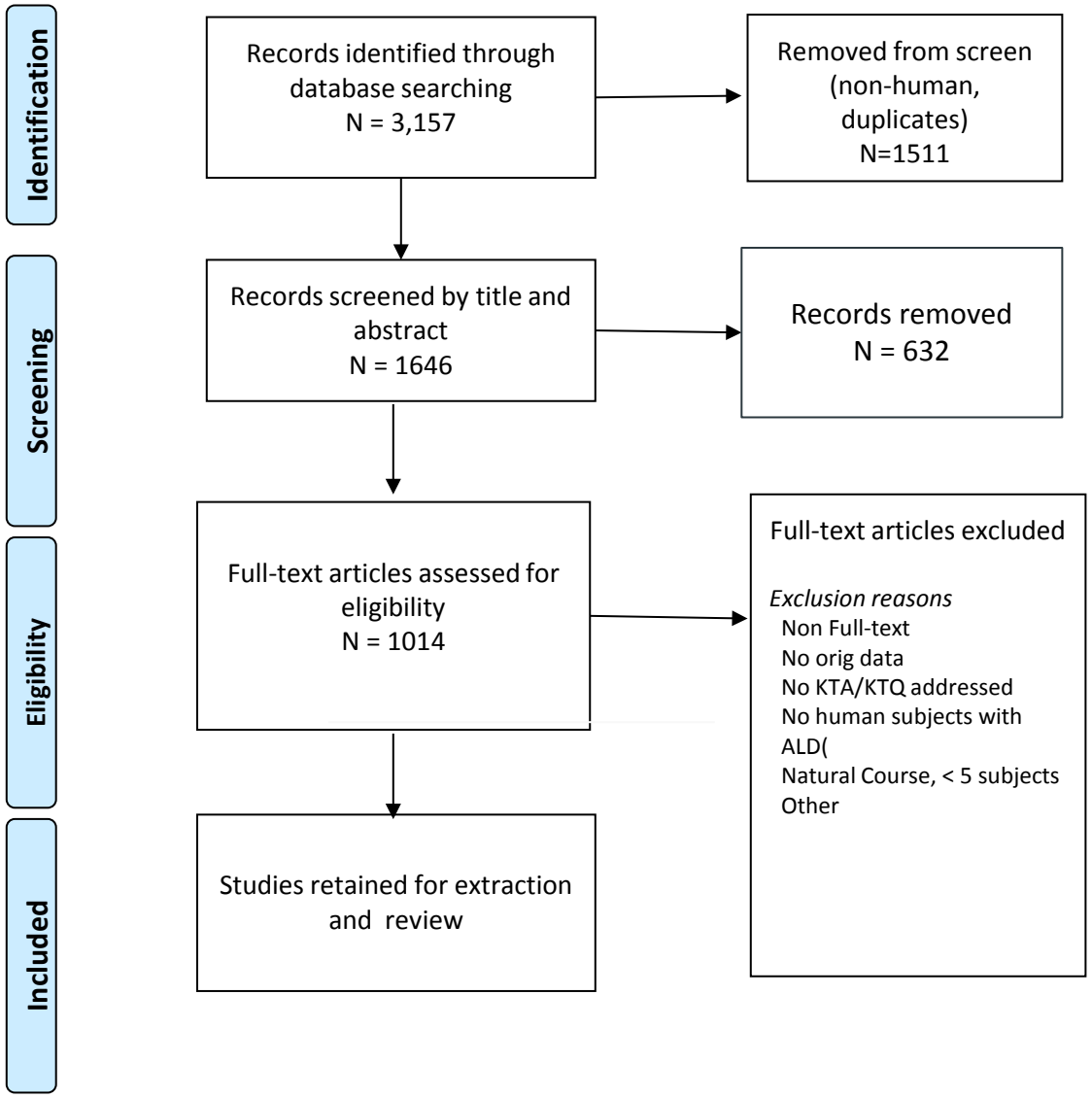


Engelen et al. 2012. X-linked adrenoleukodystrophy: Clinical presentation and guidelines for diagnosis, follow-up and management. *Orph J Rare Dis. 7*

Systematic Evidence Review: Published Literature – Through July 2015

- Keywords:
  ("Adrenoleukodystrophy"[Mesh]) OR ("Adrenoleukodystrophy"[tiab]) OR ("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 ("humans"[Mesh] NOT "animals"[mesh]) AND Limits: English.
- Articles through PubMed, EMBASE, & CINAHL since inception (3,157)
- Articles screened for title/abstract relevance (1,646)
- Articles assessed for initial eligibility (1,014)
- Screening by two independent reviewers

Figure 1. PRISMA Diagram of Published Literature Search





Technical Expert Panel

EXPERT PANEL MEMBERS
Michele Caggana, Sc.D., FAC New York State Department of Health Director, Newborn Screening Program
Ann Moser, BA Kennedy Krieger Institute Associate Director – Moser Lab
Joanne Kurtzberg, MD Duke University School of Medicine – Div of Pediatrics Director, Carolinas Cord Blood Bank
Paul Orchard, MD University of Minnesota Medical Center – Pediatric Blood and Marrow Transplantation
Gerald Raymond, MD University of Minnesota Medical Center Department of Neurology
Florian Eichler, MD Massachusetts General Hospital for Children Director of Leukodystrophy Center

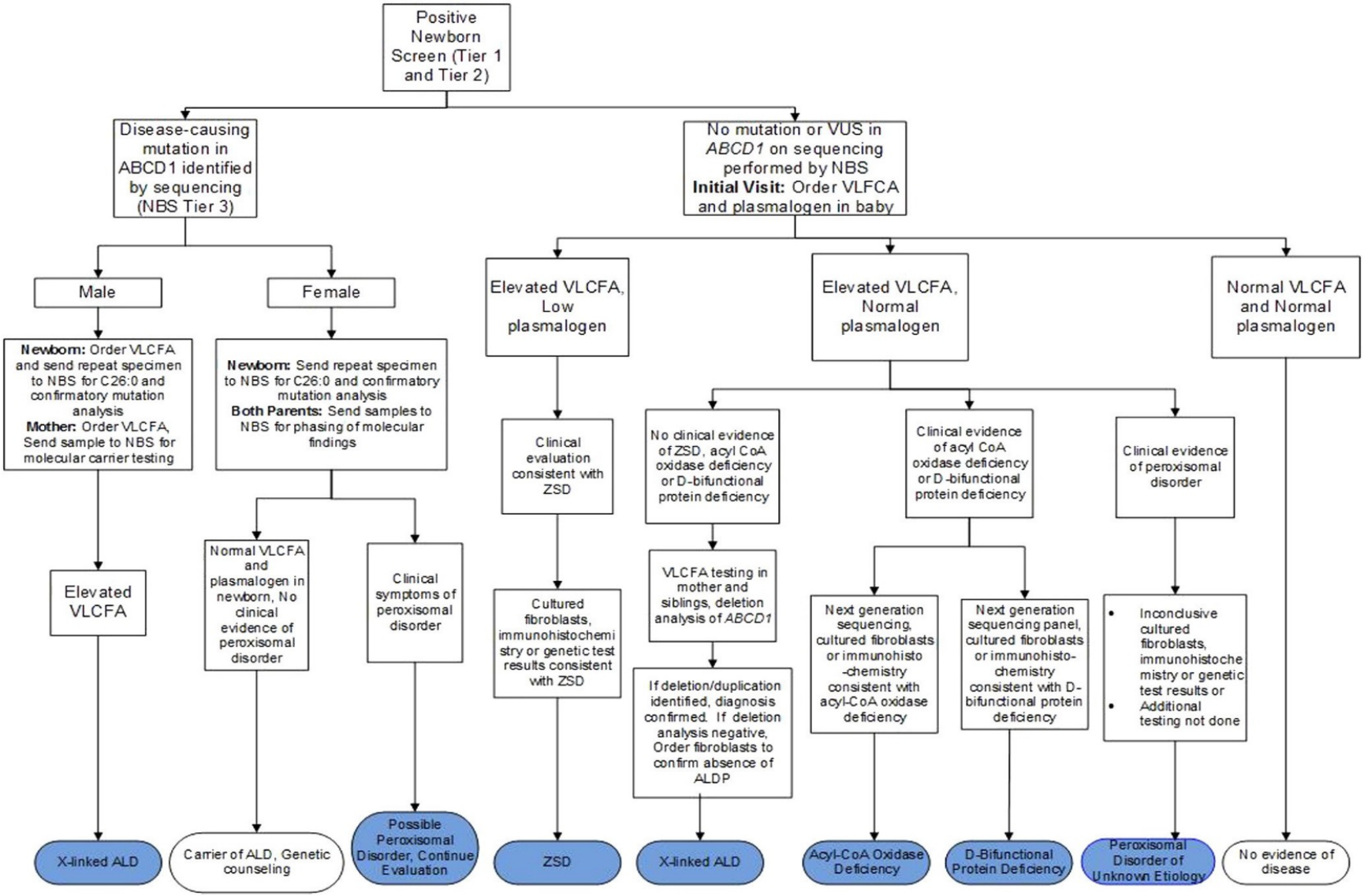
TEP Meetings

- *April 2015*
- *June 2015*
- *July 2015*

Topics

- Case Definition
- Natural History
- Prevalence, Phenotypes
- Screening & Diagnosis
- Treatment Initiation
- Available Evidence
- Unpublished data

NY NBS Short-term Follow Up Algorithm



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, 114(4), 599-603.*



NY State NBS Program – "3-Tier" Screening for X-ALD

Tier - Screening Activity		Rate Definition		Rates
TIER 1	MS/MS for C26:0 LPC	Re-test rate (same specimen)	= 6,679 of 363,755 *newborns*	=1.84%
TIER 2	HPLC & MS/MS for C26:0 LPC	Repeat rate (independent specimen)	= 43 borderline retest results, repeats requested of 363,755 *newborns* tested	= 0.0091%
⇨ Mutation analysis – ABCD1 gene		Referral rate	=33 of 363,755 newborns	= 0.0091%
	Confirmed Status:	*14 male ABCD1 mutations (7 with X-ALD dx confirmed)* *14 female carriers* *5 Other (secondary, other)* *3 ZSD confirmed* *1 Aicardi-Goutieres syndrome confirmed*		

Total 363,755 newborns screened (Dec 30 2013 – Jul 2015)



Summary: X-ALD NBS & Short-term Follow up

- The overall prevalence of X-ALD in males and females is about 6 per 100,000 and the prevalence of males with C-CALD is about 1 per 100,000
- There is no genotype-phenotype correlation
- Screening is based on the elevated VLCFA levels
- Screening will also identify most heterozygote females and other peroxisomal disorders
- The NY NBS screening program has a very low rate of positive results, and the positive predictive value if the goal is to detect males with X-ALD is likely 42% (14/33)
- Diagnostic follow-up includes brain MRIs and assessment of adrenal function over time to determine the need for either HSCT or adrenal hormone replacement



Presymptomatic v. Clinical Detection Outcomes

What are the benefits and harms associated with presymptomatic detection compared to clinical case detection?



Adrenal Insufficiency

- Untreated adrenal insufficiency can lead to death
- However, no study included in the SER compared treatment outcomes based on the timing of diagnosis of adrenal insufficiency
- One study (Polgreen et al, 2011) describes how diagnosis of adrenal insufficiency can help speed the diagnosis of X-ALD and improve outcomes.
- HSCT does not affect adrenal insufficiency
- Presymptomatic detection of adrenal insufficiency in X-ALD is not a specific focus of the rest of the report



Treatment Outcomes: Child Cerebral X-ALD

- Disease Status Measures:
  - *MRI Severity Rating (Loes Score)*

Loes Score	Clinical Guidelines
< 0.5	Normal, no neurological involvement
<8 or 9	Recommendation for HSCT
>8 or 9	Not usually recommended for HSCT

  - *Neurologic Function Score (NFS)*
  - *ALD-Disability Rating Scale (ALD-DRS)*



Survival, C-CALD untreated *(N=283 boys)*

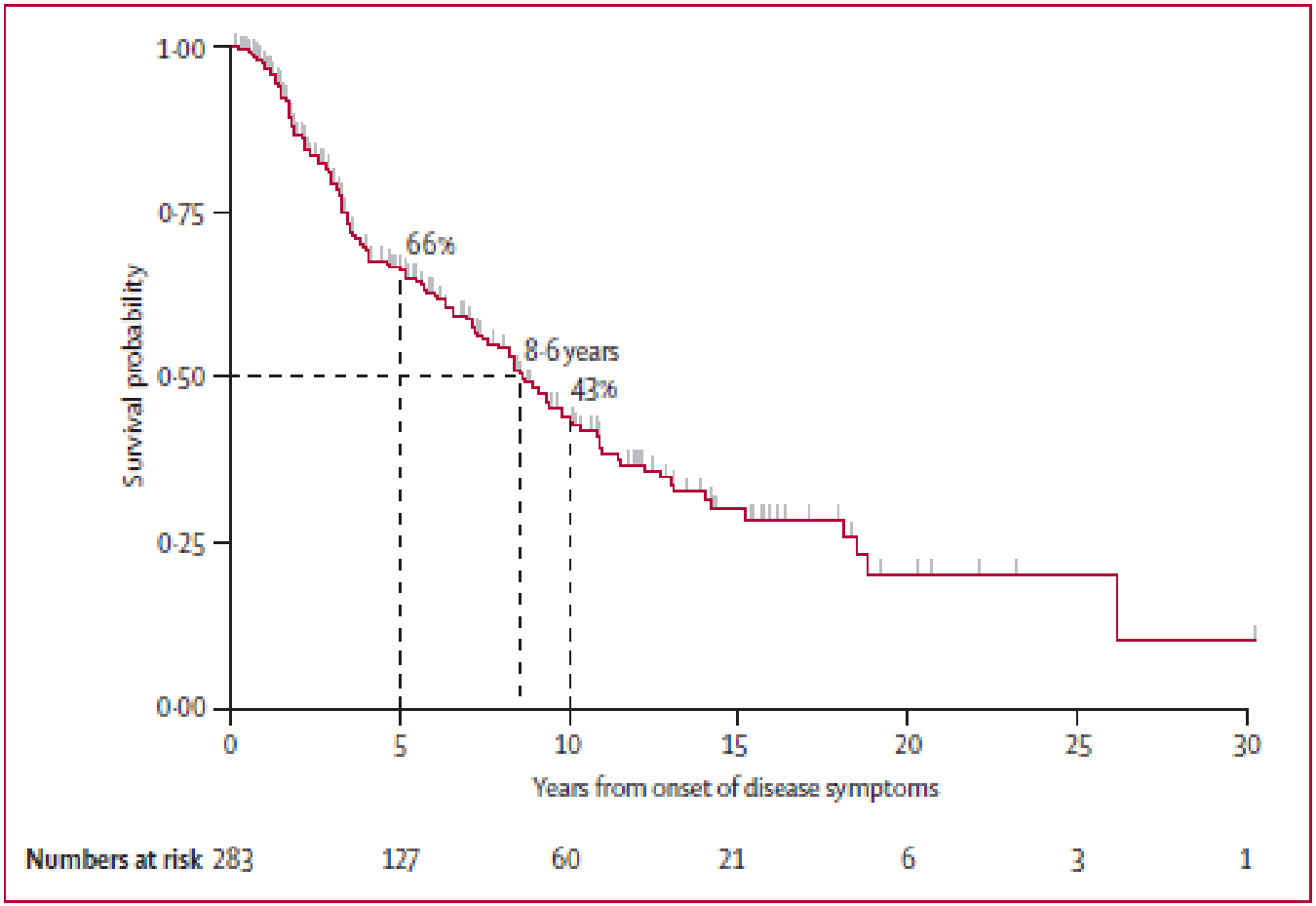


Figure 2: Kaplan-Meier estimate of survival for 283 boys with childhood cerebral X-linked adrenoleukodystrophy after development of neurological symptoms (cognitive, behavioural, or neurological symptoms)

5-yr Survival After Symptom Development

66% - survived

10-yr Survival After Symptom Development

43% - survived

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



Survival, Early stage C-CALD (*NFS≤1, Loes<9*):

Transplant vs. *No Transplant*

5-yr Survival After First Abnormal MRI (NFS=0 or 1, Loes<9)

- 95% - Transplant (n=19)
- 54% - No transplant (n=30)
- *p*=0.006

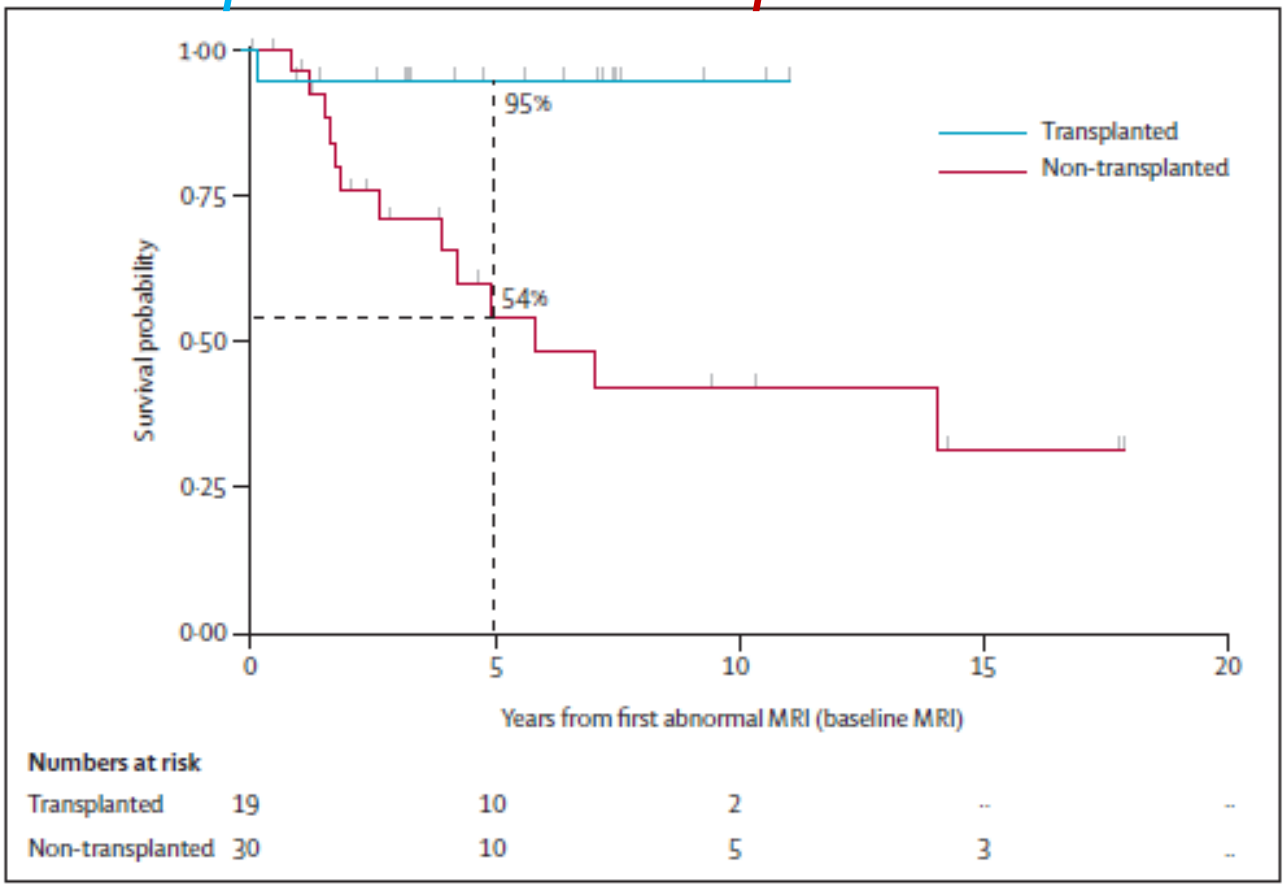


Figure 4: Kaplan-Meier estimates of survival for 19 transplanted patients with early stage cerebral adrenoleukodystrophy and for 30 non-transplanted patients with early stage cerebral adrenoleukodystrophy (ie, neurological deficit score of 0 or 1 and MRI severity score less than 9)
Survival was different in these two groups (χ^2=7·47, 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.



Outcomes, Early vs. Late Stage C-CALD

- At least 5 included outcome studies with N>6 that compare pre-post HCT outcomes between early vs. late stage C-CALD with MRI Severity/Loes scores

Pub YR, Author	Title	Journal	N
2004 Peters et al.	Cerebral X-ALD: the international hematopoietic cell transplantation experience from 1982 to 1999	Blood	94
2007 Beam et al.	Outcomes of unrelated umbilical cord blood transplantation for X-ALD	Biology of Blood & marrow transplantation	12
2011 Miller et al.	Outcomes after allogeneic HCT for childhood cerebral ALD: the largest single-institution cohort report	Blood	60
2013 McKinney et al.	Childhood cerebral X-linked ALD: Diffusion tensor imaging measurements for prediction of clinical outcome after HSCT	AJNR	8
2015 Bladowska et al.	The Role of MR Imaging in the Assessment of Clinical Outcomes in Children with X-ALD after Allogeneic HSCT	Pol J Radiol	7



Multicenter HCT Outcomes, C-CALD <19 yrs

Key Study Variables and Outcomes		
N=94	male X-ALD patients <19 years with complete data (of 126 total patients)	
Med age at HSCT	9.0 y	(rg 4.9 – 18.6)
Detection	N=28 (33%) Family hx	N=58 (67%) Symptom onset
Survival est 5- & 8-yrs (n=94)	56%	(95% CI, 44% - 68%)
Survival est 5-yrs by severity:		
Neurodeficits (ND) >1, Loes ≥9 (n=25)	**45%**	**(95% CI, 23% - 67%)**
ND ≤1, Loes <9 (n=37)	**92%***	**(95% CI, 81% -100%)**
	(**p*<0.01)	

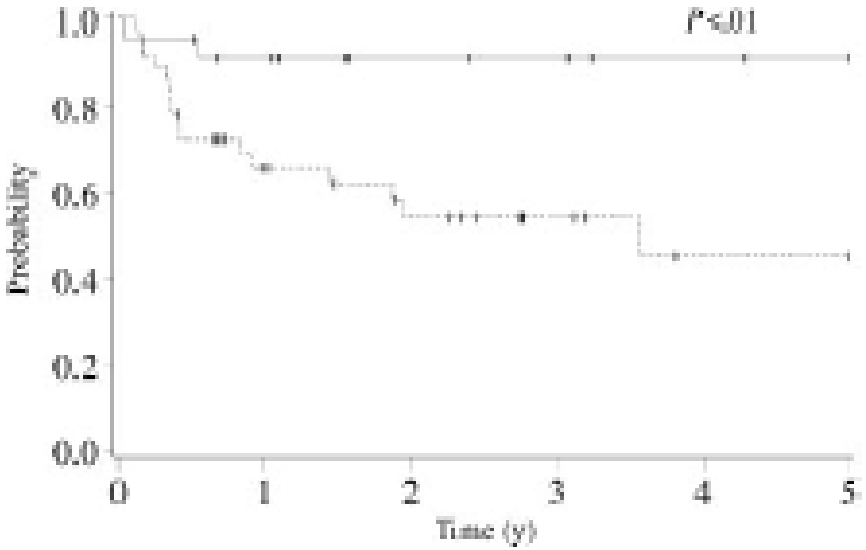


Figure. Survival, C-CALD

- *Solid line=pre-HCT neurodeficits 0, 1 and Loes <9, 92% survival.*
- *Dashed line=pre-HCT neurodeficits >2, Loes ≥9, 45% survival.*

Peters et al. 2004. Cerebral X-linked ALD: the international hematopoietic cell transplantation experience from 1982 to 1999. *Blood*, 104: 881-888.



Single-center BMT Outcomes

Key Study Variables and Outcomes		
N=12, 11 received BMT	X-ALD boys with no HLA matched donors evaluated for BMT. *11 of 12 survived pre-BMT chemo*	
Med age at dx	7.0 y	(rg 0 – 9.75)
Med age at HCT	7.41 y	(rg 2.36 – 11.71)
OS at 6.25 mos (n=11)	66.7%	(95 CI, 39.9–93.3%)

Fig a. Cognitive Development and pre-BMT Loes

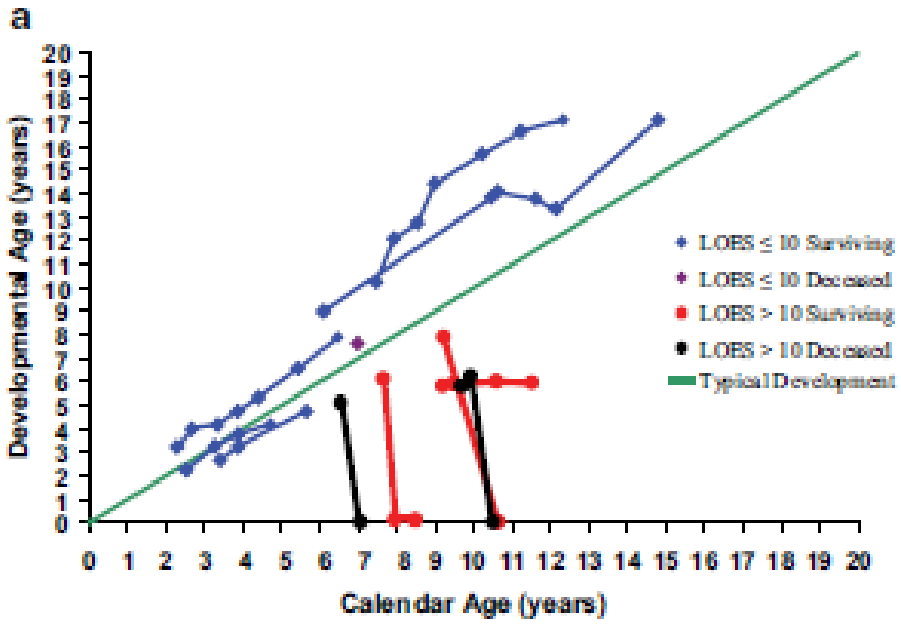
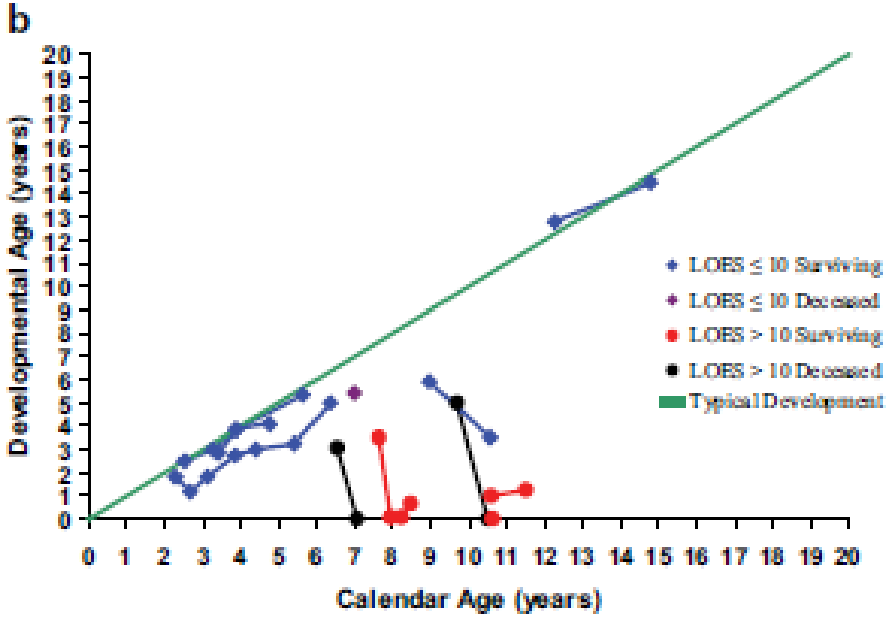


Fig b. Gross Motor Development and pre-BMT Loes



Beam et al. 2007. Outcomes of unrelated umbilical cord blood transplantation for X-linked ALD. *Biol Blood Marrow Transplant*, 13,(6) 665-74.



Does presymptomatic identification lead to improved outcomes for C-CALD compared to usual case detection?

- Case series suggest that there are improved outcomes following HSCT when the Loes score is lower.
- HSCT does not lead to restoration of significant brain involvement.
- However
  - *Is there an ideal threshold for HSCT?*
  - *Studies generally follow time from development of symptoms, without an "anchor" age*



Does presymptomatic identification lead to improved outcomes for C-CALD compared to usual case detection?

- Solution
  - *Compare outcomes from cases identified based on the development of clinical symptoms (S) to cases identified through family testing (F)*
  - *Be "agnostic" to treatment to answer the question about the benefit of knowing that a boy has X-ALD.*
  - *Restrict to cases of C-CALD*
- Two datasets identified



Single Center

- 30 Subjects treated between 2006-2015
  - *17 F*
  - *13 S*
- Outcome data on 19 subjects
  - *7 F*
  - *12 S*
- HSCT
  - *3 of the 7 F (1 undergoing eval, 3 “arrested” [“Self-halted”])*
  - *7 of the 12 S (4 advanced disease, 1 “arrested)*



Multi-Center

- 59 subjects
  - *25 F*
  - *34 S*
- All received HSCT

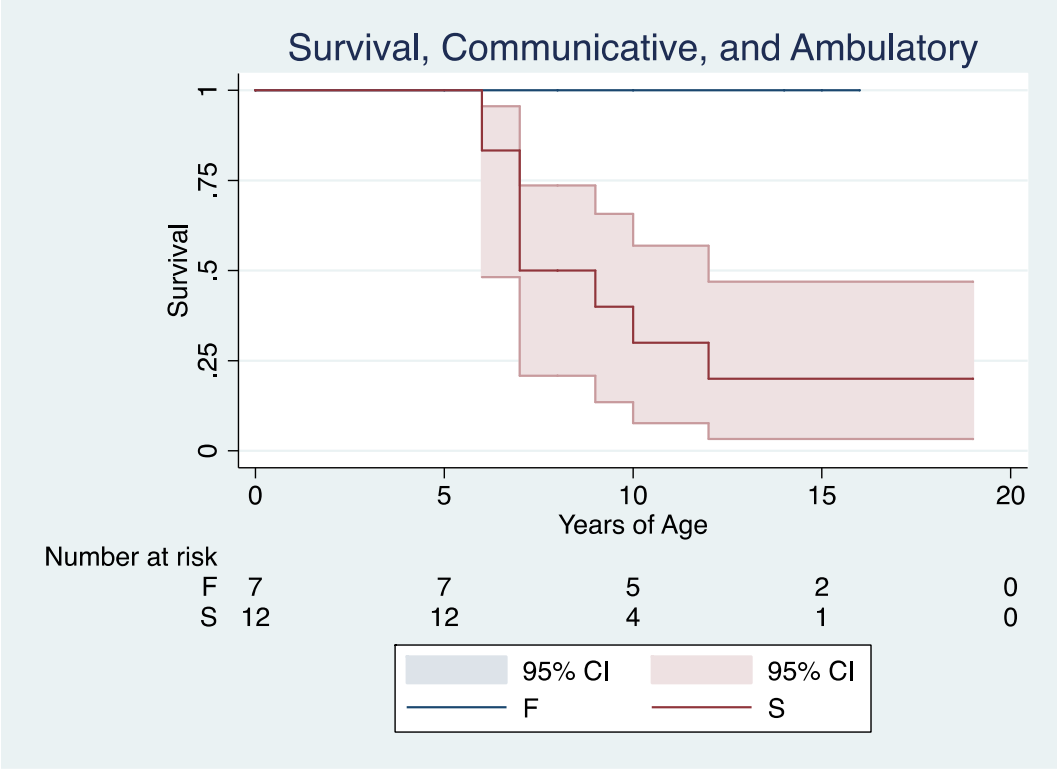


Treatment Outcomes by Detection: *(Unpublished)* Family Risk (F) vs. Symptom onset (S)

Primary Outcomes	Single Center (n=19) Detection Group			Multi-Center, Int'l (n=59) Detection Group		
	Family (F) (n=7)	Symptom (S) (n=12)		Family-risk (F) (n=25)	Symptom (S) (n=34)	
Received HSCT	3 (43%)	7 (58%)		25 (100%)	34 (100%)	
Med Age at HSCT	7 yrs (rg 4-7)	8 yrs (IQR 6-9)		8 yrs (rg 5-9)	8 yrs (IQR 7-10)	
First avail Loes (med)	0 (IQR 0-1)	12 (IQR 11-12)	$p<0.001$	4 (IQR 2-5)	7.5 (IQR 3-11)	p<0.02
Med Age, First Loes	5 yrs (IQR 4-6)	7 yrs (IQR 6-9)		8 yrs (IQR 5-8)	8 yrs (IQR 6-9)	
Most Recent Loes (med)	3 (IQR 2-4)	12 (IQR 11-20)		5.75 (IQR 2-11.5)	13 (IQR 6.5-18)	p<0.02
Med Age, Recent Loes	10 yrs (rg 8-15)	11 yrs (IQR 8-19)		10.5 yrs (IQR 9-14.5)	10 yrs (IQR 8-13)	

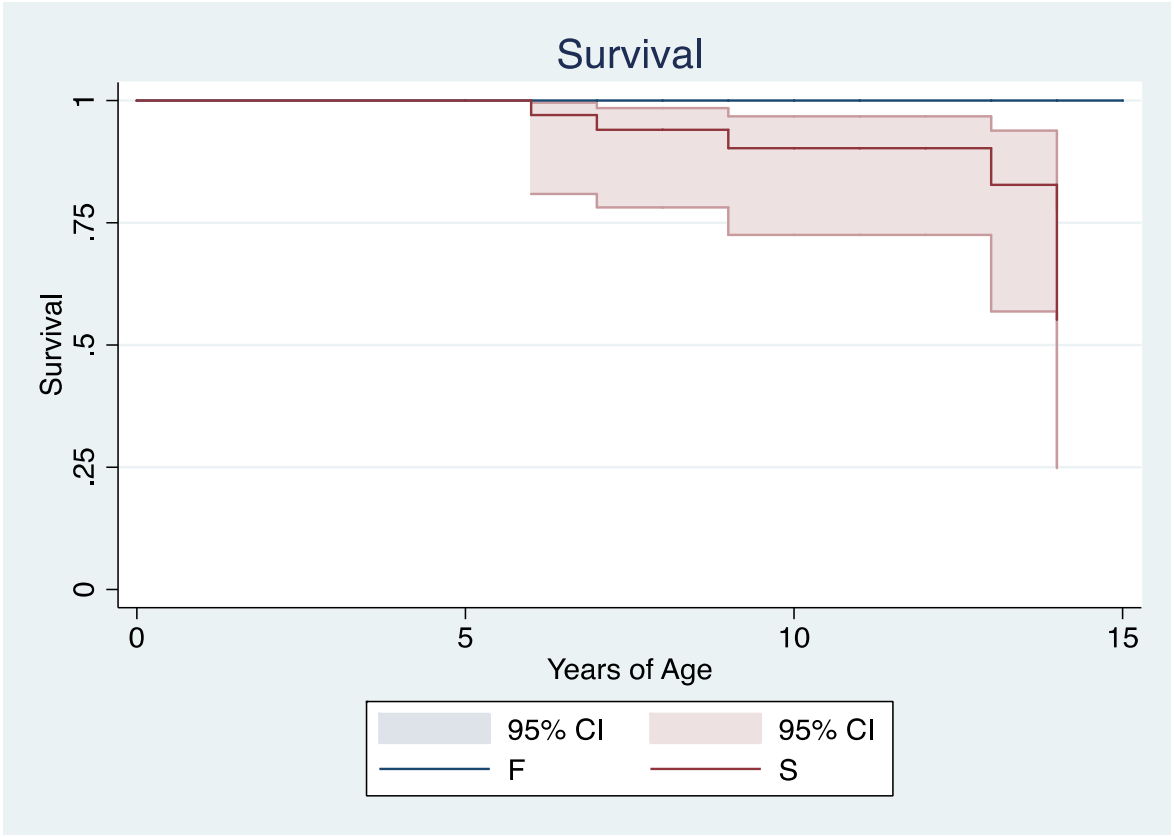


Single Center





Multi-Center





Limitations

- Only C-CALD
- Small, select number of subjects with variable follow-up
- Little information on
  - *Treatment*
  - *Disease Course, including functional status*
- May not reflect the full spectrum of cases detected through newborn screening



Treatment Summary – Presymptomatic Identification of C-CALD

- No direct evidence about the benefit of presymptomatic identification of adrenal insufficiency
- HSCT improves outcomes, and treatment with a lower Loes score is associated with better outcomes
- Unpublished data suggests that identification through family testing leads to improved survival in late childhood compared to detection after the development of symptoms

Population-Level Outcomes for Newborn Screening of X-ALD

Lisa A. Prosser, Ph.D.

August 27, 2015

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Background: Decision analysis

- Validated approach for evidence synthesis
- Using simulation modeling, ranges can be estimated for population-level health benefits
- Explicitly identify assumptions and key areas of uncertainty

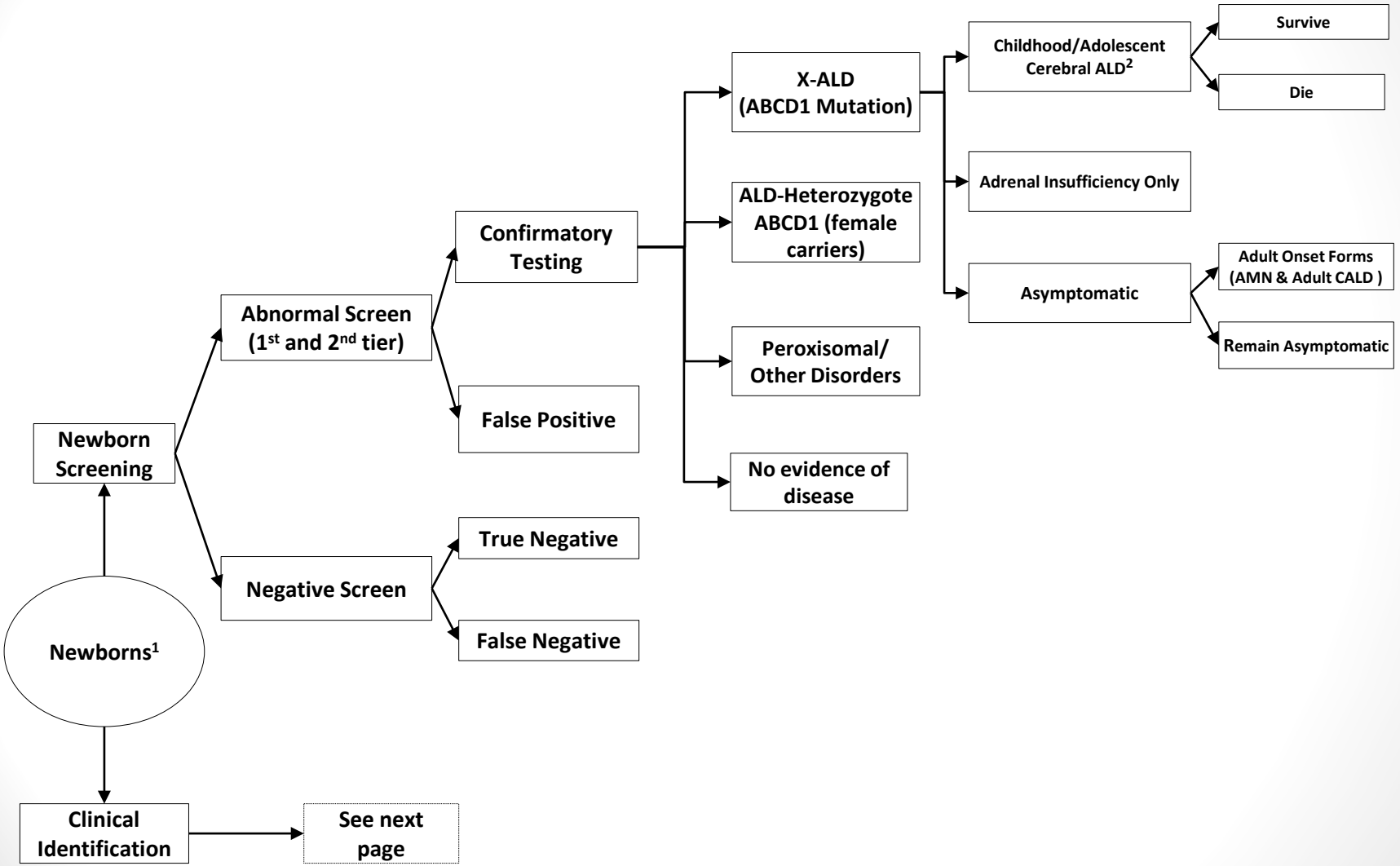
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Analytic Approach

- Computer simulation model to evaluate outcomes for:
  - Universal newborn screening for X-ALD [NBS]
  - Clinical identification of X-ALD [CI]
- 3 expert panels: April 2015, June 2015, July 2015
- Key health endpoints:
  - # cases identified
  - # deaths averted by 15 years of age

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Model Schematic: NBS Submodel

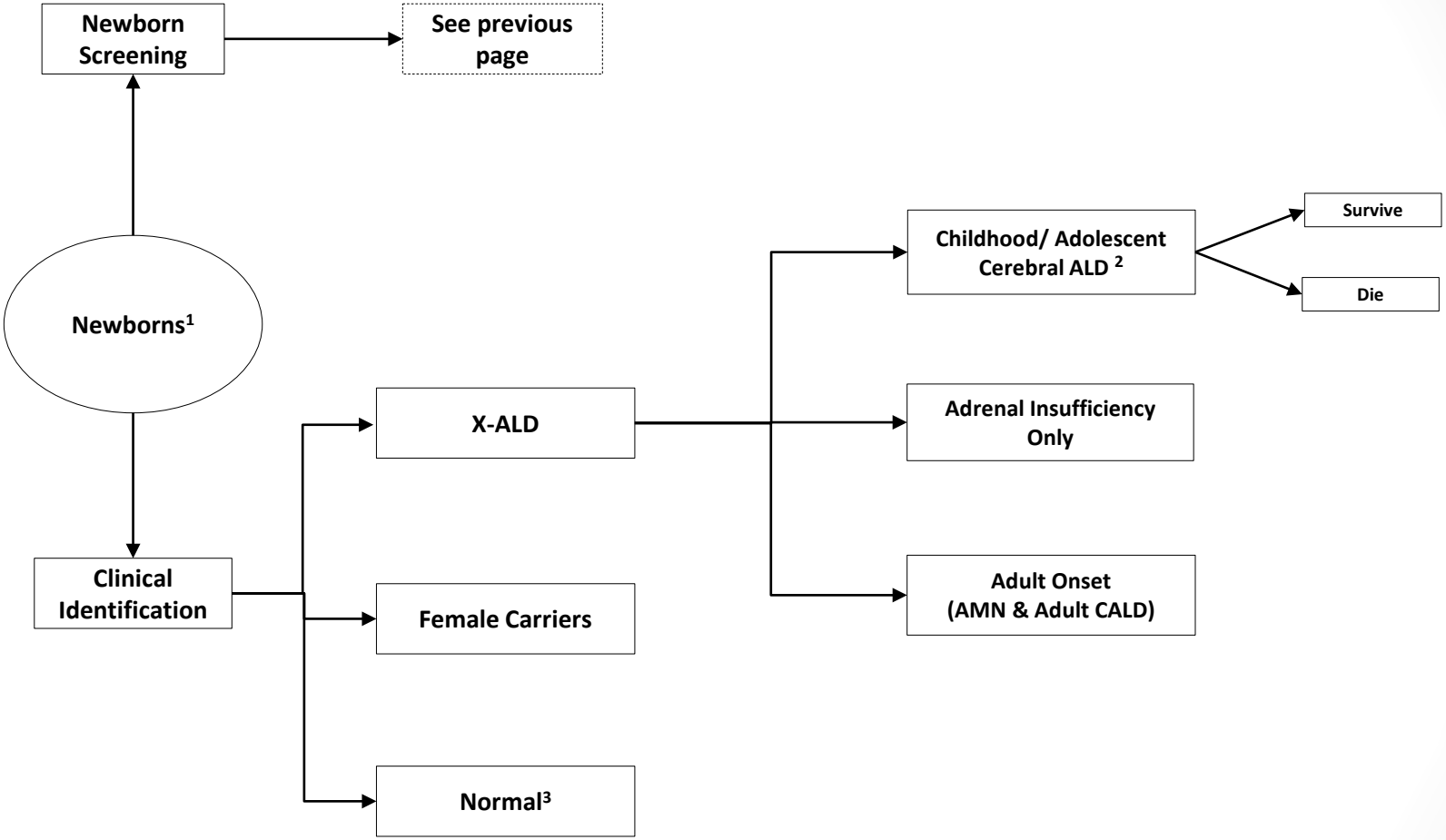


[1]Not at high risk

[2]With or without adrenal insufficiency

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Model Schematic: CI Submodel



[1]Not at high risk

[2]With or without adrenal insufficiency

[3]Can also include peroxisomal/other disorders

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Modeling Assumptions

- Screening projections based on NY data
- Other model inputs derived from evidence review, expert panel, assumptions
- Potential benefits of earlier treatment are uncertain but may include:
  - Improved survival
  - Improved cognitive outcomes (not modeled, except for NANC state)

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Results: Annual Cases of X-ALD identified[1]

	NBS	Clinical Identification
CCALD[2]	46 (32-68)	46 (32-66)
Adrenal Insufficiency Only	12 (8-18)	12 (8-17)
Adult Onset	85 (24-125)	34 (24-49)
Total X-ALD	**143 (64-211)**	**92 (64-132)**

[1]Assuming healthy annual newborn cohort of 4 million, not at higher risk of X-ALD
[2]With or without adrenal insufficiency

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Results: Survival Outcomes at 15 years of age[1]

Table 15.a. Projected survival without NANC[2]

	Survival without NANC (# cases)	Deaths or cases of NANC
Screened/Treated if Indicated		
Most Likely	46	0
(Min, Max)	(5, 68)	(0, 57)
Clinically Diagnosed/Treated if Indicated		
Most Likely	9	37
(Min, Max)	(1, 31)	(17, 64)

Table 15. b. Projected survival, treated patients only[3]

	Survival (# Cases)	Deaths
Screened/Received Transplant		
Most Likely	46	0
(Min, Max)	(22, 68)	(0, 21)
Clinically Diagnosed/Received Transplant		
Most Likely	28	18
(Min, Max)	(11, 52)	(7, 44)

[1]95% CIs derived assuming a binomial distribution; [2]NANC = Non-ambulatory, non-communicative state; unpublished data from Eichler et al, 2015; [3]Unpublished data from multisite study

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Summary

- Projected health benefits for newborn screening compared with clinical identification for cases of X-ALD by 15 years:
  - **18 deaths averted** (range: 7-44), or
  - **37 cases of death or NANC averted** (range: 17-64)
- Base case projections assume equal numbers of childhood/adolescent CALD identified under each alternative.
  - However, newborn screening may result in a higher incidence of X-ALD attributable to missed cases, and/or spectrum bias.
  - Under certain scenarios, the additional number of adult cases of AMN identified is projected to be as high as 76 cases annually.

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Public Health System Impact Assessment

X-linked Adrenoleukodystrophy

Overview

- Background
- APHL's Role
- Methods
- Results
- Summary

PHSI Background

- Recommendations are based on
  - Certainty of net benefit
  - Feasibility and readiness of implementing comprehensive screening

Definition of Readiness

- Ready
  - most NBS programs could implement within 1 year
- Developmental Readiness
  - most NBS programs could implement within 1–3 years
- Unprepared
  - most NBS programs would take more than 3 years to implement

Components of Feasibility

- An established and available screening test
- A clear approach to diagnostic confirmation
- Acceptable treatment plan, and
- Established approach to long-term follow-up plans

Why is this Assessment Important?

- Opportunity to
  - Understand the “real world” barriers and facilitators related to screening
  - Evaluate opportunity costs

Methods

- X-ALD factsheet
- Webinar and outreach
- Survey to 53 U.S. states and territories
- Informant interviews with 4 state NBS programs that are or are planning X-ALD newborn screening

Results: Interviews

	Legislative Mandate	Statewide Screening
New York	X	X
California	X	
Connecticut	X	
New Jersey	X	

Results: Interviews

Challenges from NBS program screening:

- Validating the X-ALD assay
- Determining how to multiplex the assay with LSDs to get consistent results
- Adjusting the screening cutoff to capture as many cases as possible
- Resolving follow up issues related to identifying asymptomatic males and secondary targets (e.g., female carriers and females with peroxisomal disorders)

Results: Interviews

Factors aiding implementation from NBS program screening:

- Consistent communication/developing relationships with specialty centers, health care providers, and diagnostic centers
- Not needing to procure new equipment
- Having existing resources for screening

Results: States with Mandates

State	Year Mandate Received	Screening REQUIRED immediately once added to RUSP	Conditions to be met before screening begins	Timeframe to fulfill conditions
CA	2014	Yes	None	Not specified
CT	2013	No	• Development and validation of method or FDA approved kit • Availability of necessary reagents for tests	Not specified
NJ	2013	No	• Development of a reliable test • Availability of quality assurance materials • Inclusion on the RUSP • Review by the Department of Health • Acquisition of equipment	Six months after condition is added to RUSP

Results: Interviews

Challenges from states with mandate to screen:

- Realistic time frame
- Working with neurologists for first time
- Referral process
- Duration to track patients
- Follow-up issues
- Ensuring availability of specimens for validation
- Hiring challenges

Results: Interviews

Factors that have/will aid in implementation:

- Communicating and sharing information with other NBS programs
- Attending national trainings
- Adequate clinical and follow-up data
- Addition of other disorders on the RUSP
- Insight from NBS programs screening
- Adequate time to implement

Results: Survey

- Response rate of 70%
  - 27 responses from state NBS programs
  - 6 responses from programs that contract commercially or regionally
- Four states NBS programs were excluded from the analysis because they participated in the interview

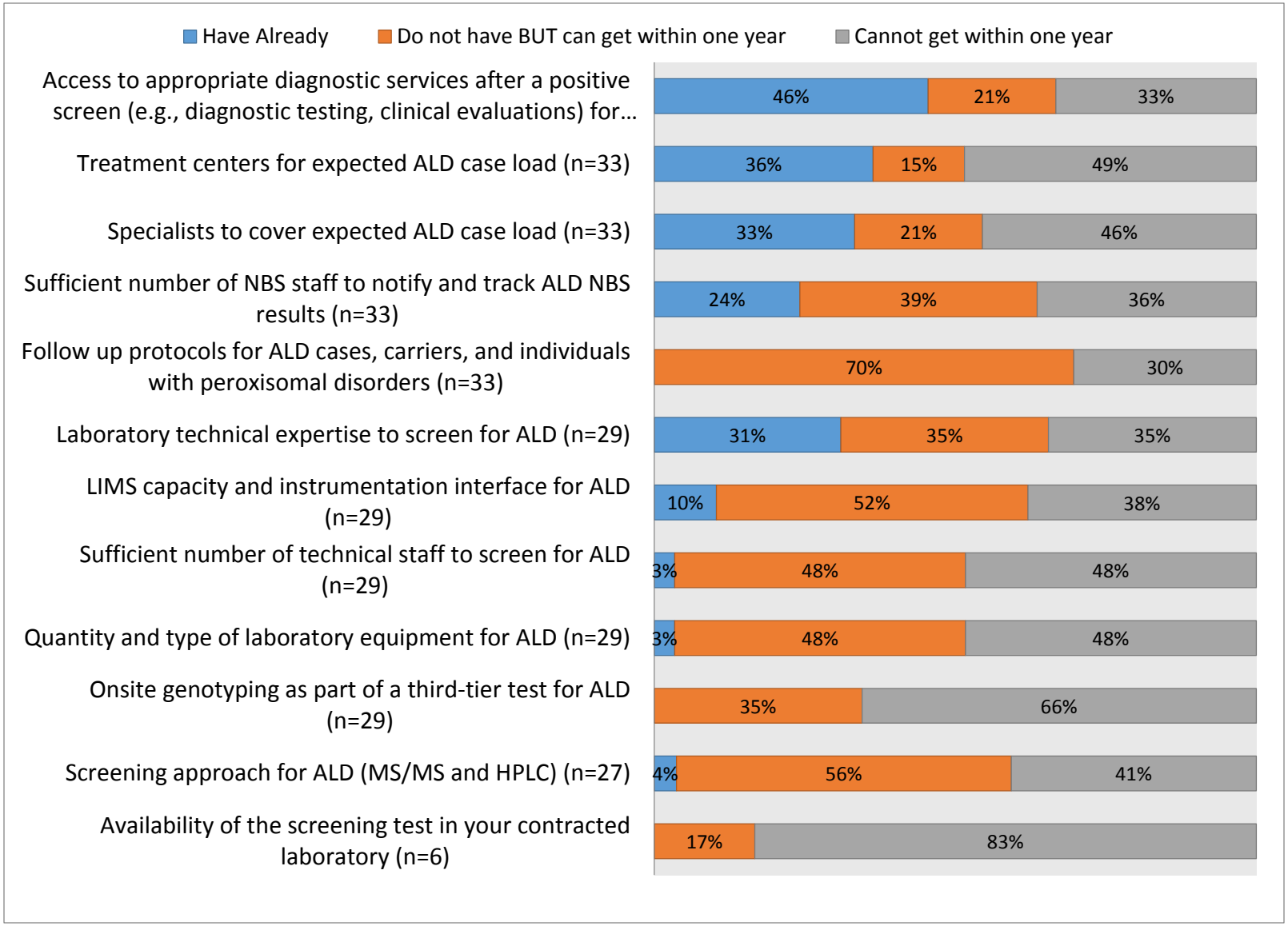
Results: Duration for Authorization

Answer	Number of Programs	%
Less than 1 year	5	15%
1 to 3 years	20	61%
More than 3 years	8	24%
Never	0	0%

Results: Implementation Challenges

Answer	Number of Programs	%
Provide screening test	20	61%
Short-term follow-up of abnormals	20	61%
Increase of NBS fee	16	49%
Long-term follow up for carriers and individuals with peroxisomal disorders	15	46%
Support to ALD specialists	12	36%
Treatment support for ALD	8	24%
Other-please specify	3	9%

Results: Implementation Resources



Results: Implementation Resources

	Major Barrier		Minor Barrier		No Impact		Minor Facilitator		Major Facilitator	
	n	%	n	%	n	%	n	%	n	%
Cost per specimen to conduct ALD screening (personnel, equipment, reagents) (n=33)	19	58%	13	39%	1	3%	0	0%	0	0%
Other ongoing NBS program activities (e.g., addition of other conditions, other quality improvements) (n=33)	16	49%	17	52%	0	0%	0	0%	0	0%
Cost of treatment for newborns diagnosed with ALD (n=33)	9	27%	11	33%	13	39%	0	0%	0	0%
Other non-NBS public health priorities within your state (n=33)	9	27%	12	36%	12	36%	0	0%	0	0%
Expected clinical outcomes of newborns identified with ALD from screening (n=33)	8	24%	4	12%	8	24%	7	21%	6	18%
Expected cost-benefit of screening for ALD in your state (n=33)	6	18%	6	18%	11	33%	7	21%	3	9%
Advocacy for screening for ALD (n=33)	2	6%	2	6%	11	33%	14	42%	4	12%
Extent to which the screening test for ALD can be multiplexed with other disorders (n=29)*	6	21%	9	31%	3	10%	4	14%	7	24%
Predicted run time to screen for ALD as it relates to other workload (n=29)*	4	14%	14	48%	9	31%	2	7%	0	0%

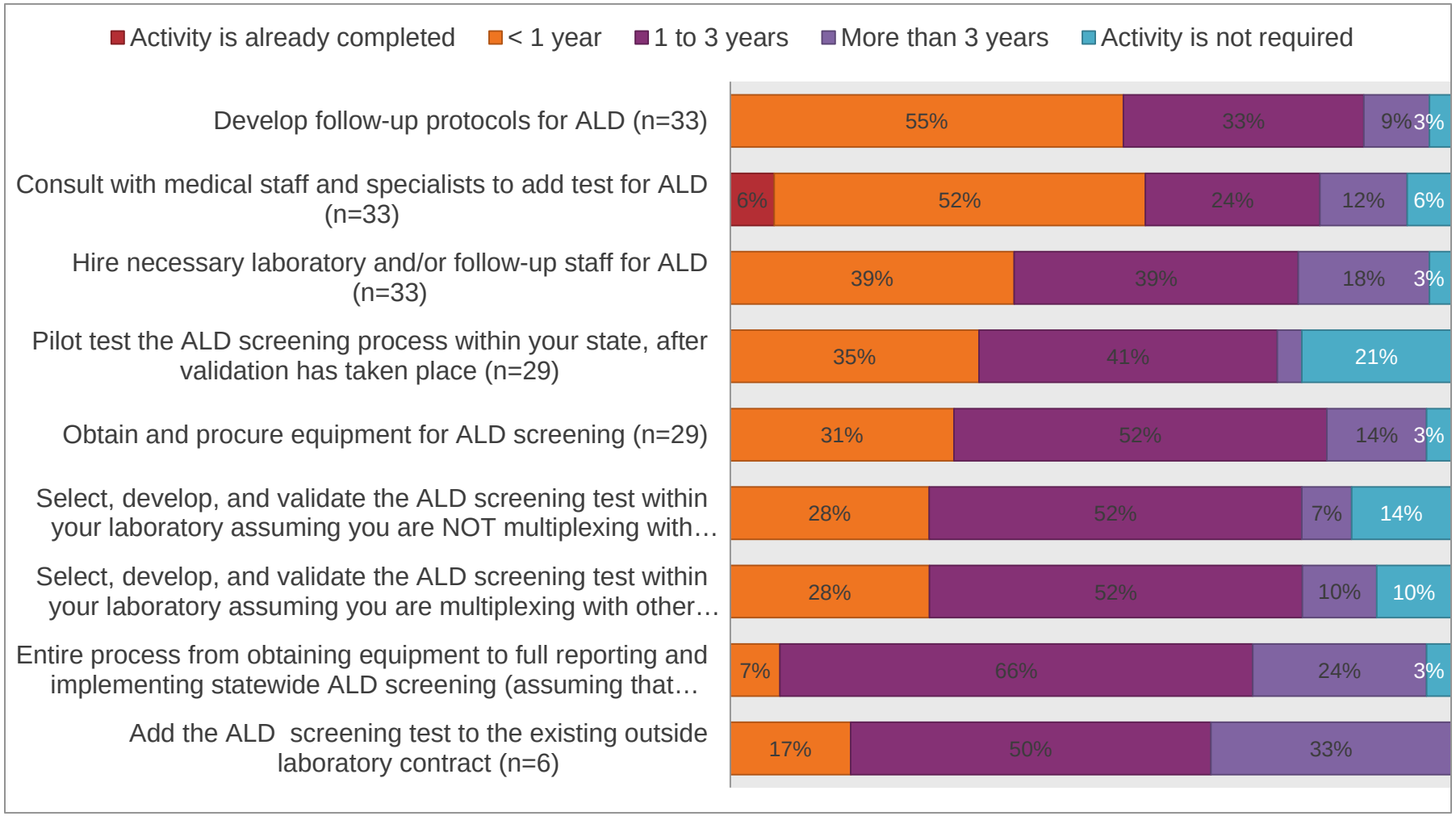
Results: Most Significant Barrier

- 15 NBS programs cited funding/costs as the most significant barrier
- Other barriers:
  - Legislative approval or not having the condition on the RUSP
  - Staffing/hiring
  - Waiting for contract laboratory to get the screening test
  - Competing public health priorities

Results: Greatest Facilitator

- Eight NBS programs cited the potential of multiplexing with other disorders as being the most significant facilitator
- Other facilitators:
  - Addition to the RUSP
  - Benefits of early detection
  - Readiness of contract laboratory/other program that can perform testing
  - Advocacy

Duration for Implementation



Strengths of PHSI

- Survey response rate of 70%
- Webinar and factsheet for survey responders
- Survey assessed perceptions about implementation based on experiences with other disorders
- Interviews assessed real world experiences

Limitations of PHSI

- Assumption that approval had occurred and funds were allocated
- Hypothetical survey questions and subjective responses
- Limited data on screening for X-ALD in NBS setting

Conclusions: Readiness

- Most (61%) of the state NBS programs that were surveyed and 2 out of 3 states with mandates reported that it would take between 1 and 3 years to implement screening for X-ALD after approval and allocation of funds
- Developmentally ready at best

Conclusions: Feasibility

- Establishing long-term follow up plans remains difficult
- Several follow-up issues were noted:
  - Uncertainty regarding age of onset (often later than most NBS disorders)
  - Length of time to track patients
  - Timing of the development of CALD or adrenal insufficiency
  - Referral process

Summary

- Costs associated with screening and competing public health interests continue to hinder implementation of other recommended conditions
- States with mandates do not have funds for sustained screening
- The NBS program that has begun screening provides important lessons



Overall Summary

- X-ALD is associated with significant morbidity and mortality in affected males
- HSCT can be an effective therapy for those with C-CALD
  - *Studies support that outcomes are improved when there is less cerebral involvement*
  - *Unpublished data suggest that there is decreased morbidity/mortality in late childhood among individuals who are diagnosed through family testing compared to after the development of symptoms*
- Adrenal insufficiency is common and can be treated with replacement therapy
  - *No data about the benefit of early identification compared to usual case detection*
- Harms
  - *Screening identifies boys with C-CALD but also identifies heterozygote females and other peroxisomal disorders*
  - *Individuals identified through screening may need many years of follow-up with uncertain course of disease*
  - *Shifting transplant earlier exposes the risk of transplant to an earlier age*
- Most states anticipate needing at least 1-3 years to adopt screening once funding becomes available



Thank You!

Questions?

Presentation Contact:

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