Secretary's Advisory Committee on Newborn Screening

Report on Nomination for Newborn Screening for Spinal Muscular Atrophy in Wisconsin

The advisory committee met on January 11, 2018 to consider whether Spinal Muscular Atrophy should be added to the Wisconsin mandatory newborn screening panel.

Spinal Muscular Atrophy (SMA) is an autosomal recessive degenerative genetic disorder that affects the motor neurons of the spinal cord. The carrier frequency is estimated as 1:54 and the disease incidence is 1:11,000, affecting approximately 4-5 infants born each per year in the state of Wisconsin. SMA is the most common lethal genetic disease of children under 2 years old.

There are four subtypes of SMA that differ by age of onset and disease severity. Type I is the most common and severe type, comprising about 50-60% of affected individuals.. Age of onset is less than 6 months, with the average age of death before two years, typically secondary to respiratory failure. Children with type 1 SMA are typically not able to sit without support.

Type II is the second most common, affecting approximately 30-40% of affected individuals. The age of onset is less than 18 months, with average age of death in the 2nd to 3rd decade of life. Those with type II SMA are typically not able to sit independently, and cannot stand or walk.

Type III SMA affects roughly 10% and the age of onset can range from 18 months to 10 years of age. Children with type II can stand and walk independently, but lose their motor skills over time. They typically have a normal life expectancy.

Type IV SMA, the least common, affects less than 5% and has an adolescent or adult onset. Those with type IV have a normal life expectancy, and retain their ability to walk, but can experience muscle pain.

Motor neurons in patients with SMA die over time. This can start in utero. Physical findings on an initial physical exam for children with SMA can be subtle and difficult to identify, resulting in delayed diagnosis and treatment. Earlier treatment appears to be associated with better outcomes. Studies have shown that patients who are treated before symptoms reach more motor milestones.

The current approved treatment is Nusinersen (trade name Spinraza), approved by the FDA in December 2016. Other treatments are being studied. The cost of Spinraza is estimated to be approximately $750,000 in the first year, and $350,000 per year thereafter.

The cause for 95% of SMA cases is a homozygous deletion of the gene SMN1 on chromosome 5q. The clinical severity type is modulated by the number of copies of another gene, SMN2. The proposed screening test would detect the presence or absence

of the SMN1 gene, which is deleted in patients with SMA. The sensitivity of this screening test will be 100%, as its purpose is to detect the presence, or in SMA the absence, of the SMN1 gene. Once identified, confirmatory testing would including measuring the number of SMN2 genes to try to determine which subtype of SMA the patient will have.

The benefit of treatment with Nusinersen is most clear in patients with Type 1, but long term outcomes are not yet known. Early evidence suggests that the benefit is greater if treatment begins as early as possible.

Because the benefits of Nusinersen are less clear in later onset cases, there is concern that these children could suffer from psychosocial harm due to years of waiting for a dread disease, possibly without the prospect of benefit. For this reason, the Committee unanimously recommended that the screening program should be linked with a study of the psychosocial harms in late onset cases, and the provision of education and support services to these families.

The committee considered whether SMA screening met each of the following nine criteria. Voting options were Yes, No, or Need More Information

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. (Yes 6-0)

2. For each condition, there should be information about the incidence, morbidity, and mortality and the natural history of the disorder. (Yes 6-0)
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. (Yes-3, Need More Information -3)
4. The interventions should be reasonably available to affected newborns. (Yes-5, Need More Information -1)
5. Appropriate follow-up should be available for newborns that have a false positive newborn screen. (Yes-1, Need More Information-2, Not Applicable-3). At least three members thought that this was not applicable because no false positives would be possible using the proposed screening tests.
6. 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). (Yes-5, Need More Information-1)
7. If a new sample collection system is needed to add a disorder, reliability and timeliness of sample collection must be demonstrated. (Yes-6)
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. (Yes-6)
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. (Yes-5, Need More Information-1)

Dr. Baker participated in the discussion but recused herself from the voting because of conflicts of interest.

A motion to add Spinal Muscular Atrophy to the panel was moved and seconded. The committee then unanimously voted (6-0, Baker recused, Chair not voting) to recommend the addition of Spinal Muscular Atrophy to the mandatory screening panel.

Addendum:

At the time of the meeting, the US Department of Health and Human Services Advisory Committee On Heritable Disorders in Newborns and Children was in the process of reviewing SMA screening but had not yet made a recommendation. Following our meeting, the federal committee recommended adding SMA screening to the Recommended Uniform Screening Panel by a vote of 8-5. The dissenting votes included concerns about the lack of data on long term outcomes, and the paucity of publications, with much of the research data as yet unpublished.

Members present:
Mei Baker MD (recused from voting)
Jeffrey Britton MD
Christine Brown
Arthur Derse MD JD
Ousmane Diallo MD MPH
Norman Fost MD MPH (Chair)
Kevin Josephson MS CGC
Stephen Leuthner MD

Report approved May 22, 2018