WISCONSIN NEWBORN SCREENING (NBS) PROGRAM – CONDITION NOMINATION

Nomination of a Condition to the Wisconsin Newborn Screening Panel

Date of Nomination

9/7/2021

NOMINATOR	
Name Jennifer M. Kwon, MD	Organization University of Wisconsin School of Medicine and Public Health
Affiliation (i.e., health professional, researcher, clinician, advocate) Child Neurologist, Professor of Neurology	
Address 1685 Highland Avenue, Madison, WI 53705	
Email Address kwon@neurology.wisc.edu	Telephone Number 608-263-4231
CO-SPONSORING ORGANIZATION #1 (as appropriate, additional sponsors may be included on page 5)	
Name Mei Baker, MD	Organization Wisconsin State Laboratory of Hygiene
Affiliation (i.e., health professional, researcher, clinician, advocate) Public Health Laboratory Director	
Address 465 Henry Mall, Madison WI 53706	
Email Address mei.baker@slh.wisc.edu	Telephone Number 608-262-5494

Condition	**STATEMENT**
Nominated Condition	X-linked Adrenoleukodystrophy (X-ALD)
Description of Disorder	X-ALD is a rare disorder caused by a change in a gene that makes a protein which helps the body break down certain types of fats. It is an X-linked disorder that affects both males and females, but females tend to develop symptoms in 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 irrevesible 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 a rapidly progressive cerebral demyelination in childhood, which 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 there are brain changes 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 Method	Elevation of very long chain fatty acids (VLCFA) using MS/MS on dried blood spot
Gene	ABCD1
OMIM or other names for condition	Adrenoleukodystrophy, ALD, X-ALD, Addison disease and cerebral sclerosis, Addison-Schilder disease
Case Definition	1) Elevation of plasma VLCFA and pathogenic variant (including deletion or duplication) in the ABCD1 gene, or 2) Elevation of plasma VLCFA and family history of X-ALD (also confirmed by elevated VLCFA in affected relatives

NOTE: Please reference each statement/answer with the corresponding reference number listed in **Key References**.

CRITERION	
Criterion 1: 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.	
Timing of Clinical Onset	*Relevance of the timing of newborn screening to onset of clinical manifestations. Must cause serious health risks in childhood that are unlikely to be detected and prevented in the absence of newborn screening.* X-ALD newborn screening (NBS) will allow early identification of boys at risk for adrenal insufficiency (AI) and the childhood cerebral form of X-ALD (CCALD) described above.(Ref 1) 1) AI develops in most males with X-ALD. AI may develop in infancy, without any clinical symptoms, so current guidelines from the Pediatric Endocrinology Society recommend laboratory testing of ACTH and cortisol every 3-4 months in the first 2 years of life, and every 4-6 months after 2 years. This laboratory testing of adrenal function will identify AI early, while clinically asymptomatic, allowing for appropriate treatment and preventing the serious and potentially fatal condition of adrenal crisis.(Ref 2) 2) CCALD is a form of rapidly progressive inflammatory demyelination that can be treated and halted with HSCT. It is well established that the best time to treat CCALD is before any clinical symptoms are present, using regular evaluations with brain MRI to detect early stages of demyelination. Without newborn screening, boys with CCALD who present clinically will not be able to benefit from treatment and will develop dementia, disability, and die. MRI surveillance screening should begin between 1-2 years of age and is repeated every 6 months between the ages of 3-12 years.(Ref 1-3)
Criterion 2: For each condition, there should be information about the incidence, morbidity and mortality, and the natural history of the disorder.	

Incidence	*Determined by what method(s): pilot screening or clinical identification?* Based on the CA NBS results from their first years of screening (i.e., population based screening) the birth prevalence was recently reported as 1/14,390 in hemizygous males and 1/9593 in heterozygous females out of 1.8 million infants screened. This report compared the CA incidence to the one reported for NY-1/18,783 males and 1/17,820 females after 1.39 million newborns were screened.(Ref 4)
Severity of Disease	*Morbidity, disability, mortality, spectrum of severity, natural history*. As noted above, this disorder can present with many forms: • Childhood Cerebral ALD (CCALD): CCALD is the most severe childhood of X-ALD and affects about 40% of males with X-ALD. Without intervention, all boys with CCALD will experience morbidity, disability and die. Boys with CCALD present in childhood with a rapidly progressive brain disease resulting in loss of cognition, vision, ambulation, and early death. Before clinical symptoms develop, brain MRI will show early brain white matter changes (demyelination). It is at this point that treatment with HSCT is most effective. With successful HSCT, boys with CCALD treated at the earliest stages will not develop a devastating brain disease. The morbidity and mortality with HSCT treatment can be 30% and 15%, respectively. If the treatment is successful, boys can expect to continue to make developmental gains and live to adulthood.(Ref 1,5) • Adrenal insufficiency (AI): This usually only affects males (rarely females have been reported to have abnormal adrenal function) and the lifetime prevalence is ~80%. The risk of developing AI is highest in the first decade of life.(Ref 6) Treatment, usually with hydrocortisone, is highly effective. Without appropriate treatment, children develop fatigue, weakness, loss of appetite, abdominal pain, and hyperpigmentation. They may also be asymptomatic with only laboratory evidence of adrenal insufficiency, though symptoms are likely at some point, without treatment. If early symptoms are ignored, some may present in adrenal crisis which can cause severe weakness, delirium, hypotension, and may lead to death if not recognized. Mortality is relatively low.(Ref 2,6) • Adrenomyeloneuropathy (AMN): AMN is due to a peripheral nerve axonopathy with variable spinal cord involvement. AMN affects adult males and females with X-ALD. Nearly all adult males develop AMN, even if they have been treated for CCALD with HSCT.(Ref 1,7) Onset of AMN symptoms in young men begins with leg weakness and spasticity, bladder and bowel dysfunction, and peripheral neuropathy. Adult women develop milder symptoms later in adulthood.(Ref 8) There is no treatment for AMN.(Ref 1) • Cerebral forms affecting older males: Brain demyelination may be seen in adolescents or adults and may have a slower progression or even stop progressing. Because of this variable progression, treatment with HSCT is controversial,(Ref 1,5) but many recommend following adult males with X-ALD with annual brain MRIs after age 12 years.(Ref 9,10)

Criterion 3: 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.

Urgency	How soon after birth must treatment be initiated to be effective? Of the forms of X-ALD described above (Criterion 2) the two forms that present in childhood are AI and CCALD, both forms affecting boys only. 1) AI: Most males with X-ALD develop AI during childhood, but not typically in infancy. Still, surveillance of adrenal function begins in infancy by testing blood levels of adrenocorticotrophic hormone (ACTH) and cortisol under the direction of a pediatric endocrinologist.(Ref 2,6) 2) CCALD: Boys with X-ALD develop CCALD in childhood, usually between 2-10 years of age.(Ref 1) In one large multicenter retrospective review of CCALD patients, the median of onset was 8 years.(Ref 11) There is value in early surveillance MRI testing starting between 1-2 years of age and continueing every 6 months until 12-15 years of age, in order to detect the earliest MRI changes of inflammatory demyelination, so that decisions about HSCT can be made at a time the benefits are maximal.(Ref 1,2,5,11)
Efficacy (Benefits)	Extent of prevention of mortality, morbidity, disability. Treatment limitations, such as difficulty with acceptance or adherence. Treatment of AI and CCALD are known to be effective in preventing morbidity, mortality, and major disability. 1) AI: Treatment of AI with glucocorticoid replacement is highly effective in preventing all symptoms of AI, including severe adrenal crisis and death.(Ref 2) Algorithms for following infant boys identified with X-ALD to monitor for AI have been developed, but there may be some uncertainty of how to address early AI with indeterminate testing results.(Ref 12) Treatment is generally tolerated by children, with the only real limitation is the need for regular monitoring by a pediatric endocrinologist.(Ref 2,12) 2) CCALD: When boys present with clinical symptoms of CCALD, there may be rapid deterioration to significant disability and death. Treatment with HSCT can be life-saving and arrest the progression of demyelination and clinical decline. For this reason, it is considered the standard of care for CCALD, though its greatest limitation is that the treatment is not effective beyond the earliest stage of brain involvement. HSCT involves significant risks, so the ideal candidate is clinically asymptomatic with limited and early findings of inflammatory demyelination in their brain MRI. In such a carefully selected cohort, nearly all would be expected to survive without developing disablity, but there remains the risks of HSCT which include infection, graft-versus-host disease, and graft failure. Furthermore, there may be difficulty identifying suitable donors. For these reasons, HSCT should only be performed in experienced pediatric HSCT centers to minimize the risks of HSCT. The lack of access to such a center pediatric center can be a barrier to treatment in some areas. In WI, there are two such HSCT centers and both are comfortable with HSCT treatment in X-ALD. The other limitation to treatment is the need for regular MRIs in boys with X-ALD, who often require sedation. Needing to have MRIs every 6 months can be burdensome to families.(Ref 1,5,11,12,13)

Potential Harms	Potential medical or other ill effects from treatment. 1) AI usually requires glucocorticoid replacement, with daily maintenance dosing as well as additional doses at times of physiologic stress. The preferred maintenance medication is oral hydrocortisone which is generally well tolerated though its administration does require close monitoring by an experienced endocrinology team.(Ref 2) 2) The treatment for CCALD is HSCT a complex intervention with significant morbidity and some risk of death. Safe administration of HSCT requires an experienced medical center and clinical team and carefully chosen patients to receive treatment. HSCT in boys with X-ALD is best suited for those with early MRI changes, no clinical neurologic deficits, and a well matched donor. The morbidity in HSCT starts with the need for initial myeloablative conditioning and is also due to immunosuppression, graft failure, and development of graft versus host disease; complications can affect 20-40% of recipients. (Ref 11,14) The mortality is estimated at 10-20%.(Ref 11,14) Furthermore, the disease may continue to progress for several months after HSCT.(Ref 5,11,13) Effective treatment of both AI and CCALD require that infants identified with X-ALD be monitored closely BEFORE the development of any clinica, laboratory, or imaging abnormalities. This commits the child and family to years of close medical surveillance while the child is clinically and physiologically completely well. This type of monitoring can be stressful and burdensome to families and children.(Ref 1,15,16)
Criterion 4: The interventions should be reasonably available to affected newborns.	
Modality	*Drug(s), diet, replacement therapy, transplant, surgery, other. Include information regarding regulatory status of treatment.* 11) For AI, the treatment is with hydrocortisone which is commerically available as an oral drug for maintenance management and as an injection for times of physiologic stress or emergency administration. Hydrocortisone treatment as well as other glucocorticoid replacements are widely available but require the involvement of pediatric endocrinologists for safe and effective management.(Ref 2) 2) In the case of CCALD, HSCT is accepted as the only available treatment to halt disease progression but it is only available at selected centers.(Ref 1,12,13) In WI, there are two pediatric HSCT centers which can offer this treatment to boys with CCALD. Recently, gene therapy delivered via HSCT has shown promising results for CCALD.(Ref 17) While not currently available, except through an ongoing clinical trial (NCT03852498), this treatment uses the patient's own CD34+ cells that have been transduced with the elivaldogene tavalentivec (Lenti-D) lentiviral vector. This treatment has the potential to greatly reduce the morbidity associated with standard matched donor HSCT.(Ref 13,17)
Availability	*Describe scope of availability and note any limitations.* 1) For AI, the treatment is readily available, as noted above, but requires close management by a specialist in pediatric endocrinology. 2) For CCALD, proximity to an experienced HSCT center is important. Fortunately, WI has two HSCT centers with experience.
Criterion 5: Appropriate follow-up should be available for newborns that have a false positive newborn screen.	

Follow-up for False Positives	*Define the follow-up process.* Consistent with existing Wisconsin NBS practices, the state NBS laboratory at WSLH will communicate the positive VLCFA screening result to the primary care provider and the metabolic center designated to engage in confirmatory testing and short term follow-up. At the center, the metabolic geneticist will reach out to the primary care provider to provide further consultation and to reach out to the baby's family about the initial appointment where confirmatory testing will be performed. This confirmatory testing will include biochemical testing of very long chain fatty acids and a gene panel testing for several peroxisomal disorders including the ABCD1 gene and other genes that cause disorders that can lead to abnormal elevations in VLCFA. This will help determine those who: 1) do NOT have a disorder because their repeate VLCFA are normal and they can be discharged from further follow-up or 2) DO have a disorder, which may be X-ALD (either male or female), or another peroxisomal disorder (such as Zellweger spectrum disorder) or another disorder such as Aicardi-Goutières syndrome (AGS).(Ref 1, 3, 4, 18) Those found to have X-ALD will be followed by a multidisciplinary team of medical providers, as detailed below in Criterion 8. For other peroxisomal disorders, follow-up will primarily be with the metabolic geneticist.
Criterion 6: The characteristics of mandated tests in the newborn population should be known, including specificity, sensitivity, and predictive value.	
Screening test(s) to be used	*Description of the high volume method, instrumentation and if available as part of multi-analyte platform.* Measurement of C26:0-lysophosphatidylcholine (C26:0-LPC) on routine NBS specimens. The concentration of C26:0-LPC in the neonatal dried blood spots (DBS) is determined using a flow injection analysis, electrospray ionization, tandem mass spectrometry (FIA-ESI-MSMS).
Modality of Screening	*Dried blood spot, physical or physiologic assessment, other* Dried blood spots
Does the screening algorithm include a second tier test? If so, what type of test and availability?	*Dried blood spot, physical or physiologic assessment, other* No

Clinical Validation	*Location, duration, size, preliminary results of past/ongoing pilot study for clinical validation, positive predictive value, false positive rate, analytical specificity, sensitivity.* The NBS Laboratory at WSLH has developed and validated an NBS for X-ALD test that measures C26:0-lysophosphatidylcholine (C26:0-LPC) on routine NBS specimens. The concentration of C26:0-LPC in the newborn dried blood spots (DBS) is determined using a flow injection analysis, electrospray ionization, and tandem mass spectrometry (FIA-ESI-MSMS). After validation of the assay's linearity, accuracy, and precision, the C26:0 LPC level distribution in newborn population was assessed using 5,881 de-identified sequential residual newborn specimens received from 8/21/2020 to 9/21/2020. A mean C26:0 LPC value of 0.07 μM was observed with a standard deviation of 0.02 μM. Based on four and eight standard deviations, C26:0 LPC concentrations of ≥ 0.15 μM and ≥ 0.23 μM were determined to be borderline and presumptive positive X-ALD cut-off levels, respectively, where borderline samples would be subjected to re-collect a newborn screening specimen for repeating testing, and presumptive positive X-ALD infants would be subject to confirmatory testing. Clinical validity was assessed using a set of de-identified and blinded NBS residual specimens that contained both true X-ALD screening positive and true X-ALD screening negative cases provided by the Minnesota Newborn screening program. In a panel of 12 samples, the five true screening negative samples were correctly identified with C26:0 LPC concentrations from 0.07 μM to 0.10 μM, while six true screening positive samples were correctly identified with C26:0 LPC concentrations from 0.22 μM to 0.83 μM, including one sample identified as borderline positive. Based on the validation study, the proposed X-ALD screening tests' sensitivity is 100%, specificity is 100%, and positive predictive value 100%.
Analytic Validation	*Limit of detection/quantitation, detection rate, reportable range of test results, reference range. Include regulatory status of test, information about reference samples and controls required for testing and availability of or potential for external quality assurance system, e.g., QC and PT for both screening and confirmatory tests.* The validated NBS assay for X-ALD developed at WSLH has a limit of detection/quanititation of C26:0 LPC at 0.0125 μM. Infants with C26:0 LPC < 0.15 μM would be reported as X-ALD screening negative. The CDC currently provides regular QC and PT assessments to the states that have implemented NBS for X-ALD programs.
Potential Secondary Findings	*May other disorders be identified by the screening test for the nominated condition?* ☒ Yes ☐ No ***If yes:*** • *How should that identification be handled—should those screening results be disclosed to the physicians or parents?* Zellweger spectrum disorder, a peroxisomal disorder, can be identified via elevated C26:0 LPC, and confirmed during confirmatory testing and clinical evaluation process.(3,4) 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 as this condition has management, prognostic, and reproductive implications.(Ref 18) • *Would that disorder(s) meet the outlined criteria?* ☐ Yes ☒ No o *If yes, please prepare a separate nomination form for the secondary disorder(s)* N/A o *If no, what criteria does it not meet?* Availability of effective treatments

Summary of Population-based Pilot Study(ies)

Location of Prospective Pilot	N/A
Number of Newborns Screened	N/A
Number of Positive Results	*Positive by primary test versus 2nd tier test if applicable.* N/A

False Positive Rate; False Negative Rate (if known)	*False positive by primary test versus 2nd tier test if applicable.* N/A
Number of Infants Confirmed with Diagnosis	*How are diagnosis confirmed [clinical, biochemical, molecular]?* N/A
Criterion 7: If a new sample collection system is needed to add a disorder, reliability and timeliness of sample collection must be demonstrated.	
Is this a new sample collection system?	*If yes, demonstrate reliability and timeliness of sample collection process, including data collection, analysis, and reporting of new results.* N/A
Criterion 8: 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.	
Considerations of Screening and Diagnostic Testing	*False positives, carrier detection, invasiveness of method, other* X-ALD newborn screening 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 Newborn Screening 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. In this way, the genetic provider will be able to determine the clinical status and location of the infant and contact details for the parents. The primary care provider will learn of the newborn screen results, the natural history of X-ALD and other potential conditions from the genetics consultant. The consultant will request that the primary doctor contact the parents. If the infant is clinically well (feeding well, alert, no reduced tone) the child can be referred to the metabolic center within 2-4 weeks for evaluation and confirmatory testing (VLCFA levels in blood). Alternatively, if the primary care provider can arrange for a blood draw for VLCFA levels then the infant can have this done locally. If the VLCFA is confirmed as abnormal, then the family will be counselled about additional genetic testing. This can confirm the diagnosis of X-ALD (ABCD1 testing only) or other peroxisomal disorders (peroxisomal gene panel testing that includes ABCD1 testing). 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 by sending a genetic panel specific for peroxisomal disorders, which also includes the ABCD1 gene for X-ALD. .
Is test FDA cleared/approved	*Include availability of information, sole source manufacturer, etc.* This is a test developed by the WSLH NBS laboratory.
List all CLIA or CAP certified labs offering testing in the US	*Link to GeneTests, and Genetic Test Reference if applicable.* • VLCFA testing: Many large laboratories such as Quest, Mayo, and ARUP, are able to test for VLCFA levels. Some laboratories will send their specimens to the Kennedy Kreiger laboratories. • Peroxisomal gene panel testing: Several genetic testing companies (e.g., Invitae, GeneDx, PreventionGenetics) have next-generation sequencing panels with deletion/duplication testing of genes associated with elevated VLCFA levels and peroxisomal disorders.

Follow-up and management process	*Development of standard instructions, identification of consultants, identification of appropriate referral centers throughout the state/region, follow-up for results, management of ongoing care, education, and outreach.* Infants are diagnosed with X-ALD if they have elevated VLCFA levels and a pathogenic mutation the ABCD1 gene have X-ALD. Families of infants with X-ALD should receive information about X-ALD using resources for newly diagnosed X-ALD families as a guide, (e.g., see https://aldconnect.org/what-is-ald/; https://www.babysfirsttest.org/newborn-screening/conditions/adrenoleukodystrophy). They should also receive early genetic counselling with the goal of identifying at-risk family members, especially younger male relatives who could develop AI or CCALD. A male infant with X-ALD will need surveillance monitoring during childhood. During infancy, adrenal function will be tested, usually every 3-4 months during the first 2 years of life and every 4-6 months when they are older than 2 years.(Ref 2). In their first year of life, they should meet with the pediatric neurologist to discuss the rationale and process of CCALD screening. This consists of regularly scheduled brain MRIs that begin between the ages of 1-2 years and occur every 6 months, usually between the ages of 3-12 years.(Ref 1, 2) Most children under the age of 9 years will need sedation for MRIs, and neurologic assessments should be timed to coincide with these MRIs. Whenever possible neurology and endocrinology should try to conduct joint evaluations to minimize family travel. For example, adrenal function testing can be done when children come for their MRIs since they will likely need an intravenous line placed and blood can be drawn then. Girls with X-ALD are unlikely to develop adrenal dysfunction. (Ref 6) They can, as older adults, develop symptoms of AMN, and their families should be counselled about this. (Ref 1,8)

Criterion 9: 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.

Screening test	The currently estimated cost for screening testing is $10.00 per infant
Confirmatory testing	
Treatment	
Counseling	
False positives	
Mechanism of funding	

Key References to support each criterion. Please list and attach as PDF(s). If mailing, include hard copies.	
#	**Criterion 1**
	1. Kemper AR, Brosco J, Comeau AM, et al. Newborn screening for X-linked adrenoleukodystrophy: evidence summary and advisory committee recommendation. Genetics in medicine : official journal of the American College of Medical Genetics 2017; 19(1): 121-6.
	2. Eng L, Regelmann MO. Adrenoleukodystrophy in the era of newborn screening. Curr Opin Endocrinol Diabetes Obes 2020; 27(1): 47-55 3. Vogel BH, Bradley SE, Adams DJ, et al. Newborn screening for X-linked adrenoleukodystrophy in New York State: diagnostic protocol, surveillance protocol and treatment guidelines. Molecular genetics and metabolism 2015; 114(4): 599-603
	Criterion 2
	4. Matteson J, Sciortino S, Feuchtbaum L, Bishop T, Olney RS, Tang H. Adrenoleukodystrophy Newborn Screening in California Since 2016: Programmatic Outcomes and Follow-Up. Int J Neonatal Screen 2021; 7(2). 5. Turk BR, Theda C, Fatemi A, Moser AB. X-linked adrenoleukodystrophy: Pathology, pathophysiology, diagnostic testing, newborn screening and therapies. Int J Dev Neurosci 2020; 80(1): 52-72. 6. Huffnagel IC, Laheji FK, Aziz-Bose R, et al. The Natural History of Adrenal Insufficiency in X-Linked Adrenoleukodystrophy: An International Collaboration. The Journal of clinical endocrinology and metabolism 2019; 104(1): 118-26. 7. van Geel BM, Poll-The BT, Verrips A, Boelens JJ, Kemp S, Engelen M. Hematopoietic cell transplantation does not prevent myelopathy in X-linked adrenoleukodystrophy: a retrospective study. Journal of inherited metabolic disease 2015; 38(2): 359-61.
	8. Habekost CT, Pereira FS, Vargas CR, et al. Progression rate of myelopathy in X-linked adrenoleukodystrophy heterozygotes. Metab Brain Dis 2015; 30(5): 1279-84. 9. Kühl JS, Suarez F, Gillett GT, et al. Long-term outcomes of allogeneic haematopoietic stem cell transplantation for adult cerebral X-linked adrenoleukodystrophy. Brain : a journal of neurology 2017; 140(4): 953-66. 10. Waldhüter N, Köhler W, Hemmati PG, et al. Allogeneic hematopoietic stem cell transplantation with myeloablative conditioning for adult cerebral X-linked adrenoleukodystrophy. Journal of inherited metabolic disease 2019; 42(2): 313-24.
	Criterion 3
	11. Raymond GV, Aubourg P, Paker A, et al. Survival and Functional Outcomes in Boys with Cerebral Adrenoleukodystrophy with and without Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant 2019; 25(3): 538-48. 12. Zhu J, Eichler F, Biffi A, Duncan CN, Williams DA, Majzoub JA. The Changing Face of Adrenoleukodystrophy. Endocr Rev 2020; 41(4): 577-93. 13. Mallack EJ, Turk B, Yan H, Eichler FS. The Landscape of Hematopoietic Stem Cell Transplant and Gene Therapy for X-Linked Adrenoleukodystrophy. Curr Treat Options Neurol 2019; 21(12): 61.
	14. Kühl JS, Kupper J, Baqué H, et al. Potential Risks to Stable Long-term Outcome of Allogeneic Hematopoietic Stem Cell Transplantation for Children With Cerebral X-linked Adrenoleukodystrophy. JAMA Netw Open 2018; 1(3): e180769. 15. Schwan K, Youngblom J, Weisiger K, Kianmahd J, Waggoner R, Fanos J. Family Perspectives on Newborn Screening for X-Linked Adrenoleukodystrophy in California. Int J Neonatal Screen 2019; 5(4): 42. 16. Timmermans S, Buchbinder M. Patients-in-waiting: Living between sickness and health in the genomics era. J Health Soc Behav 2010; 51(4): 408-23.
	Criterion 4
	17. Eichler F, Duncan C, Musolino PL, et al. Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy. The New England journal of medicine 2017; 377(17): 1630-8.

	Criterion 5
	18. Tise CG, Morales JA, Lee AS, et al. Aicardi-Goutières syndrome may present with positive newborn screen for X-linked adrenoleukodystrophy. American journal of medical genetics Part A 2021; 185(6): 1848-53.
	Criterion 6
	Criterion 7
	reference already cited above
	Criterion 8
	references already cited above
	Criterion 9

Additional Co-sponsoring Organizations

CO-SPONSORING ORGANIZATION #2	
Name	Organization
Affiliation (i.e., health professional, researcher, clinician, advocate)	
Address	
Email Address	Telephone Number

CO-SPONSORING ORGANIZATION #3	
Name	Organization
Affiliation (i.e., health professional, researcher, clinician, advocate)	
Address	
Email Address	Telephone Number

CO-SPONSORING ORGANIZATION #4	
Name	Organization
Affiliation (i.e., health professional, researcher, clinician, advocate)	
Address	
Email Address	Telephone Number

CO-SPONSORING ORGANIZATION #5	
Name	Organization
Affiliation (i.e., health professional, researcher, clinician, advocate)	
Address	
Email Address	Telephone Number

Submission Checklist	
☒	Nomination form
☒	Conflict of Interest Forms completed by Nominator and all Co-Sponsoring Organizations
☒	PDF(s) or hard copies of references

Contact information of Nominator: Jennifer Kwon, MD; kwon@neurology.wisc.edu

Submit Nominations to: DHSWICongenitalDisorders@wisconsin.gov
Or mail to:

WI Division of Public Health
Newborn Screening Program
1 West Wilson Street – Room 233
Madison, WI 53703