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**Information about the Newborn Screening X-Linked Adrenoleukodystrophy Demonstration Project**

Dear Physician/Nurse Midwife:

We are writing to inform you of the implementation of a newborn screening (NBS) demonstration project for X-linked adrenoleukodystrophy (X-ALD). In February 2016, the US Secretary of Health and Human Services accepted the recommendation by the Advisory Committee on Heritable Disorders in Newborns and Children that X-ALD be added to the Recommended Uniform Screening Panel. The nomination to add X-ALD to the Wisconsin NBS panel was reviewed and recommended to be accepted by the Metabolic Subcommittee on September 21, 2021, and then reviewed and also recommended to be accepted by the Umbrella Committee on December 3, 2021. On March 4, 2022, the Wisconsin Secretary's Advisory Committee on Newborn Screening reviewed the nomination and voted unanimously in favor of adding X-ALD to the Wisconsin NBS panel. On May 12, 2022, the Secretary approved the addition of X-ALD to the NBS panel through the administrative rule-making process.

Wisconsin has received CDC funding to support a demonstration project. As a result, the Wisconsin State Laboratory of Hygiene, in conjunction with several pediatric metabolic and neurology specialists in the state, will be conducting Wisconsin's X-ALD NBS. It is anticipated that the project will start on September 20, 2023 and will last about 18 months.

X-ALD is a rare disorder caused by a change in a gene that makes a protein that helps the body break down certain types of fats. It is an X-linked disorder that affects both males and females, but females tend not to develop symptoms until adulthood. Males with X-ALD are often normal in infancy, but they may go on to develop problems with their adrenal glands, brain, and spinal cord. Without treatment, these boys may become seriously ill or develop irreversible neurologic injury during childhood. Treatments for X-ALD include cortisol replacment for adrenal dysfunction and hematopoietic stem cell transplantation (HSCT) to arrest progressive brain abnormalities. There is no cure for X-ALD, but early diagnosis means that children with X-ALD can avoid serious adrenal insufficiency, degenerative brain disease, and death, by having regular monitoring to detect endocrine and brain abnormalities at early stages when treatment is most likely to be be effective.

X-ALD is caused by pathogenic variants in the *ABCD1* gene. There is no genotype-phenotype correlation, and in the same family, X-ALD can take different clinical forms. These include:

- Adrenal Insufficiency: By the time they are adults, most men (~85%) will develop some degree of adrenal insufficiency, which usually begins in childhood.

- Childhood Cerebral ALD: 40% of males affected will develop rapidly progressive cerebral demyelination in childhood; this is called childhood cerebral ALD (CCALD). CCALD leads to cognitive loss, blindness, severe disability, and death. CCALD can be treated with HSCT, but treatment is only effective when CCALD is identified at an early stage, when brain changes can be seen on imaging studies (i.e., magnetic resonance imaging (MRI)) but before the development of clinical symptoms. When boys are diagnosed with X-ALD because they are presenting with clinical symptoms, such as inattention or vision changes,

treatment will not slow the progression of CCALD. Therefore, early presymptomatic diagnosis can allow boys to be closely monitored with serial MRIs so as not to miss the best therapeutic window for providing HSCT.

- Adrenomyeloneuropathy: Nearly all adult males with X-ALD will develop stiffness in their legs (spasticity) and gait abnormality due to X-ALD's spinal cord and peripheral nerve effects, causing adrenomyeloneuropathy (AMN).

- Females: the majority of adult women "carriers" will develop some central nervous system effects in adulthood or mild AMN, but they rarely get adrenal disease.

Screening for X-ALD is done by measurement of C26:0-lysophosphatidylcholine (C26:0-LPC) on routine NBS specimens. Zellweger spectrum disorder, a peroxisomal disorder, can be identified via elevated C26:0 LPC and confirmed during the confirmatory testing and clinical evaluation process. Those screening results should be disclosed to the physicians, since at least some of the manifestations of the condition may be treatable. Aicardi-Goutieres Syndrome may also be identified. Physicians should be notified in this instance because this condition has management, prognostic, and reproductive implications.

Recognizing both the potential benefits to CCALD cases and the dilemma related to the diagnosis of late-onset cases, the project includes the option to “opt out.” Parents can inform the WSLH that they do not wish to have their child tested for X-ALD by calling a toll-free number (see attached opt-out form). Opting out of the X-ALD project will not affect a family’s participation in Wisconsin’s routine NBS panel.

The opt-out form will be distributed along with routine NBS education materials at birthing hospitals and by the midwife at out-of-hospital births. We acknowledge that you may also be approached by families for your opinion on the project and appreciate your time in discussing the process with the families you serve. We are also ready to serve as information resources for you and your patients.

*What happens if a patient screens positive?*

Consistent with when infants screen positive for other conditions present on the newborn screen, their diagnosis must be confirmed, as some screens will be false positives.

X-ALD NBS will be integrated into the ongoing NBS workflow, and the testing will follow the general principles established for other metabolic disorders. Clinical geneticist physicians who are consultants for the WI NBS Program will be contacted by phone by the WI NBS laboratory about presumed X-ALD positives. These genetic consultants will contact the primary care provider, who will already have been notified by the WI NBS laboratory.

If the infant is clinically well (feeding well, alert, no reduced muscle tone, the child can be referred to the metabolic center within 2-4 weeks for evaluation and confirmatory testing of very long chain fatty acid (VLCFA) levels in blood. Alternatively, if the primary care provider can arrange a blood draw for VLCFA levels, then the infant can have this done locally. If the VLCFA level is confirmed as abnormal, then the family will be counseled about additional genetic testing. This can confirm the diagnosis of X-ALD (*ABCD1* gene testing only) or other peroxisomal disorders (peroxisomal gene panel testing that includes *ABCD1*).
If the infant is not well (poor feeding, listless, hypotonic) and requires medical oversight, the child may have Zellweger syndrome, a peroxisomal disorder with a poor prognosis. If appropriate, the child should

be referred for medical care and support. Diagnosis of Zellweger syndrome can by determined with a genetic panel specific for peroxisomal disorders, which also includes *ABCD1*.

We are very excited to offer X-ALD screening to Wisconsin's newborns and their families and recognize your place in this team effort to provide the highest quality care to children in our state. We greatly appreciate your assistance in this project; please do not hesitate to contact one of us for further discussion regarding this upcoming project.

Sincerely,


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