Clinical Considerations: Newborn Screening for ALD

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Discussion

- Phenotypes associated with ALD
- Diagnosis; implications for the family
- Monitoring of patients post diagnosis
- Current treatment; transplant outcomes
- Importance of newborn screening

Adrenoleukodystrophy

- Frequency **≈1:20,000** boys
- X-linked peroxisomal
- Defect in ABCD1 gene; many described mutations
- Defective metabolism of very long chain fatty acids (VLCFA)
- High plasma VLCFA; establishes the diagnosis

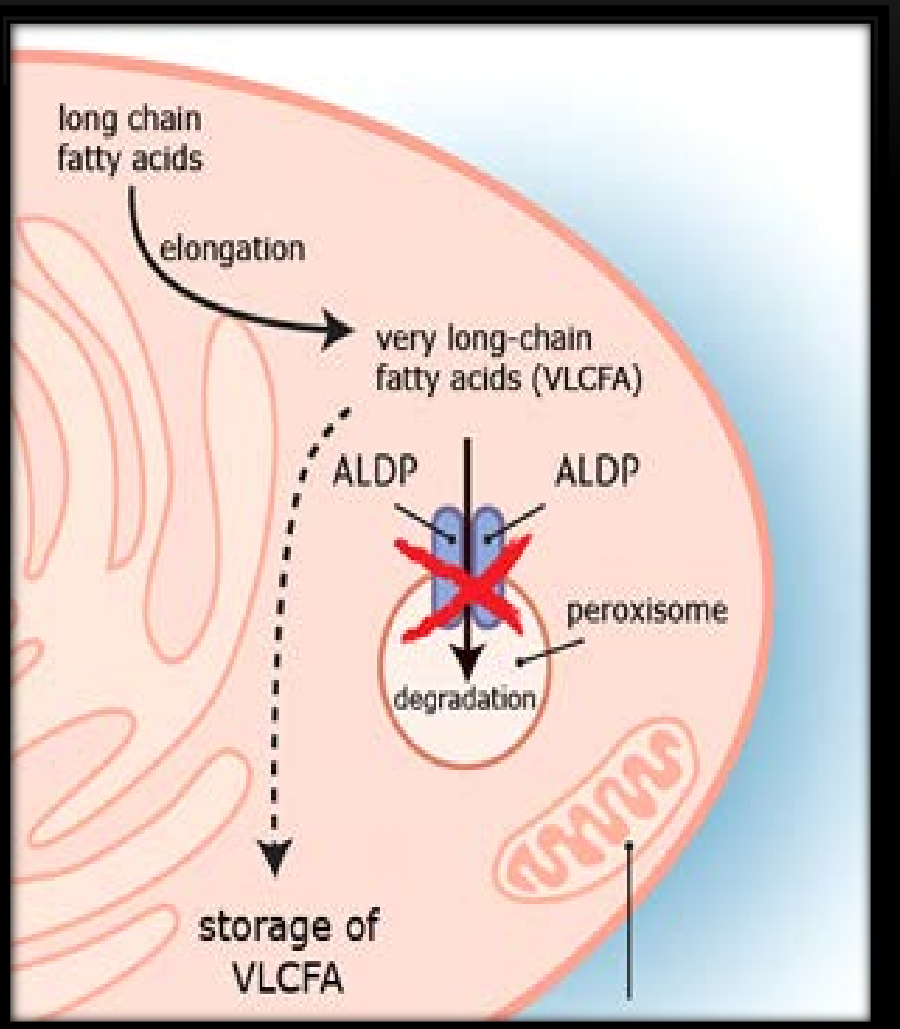
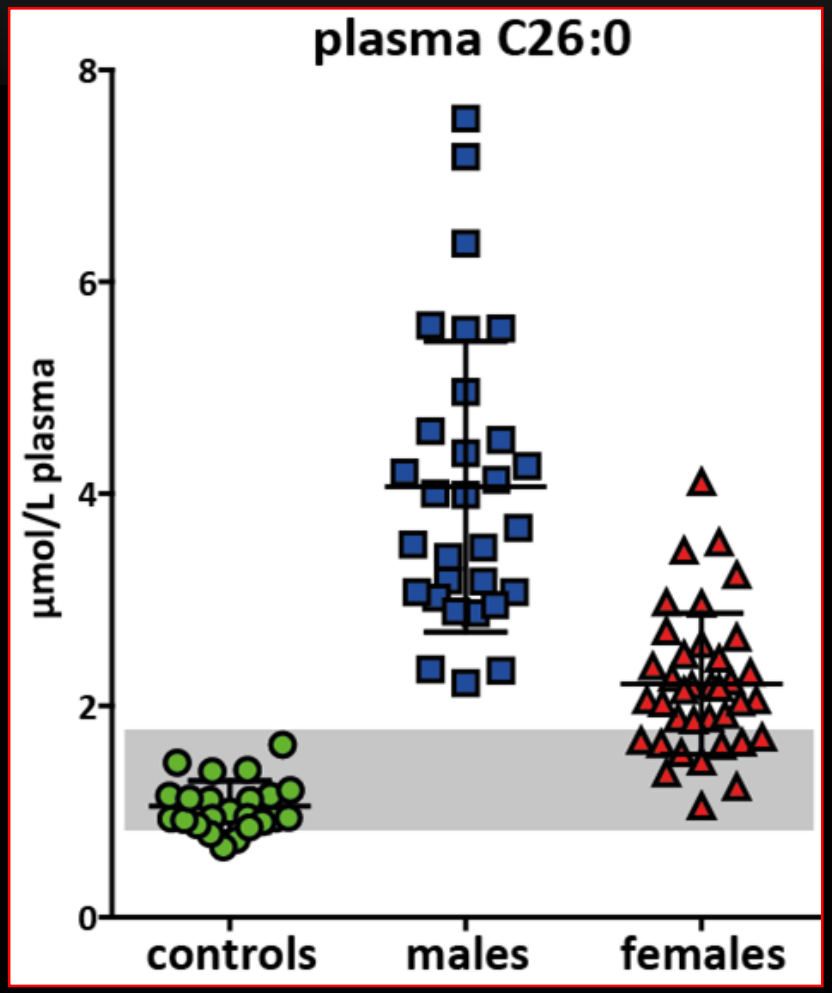


Figure: Dr. Kemp, Emma Children's Hospital, Amsterdam, Netherlands

Diagnosis of ALD

- Very Long Chain Fatty Acid (VLCFA) accumulation in ALD esp. C24 and C26
- Defective gene (ABCD1) mapped to Xq2; >750 mutations described
- Other peroxisomal disorders can also have increased VLCFA



http://www.x-ald.nl/biochemistry-genetics/vlcfa/

Phenotypes: ALD

• Childhood Cerebral ALD (C-ALD) 2.75-10 years; median age 7.2 years	30 - 35%
• Adolescent Cerebral ALD; 11-21 years	4 - 7%
• Adrenomyeloneuropathy (AMN) Spinal cord disease (40% develop C-ALD)	40 - 46%
• Adult C-ALD alone	2 - 5%
• Addisonian Disease alone	50%
• Asymptomatic: Decreases with age	Rare <40

Adrenomyeloneuropathy (AMN)

- Most frequent phenotype of ALD
- Symptom onset usually 20 - 30 yrs
- Slowly progressive motor disability. Stiffness, weakness in legs initially
- Leads to use of cane, then wheelchair
- Defects in spinal cord; non-inflammatory
- Also occurs to a lesser degree in women carriers

Kemp, Biochimica et Biophysica, 2012; (1822):1465-74

Adrenal Insufficiency (AI) in ALD

- VLCFA accumulate in adrenal glands
- IN ALD, production of cortisol and aldosterone can be impaired
- Chronic symptoms may include
  - Fatigue, weakness, weight loss, nausea
- Stress (infection, trauma) can cause
  - Severe N/V, dehydration, hypotension, hypoglycemia, low Na, high K
  - Deaths occur with common viral infections

Adrenal Insufficiency (AI)

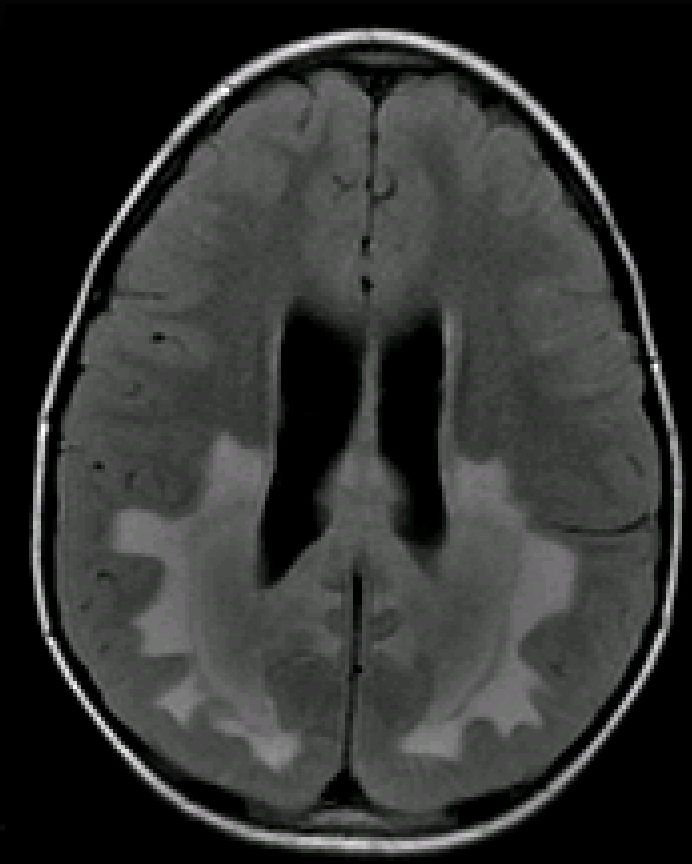
Studies of AI in ALD:

- 49 asymptomatic pts (mean 4.5 yrs)
  - 39 (80%) showed adrenal dysfunction*
- 90 pts with cerebral ALD (mean 6.3 yrs)
  - 79 (88%) showed adrenal dysfunction**
  - 17 (22%) of these – AI first sign of ALD
- Transplantation does not reverse AI***

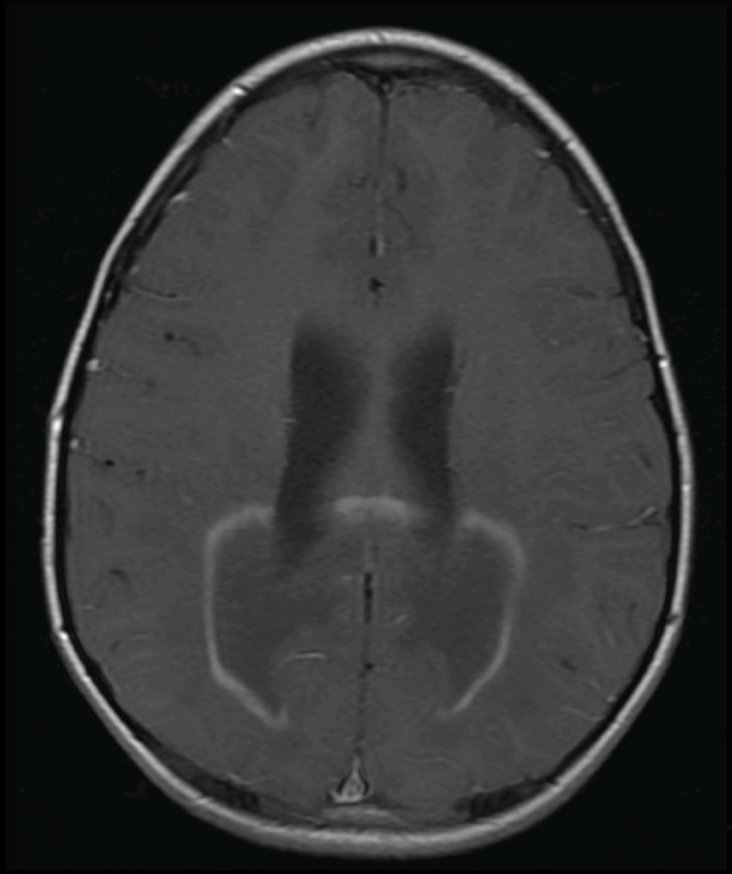
**Kemp, Biochimica et Biophysica, 2012; (1822):1465-74*
***Polgreen, Eur J Pediatr, 2011 (170): 1049-1054*
****Petryk, Bone Marrow Transpl, 2012 (47): 1377-8*

Cerebral ALD: MRI Findings

Occipital Disease



Gadolinium Enhancement



Cerebral ALD (CALD)

- Most lethal form of ALD
- Acute, neuroinflammatory process leading to demyelination in 35-40% of boys
- Peak age of onset of clinical disease is 7 years of age; MRI changes ~2 yrs earlier
- Occurs with other phenotypes
- Not clear what initiates disease
- Progressive and lethal; bone marrow transplantation is the only approved Rx

History Of Transplantation For Cerebral ALD

- Rationale based on transplant successes with LSD
- ALD known to be a peroxisomal disease, but thought to be an enzyme deficiency
- 1984; Moser - first report of HSCT for ALD; advanced patient; progressed, died
- 1990; Aubourg - reported disease stabilization in a patient with early cerebral ALD
- 1993; Aubourg cloned the gene, showing it is a transmembrane, non-secreted protein
- Allogeneic HCT now standard of care for early cALD (but why how does it work??)

What are the outcomes of transplantation for CALD?

1. Survival
2. Neurologic Outcomes
3. Neuropsychological Findings

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Grading Radiographic Severity

Loes scoring: (0–34) Point system

- parieto-occipital WM
- antero-temporal WM
- frontal WM
- corpus callosum
- visual pathways
- auditory pathways
- pyramidal system
- basal ganglia
- anterior thalamus

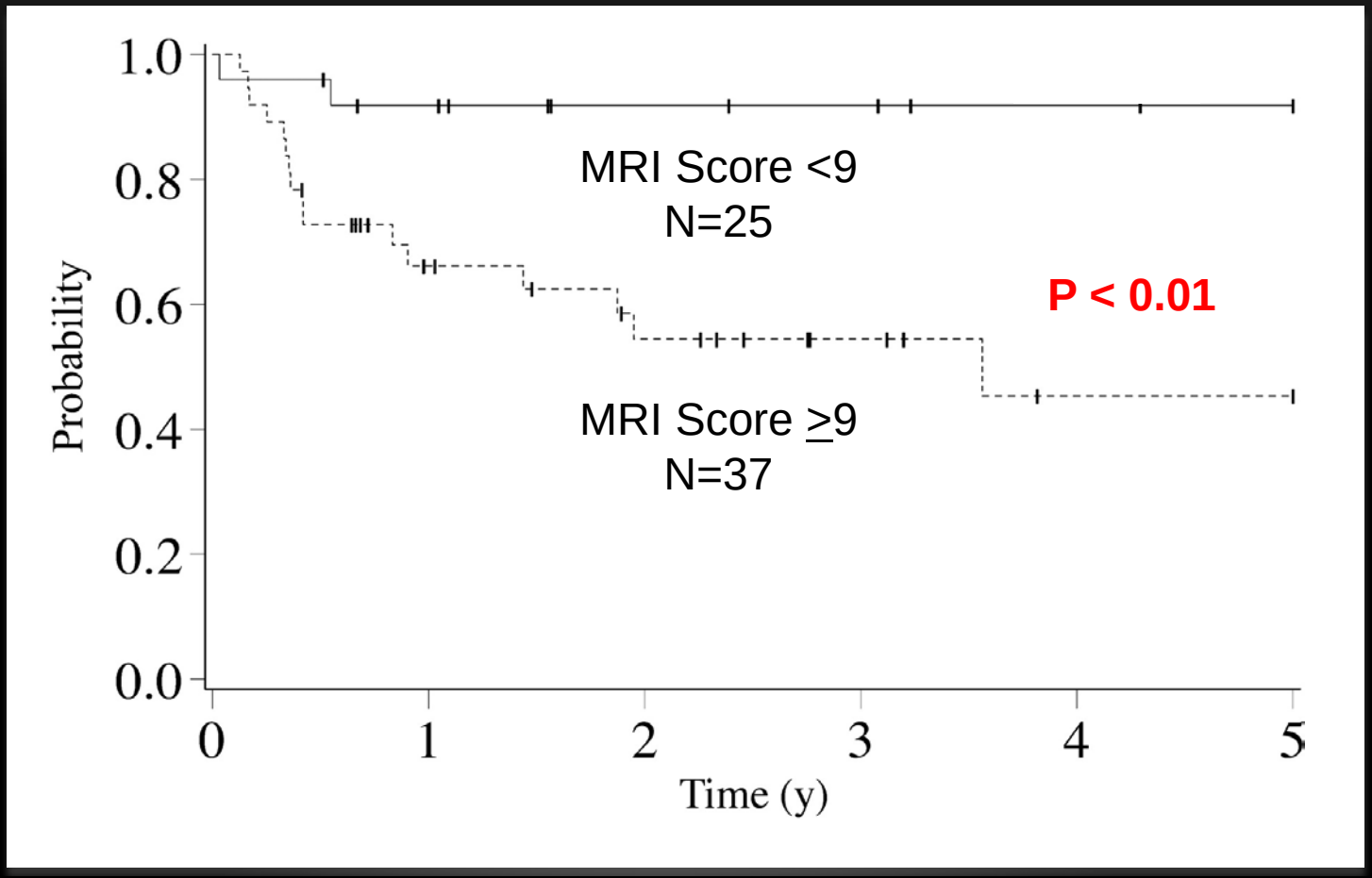
Loes et al. AJNR Am J Neuroradiol 1994;15:1761-1766

Cerebral ALD: HCT Experience

- 2004; International experience (43 centers)
- 94 patients transplanted through 1999
- numerous preparative regimens used
- Overall survival 56% over entire group
- Leading cause of death: disease progression
- Amount of disease at the time of BMT crucial

Peters et al. Blood 2004; 104:881-888

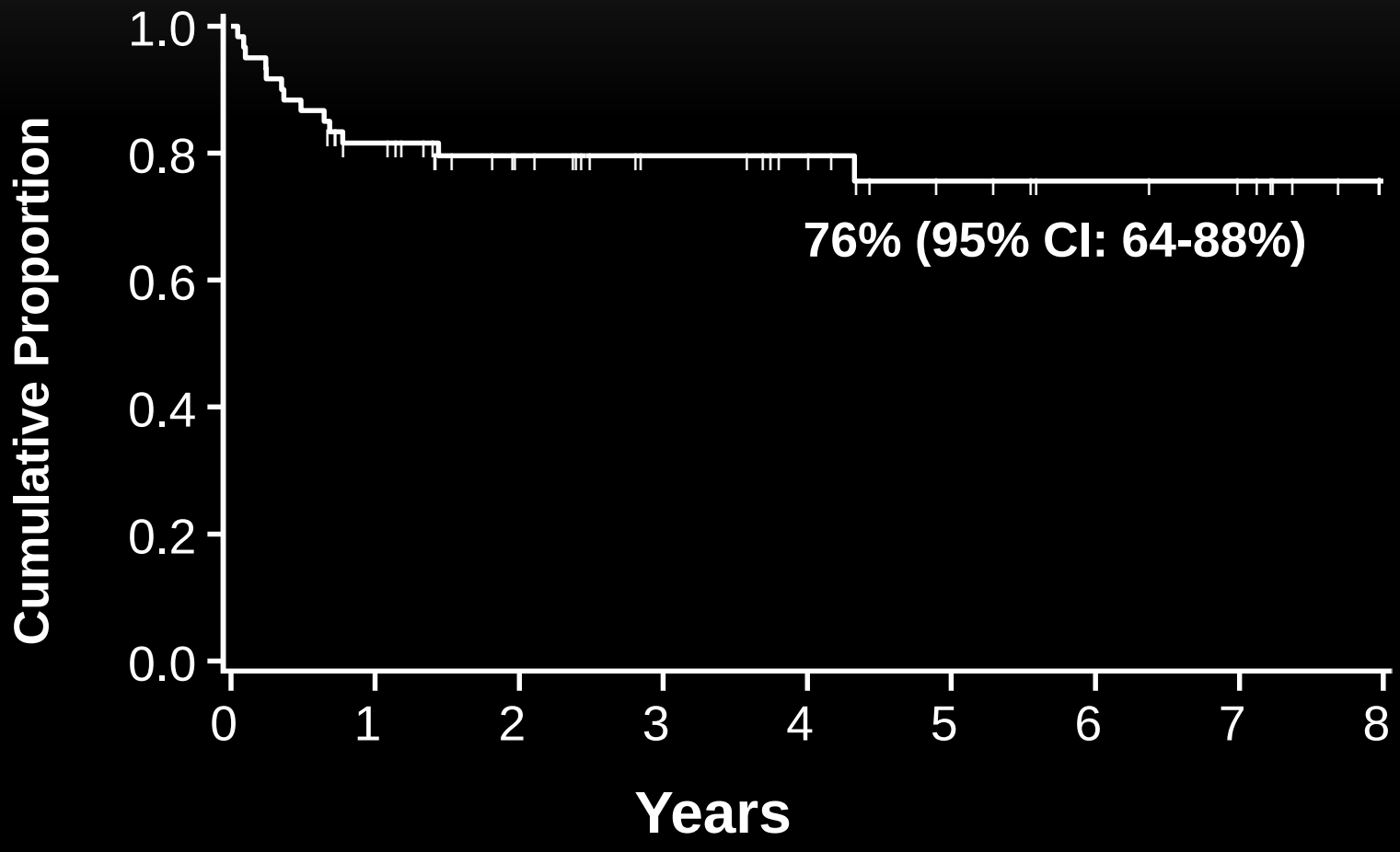
Survival Based On MRI Score



MRI score prior to transplant predicts survival

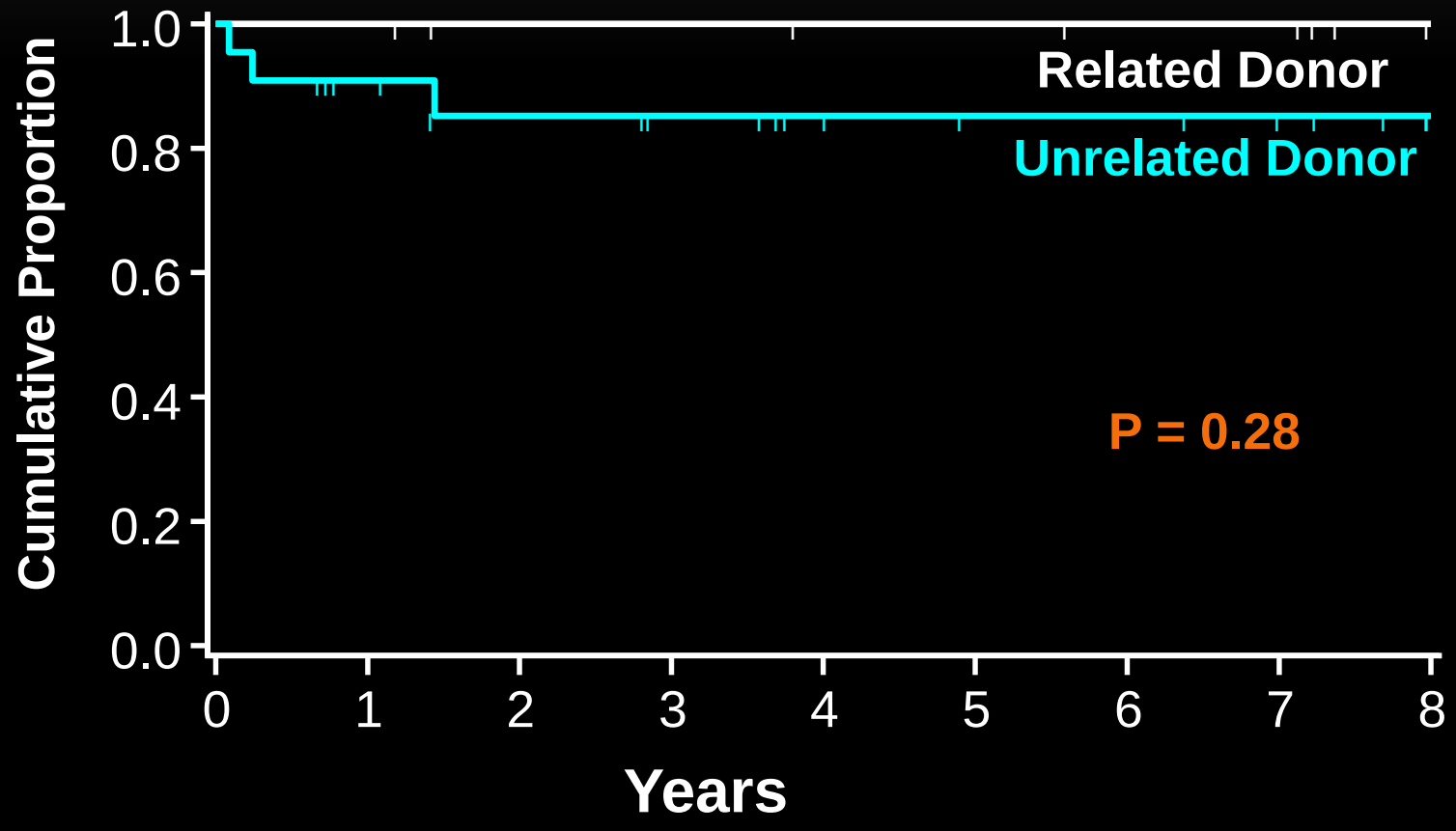
Peters et al. Blood 2004; 104:881-888

Minnesota Study: Overall Survival: All Transplanted ALD Patients (n=60)



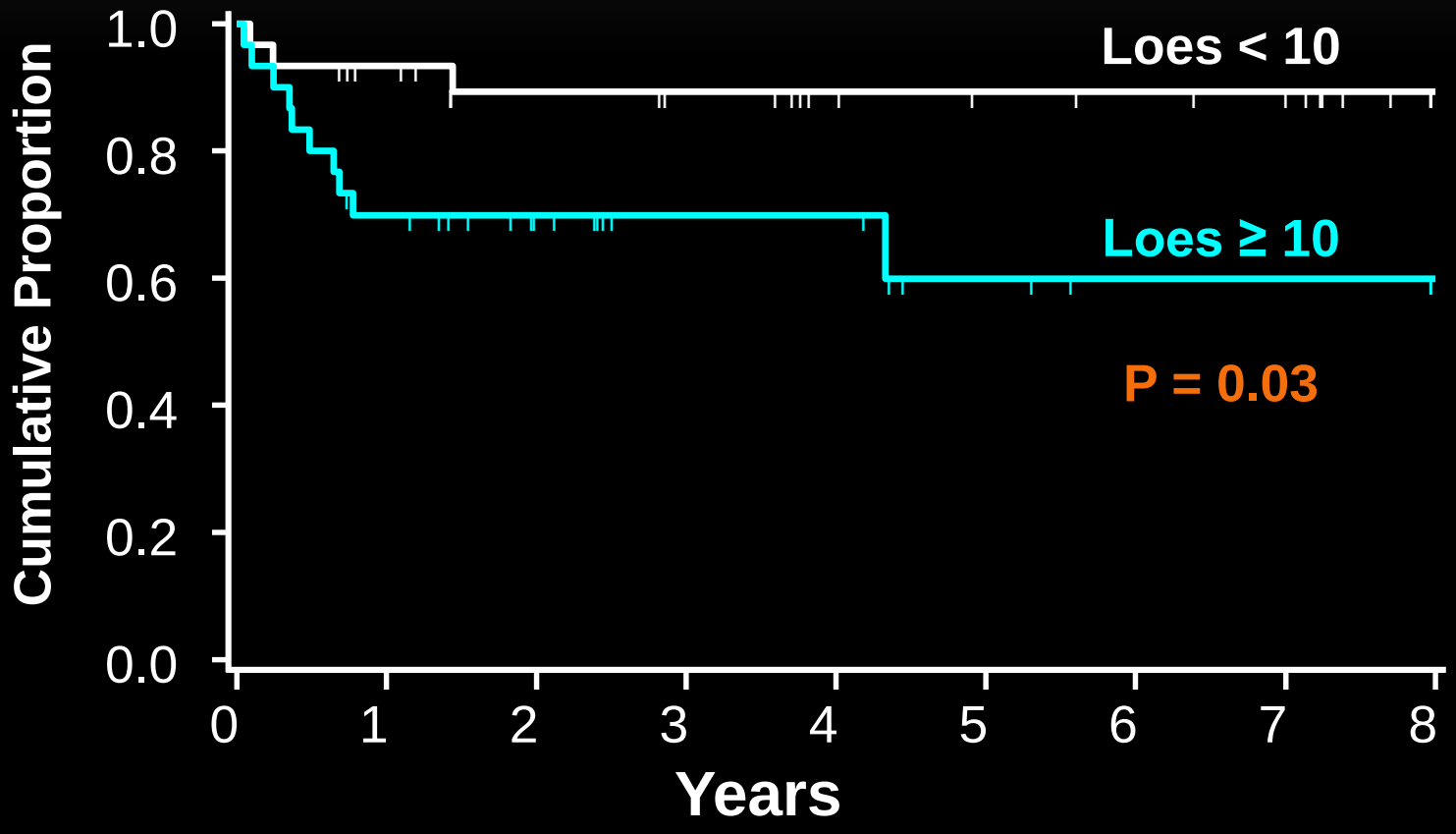
Miller, Blood, 2011; 18(7):1971-8

Survival by Graft Source; Early cALD (Loes Score <10; N=30)



Miller, Blood, 2011; 18(7):1971-8

Survival by pre-Transplant Loes Score (Early vs. Late Disease)



Miller, W. et al. Blood, 2011; 18(7):1971-8

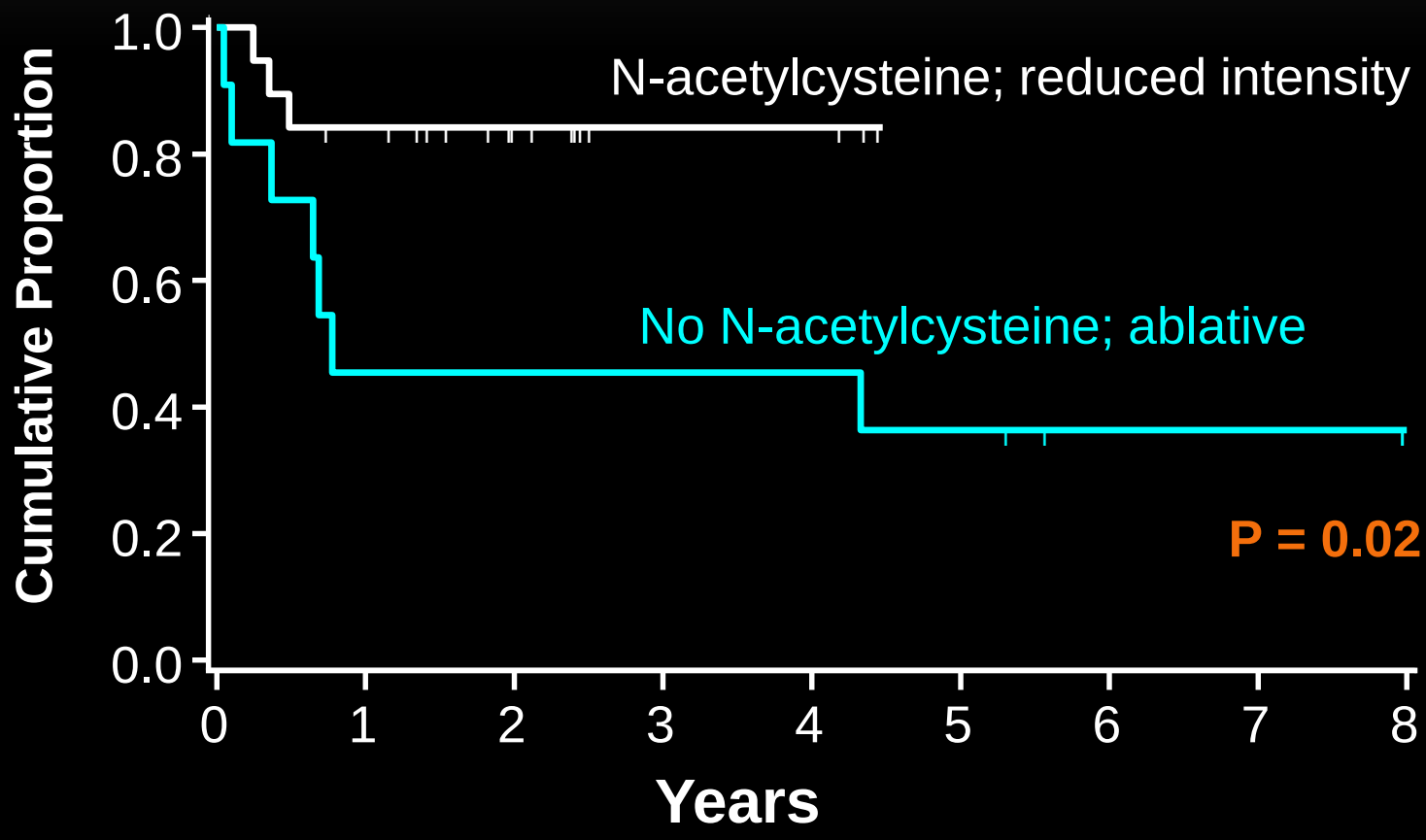
Could Modification of the Transplantation Approach Improve Outcomes in CALD?

1. Powers; 2005 – autopsy study
   Oxidative stress in brains of patients with ALD
2. Pujol; 2008 – murine data
   Confirmed oxidative stress in *ABCD1*$^{-}$ mice

Powers et al. J Neuropathol Exp Neurol. 2008 64(12):1067-1079

Fourcade et al. Human Molecular Genetics. 2008 17(12):1762-1773

Advanced ALD; Modified Protocol (Loes Score >10; N=30)



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Survival can be improved with transplant modification in advanced cALD

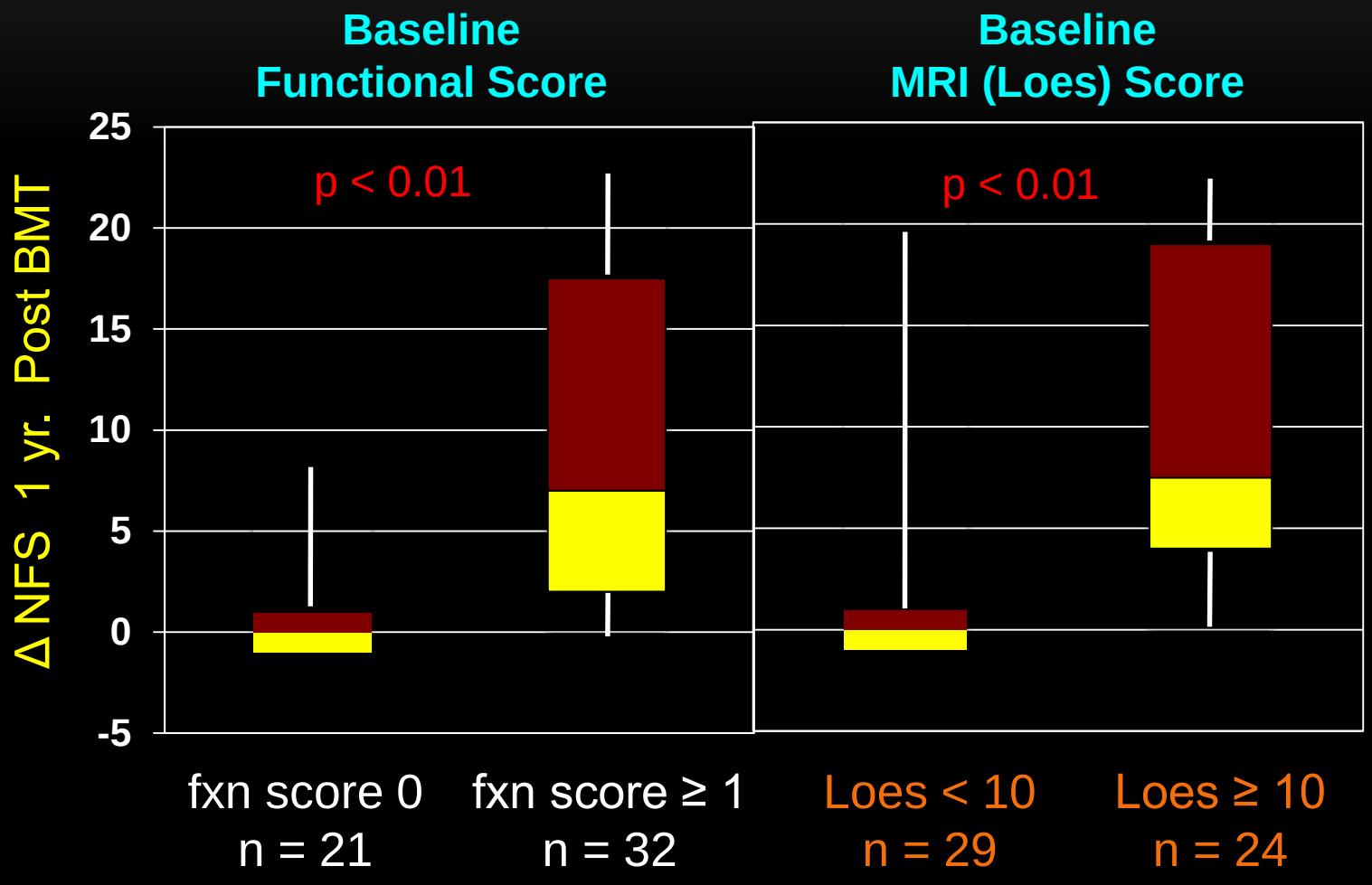
What about neurologic outcomes?

Assessing Functional Outcome: Moser/Raymond NFS Scale

Hearing/auditory processing problems	1
Aphasia/apraxia	1
Loss of communication	3
Vision impairment/fields cut	1
Cortical blindness	2
Swallowing difficulty or other CNS dysfunction	2
Tube feeding	2
Running difficulties/hyperreflexia	1
Walking difficulties/spasticity/spastic gait (no assistance)	1
Spastic gait (needs assistance)	2
Wheelchair required	2
No voluntary movement	3
Episodes of incontinency	1
Total incontinency	2
Nonfebrile seizures	1
Possible Total:	**25**

from Moser, Arch Neurol 2005;62:1073-1080

Change In Neurologic Function Score (NFS) Based on Baseline Score, Loes Score



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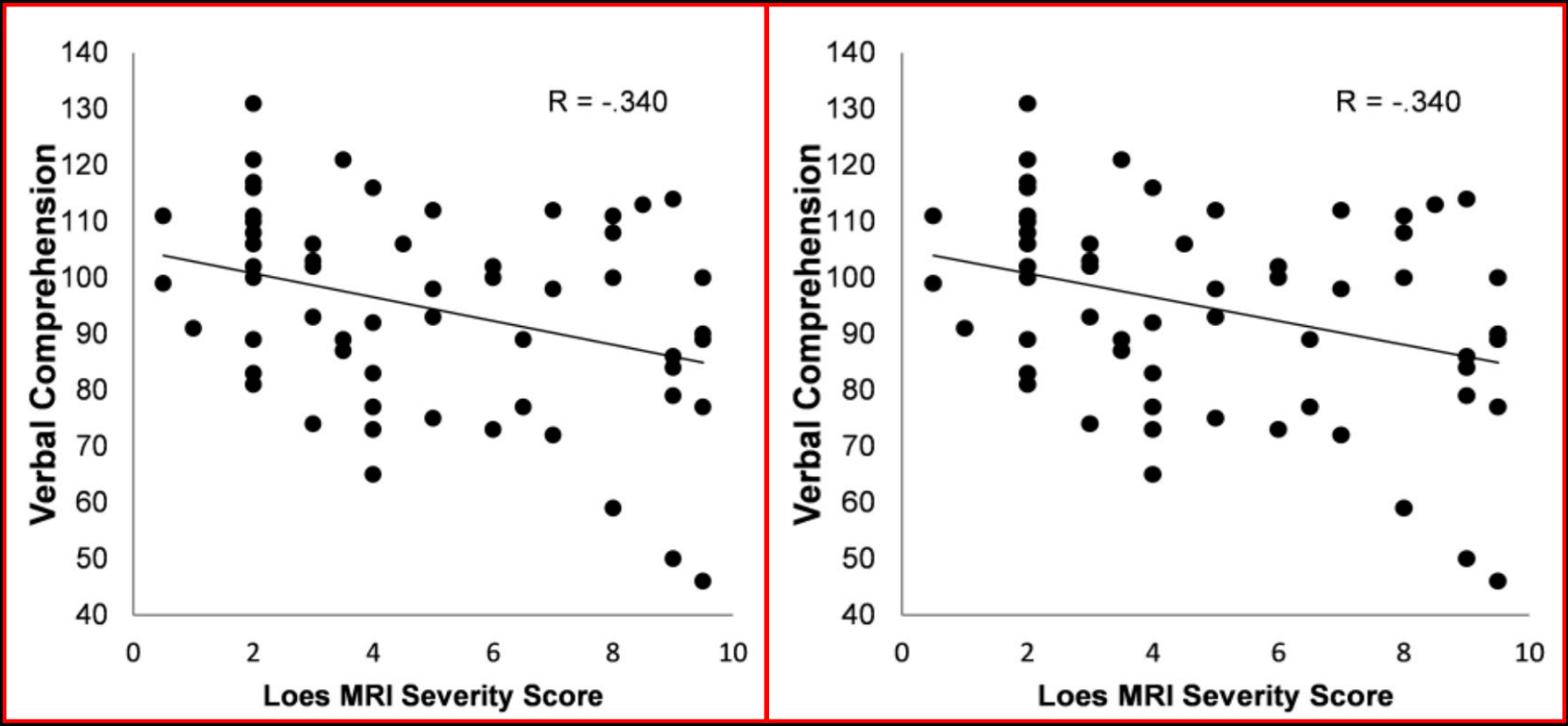
Neurocognitive Assessments Standard Risk cALD Patients

1. 139 cALD patients transplanted at Minnesota between 1991-2014
2. 62 patients had pre-BMT MRI scores <10 and pre-HCT neurocognitive testing (baseline group)
3. 33 had neurocognitive data obtained at least 2 years post HCT (long-term group)
4. Median age of all patients was 8 years
5. Testing included verbal reasoning, visual/perceptual reasoning, verbal reasoning, working memory and processing speed

Pierpont; JAMA Neurology, 2017; in press

Neurocognitive Functioning Pre-HCT Correlation: Increased MRI Severity



Pierpont; JAMA Neurology, 2017; in press

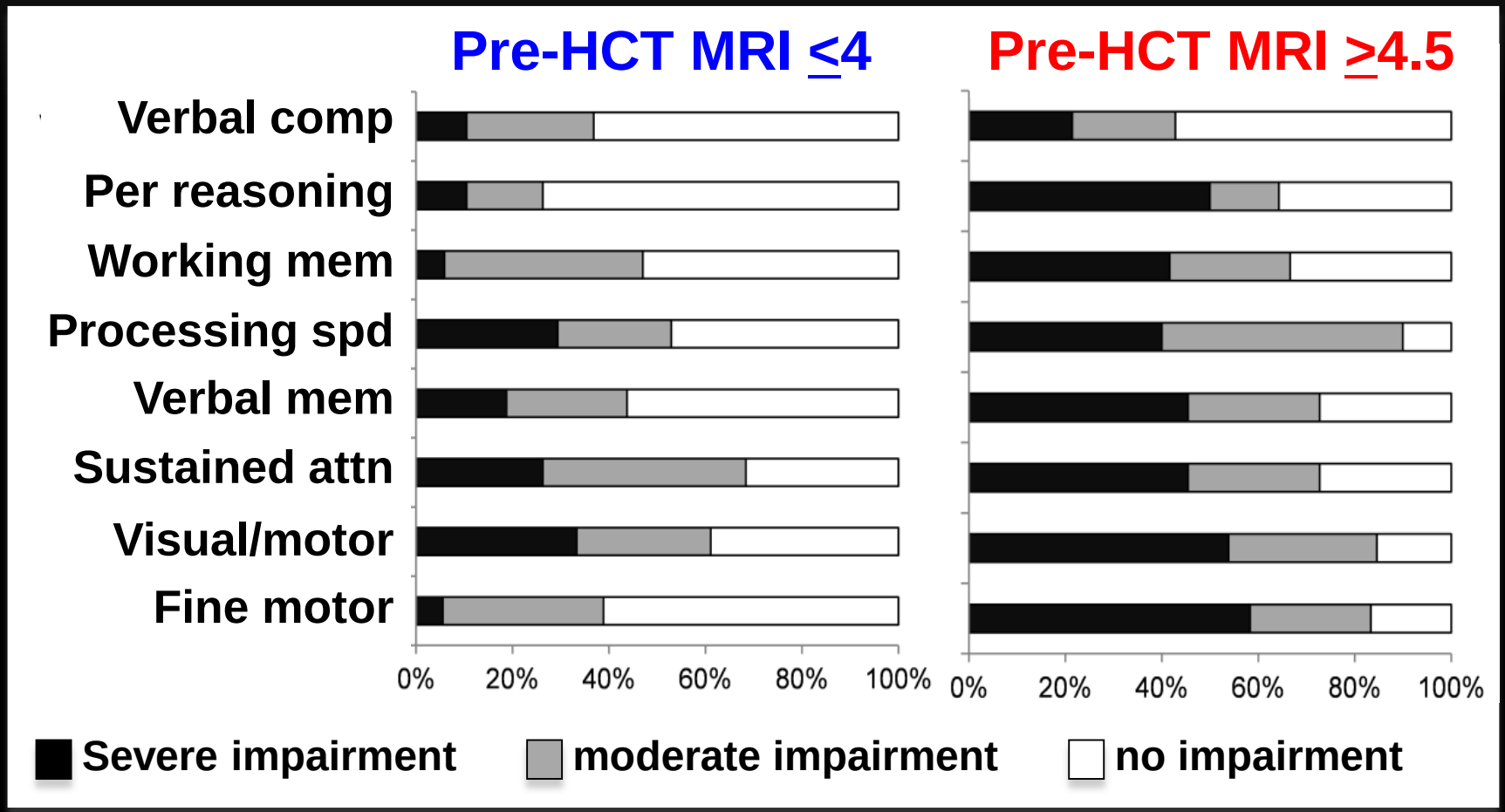
Effect Of Severity of Baseline MRI On Neurocognitive Functioning pre-HCT

Testing	p value
Verbal comprehension	0.008
Perceptual reasoning	0.001
Working memory	NS
Processing speed	0.03

Conclusion: Despite being identified as being in a "standard risk" ALD group, significant deficits are observed, related to MRI based severity

Pierpont; JAMA Neurology, 2017; in press

Impairments at Most Recent Evaluation: Boys With Standard Risk cALD



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Predicted Outcome; Effect of Pre-HCT MRI On Neurocognitive Functioning post-HCT

MRI Score	HCT	Verbal Comp	Percept Reason	Working Memory	Process Speed
2	pre	99	102	94	95
2	5 yr	93	102	93	86
7	pre	90	88	86	85
7	5 yr	65	63	79	46

Outcomes based on linear mixed model
Hypothetical 8 year old with cALD undergoing HCT

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Summary: Neurocognitive Testing in "Standard-Risk" cALD and HCT

1. At baseline, as MRI scores increase, prior to HCT there is more impairment of verbal & visual reasoning and processing speed
2. Post transplant, patients with more advanced disease have a steeper decline in functioning
3. Two-thirds of all patients had severe impairment in ≥1 neurocognitive domain at the time of last testing

Implication: Even boys with "standard-risk" disease are at risk for long term deficits. Earliest diagnosis of cALD possible provides the best opportunity for good outcomes

Pierpont; JAMA Neurology, 2017; in press

Summary: NBS for ALD

1. **Newborn screening will save lives!**
2. Deaths due to adrenal insufficiency will be decreased
3. Deaths and life-long disability will be decreased because of earlier transplantation.
4. With NBS, other boys at risk (brothers, cousins) will be identified as well.
5. For NBS to be effective, ongoing monitoring will be required to establish when intervention (hydrocortisone, BMT) will be necessary
6. Can we identify CALD before demyelination occurs? May allow us to better preserve function

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