

Secretary's Advisory Committee on Newborn Screening Meeting

Friday, March 4, 2022

*Report on the Nomination to Add X-Linked Adrenal Leukodystrophy
to the Newborn Screening Panel in the State of Wisconsin*

On March 4, 2022, the Secretary's Advisory Committee on Newborn Screening (SACNBS) met via Zoom to review the nomination to add X-linked adrenal leukodystrophy (X-ALD) to the Wisconsin mandatory newborn screening (NBS) panel. X-ALD was initially nominated on September 7, 2021 by Jennifer Kwon, MD (Child Neurologist, University of Wisconsin School of Medicine and Public Health) with co-sponsor Mei Baker, MD (Newborn Screening Laboratory Director at the Wisconsin State Laboratory of Hygiene). The nomination was then reviewed by the Metabolic Subcommittee, which recommended acceptance, and then by Umbrella Committee on December 3, 2021, which also recommended acceptance. The SACNBS voted unanimously in favor of adding X-ALD to the Wisconsin NBS panel.

X-ALD is a rare peroxisomal disorder caused by changes in a gene on the X-chromosome. Both males and females can be affected, though males typically experience onset in childhood and experience greater severity of disease. Affected individuals are unable to properly metabolize fat, resulting in the accumulation of very long chain fatty acids (VLCFA) in the cells of the adrenal glands, spinal cord, and brain. There are three primary clinical manifestations of disease: 1) adrenal insufficiency (AI), particularly the inability to produce steroids in the normal physiologic stress response, 2)

adrenomyeloneuropathy (AMN), which affects the spinal cord and results in leg pain and difficulty walking, and 3) childhood cerebral adrenoleukodystrophy (CCALD), which affects the white matter of the brain and results in severe cognitive and physical disabilities. Both AI and CCALD can be fatal, but both conditions are treatable if diagnosed early. Infants, and particularly male infants, who are identified by NBS can be monitored throughout childhood for disease progression.

NBS for X-ALD involves measuring VLCFA levels in dried blood spots (DBS). Infants with screen positive results must undergo confirmatory diagnostic testing with serum VLCFA levels and genetic testing. If a diagnosis of X-ALD is established, male infants are seen by a pediatric endocrinologist and neurologist at regular intervals throughout childhood to monitor for development of AI and CCALD. Treatment of AI with oral and intravenous steroid medications is highly effective. Treatment of CCALD with a hematopoietic stem cell transplant (HSCT) significantly improves neurologic outcomes and allows affected individuals to live into adulthood.

X-ALD was added to the national Recommended Uniform Screening Panel in 2015. Currently, 21 states including Minnesota, Illinois, Indiana, and Michigan, and the District of Columbia screen for X-ALD disease. Conditions added to the Wisconsin mandatory newborn screening panel must meet nine criteria. The committee considered and voted on each criterion in turn.

First, mandated testing should be limited to conditions that cause serious health risks in childhood that are unlikely to be detected and prevented in the absence of newborn screening. X-ALD is not clinically detectable in infancy until symptoms develop; symptom development typically occurs in childhood and is insidious. The two

primary clinical manifestations of X-ALD in males are adrenal insufficiency (AI) and childhood cerebral ALD (CCALD). Both conditions are life-threatening and require early surveillance and timely treatment to prevent serious health consequences. Untreated, individuals with AI are at risk for adrenal crisis, which can be fatal. Those who develop CCALD are at risk for rapid neurological deterioration and early death. Treatment of CCALD with HSCT is only performed after the appearance of brain changes on MRI suggestive of CCALD and is only effective when performed before the onset of clinically apparent neurologic disability. Therefore, early diagnosis prior to symptom onset is critical to halt or slow disease progression. Studies demonstrate that males diagnosed with X-ALD by NBS have significantly better outcomes than those diagnosed clinically.

Second, for each condition, there should be information about the incidence, morbidity and mortality and the natural history of the disorder. Extensive literature has been published on the epidemiology and natural history of X-ALD. Based on NBS data from California and New York, the overall incidence of X-ALD is approximately 1 in 10,000 to 15,000 live births. The birth prevalence of hemizygous males has been estimated as 1 in 14,000 to 18,000, and the birth prevalence of heterozygous or carrier females has been estimated as 1 in 10,000 to 17,000. Of males born with X-ALD, 80-90% will develop AI, about 60% will develop AMN, and 30-40% will develop CCALD. Untreated AI associated with X-ALD confers significant morbidity from adrenal crisis.

Third, conditions identified by newborn screening should be linked with interventions that have been shown in well-designed studies to be safe and effective in preventing serious health consequences. Without treatment, males with CCALD universally experience significant neurological disability including cognitive losses,

visual impairment, difficulty walking, and early death. If signs of CCALD are detected on a screening brain MRI prior to symptom onset, treatment with HSCT is effective at preventing neurologic devastation and extending lifespan significantly.

Diagnosis of X-ALD in males in infancy allows for the initiation of laboratory screening of adrenal function and regular brain imaging to screen for CCALD. Early treatment of AI with glucocorticoid replacement is highly effective in preventing adrenal crisis and death. Treatment with maintenance and stress doses of oral hydrocortisone is directed by a pediatric endocrinologist and is generally well-tolerated. Treatment of CCALD with HSCT is most effective when performed early in the course, when the child is asymptomatic. However, HSCT involves significant risk with associated morbidity of 20-40%, including immunosuppression, and graft versus host disease, and mortality of 10-20%, so it is only undertaken when there are MRI findings of demyelination; it is not performed prophylactically in males with ALD without signs of CCALD. HSCT mortality specific to patients with X-ALD at the two transplant centers in Wisconsin is not known. Currently, there are no effective treatments for X-ALD-associated AMN.

Fourth, *the interventions should be reasonably available to affected newborns.* Steroid treatment of AI with oral maintenance hydrocortisone and intravenous stress dosing during illness is widely available, though requires management by a pediatric endocrinologist. HSCT requires the availability of a well matched donor, and is only performed at select centers, with two such centers located in Wisconsin. Clinical trials of gene therapy for X-ALD have provided hopeful results, and gene therapy may become available in the coming years. However, at present, there are no gene therapy trails

actively recruiting patients. Patients who undergo either HSCT or gene therapy would not be eligible for the other therapy unless they experience treatment failure.

Fifth, appropriate follow-up should be available for newborns who have a false positive newborn screen. All infants who screen positive with elevated VLCFA on DBS will undergo confirmatory testing and follow-up with a metabolic specialist. Specifically, confirmatory testing includes serum VLCFA levels and a gene panel for peroxisomal disorders (including the *ABCD1* gene implicated in X-ALD and several other genes associated with disorders causing elevated VLCFA). Infants whose follow-up testing is negative will be counseled on the results and discharged from further follow-up. Infants who test positive for another disorder such as Zellweger spectrum disorder or Aicardi-Goutières syndrome will be referred to the appropriate subspecialists for further care.

Sixth, the characteristics of mandated tests in the newborn population should be known including specificity, sensitivity, and predictive value or other convincing medical evidence (experience, natural history, or literature). NBS for X-ALD involves measurement of C26:0-lysophosphatidylcholine (C26:0-LPC) in neonatal DBS NBS samples using flow injection analysis, electrospray ionization, and tandem mass spectrometry. In a validation study performed by the NBS Laboratory at WSLH, 12 samples from the Minnesota NBS program (5 true screening negative, six true screening positive, and one borderline positive sample) were all correctly identified, based on the screening cutoffs established with Wisconsin 5,881 de-identified residual routine NBS specimens. Thus, based on this small sample set, the sensitivity, specificity, and positive predictive value of the proposed X-ALD screening test are expected to be 100%.

Seventh, *if a new sample collection system is needed to add a disorder, reliability and timeliness of sample collection must be demonstrated.* This criterion does not apply to X-ALD, as the screening test employs existing collection methods; measurement of VLCFA can be done on DBS collected on filter paper.

Eighth, *before a test is added to the panel the details of reporting, follow-up, and management must be completely delineated including development of standard instructions, identification of consultants, and identification of appropriate referral centers throughout the state/region.* Reporting, follow-up, and management for identified cases of X-ALD will follow the typical workflow for other metabolic disorders on the Wisconsin newborn screening panel. In the event of a positive test, the state lab will contact the consulting clinical geneticist and, the infant's primary care provider (PCP). The geneticist and PCP then work together to communicate the positive screen to parents and coordinate confirmatory testing. In the case of a clinically well infant, these tests may be done over the next 2-4 weeks, as diagnosis of X-ALD is not as time-sensitive as many other disorders on the NBS panel. If testing confirms a diagnosis of X-ALD, initial clinical evaluations will be arranged with appropriate subspecialist consultants (a pediatric neurologist and endocrinologist). Genetic counselors will also be involved in communication, education, care coordination, and counseling at-risk family members. Families of newly diagnosed infants will be directed to informational print and online resources. Unwell infants should be evaluated more expediently and may require testing for Zellweger syndrome, a more severe peroxisomal disorder that also results in elevated VLCFA on DBS.

Finally, *recommendations and decisions should include consideration of the costs of the screening test, confirmatory testing, accompanying treatment, counseling, and the consequences of false positives. The mechanism of funding those costs should be identified. Expertise in economic factors should be available to those responsible for recommendations and decisions.* The cost of newborn screening for X-ALD is estimated at \$10 per sample. The additional cost would be funded through the newborn screening fee, which is obtained from NBS submitters. Screening for clinical manifestations of X-ALD (such as serial brain MRIs) and treatment of complications (such as steroids and HSCT) are generally covered by private and state health insurance.

In addition to the criteria discussed above, specific concerns were raised over the appropriateness and utility of screening female infants for X-ALD. Female “carriers” of X-ALD are typically unaffected in childhood. Most women develop symptoms in adulthood related to central nervous involvement or AMN, though adrenal insufficiency is rare. There is no consensus recommendation for routine screening of females for subclinical or clinical manifestations of X-ALD. Potential harms of such screening include psychosocial distress for families and parents, the “vulnerable child” syndrome, and inefficient use of healthcare resources on clinical screening (e.g., brain MRIs) of unknown utility. Potential benefits of screening and identifying female infants with X-ALD include anticipatory reproductive counseling on the risk to male offspring, the avoidance of a diagnostic odyssey for females who become symptomatic later in life, and the ability to test and diagnose male relatives who were born prior to the implementation of NBS for X-ALD in their state. One proposed solution to this problem would be to withhold the results of X-ALD screening from female infants. However, with evidence of

up to 5% inaccuracy of sex designations on DBS cards, there was concern for the potential to miss affected males who were mislabeled as female. Additionally, there were concerns over the societal implications of withholding health information from patients, though it was noted that this is a common and widely accepted practice in medicine. Ultimately, the committee favored the screening of all infants, male and female, for X-ALD.

The committee was unanimous in agreement that X-ALD met conditions 1-9 (with the exception of condition 7, which does not apply to X-ALD). A motion was made to add X-ALD to the NBS panel; that motion was seconded. The committee then voted unanimously in favor of the addition of X-ALD to the required newborn screening panel in the state of Wisconsin.

Submitted by The Secretary's Advisory Committee on Newborn Screening

Norman Fost MD MPH (Chair)
Jeffrey Britton MD
Christine Brown
Stephen Leuthner MD MA
Kevin Josephson MS, CGC
David Wargowski MD

Absent:
Arthur Derse MD JD

Recused:
Mei Baker MD (Co-nominator)