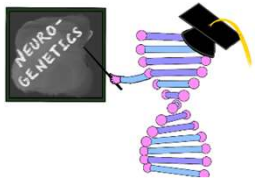
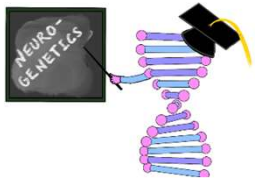
Inborn Errors of Metabolism: Leukodystrophies

MODULE 9



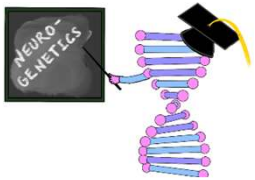
Learning Objectives

- Diagnose X-ALD after a positive newborn screen and describe cascade testing.
- Describe the diagnostic features of X-ALD based on typical clinical features, brain MRI, and biochemical and genetic testing.
- Distinguish X-ALD from other typical leukodystrophies based on MRI and symptoms.
- Discuss treatments for X-ALD and how to determine a patient's eligibility.
- Understand ethical and broader family implications of screening for and diagnosis of a genetic condition.



What is Newborn Screening?

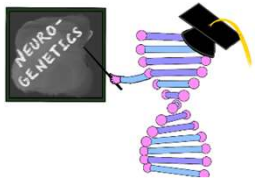
- Federal Recommended Uniform Screening Panel (RUSP) of conditions created by the Secretary of Health and Human Services.
- Individual states decide what conditions they will screen for.
- Screening is generally compulsory with states having various requirements to opt-out.
- Heel stick before discharge from birth hospital → metabolic and genetic testing in the state's newborn screening lab.



Chief Complaint – Positive NBS

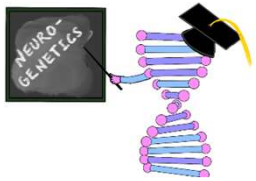
- Baby girl born at term screened positive for X-ALD on newborn screen. The family comes to you for counseling and further testing.

- *Name some disorders, of special interest to neurologists, that have had newborn screening initiated in recent years.*



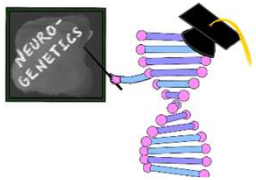
Newborn Screening Conditions

	Year and location for first state-based screening program	Year added to the RUSP	Primary childhood neurologic presentation
Pompe disease	MO 2013	2015	Weakness
X-ALD	NY 2013	2016	Developmental regression, leukodystrophy
MPS 1 (Hurler disease)	MO 2013	2016	Developmental delay
SMA	UT 2018	2018	Weakness
MPS 2 (Hunter disease)	IL 2017	2022	Developmental delay
GAMT deficiency	UT 2015	2023	Developmental delay, epilepsy
Krabbe disease	NY 2006	Voted to recommend for the RUSP in Jan 2024	Developmental regression, leukodystrophy
Duchenne muscular dystrophy	OH 2024	Under consideration 2024	Weakness



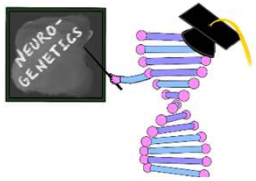
Newborn Screening and You

- **Be sure to know what's on your state's newborn screening panel.** Different states screen for different lists of conditions.
- **Screening is not a diagnostic test.**
  - If a given condition is in your differential diagnosis for a patient, you should test for it. Don't rely on the newborn screen to rule out a condition.
    - For example, the newborn screen will identify approximately 95% of SMA. That means 5% of patients will present for diagnosis based on symptoms.



Neurologic Disorders Added to NB

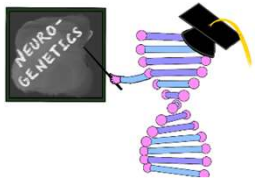
- Newborn screen for X-ALD looks for elevation of a lysophosphatidylcholine derivative of a very-long-chain fatty acid marker in dried blood spots, abbreviated C26:0-LPC.
- What group of conditions can cause elevated VLCFA?
  - Peroxisomal disorders. Peroxisomes break down VLCFA for removal from the cell.
- Many states also screen for Krabbe disease in newborns. What group of disorders does Krabbe belong to and how is it screened for on NBS?
  - Lysosomal storage disorders
  - Galactocerebrosidase (GALC) activity in dried blood spots. If low, 2nd tier test measured psychosine, the neuro-toxic product that builds up in GALC deficiency.
- What are some other lysosomal disorders on the RUSP?
  - Pompe disease, MPS I, MPS II



X-ALD_Female (X-Linked Adrenoleukodystrophy) – newbornscreening.info

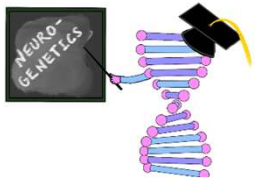
Differential Diagnosis for X-ALD Positive NBS

- Single gene peroxisomal disorders → reduced function of otherwise intact peroxisomes
  - X-ALD – due to impaired transport of VLCFA into the peroxisome
- Peroxisomal biogenesis disorders → reduced number of functional peroxisomes
  - Zellweger Spectrum
- Aicardi Goutières Syndrome → heritable interferonopathy associated with systemic autoinflammation
  - Causes interferon elevation and increased C26:0 lysophosphatidylcholine



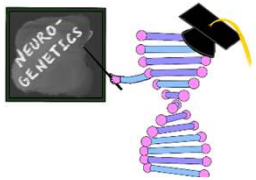
Physical Exam

- The infant is healthy with normal exam and normal growth parameters.
- Her state newborn screen reported elevated VLCFA.
- Family brings their other kids whom we'll discuss later.



Clinical Tests

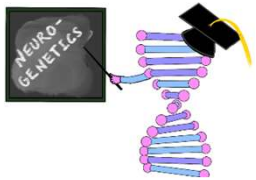
- First determine patient has X-ALD or another condition:
  - Clinically confirm elevated VLCFA.
  - Genetic testing:
    - ABCD1 sequencing panel
    - Peroxisomal disorders gene panel (if ABCD1 is normal)



Genetic Results

- The patient has abnormal VLCFA and a pathogenic variant in the ABCD1 gene

- *What are the next steps?*

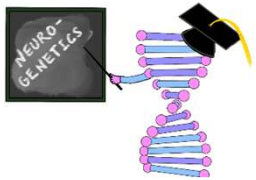


Immediate Actions After Confirme X-ALD Newborn Diagnosis

- If it's a girl,
  - She only requires genetic counseling. Girls will be not symptomatic in childhood. They have a risk of myeloneuropathy in adulthood.

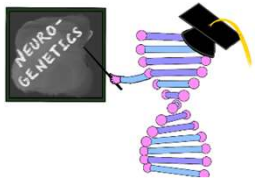
- If it's a boy,
  - Refer to endocrinology and neurology as soon as diagnosis is confirmed.

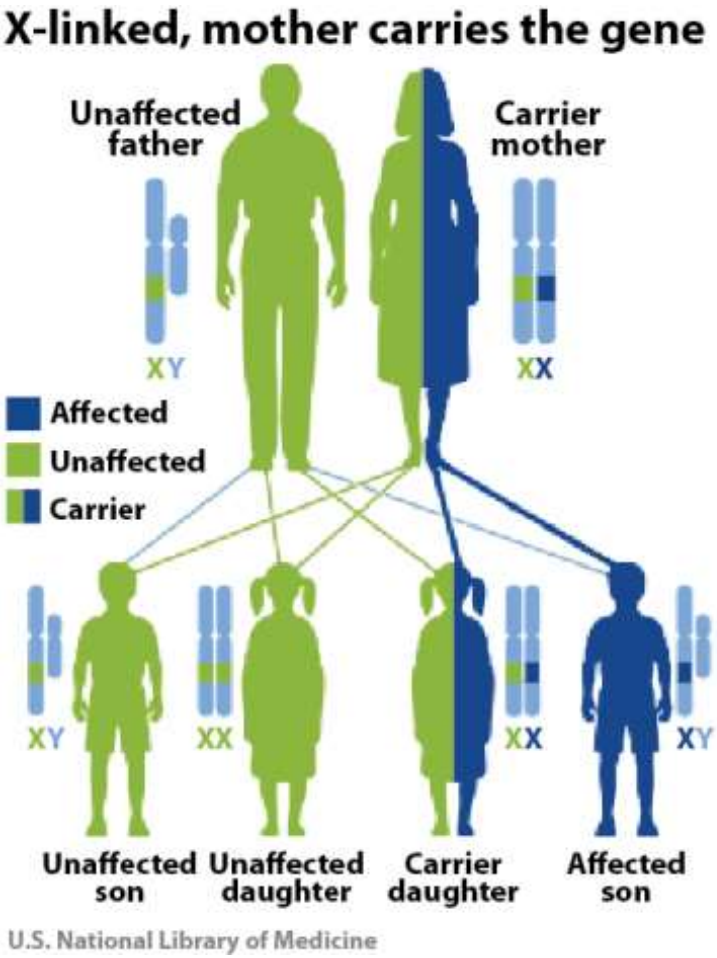
- In either case, at risk family members should be identified and offered testing.



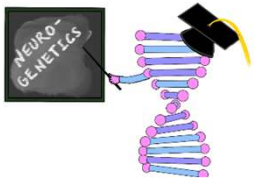
Cascade Testing of Family Members

- If X-ALD is confirmed in the index patient, determine if it is de novo or inherited
  - 5-10% of ABCD1 pathogenic variants are de novo
  - Offer genetic testing to mom
- If inherited
  - Offer genetic testing to mom's female siblings and her adult female offspring
  - Offer biochemical testing to mom's male siblings and male offspring
  - 100% of males with X-ALD and 80% of female carriers of X-ALD will have elevated VLCFA
- Take a family history to identify others who need testing

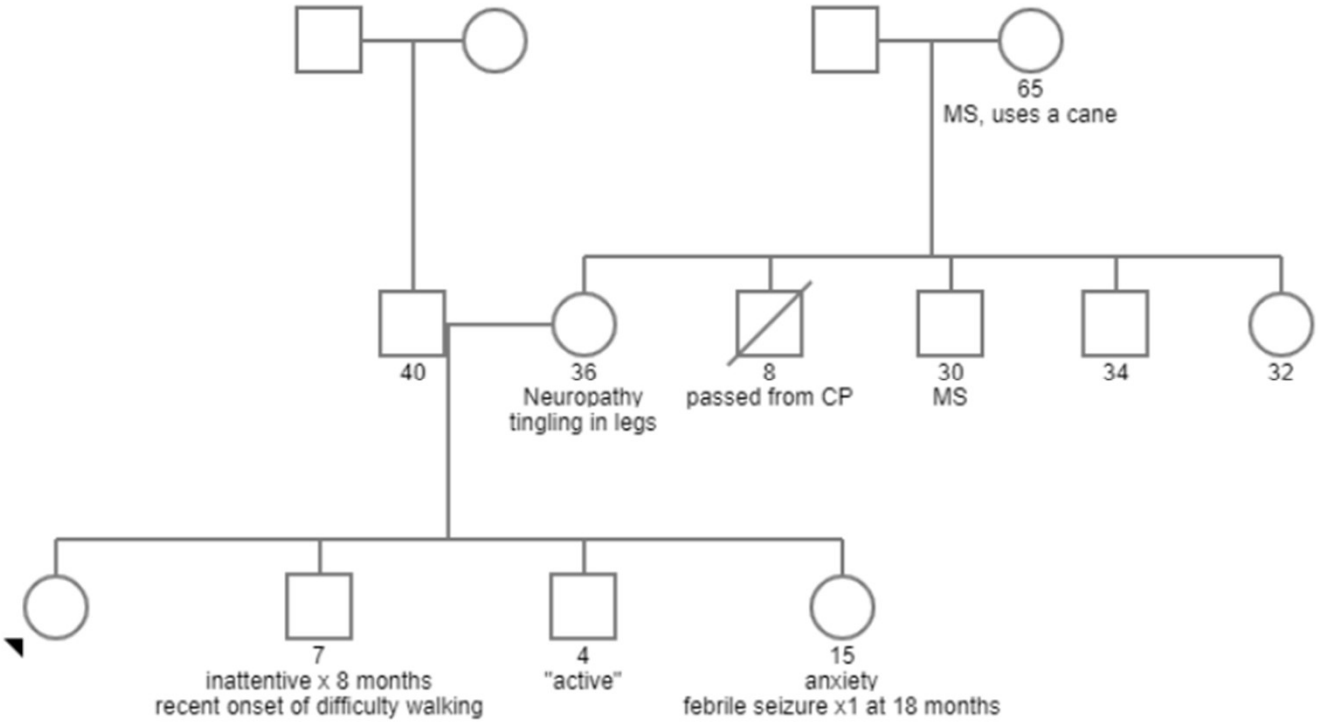


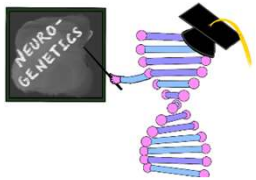


- In the case of X-ALD, a “carrier” female may be pre-symptomatic rather than unaffected. Symptoms relate to myeloneuropathy.
- Always ask the mothers of male X-ALD patients about neurologic symptoms and recommend they seek evaluation by a neurologist.



Who Should be Offered Testing from the Patient's Family?





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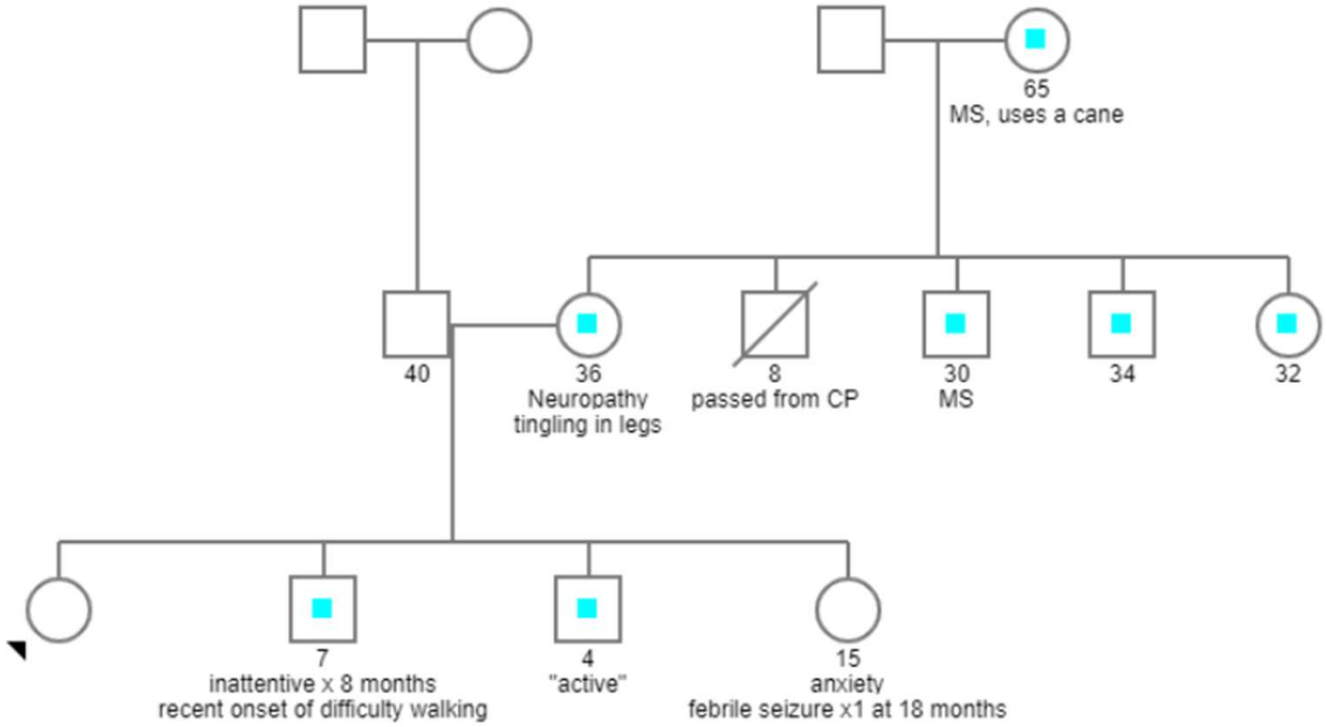
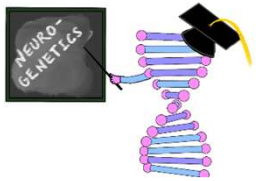
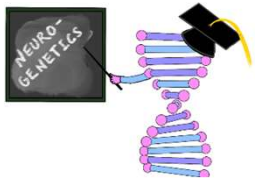




Familial Testing

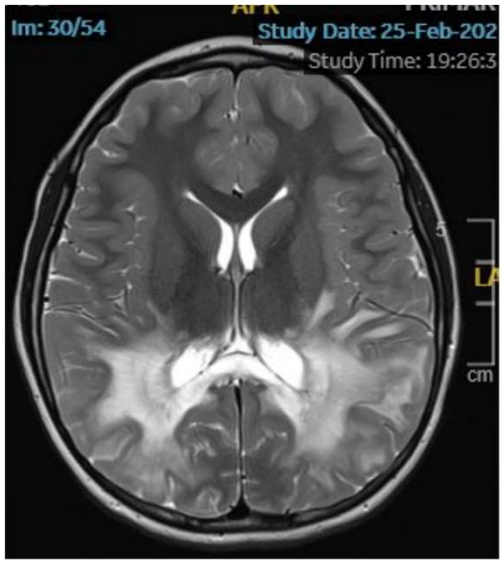
- Since both of the patient's brothers are potentially symptomatic, urgent evaluation is warranted
  - Their VLCFA are elevated
  - They carry the same ABCD1 variant

  - *What do you do next for the boys?*

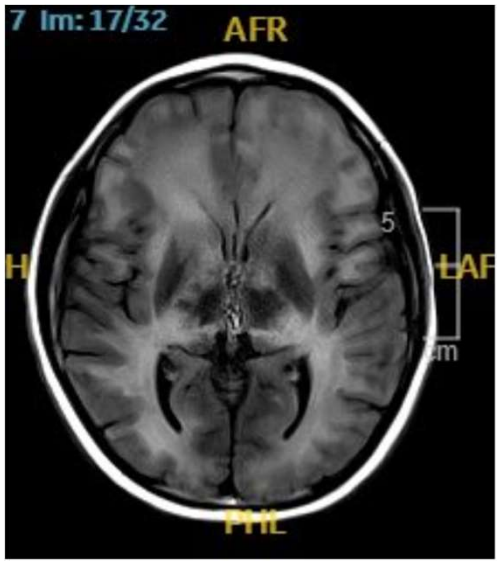


Investigations (Non-Genetic)

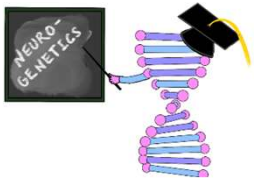
- MRI for the two boys. Girls do not need MRI in childhood.
- Adrenal function for the boys (can start with random cortisol) and refer to endocrinology.



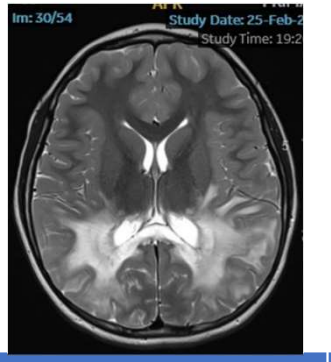
4-year-old

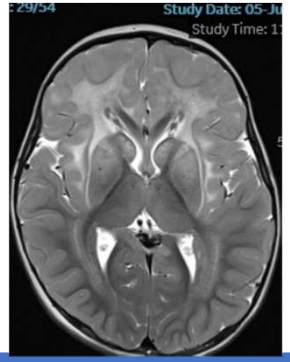


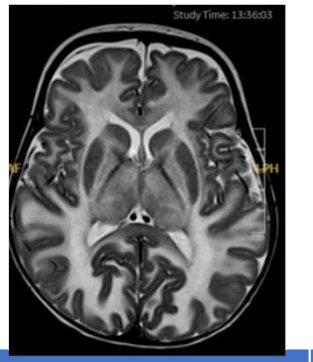
7-year-old

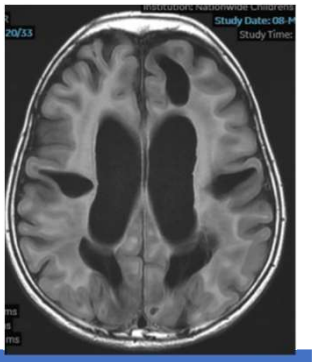


Common Imaging Findings

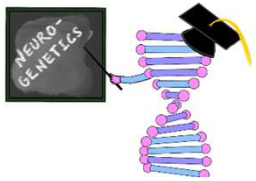




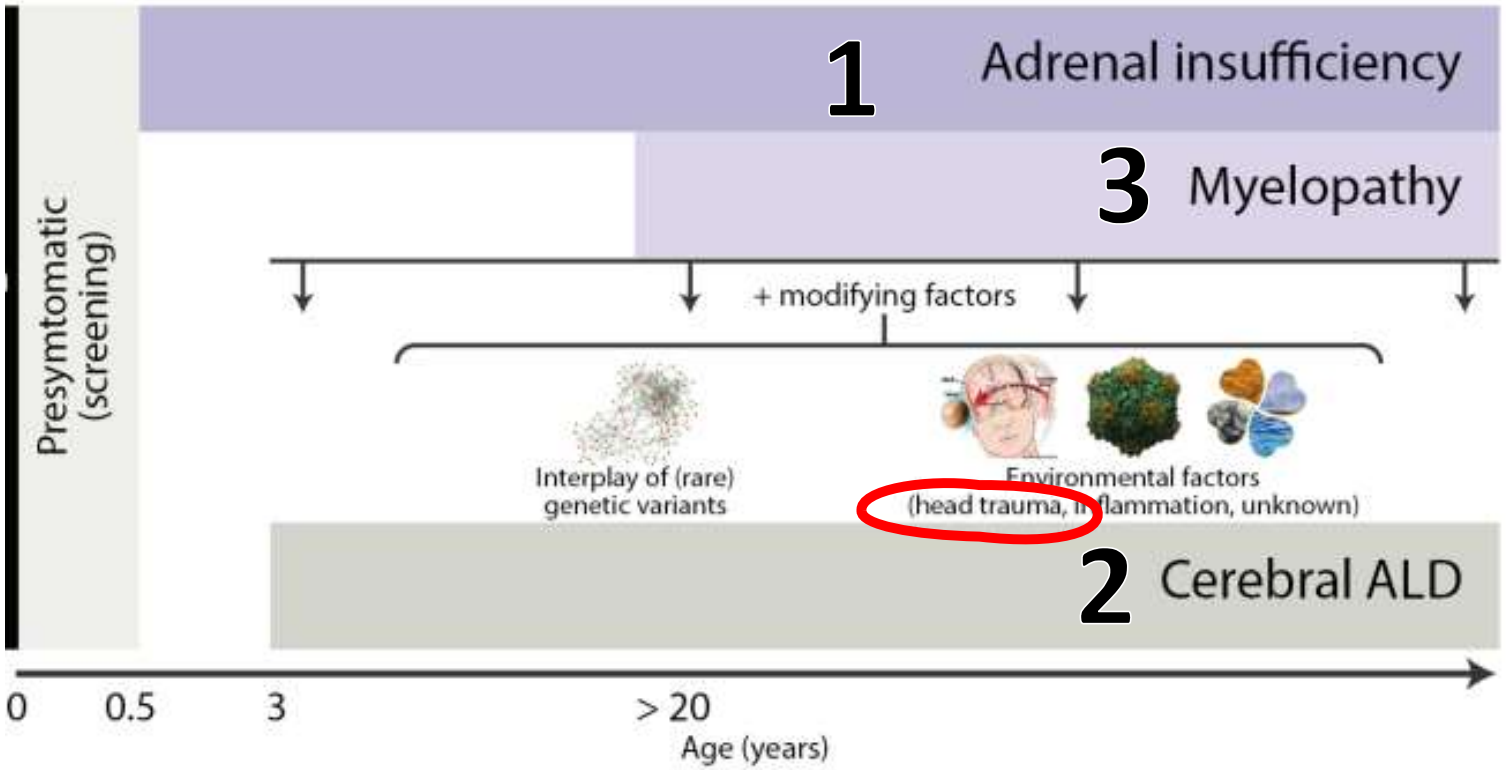


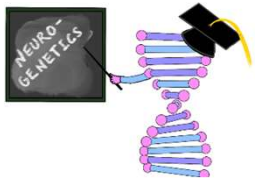


Condition	X-ALD	Alexander Disease	Canavan Disease	Megalencephalic leukoencephalopathy with subcortical cysts
Typical MRI findings	Posterior predominant demyelination with rim enhancement	Frontally predominant demyelination. Notice U fiber sparing here.	Diffuse white matter hyperintensity. No U fiber sparing.	Diffuse white matter hyperintensity with frontal & temporal cysts
Gene	ABCD1	GFAP	ASPA	MLC1
Inheritance pattern	X-linked	De novo, dominant	Autosomal recessive	Autosomal recessive
Typical presentation	Elementary-aged male, inattention, decreased school performance	Infant/preschooler with macrocephaly, seizures, motor delay, spasticity	Infant with increasing macrocephaly, motor regression	Preschooler with mild motor delay, macrocephaly, seizures



X-ALD: Phenotypes Across the Lifespan

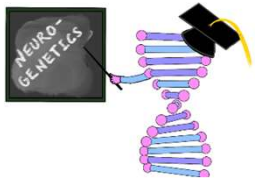




12. Kemp S, Huffnagel IC, Linthorst GE, Wanders RJ, Engelen M. *Nat Rev Endocrinol.* 2016;12(10):606-615.

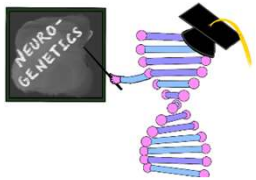
X-ALD Has Three Phenotypes

- X-linked dominant inheritance pattern
- Adrenal insufficiency affects 50-86% of males with ALD mutations, <1% of females.
- Childhood cerebral disease affects 35-40% of males with ALD (peak 4-8 years old).
- Adrenal myeloneuropathy affects almost all ALD males, 60% of ALD females.
  - Onset in males average 28 years old, always by 55.



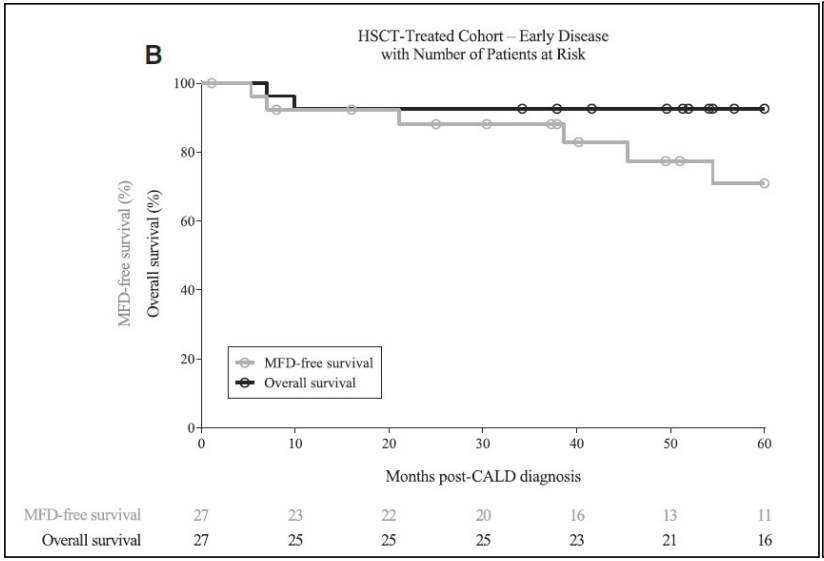
Treatment

- Eligibility depends on disease severity
- Disease severity is measured by:
  - Symptoms: neurologic function score (25-point scale)
  - MRI findings: Loes score (34-point scale)
- If NFS ≤1, Loes < 9, treatment benefit outweighs risk
  - Hematopoietic stem cell transplant
    - Donor source could be a matched relative, unrelated matched donor or umbilical cord blood
  - Ex vivo (lentiviral) gene therapy can be offered when there is not an adequately matched donor source.

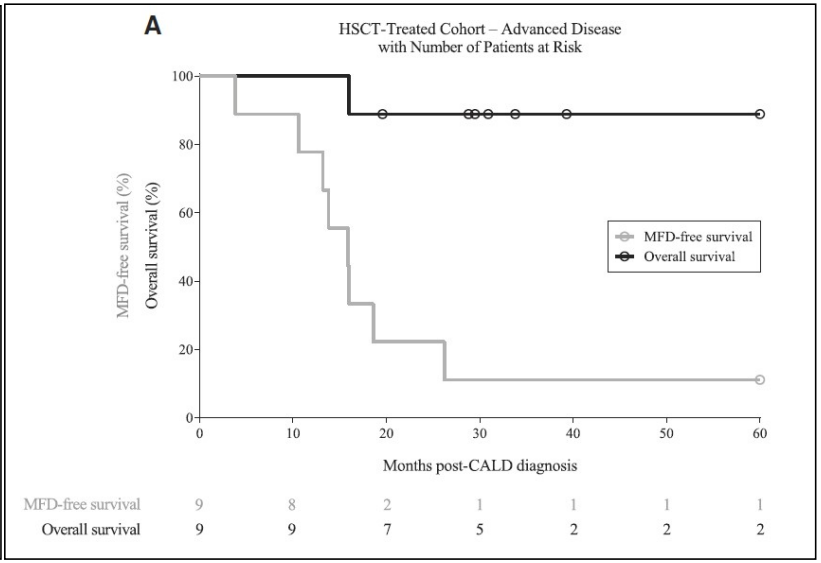


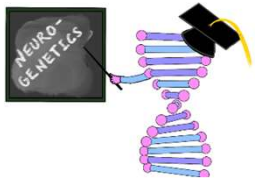
Transplant Reduces Mortality and Disability if Done Early (NFS≤1, Loes ≤9)

Treated early disease



Treated advanced disease



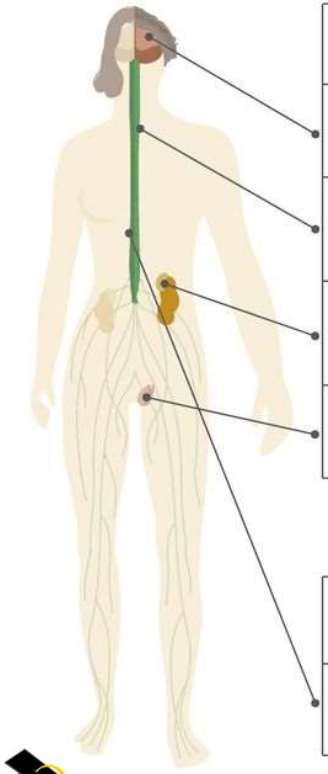


5-year overall survival from the time of cerebral ALD diagnosis

- 55% untreated cohort
- 78% HSCT

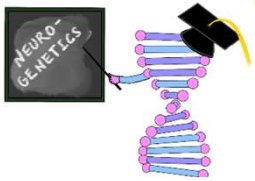
Raymond GV, Aubourg P, Paker A, et al. *Biol Blood Marrow Transplant.* 2019;25(3):538-548.

Guidelines for NBS-Identified X-ALD



Male	Screening or diagnostic tool	Screening protocol			Treatment
Cerebral ALD	MRI	2 years old, baseline scan	2–12 years old, every 6 months	>12 years old, yearly	HSCT or gene therapy
Myeloneuropathy	History and neurologic examination	>18 years old, only in parallel with any other testing			Supportive
Adrenal insufficiency	Morning fasted cortisol, ACTH, renin, electrolytes	0–6 months, start screening	6 months–10 years old, every 3–6 months	>10 years old, yearly	Hormone replacement therapy
Gonadal insufficiency	Symptoms biomarkers: Testosterone, LH, FSH	No screening test if symptoms			Hormone replacement therapy

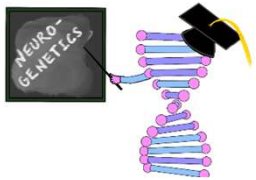
Female	Screening or diagnostic tool	Screening protocol	Treatment
Myeloneuropathy	History and neurologic examination	>18 years old	Supportive



Engelen et al. Neurology, 2022

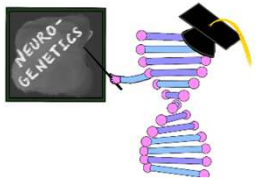
Discussion of Ethics

- How do you think an NBS diagnosis of X-ALD affects a family?
- Would you test the 15-year-old sister?
- What are the implications for universal NBS?



Suggested Reading

- Adang et al. Global Leukodystrophy Initiative (GLIA) Consortium. Revised consensus statement on the preventive and symptomatic care of patients with leukodystrophies. Mol Genet Metab. 2017 Sep;122(1-2):18-32.
- Eichler et al. Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy. N Engl J Med. 2017 Oct 26;377(17):1630-1638.
- Engelen et al. International Recommendations for the Diagnosis and Management of Patients With Adrenoleukodystrophy: A Consensus-Based Approach. Neurology. 2022 Nov 22;99(21):940-951.
- Gupta et al. Treatment of cerebral adrenoleukodystrophy: allogeneic transplantation and lentiviral gene therapy. Expert Opin Biol Ther. 2022 Sep;22(9):1151-1162.
- Page et al. Hematopoietic Stem Cell Transplantation to Treat Leukodystrophies: Clinical Practice Guidelines from the Hunter's Hope Leukodystrophy Care Network. Biol Blood Marrow Transplant. 2019 Dec;25(12):e363-e374.
- Raymond et al. Survival and Functional Outcomes in Boys with Cerebral Adrenoleukodystrophy with and without Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2019 Mar;25(3):538-548.



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- Margie Ream (Nationwide)
- Julie Ziobro (UM)

Additional Members:
- Alexa Taylor (CNMC)