Duke Clinical Research Institute

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

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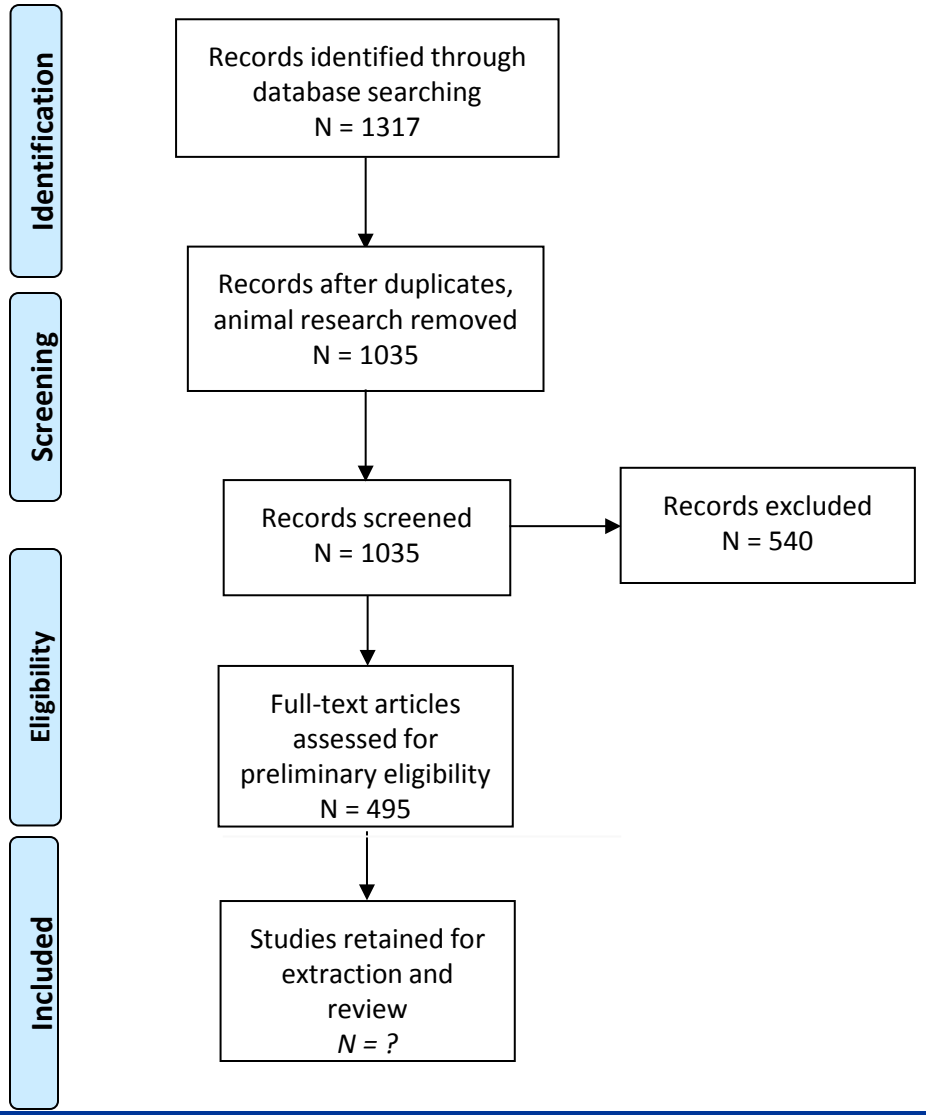
Overview: X-Linked Adrenoleukodystrophy (X-ALD)

- 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)
- Screening by two independent reviewers

Figure 1. Preliminary PRISMA Diagram of Published Literature Search



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, adrenal hormone replacement therapy, N-acetyl-L-cysteine, Gene therapy

X-ALD Phenotypes

	Cerebral ALD *(about 90% of CCALD have adrenal insufficiency [Addison's disease])			**Adrenomyeloneuro-pathy (AMN)**	**Addison Only** (adrenal insufficiency)	**Women with X-ALD**
Frequency (%)	**CHILD** (CCALD) 31 – 35	**ADOL** (AdolALD) 4 – 7	**ADULT** (AALD) 2 – 5	40 - 46	*(decreasing with age)*	unknown symptomatic
Onset Age (Yrs)	2.5–10	10–21	>21	>18	>2	Mostly >40
Progression	Rapid			Slow *(if no cerebral involvement)*	–	Slow
Myelopathy	–	+ / -		+	–	+
White matter lesions on brain MRI	Extensive			Some	–	Occasional-Rare
Behavioral & Cognitive Disorder	+			– (+ *if cerebral involvement)*	–	Very rare
Peripheral Neuropathy	–	rare	possible	Sensory-motor, axonal	–	+ / -
Life Expectancy *(if 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*
  - *Unknown sensitivity (false-negative rate)*
  - *Clinical validity with confirmation not established*
- Primary Screening Methods:
  - *Tandem mass spectrometry (MS/MS)*

Current X-ALD Newborn Screening

- **NY, CT,** and **NJ** State Newborn Screening– legislation approved 2013
- **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 data still being gathered)

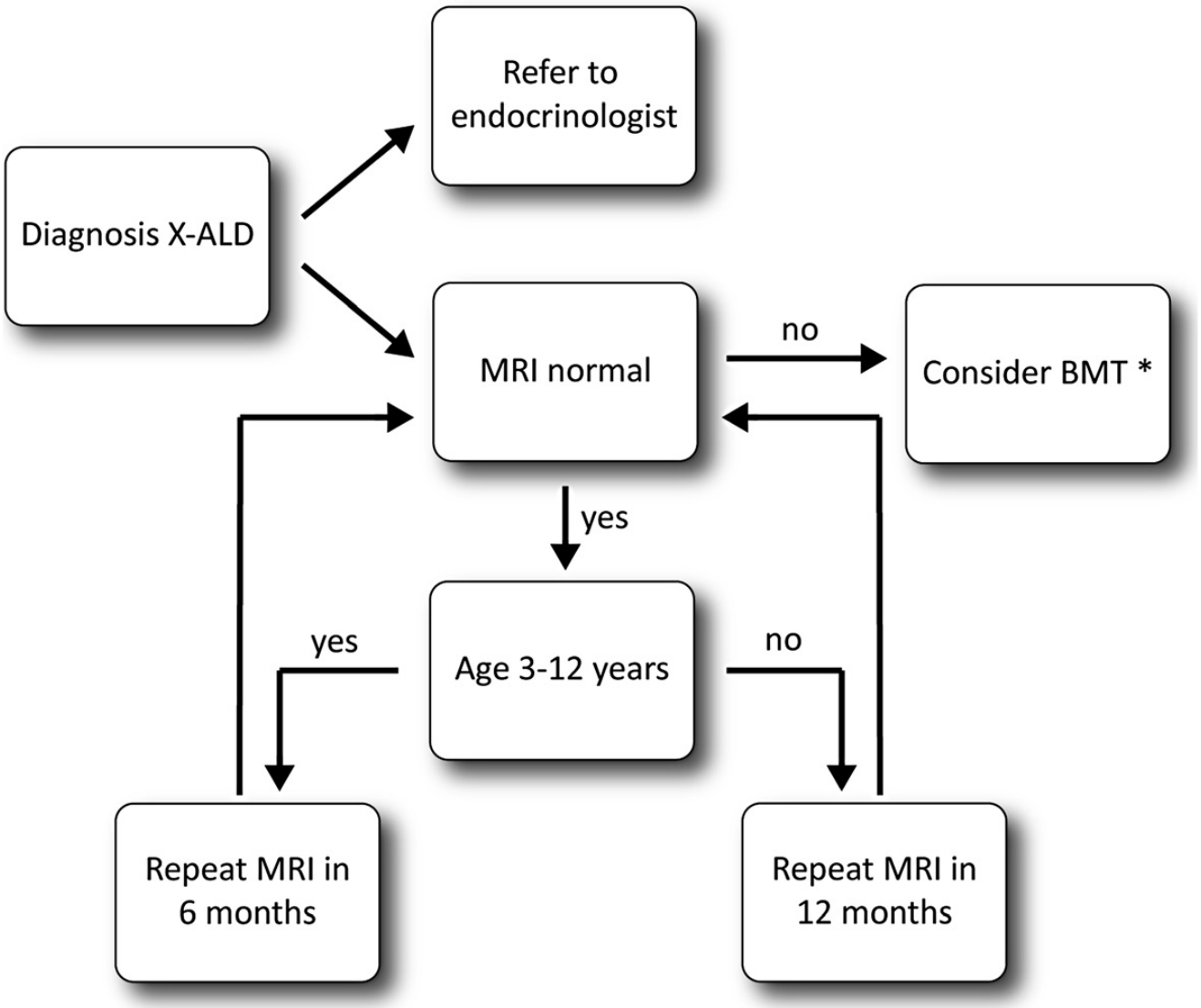
X-ALD Newborn Screening

- **What is the primary target of screening?**
- **What are the secondary targets?**
- **What would most help inform the Advisory Committee?**
- **Proposal**
  - *Screening: Summarize all cases detected*
  - *Focus on expected outcomes from newborn screening: Cerebral ALD, Addison's (in childhood), ?other peroxisomal disorders detected through newborn screening (Zellweger syndrome)? [SECONDARY TARGET]*
  - *Exclude evaluating expected outcomes of early diagnosis of adult-onset conditions; will summarize guidelines/ recommendations of care for early detected cases*

Establishing the X-ALD Diagnosis

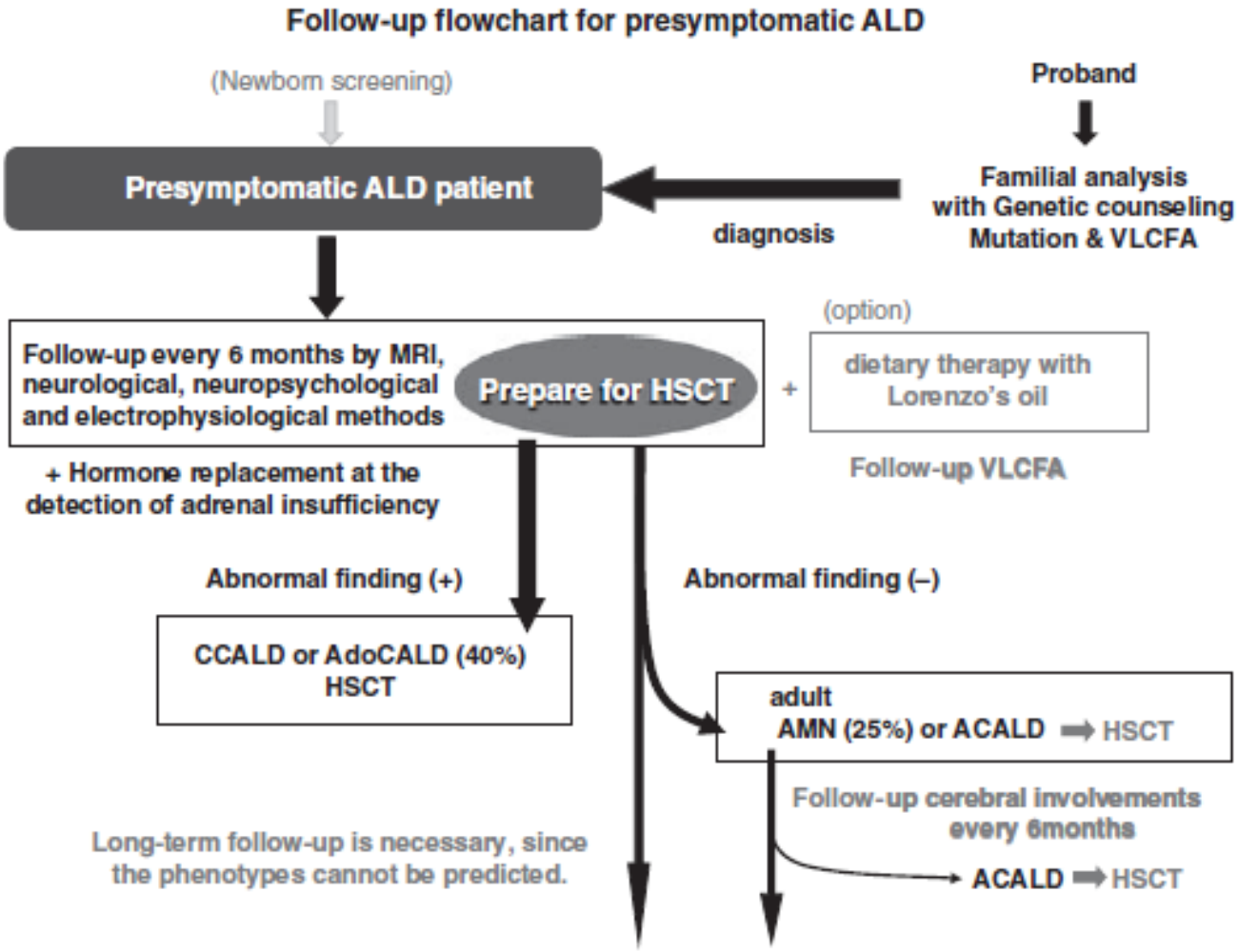
- **Definitive X-ALD diagnosis**
  - *DNA diagnostic test for X-ALD involving non-nested genomic amplication of the ABDC1 gene, followed by sequencing and analysis with fluorescence.*
- **Neuroimaging**
  - *Brain MRI/(& Loes scale for MRI) – always abnormal in neurologically symptomatic males*
- **Increased Very long-chain fatty acids**
  - *Most important laboratory assay is VLCFA concentration in plasma*
- **Clinical Diagnosis in CALD (Boys) –**
  - *Symptoms of ADD, with signs of dementia and understanding of spoken language, progressive disturbance in behavior, coordination, handwriting, vision, other neurological disturbances.*
  - *Primary adrenocortical insufficiency (with additional diagnostic confirmation)*

Management of Presymptomatic X-ALD



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

Management of Presymptomatic X-ALD



Shimozawa et al. 2011. X-linked adrenoleukodystrophy: Diagnostic and follow-up system in Japan. *J of Hum Gen*, *56*, 106-109.

Treatment Strategies

- **Hematopoietic Stem Cell Transplantation (HSCT)**
  - *May reduce risk or progression of neurological degeneration in early stage CCALD*
- **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**
  - *2 successful case studies in France (2 7 yr old boys, early CALD), cerebral disease progression halted after 14-16 mos*
- **Lorenzo's oil**
  - *Aims to normalize Saturated VLCFA plasma levels, controversial and mixed results. Efficacy and application studies continue.*
- **Lovastatin in X-ALD**
  - *Aims to lower VLCFA*
  - *Mixed findings, strongest study (Engemen, 2010, NEJM) show small VLCFA decrease in plasma, but not red and white blood cells*

Survival Outcomes with Clinical Detection, with and without HCT

- Subjects: Boys with early stage CALD
  - *N=283 non-transplanted*
  - *N=19 transplanted*
- Mean age at symptom onset among 283 non-transplanted group was 7 years (SD 2 years).
- 131 (46%) patients died during the mean follow-up period of 5.9 years (5.3) at a mean age of 12.3 years (4.9), 5-year survival was 66%.
- The 5-year survival probability of 54% in the early stage group was significantly poorer (p=0.006) than the 5-year survival of 95% in the transplanted group with early stage cerebral disease.

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

Survival, CALD untreated (N=283 boys)

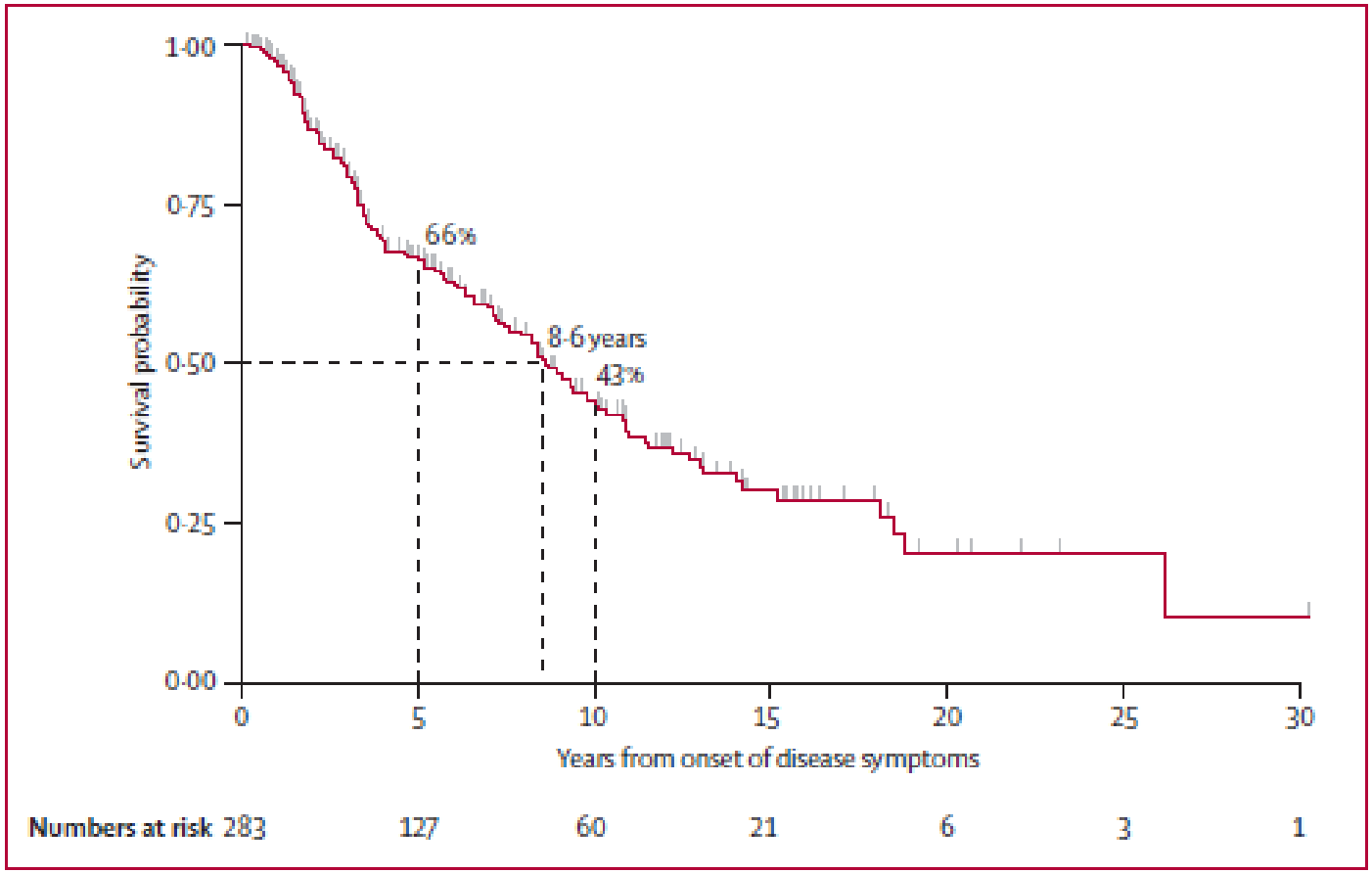


Figure 2: Kaplan-Meier estimate of survival for 283 boys with childhood cerebral X-linked adrenoleukodystrophy after development of neurological symptoms (cognitive, behavioural, or neurological symptoms)

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

Survival outcomes, CALD with (n=19) and without transplants (n=30)

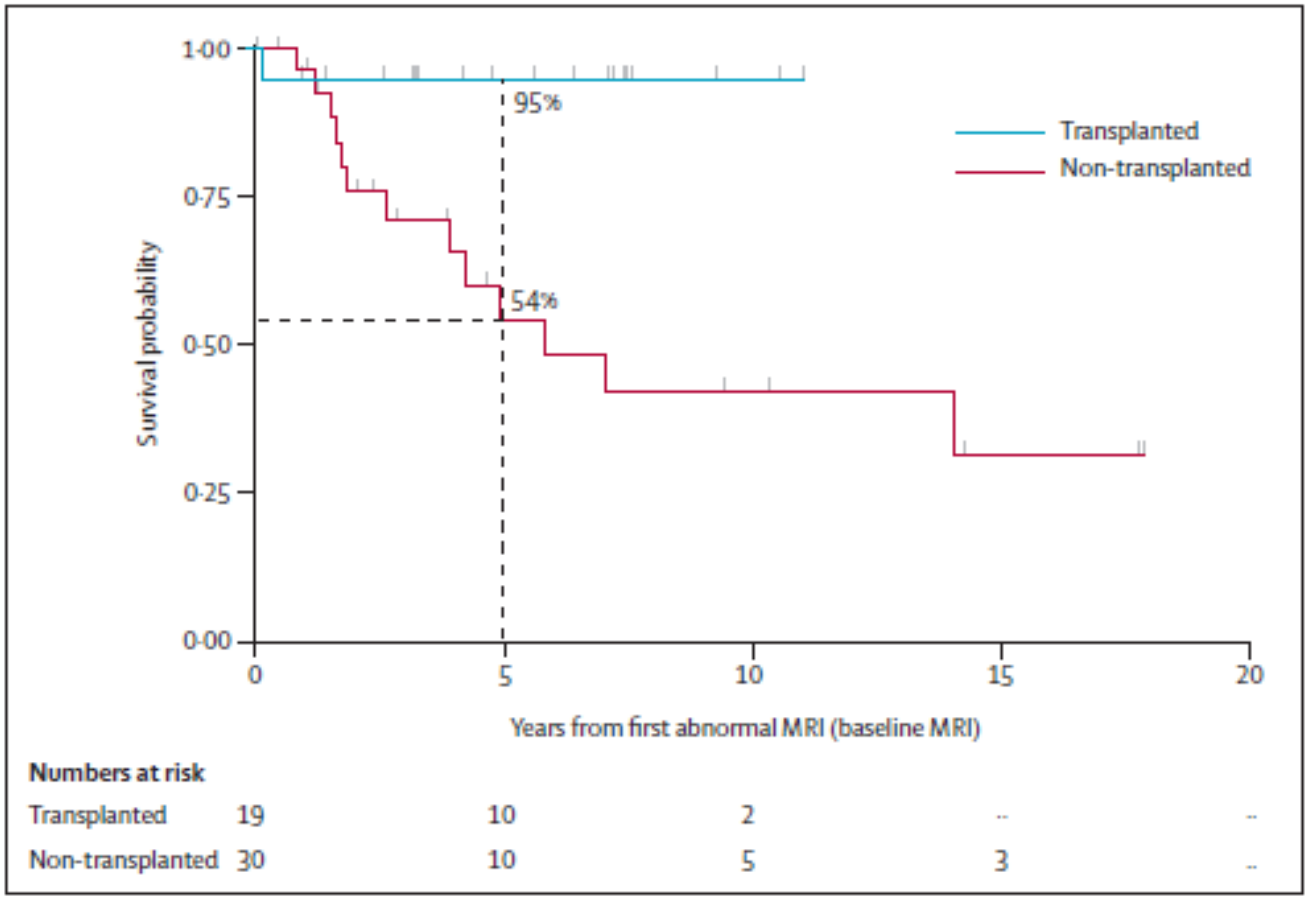


Figure 4: Kaplan-Meier estimates of survival for 19 transplanted patients with early stage cerebral adrenoleukodystrophy and for 30 non-transplanted patients with early stage cerebral adrenoleukodystrophy (ie, neurological deficit score of 0 or 1 and MRI severity score less than 9)
Survival was different 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.

Thank You!

Questions?

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