COMPASS

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Newborn Screening Requirement for SMA to Accelerate Diagnoses

The early diagnosis of spinal muscular atrophy (SMA) is a critical factor in preventing the debilitating loss of neurons in the early stages of a child's life and achieving the maximal therapeutic benefits of treatment. Infants diagnosed with SMA type 1, which accounts for about 60 percent of cases, generally experience severe denervation by three months of age. This means that motor neurons begin to be irreversibly lost, causing children to never gain the ability to sit or walk. However, regulatory authorities in the United States have now taken a positive step forward in preventing diagnostic delays that hinder early intervention.

On February 8, 2018 the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) issued a recommendation to the Secretary of Health and Human Services that all states should include SMA in routine newborn screenings. This is a significant milestone in the quest to have every infant born in the United States tested for the disease. With an incidence of approximately one in 11,000, more than 360 infants will be born annually with SMA. Widespread early diagnosis is a critical first step toward ensuring these infants can receive prompt treatment and are given the best chance at improved development and survival.

What is newborn screening?

At birth, infants are tested for certain serious conditions, allowing doctors to begin treatment before harmful effects occur. To screen for diseases, such as SMA, a blood test is performed 24 to 48 hours after birth. If a condition is identified, parents are immediately notified and follow-up diagnostic testing is conducted. This routine process for early diagnosis provides both medical care teams and families with the ability to seek out resources and treatments before the onset of serious and often irreversible symptoms that could drastically affect a child's life.

Newborn screenings are a state public health service that reaches each of the nearly 4 million infants born in the United States annually. There are currently screening tests available for more than 60 diseases, but conditions included in each state's newborn screenings vary.

For a condition like SMA to become part of routine newborn screening, it must be submitted to the federal Recommended Uniform Screening Panel (RUSP). The process for including new conditions involves the submission of a nomination to the ACHDNC, committee review and deliberation, a committee vote, and a final decision by the Secretary of the Department of Health and Human Services (HHS). For SMA, a nomination was submitted and reviewed and the ACHDNC provided a recommendation to include SMA in newborn screening. Now, the HHS Secretary has 120 days by federal law to issue a final decision based on this recommendation and, if positive, the HHS will send notices to states in support of the addition of SMA to state newborn screening panels.

To support the nomination of SMA to be included by the RUSP, Cure SMA worked alongside subject matter experts to write and submit the nomination. In addition, Cure SMA and other stakeholders supported testimonies before the advisory committee on heritable disorders in newborns and children (ACHDNC), compiled and prepared data to support the submission, worked with Congress and the Centers for Disease Control and Prevention (CDC) to secure necessary appropriations, and conducted state-level advocacy efforts.

What is the RUSP?

The Recommended Uniform Screening Panel (RUSP) is a list of heritable disorders recommended by the HHS Secretary to be included by states in routine newborn screenings. In 2006, the panel initially included 29 conditions. There are now 35 conditions on the RUSP, including SMA once the HHS secretary gives final approval.

To support the nomination of SMA to be included on the RUSP, Cure SMA worked alongside subject matter experts to write and submit the nomination. In addition, Cure SMA and other stakeholders gave testimonies before the ACHDNC, and compiled and prepared data to support the submission. While the nomination was being reviewed, Cure SMA and the community also worked with Congress and the Centers for Disease Control and Prevention (CDC) to secure necessary appropriations, and conducted state-level advocacy efforts.

Ultimately, a full nomination package was reviewed by the committee, who considered the following information and data on newborn screening for SMA:

I. There is strong natural history data indicating the natural progression of SMA.

II. There is an approved treatment for SMA.

III. There is evidence that pre-symptomatic treatment for SMA is more effective than treatment after the onset of symptoms.

IV. The application is supported by pilot screening data from New York and Taiwan.

V. There is a reliable and cost-effective diagnostic test for SMA that can be used on a broad scale.

An essential part of our efforts focused on collaborating with the SMA community, as families of those affected by SMA and local advocates played a critical role in telling their stories to both federal and state policymakers. Both physicians and caregivers testified before the ACHDNC to support the nomination, describing the urgent importance of early detection and intervention to achieve the best outcomes for their children. Doctors highlighted the drastic motor improvements children who are treated earlier are able to achieve and parents described first-hand the need to reduce the "diagnostic odyssey" so many families face when trying to detect and treat SMA.

Additionally, Cure SMA established the SMA Newborn Screening Coalition to bring stakeholders together to support the nomination through its approval. The Coalition included staff from Cure SMA and representatives from Biogen, AveXis, and Genentech/Roche.

How can newborn screening help those affected by SMA?

There are about 360 infants born with SMA annually, which means that there are 360 opportunities each year for newborn screening to improve a child's chances of achieving age-appropriate developmental milestones. Newborn screening can help to:

- Pre-empt irreversible motor neuron loss;
- Increase prompt intervention; and
- Eliminate long diagnostic delays.

By including SMA in newborn screenings, infants may receive treatment before showing symptoms caused by motor neuron loss, which often occurs by three months of age for children with SMA type 1. Research suggests that early treatment may allow therapies to be more effective and improve outcomes. Additionally, routine newborn screenings for SMA can help eliminate long and difficult diagnostic delays, which can range from three months for SMA type 1 to three years for SMA type 3, and often lead to SMA being identified after the onset of motor neuron loss.

DR. RICHARD FINKEL

Dr. Richard Finkel, a principal investigator for NURTURE, a trial used to support the nomination of SMA to be added to the RUSP, commented, *"**Newborn screening for SMA really is a priority** to be able to get treatments to these infants so they can have the **best chance for a hopefully normal lifespan**, as well as normal growth and development."*

AMY MEDINA

Amy Medina, a parent of two children with SMA, one of whom is enrolled in the NURTURE trial, described a ***"night and day difference"*** *for her child who received pre-symptomatic treatment. Amy described feeling "isolated" and lacking information when her first son was diagnosed, but was able to seek out clinical trials and support groups when her family received an early diagnosis for their second son.* ***Amy noted that routine newborn screening will give families both hope and time to prepare.***

The impact of early diagnosis has been demonstrated through several studies that reinforce the importance of newborn screening. Data from both the ENDEAR and NURTURE trial, which each tested the efficacy of the treatment nusinersen at different stages of disease development, were used to support the nomination of SMA to the RUSP.

The ENDEAR trial evaluated infants with SMA type 1 that were treated with nusinersen after the onset of symptoms. The study found that infants treated with nusinersen demonstrated a significantly greater percentage of motor milestones than those in the control arm, who did not receive the treatment. Importantly, the study also showed that earlier treatment in symptomatic patients could lead to improved development. As the existence of a treatment for SMA is an essential part of the RUSP submission, data from ENDEAR strongly support the positive effects that early intervention can have.

The NURTURE trial expanded upon these results. NURTURE examined infants who were identified through genetic testing, carried two or three copies of the survival motor neuron 2 (SMN2) gene, and were treated pre-symptomatically with nusinersen. This means infants were able to receive intervention before the onset of motor neuron loss or observable disease.

The trial demonstrated several important findings, including:

- Infants with three copies of SMN2, which is typically associated with SMA type 2, who received nusinersen met motor milestones at a normal rate, consistent with those of children who did not have SMA.
- Infants with two copies of SMN2, which is generally consistent with the genotypes of those diagnosed with SMA type 1, developed ahead of infants enrolled in the ENDEAR trial.
- No infant enrolled in the NURTURE study died or needed permanent ventilation, which was not the case for those treated after the onset of symptoms in ENDEAR.

The results of the NURTURE trial highlight the critical difference that pre-symptomatic intervention can make, something which can only be achieved on a broad scale through routine newborn screening. Dr. Finkel noted that all three of the patients he is treating that are enrolled in the trial are making "remarkable gains" and meeting the same developmental milestones as children without SMA, including walking. Amy Medina described a similar experience for her family. Amy commented, ***"My child is almost two years old and can independently walk on his own. What children with SMA could never accomplish, I am witnessing in my day-to-day life with him going above and beyond this."***

As the committee considered whether or not there was evidence that pre-symptomatic treatment for SMA would be more effective than treatment after the onset of symptoms, NURTURE provided essential findings that demonstrated to the committee the importance of prompt treatment and early diagnosis.

What now?

While the addition of SMA to the RUSP is an important first step, each state must act to implement newborn screening for SMA. Throughout the nomination and review process, Cure SMA worked alongside advocates to educate state-level "SMA champions" across the country to ensure that this recommendation would be executed upon when the time came. Educational efforts included holding a newborn screening symposium at the Annual SMA Conference, hosting a newborn screening webinar, and releasing an advocacy toolkit.

With these resources, champions, and local advocates, Cure SMA will now work with state health leaders to ensure that all states include SMA in routine newborn screenings.

Our efforts will be two-pronged:

1. **We will engage in critical state-level advocacy.** Several states will roll out newborn screening requirements for SMA in the coming year, but more state-level advocacy is needed to ensure that newborns with SMA throughout the country receive early diagnoses. Some states, such as Missouri and Minnesota, have already taken legislative action to implement permanent SMA screening for newborns. This legislative movement is an important vehicle to ensuring that all newborns in the US are screened for SMA. We hope that our advocacy efforts, alongside those of families and patient groups, will implore the other 48 states to follow the necessary steps outlined by their legislative bodies to incorporate SMA in newborn screenings, as well.

2. **We will conduct nationwide education.** Education will be needed to inform states on why SMA screening is necessary, but also to assure that physicians are equipped with the correct information to support patients once a diagnosis is made. Many parents or caregivers of children diagnosed with SMA describe a gap in information following the initial diagnosis. During the submission process, our team worked to create treatment plans for infants who screen positive, which will help families be connected to physicians who can manage the full range of care required for SMA. Now, this education on SMA will be an important tool to ensure that children receive proper interventions and families have the resources that they need.

3. **We will continue to advocate for necessary federal funding of newborn screening.** This includes funding for the Health Resources and Services Administration (of which the ACHDNC is a part), the CDC, and the NIH.

We would like to extend our sincerest thanks to the ACHDNC for this important decision, as well as all those who supported the nomination and its review. In particular, we would also like to thank all of the families affected by SMA who advocated or testified for the inclusion of SMA in newborn screening at both the federal and state levels. We also thank the workgroup that assembled this nomination. Without all your support, this milestone would not have been reached.

While this is a critical first step, we will continue to work to ensure that states implement the recommendation and all newborns in the United States are screened for SMA. We urge the HHS Secretary to formally adopt the nomination of SMA without delay and provide those whose families have been impacted by the disease with reinvigorated hope for the future.

> ***"A large educational effort will be needed to ensure professionals in state health departments understand why treatment needs to be initiated as soon as possible after genetic diagnosis has been established and confirmed, and why the review and approval process [for treatments] needs to be expedited in particular for those infants identified by newborn screening."***
>
> – Dr. Richard Finkel

For more information on our surveys visit **cureSMA.org/communitysurvey**

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