DEPARTMENT OF HEALTH AND HUMAN SERVICES

Advisory Committee on Heritable Disorders in Newborns and Children
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March 8, 2018

The Honorable Alex Azar
Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Dear Secretary Azar:

It is an honor to welcome you to your new position as Secretary of Health and Human Services. The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) looks forward to serving you in your efforts to improve the health and wellbeing of the population of the United States.

The Committee is charged to make systematic evidence-based recommendations to the Secretary on heritable disorders that have the potential to significantly impact public health for which all newborns should be screened. The list of conditions for which screening is recommended at birth as part of states' newborn screening programs is referred to as the Recommend Uniform Screening Panel (RUSP). Newborn screening is a state public health function. Most states screen for the majority of disorders on the RUSP.

The Committee has a process in place for considering conditions for the RUSP, which begins with a nomination. The Committee encourages individuals and organizations to form multi-disciplinary teams to submit nominations. The Committee then determines whether sufficient evidence is available to recommend a formal evidence-based review. If the Committee votes to proceed to evidence review, an independent external group conducts a systematic evidence-based review and reports its findings to the Committee. The Committee discusses and deliberates on the evidence presented and uses a decision matrix to guide the decision whether to recommend adding a condition to the RUSP. This letter is to inform you of a new recommendation from the Committee.

During its February 8, 2018 meeting, the Committee reviewed the evidence-based report for the nominated heritable disorder – spinal muscular atrophy (SMA). Based on this report and deliberations on all associated clinical data, testing platforms, available treatments, benefits and harms, an assessment of the public health systems impact, and public comment, the Committee voted to recommend to you the following:

Expand the Recommended Uniform Screening Panel (RUSP) to include the addition of spinal muscular atrophy (SMA) due to homozygous deletion of exon 7 in SMN1.

SMA is a heterogeneous group of inherited neuromuscular disorders affecting the motor neurons in the spinal cord and brainstem, resulting in motor weakness and atrophy. The estimated prevalence of SMA is 1 in 11,000 births. SMA is an autosomal recessive disorder caused by mutations in the Survival Motor Neuron 1 (SMN1) gene. Approximately 95% of cases are caused by a deletion of exon 7 in both alleles of SMN1. These changes result in the absence of production of the SMN protein. Without the SMN protein, motor neurons are lost leading to increasing muscle weakness and loss of muscle function. There is another gene, SMN2, which allows the production of small amounts (estimated <10%) of functional protein. More than one copy of SMN2 can be present in affected persons; the number of copies can influence the amount of functional protein made and slows the overall disease process.

The disease spectrum is divided into 5 types, based on age of onset and highest motor milestone achieved. Type 0 often leads to fetal loss or newborns with significant involvement and death in early infancy. Type I leads to progressive weakness in the first six months of life and death within the first few years of life (68% die by age 2 and 82% by age 4). Type II is associated with progressive weakness by 15 months of life and respiratory failure and death after the third decade of life. Types III and IV are associated with progressive weakness that develops after 1 year of life or in adulthood, and most individuals have a normal lifespan. It has been estimated that 54% of cases are Type I and 18% are Type II.

Until recently, intervention for SMA patients has been palliative care (nutritional support, physical therapy, and ventilation/respiratory support). In December 2016 the FDA approved the first targeted treatment for SMA, nusinersen. Nusinersen is an antisense oligonucleotide that alters splicing of SMN2 pre-mRNA to increase the amount of full-length SMN2 mRNA, leading to an increase in the amount of functional SMN protein produced. Controlled studies have shown a significant preservation of muscular function and achievement in motor milestones in patients with onset of symptoms in the first six months of life and in patients with onset of symptoms by 15 months of life when compared to palliative care. Affected patients had better outcomes with treatment if therapy was begun early after the onset of symptoms. Limited data suggest that treatment effect is greater when the treatment is initiated before symptoms develop and when the individual has more copies of SMN2. No data on long-term outcomes is available at this time, as follow up in studies has been less than 2 years.

The Committee deliberated on the net benefits, certainty of available evidence and feasibility of newborn screening for SMA and concluded that there is moderate certainty of significant benefits to affected infants through newborn screening for SMA. There is a reliable screening test. Pilot studies thus far have indicated the screening test designed to identify cases of SMA due to a homozygous deletion has a 100% positive predictive value. No false positives have been reported in the pilot studies to date. The screening test can also be multiplexed with screening for SCID, which could result in more efficient

testing. The Centers for Disease Control and Prevention has developed quality assurance/quality control and proficiency testing materials for newborn screening laboratories to aid in implementation of testing for SMA. According to the public health impact assessment for SMA, a majority of the states that responded to the survey indicated that it would take one to three years to implement SMA screening provided that the newborn screening program had the regulatory authority and funding to screen for SMA. Enclosed is the report of the evidence-based review on SMA.

The Committee recognizes there are no data that compare long-term outcomes from identification through newborn screening and usual clinical detection which is often delayed for months following the onset of symptoms and can result in permanent loss of muscle function during this period before a diagnosis is made. However, the Committee believes that the available evidence warrants the decision to add SMA to the RUSP. As with any new therapy, additional data will be developed on long-term outcomes for patients affected with this condition. Early adopter states that are already moving forward with implementing screening for SMA will be a source of additional evidence on the effectiveness of detection from newborn screening compared to clinical diagnosis after the onset of symptoms and provide data on implementation and laboratory quality improvement in addition to long-term outcomes of each of the SMA types.

The Committee believes that screening for SMA will lead to significant benefits for infants born with this rare condition and respectfully requests that you accept the recommendation to add SMA to the RUSP.

Sincerely yours,

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

Enclosure:
Report - *Evidence-based Review of Newborn Screening for Spinal Muscular Atrophy (SMA)*

cc: Catharine Riley, PhD, MPH
Designated Federal Official
Health Resources and Services Administration