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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Advisory Committee on Heritable Disorders
in Newborns and Children
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September 25, 2015

The Honorable Sylvia Mathews Burwell
Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Dear Secretary Burwell:

The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) is charged with making systematic evidence-based recommendations on heritable disorders that have the potential to significantly impact public health for which all newborns should be screened.

During the Committee's August 2015 meeting, we reviewed the evidence-based report for the nominated heritable disorder – Adrenoleukodystrophy (X-ALD). Based on this report and deliberations on all associated clinical data, testing platforms, available treatments, benefits and harms, public comment, and the public health impact assessment, the Committee voted to recommend to you the following:

1. Expand the Recommended Uniform Screening Panel (RUSP) to include the addition of X-ALD.
2. Provide federal funding to State newborn screening programs to implement the screening of X-ALD, including funding to collect data and disseminate information that further defines short and long term follow-up procedures for pre-symptomatic infants diagnosed with ALD.

X-ALD is a lysosomal storage disorder (LSD) caused by mutations in the ABCD1 gene located on the X chromosome. The clinical phenotype is broad, with severe forms affecting more males than females. The overall incidence of X-ALD in the United States is estimated at 6 per 100,000 births regardless of sex. There are three phenotype classifications of X-ALD: adrenocortical insufficiency ("Addison's-only"), cerebral demyelination (child, adolescent, and adult cerebral ALD), and progressive paraparesis (adrenomyeloneuropathy or AMN). The most serious form of X-ALD is the childhood cerebral X-ALD with symptoms appearing between 2.5 and 10 years of age and is associated with rapid neurologic decline and death or disability within 3 years after

onset. The most prevalent symptoms of children with ALD are adrenal insufficiency and cerebral demyelination. Adrenal insufficiency has been identified in up to 86% of asymptomatic males prior to any other signs of neurologic involvement, with onset as early as the first year of life. Diagnosis is based on clinical findings, biochemical tests, and mutation analysis. Treatment includes adrenal cortisol replacement therapy or hematopoietic stem cell transplantation (HSCT) based on routine monitoring for symptoms of adrenal insufficiency and neurological involvement. Modeling of outcomes of affected persons identified through newborn screening based on available data on earlier detection suggests reduced mortality and morbidity as compared to clinical case detection of persons affected with X-ALD.

The Committee deliberated on the net benefits, certainty of available evidence and feasibility of newborn screening for X-ALD, and concluded that there are significant benefits to newborn screening for X-ALD. There is a reliable screening test that has a positive predictive value of 96%. The screening test for X-ALD can be multiplexed with screening tests for other LSDs, which could result in more efficient testing. The Centers for Disease Control and Prevention is in the process of producing quality assurance/quality control and proficiency testing materials for newborn screening laboratories to aid in implementation of testing for X-ALD. According to the public health impact assessment for X-ALD, a majority of the states that responded to the survey indicated that it would take one to three years to implement X-ALD screening provided that the newborn screening program had the regulatory authority to screen for X-ALD and funding in place.

The Committee recognizes that there are no data that compare long-term outcomes from identification through newborn screening and usual clinical detection. This is why I hope that early adopter States that are already moving forward with implementing screening for X-ALD will be a source of additional evidence on the effectiveness of detection from newborn screening compared to clinical discovery and provide data on implementation and quality improvement in addition to long-term outcomes of each of the three phenotype classifications.

The Committee strongly believes that screening for X-ALD will lead to significant benefits for infants born with this rare condition and hopes that you will add X-ALD to the RUSP.

Sincerely yours,

Joseph A. Bocchini, Jr., M.D.
Chairperson

Enclosure:

Report - *Newborn Screening for Adrenoleukodystrophy (X-ALD): A Systematic Review of Evidence, Report of Final Findings*

cc: Debi Sarkar, M.P.H.
Designated Federal Official
Health Resources and Services Administration