Research Prioritization Topic Brief

Topic 5: “Cerebral Adrenoleukodystrophy (ALD)”

Comparative effectiveness of early versus late bone marrow transplant treatment for children affected by adrenoleukodystrophy (ALD).

PCORI Scientific Program Area: Assessment of Prevention, Diagnosis and Treatment Options

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### Overview/definition of topic

**DESCRIPTION OF CONDITION**
- Adrenoleukodystrophy (ALD) is an inherited disorder that affects how cells break down nutrients called very long chain fatty acids. These acids accumulate in cells and affect organs including the brain, adrenal glands, and testes. The childhood cerebral form of the disease is the most severe form.
- ALD may be familiar from the movie “Lorenzo’s Oil.”
- ALD is linked to the X chromosome:
  - Boys have only one X chromosome, so carriers almost always develop symptoms.
  - Girls have two X chromosomes, but 50-65% of carriers may still develop symptoms later in life.

### Relevance to patient-centered outcomes

**SYMPTOMS/OUTCOMES**
- Symptoms vary in severity and timing:
  - 35% of male patients develop severe nerve symptoms during childhood, starting with behavioral problems and progressing to cognitive deficits, blindness, and quadriplegia. The adrenal glands are often affected.
    - Average age of onset is 7 years.
    - Progresses to vegetative state (similar to a coma) within one to two years.
    - Death occurs within five to ten years.
  - 45-50% of male patients develop a less severe form of the disease during adulthood (called adrenomyeloneuropathy or AMN). This causes a slowly progressing paralysis and can affect the adrenal glands. When female patients develop symptoms, it resembles AMN.
    - 5-10% of patients develop adrenal gland problems only.
- Other outcomes:
  - Decreased quality of life for both patient and family
  - Reproductive concerns (female carrier has 50% chance of having an affected son and a 50% chance of passing the gene to a daughter)
  - Considerable uncertainty about benefits and harms of screening (among male patients, there is no good way to predict who is going to develop symptoms, when they will occur, or their severity)

### Burden on Society

**INCIDENCE (NEW CASES)**
- 1 in 42,000: hemizygotes (having only one of a given pair of genes, ie, males)
- 1 in 16,800: including both hemizygotes and heterozygotes (having two different forms of the gene, ie, females)

**PREVALENCE (PROPORTION OF POPULATION LIVING WITH THE CONDITION)**
- Approximately 27,000 people in the United States (0.001-0.009% of population)

**QUALITY OF LIFE**
- Severity of ALD varies, but all patients who develop symptoms experience some decrease in quality of life. In the severe childhood form (30-35% of patients), the impact on quality of life is major.
- Like all childhood illnesses, cerebral ALD has substantial effects on the whole family.

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| mortality, use of health care services | PRODUCTIVITY  
- Affected children have an impact on parents’ productivity.  
- The impact for affected adults depends on the severity of symptoms.  
FUNCTIONAL CAPACITY  
- The severe childhood form limits patients’ ability to do normal daily activities.  
- The less severe form (AMN) can lead to total disability in up to 20% of cases.  
MORTALITY  
- Mortality is close to 100% within five to ten years of diagnosis for the severe childhood form. AMN is also associated with early death in up to 20% of cases.  
| How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?  
Though ALD is rare, it carries a severe burden for people who have it and their families. |  
| **Options for Addressing the Issue**  
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options? | There are no systematic reviews on the severe childhood form of ALD, although there was a narrative review in 2012 of hematopoietic stem cell transplantation (HSCT) as a treatment in pediatric populations. This report attempted to conduct a systematic review of AMN, but pediatric data were too limited. A summary of the available evidence follows.  
SCREENING/EARLY DIAGNOSIS  
- Tests are available, but there is no direct evidence of improved outcomes for symptoms or mortality based on identification of ALD in newborns.  
  - Potential benefits include family planning, avoiding a lengthy process of diagnosis after symptoms develop.  
  - Potential harms include false-positive results, identification of newborns who will not develop symptoms until later in life, complications of unproven therapies, identification of carriers and the resulting potential negative impact on quality of life.  
TREATMENT  
- Replacement of adrenal gland hormones  
  - No uncertainty; benefits (prevention of mortality) greatly outweigh harms when adrenal insufficiency is present (70% of patients with ALD).  
- Dietary therapy (Lorenzo’s oil)  
  - Uncontrolled studies have been conducted in asymptomatic boys discovered on screening, boys with the severe childhood form, and adults with AMN.  
  - Potential benefits include a reduction or delay in onset of developing cerebral disease in asymptomatic patients (but no benefit if already present); may also slow pace of symptom progression in AMN.  
  - Potential harms include causing low platelet count, abnormal liver tests.  
- HSCT  
  - Potential benefits include improving neurologic symptoms and mortality in boys with... |
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<tr>
<th>What could new research contribute to achieving better patient-centered outcomes?</th>
<th>New research in three main areas could contribute to better patient-centered outcomes:</th>
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<td>1) Better understanding of benefits, harms, and costs associated with screening for ALD in newborn males would potentially facilitate starting dietary therapy early and improving survival and neurologic outcomes. Additional outcomes to study could be patient and family quality of life and reproductive decisionmaking.</td>
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<td>2) Further study is needed to define which patient subgroups benefit most from HSCT in terms of neurologic symptoms and survival. Existing data are limited to case series studies.</td>
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<td>3) Research comparing novel, less-established therapies (gene therapy, treatment with lovastatin) to better established therapies (HSCT, dietary therapy) in predefined patient subgroups is needed to increase understanding of whether and how these therapies improve patient-centered outcomes.</td>
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<td>Have recent innovations made research on this topic especially compelling?</td>
<td>The development of gene therapy as an option for treating ALD is a promising innovation and merits further research.</td>
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<td>How widely does care now vary?</td>
<td>VARIABILITY IN CARE</td>
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<td>• Because ALD is a rare disease with variable presentation among patients, care requires special expertise. Variability in care exists now but likely is appropriate given that patients present very differently.</td>
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<td>What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?</td>
<td>RECENT PUBLICATIONS</td>
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<td>• In 2012 there was a comparative effectiveness review that evaluated four case-series studies of HSCT in pediatric patients with severe childhood form of ALD. One additional case-series report of HSCT on the severe form of ALD has since been published.</td>
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<td>ONGOING TRIALS</td>
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<td>• There are at least eight ongoing studies in ClinicalTrials.gov relating to ALD, three of which address HSCT, and two which address dietary or medical therapies. There is a recently completed study comparing Lorenzo’s oil with placebo in adults with AMN, but results are not yet available. Outcomes assessed in these studies include neurological function and survival.</td>
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<td>How likely is it that new CER on this topic is needed?</td>
<td>The greatest limitation is the lack of randomized controlled trials and other controlled studies of HSCT, dietary therapy, gene therapy, and other treatments. Carrying out controlled studies may...</td>
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KEY UNCERTAINTIES IN CLINICAL DECISIONMAKING:
- What are the comparative benefits and harms of screening with different tests compared with each other and with no screening?
- Do the benefits of HSCT outweigh the potential harms in specific subgroups of patients with ALD?
- What is the role of newer therapies for ALD, such as gene therapy, compared with other therapies?

LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES:
- Because accurate screening tests exist, additional well-designed studies would likely be able to reduce uncertainty in the area of ALD screening. Well-designed studies comparing different therapies (HSCT, dietary therapy, gene therapy) in different patient subgroups would help reduce uncertainty in treating ALD.

### Potential for New Information to Improve Care and Patient-Centered Outcomes

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<th>What are the facilitators and barriers that would affect the implementation of new findings in practice?</th>
<th>FACILITATORS</th>
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<td>• Technical experience with HSCT at specialized centers for ALD and other conditions</td>
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<td>• Potential high degree of acceptance for positive findings since ALD is a condition with extremely poor prognosis and high impact on families</td>
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<th>BARRIERS</th>
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<td>• Variability in clinical presentation making it difficult to generalize findings to all patients</td>
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<td>• Costs of treatment</td>
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<td>• Availability of donor stem cells and access to specialized therapies such as HSCT</td>
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<td>• Potential for reluctance to accept negative findings since ALD is a condition with extremely poor prognosis and high impact on families</td>
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<th>How likely is it that the results of new research on this topic would be implemented in practice right away?</th>
<th>EVIDENCE OF BENEFIT</th>
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<td>• If there is evidence of benefit, it is extremely likely that research results would be implemented quickly.</td>
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<th>EVIDENCE OF NO BENEFIT OR HARM</th>
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<td>• Depending on the balance of benefits and harms, implementation may be less likely if there is insufficient patient demand or provider uncertainty.</td>
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<p>| Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by | Because ALD is a rare disease, often having a long delay between diagnosis and outcomes, the number of studies is necessarily small, and so findings from completed studies are likely to be relevant for a relatively long period compared with more common diseases having a shorter time to measurement of outcomes. |</p>
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<th>subsequent studies?</th>
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*PCORI Topic Brief: Assessment of Prevention, Diagnosis and Treatment Options*
REFERENCES:


**Appendix: Topic Question**

Nominated by ‘Web’

1) Adrenoleukodystrophy (ALD) is an X-linked disorder with an incidence of 1 in 17,000 males. It is characterized by an increase in very long chain fatty acids (VLCFA) in plasma and brain. In approximately 40% of boys with ALD, an acute inflammatory process develops within the central nervous system (CNS). The median age of onset of this neuroinflammatory process is age 7. Untreated, it is rapidly progressive and lethal, generally within several years of onset. Early in the course of cerebral ALD (C-ALD), bone marrow transplantation is effective in achieving disease stabilization. While patients early in the course of
their disease have good outcomes with transplantation, many boys are not diagnosed until they are more advanced, limiting the ability of transplantation to stabilize the disease process. The question therefore becomes “Can we tell parents making decisions for their affected boys who is likely to have a reasonable outcome, and who is not?”

a. **Population:** This disease is limited to boys, based on how it is inherited. In regards to demographics, it affects all ethnic groups relatively similarly.

b. **Importance:** Imagine that you have a boy that you have always thought is absolutely healthy, but he starts doing worse in school, is complaining of vision issues or hearing issues, and at some point an MRI is done. The MRI scan suggests ALD and the disease is confirmed with a blood test. Then the parents learn that not only does their son have an inherited disease affecting the brain, but that it is progressive and will be lethal within a few years. There is one potential intervention, which is bone marrow transplantation. However, in some situations, a transplant may stop the disease from getting worse, but in others a transplant may lead to a boy that is devastated neurologically and will require virtually total care, possibly for decades. It is extremely important to develop methods to determine who should be transplanted and who should not. This is the goal of our proposed study.